Farid Moinfar

Essentials of Diagnostic Breast Pathology

A Practical Approach

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With 116 Figures in 1128 Seperate Illustrations and 6 Tables

Springer

Farid Moinfar, MD
Associate Professor of Pathology
Director, Unit of Breast & Gynecologic Pathology
Department of Pathology
Medical University Graz
Auenbruggerplatz 25
8036 Graz
Austria

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Dedication

This work is dedicated with great appreciation and gratitude to

My dear parents, Shamsi and Ali Akbar Moinfar

My wonderful wife, Shokufeh Sodeifi-Moinfar

and

All my teachers and mentors, particularly
Dr. John G. Azzopardi, whose magnificent book
and other papers inspired me,
and Dr. Fattaneh A. Tavassoli, a great mentor and friend.

Preface

Several excellent and comprehensive textbooks have been written on breast pathology [1–5]. The magnificent book *Problems in Breast Pathology* [1] written by John G. Azzopardi, and two more recent great works by Fattaneh A. Tavassoli [4] and Paul P. Rosen [3] cover almost all aspects of classic and modern breast pathology. So why should one dare to write a new book on this subject?

Over the past few years, the Department of Pathology, Medical University Graz has organized annual intensive 5-day courses on diagnostic breast pathology in order to share the experience in this field and demonstrate and discuss several common diagnostic problems, including tumor-like lesions, intraductal proliferative lesions, variants of ductal and lobular intraepithelial neoplasias, papillary neoplasms, and a variety of infiltrating breast carcinomas. During these courses, it has been my constant experience that most practicing pathologists and pathologists in training appreciate receiving a precise summary of the diagnostic criteria for each entity combined with a brief and accurate discussion of the main differential diagnoses. In dealing with a variety of breast lesions in daily practice, surgical pathologists want and need to know the essentials of diagnostic breast pathology.

So, the idea to write this book gradually evolved from these diagnostic courses, with a main focus on the essentials. This book is therefore designed as a diagnostic aid for pathologists when they encounter common as well as unusual or even challenging and very difficult cases. In trying to achieve this goal, it was necessary to reduce the text but emphasize case presentations that deal with the described entities. Indeed, this book contains over 1,100 full-color illustrations demonstrating gross, histologic, cytologic, and immunohistochemical findings of common as well as challenging benign and malignant breast lesions.

I am most grateful to Dr. Fattaneh A. Tavassoli for her constructive comments, suggestions, and encouragement throughout the preparation of this book. I am indebted to the staff pathologists at the Department of Pathology, Medical University Graz, who have supported me during the preparation of this book. I am thankful to Drs. Helmut Denk, Manfred Ratschek and Wolfgang Öhlinger for their kind support. I would like to acknowledge the excellent assistance and expertise of Mrs. Andrea Kaps in preparing the photomicrographs. I would like to thank the staff of the publisher, Springer, in particular Mrs. Gabriele M. Schröder and Mrs. Ellen Blasig for their professional and efficient cooperation and consideration in the production of this book.

Once again, I would like to express my special thanks to my wife, Shokufeh Sodeifi-Moinfar, for her support and tolerance over the past three years.

Graz, Austria
November 2006

Farid Moinfar

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"One relies on one's experience. But "experience" can be merely the repetition of the same error often enough… One must be willing, even anxious, to learn from one's error. This requires a degree of humility, a readiness to listen to the arguments of others, including those of one's juniors, and the inclination to re-examine cases in which a mistaken diagnosis has been made and to analyse the reasons for the original mistake."

John G. Azzopardi
Problems in Breast Pathology

"Thus I learned early on the great importance of a close correlation between clinical and pathological studies. Each complements and supplements the other; it is impossible to do intelligent surgery without a thorough understanding of the pathology of disease and it is equally impossible to make an intelligent interpretation of pathology without a clear understanding of its clinical implications."

Arthur Purdy Stout
Guiding the Surgeon's Hand:
The History of American Surgical Pathology
Juan Rosai (Editor)

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Abbreviations

ADH	Atypical ductal hyperplasia
CK	Cytokeratin
CNB	Core needle biopsy
CSL	Complex sclerosing lesion
DLBCL	Diffuse large B-cell lymphoma
DCIS	Ductal carcinoma in situ
DIN	Ductal intraepithelial neoplasia
FA	Fibroadenoma
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FS	Frozen section
H&E	Hematoxylin and eosin
HMW	High molecular weight
IDC	Infiltrating ductal carcinoma
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
LCIS	Lobular carcinoma in situ
LIN	Lobular intraepithelial neoplasia
LMW	Low molecular weight
MALT	Mucosa-associated lymphoid tissue
MEC	Myoepithelial cells
MFH	Malignant fibrous histiocytoma
MSA	Muscle-specific actin
N/C	Nucleus/cytoplasm
NDA	Nipple duct adenoma
PASH	Pseudoangiomatous stromal hyperplasia
PSA	Prostatic specific antigen
PT	Phylloides tumor
RS	Radial scar
SA	Sclerosing adenosis
SLN	Sentinel lymph node
SMA	Smooth muscle actin
SMMHC	Smooth muscle myosin, heavy chain
TDLU	Terminal duct-lobular unit
UDH	Usual ductal hyperplasia

The Normal Breast

Contents

CHAPTER 1 The Normal Breast

1.1 Anatomy

The "normal" mature female breast ranges from 50 g to greater than 400 g. A typical nonlactating breast weighs between 150 and 250 g, while the lactating breast may exceed 400 g. The size and density of the breast are influenced by the individual's body habitus. The average breast measures 10–12 cm in diameter, and its average thickness centrally is 5–8 cm. The adult breast lies between the 2nd and 6th ribs in the vertical axis and between the sternal edge and the midaxillary line in the horizontal axis. The breast is attached to the dermis by fibrous bands called suspensory (Cooper's) ligaments anteriorly, and the posterior surface is the pectoral fascia. Approximately three-quarters of the breast is on the pectoralis major muscle (superior and medial portions).

The breast tissue is divided into upper outer, upper inner, lower outer, and lower inner quadrants; the subareolar area; and the axillary tail of the upper outer quadrant. The arterial blood supply is derived from the axillary, intercostal, and internal mammary arteries, and venous drainage is into the axillary and internal mammary veins. Lymphatic drainage is to the axillary, subclavicular, and internal mammary lymph nodes. While drainage from the upper outer quadrant is predominantly to the axillary lymph nodes, drainage from the inner quadrants is to the internal mammary chain of nodes. The nerves are branches of the thoracic segmentals.

1.1.1 Nipple-Areolar Complex

The nipple is located in the center of the complex surrounded by the areola. Numerous sebaceous glands (the glands of Montgomery) and apocrine glands are present within the areolar dermis. The nipple dermis and subcutaneous tissue contain smooth muscle bundles arranged radially and longitudinally that serve to identify the nipple histologically. The nipple is rich in sensory nerve endings. Stratified squamous epithelium covers the nipple and areola. Clear cells without cytologic atypia may be present in the surface of the epithelium. Lactiferous ducts course through the nipple dermis and open onto the epidermis. On cross-sections of the nipple, 14–24 ducts may be seen. Lobules can be observed in about 15% of nipples [5, 6, 8, 10].

1.1.2 Structure of the Adult Duct System (Fig. 1)

The breast consists of 15–20 segments (lobes). Each segment is drained by a collecting duct. The segments are ill defined and cannot be identified by gross examination.

Collecting ducts connect the nipple with lactiferous sinus. Segmental (lactiferous) and subsegmental (major) ducts connect lactiferous sinus with terminal duct-lobular units (TDLUs).

Lobules are composed of terminal ducts and acini and their specialized supporting stroma. The terminal ducts are either extralobular or intralobular depending on their location relative to the specialized lobular stroma.

The stroma within the lobules is specialized containing fine collagen fibers, abundant reticulin and numerous small vessels. It is much more cellular than the interlobular stroma. Due to quantitative and qualitative differences, the intralobular stroma is much more distinctive than the periductal stroma. Intralobular stroma also often displays a mucoid character (positive for alcian blue). One should keep in mind that while the mammary ducts are invested with elastic tissue, the lobules are completely devoid of it.

Except for a small portion of the collecting ducts at the nipple where squamous epithelium lines the duct, the entire duct system is lined by two cell layers: luminal epithelial cells and basally located myoepithelial cells. Depending on their functions, the luminal epithelial cells can be flattened, low cylindrical, or columnar. Myoepithelial cells are located in close contact with cytoplasm of the epithelial cells and are surrounded by basal lamina (Figs. 1.5 and 1.6). Myoepithelial cells often show ovoid to elongated "bipolar" dense nuclei and small cytoplasms; in the luteal phase of the cycle, however, there is glycogen accumulation, which gives a cleared appearance of cytoplasm in sections stained with hematoxylin and eosin.

Normal breast lobules during the early follicular phase of the cycle show poorly defined lumina of acinar structures, luminal epithelial cells with dark, centrally located nuclei, and eosinophilic cytoplasm.

Normal breast lobules in the luteal phase show vacuolization and ballooning of the basally located myoepithelial cells due to an increase in glycogen cytoplasmic content. "Apical snouts" of luminal epithelial cells are present due to the secretory activity. The lumina are enlarged and contain eosinophilic secretory material. Prominent stromal edema is present [1, 5–8].

1.2 Pregnancy and Lactation

Organoid enlargement and dilation of lobular units occur at the expense of fibrofatty stroma.

The luminal epithelial cells of the enlarged acini show loss of apical aspect of cells through the secretory process, vacuolated cytoplasms, and enlarged round nuclei, often with a "hobnail" pattern. Prominent nucleoli and increased mitotic activity are common.

There is no intraluminal epithelial proliferation [2–4].

1.3 Menopause

Postmenopausal breast involution is generally characterized by regression of the parenchymal TDLUs revealing marked reduction of glandular tissue with an increase in fat deposition and relative predominance of fibroconnective tissue. At the end stage of menopausal involution of the breast, only small islands of lobules (TDLUs) embedded in dense, hyalinized fibrous tissue remain [4, 7].

1.4 Immunoprofile

The luminal epithelial cells are typically immunoreactive for low molecular weight (LMW) cytokeratin (CK) such as CK8, CK18, and CK19. These cells also show a heterogeneous reaction for high molecular weight (HMW)-CK such as CK34BE12 (K-903) and CK5/6. In contrast, the vast majority of myoepithelial cells are negative (or only focally and weakly positive) for LMW-CKs. The myoepithelial cells may show a heterogeneous immunoreaction for HMW-CKs such as CK5/6 or CK34BE12.

Myoepithelial cells can be decorated with a variety of antibodies against actin (smooth muscle actin or muscle-specific actin); smooth muscle myosin, heavy chain; calponin; S100 protein; p63; CD10; 14-3-3 sigma; and so on (Figs. 1.7 and 1.8).

Estrogen receptors (ER), progesterone receptors (PR), and androgen receptors (AR) are sporadically positive in luminal epithelial cells (some areas are, however, completely negative for ER, PR, and AR). ER, PR, and AR are almost always negative in myoepithelial cells [9, 11].

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1

Fig. 1: Normal breast.

Figs. 1.1 and **1.2:** Low magnification of normal breast shows several lobules composed of terminal ducts and acini (ductules) within a specialized supporting stroma.

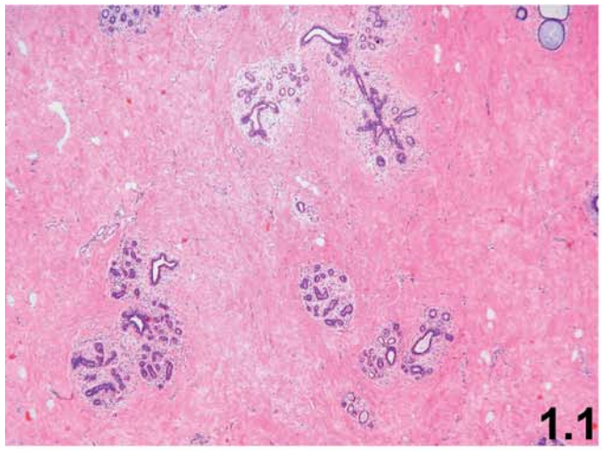
Fig. 1.3: A terminal duct-lobular unit (TDLU) with regular acinar structures and a small segment of extralobular (terminal) duct. The vast majority of benign and malignant proliferations of the breast develop in the TDLUs.

Fig. 1.4: A lobule showing acini and specialized stromal cells. The stroma is more cellular than the interlobular stroma. The intralobular stroma contains fine collagen fibers and abundant reticulin but characteristically lacks elastic fibers (not shown).

Figs. 1.5 and **1.6:** The acini (ductules) are lined by luminal epithelial and basally located myoepithelial cells. The myoepithelial cells often show elongated or bipolar nuclei. The acini are surrounded by a continuous layer of basal lamina.

Fig. 1.7: Immunohistochemistry for smooth muscle actin showing cytoplasmic positivity in the myoepithelial cells.

Fig. 1.8: The myoepithelial cells typically display nuclear positivity for p63.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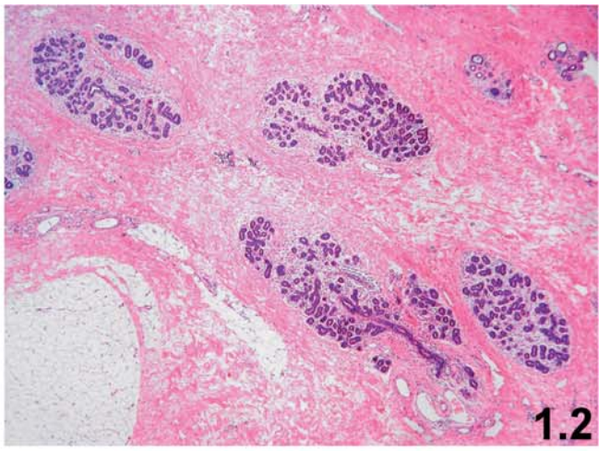
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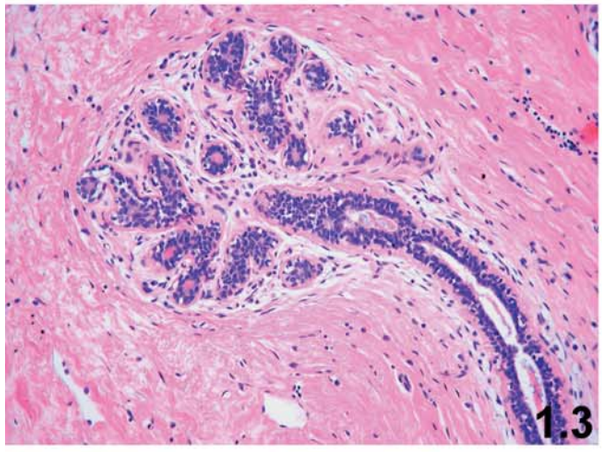
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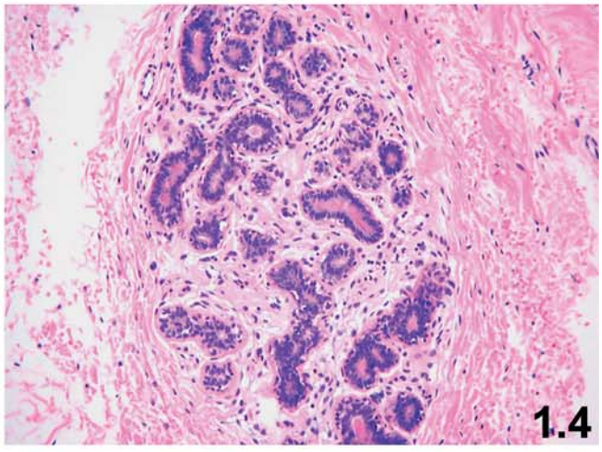
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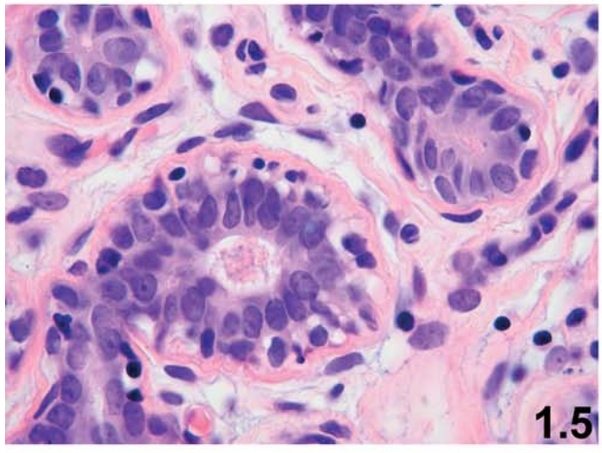
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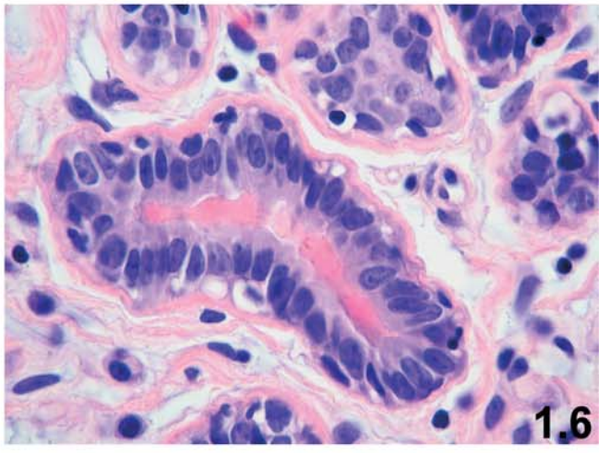
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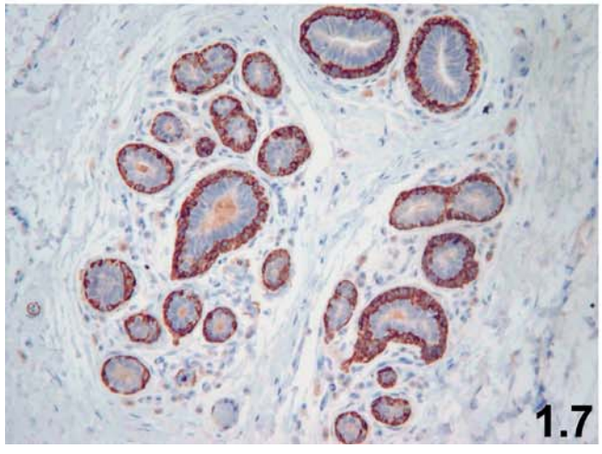
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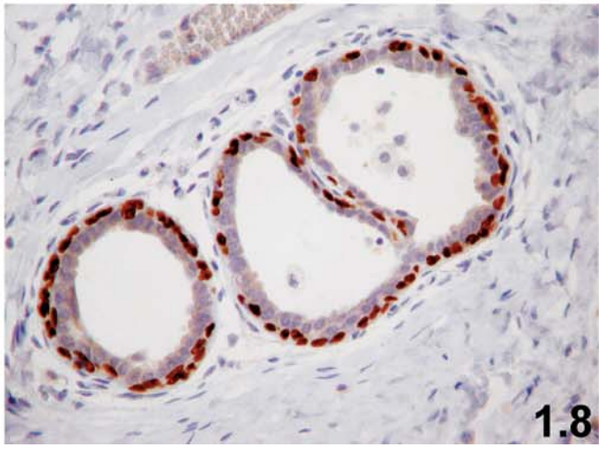
1.8

Specimen Processing

Contents

CHAPTER 2

Specimen Processing

2.1 Frozen Section

Frozen section (FS) is a useful method for confirming the diagnosis of carcinoma suspected clinically when an immediate intraoperative therapeutic decision will be based on its results. The increasing use of preoperative core needle biopsies, however, has dramatically reduced the need for FS examination of the breast specimens [2, 4, 6, 11, 13, 15, 18].

An FS evaluation is no longer automatically anticipated for every scheduled breast biopsy. Even if it is required by some surgeons, pathologists should refrain from taking random samples for FS in the absence of a grossly visible mammary lesion [2, 15].

Visual inspection of fresh breast specimens for cysts, streaks, and abnormal color and texture is useful, but frequently palpation is of even greater value. Infiltrating carcinomas (usually of ductal type) often have a hard consistency due to desmoplastic stromal reaction/proliferation. The fat tissue close to the infiltrating carcinoma usually shows a very intense yellow color that differs from the color of the adipose tissue away from carcinoma [6, 11, 13, 16, 18].

Frozen section can be used for intraoperative assessment of the resection margins. Gross examination of the resection specimen alone does not accurately reflect margin status in at least 25% of the cases [3]. It has been shown that intraoperative analysis of margins using FS is effective for minimizing the number of additional operations [7].

Sentinel lymph nodes can reliably be examined by FS [1, 5, 14]. This method, however, usually cannot detect small areas of micrometastases [1, 5].

2.1.1 Contraindications to FS Histology

If on the cut surface there is no tumor or a suspicious area (excisional biopsy performed for suspicious microcalcification), FS should not be performed [2, 11, 13, 15].

Small breast tumors (≤5 mm) on the cut surface should not be examined by FS (see additional comments) [2, 13].

Caution

- One should not report FS without gross examination of the specimen!
- Underdiagnosis of ductal intraepithelial diagnosis, DIN (DCIS) on frozen section is not a serious problem. Overdiagnosis of benign complex lesions (sclerosing papilloma with pseudoinvasion, severe epithelial hyperplasia in a fibroadenoma, sclerosing adenosis, radial scar, etc.) as infiltrating carcinomas, however, is a serious error. *If in doubt, await permanent sections.*
- The diagnosis of lobular intraepithelial neoplasia, LIN (lobular carcinoma in situ, LCIS) is extremely difficult on FS. The diagnosis should be made on permanent sections. LIN does not differ grossly from normal breast tissue.
- The diagnosis of invasive lobular carcinoma (ILC) can be difficult on FS. The uniform and small tumor cells can easily be mistaken for chronic inflammatory cells (chronic mastitis). It is important to keep in mind that the gross appearance of ILC can be very similar to that of normal breast tissue, fibrocystic change, or mastitis in 20–30% of cases.
- Small tubular carcinomas and radial scars both represent as stellate firm lesions often with chalky or yellow streaks. The gross appearance of these lesions often suggests malignancy. The histologic evaluation of FS in such cases can be very difficult. In that setting, a definite diagnosis should be made on permanent sections.
- Regarding solid or cystic tumors with prominent papillary projections (papilloma versus papillary carcinoma): *If FS histology reveals a papillary neoplasm, as a rule, a definitive intraoperative diagnosis should not be made. One needs to wait for permanent sections after proper formalin fixation!*

2.1.2 Additional Comments

Some experts (particularly in the United States, following the recommendation of the Association of Directors of Anatomic and Surgical Pathology) require a minimum size of 1 cm for breast lesions in order to be evaluated by FS [2]. Others continue to use FS even in nonpalpable breast lesions [10, 12].

Touch preparation cytology (imprint cytology) of fresh breast specimens is a valuable method that can be used intraoperatively. It often adds additional cytomorphologic details to the gross and histological patterns.

Imprint cytology provides an accurate, simple, rapid, and cost-effective evaluation of lumpectomy margins for patients undergoing breast conservation treatment [8, 9, 17].

Sentinel lymph nodes can reliably be examined by imprint cytology. With this method, however, isolated tumor cells or micrometastases often remain undetected [1, 5]. The combination of FS and imprint cytology may improve the sensitivity over that achieved by a single method.

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2.2 Core Needle Biopsy

Lesions presenting as a mass can be accurately diagnosed with core needle biopsy (CNB) using three to four cores. The Abbey core biopsy technique or vacuum-assisted core biopsy (Mammotome) may completely excise some of the small radiologically detected breast lesions [5, 12]

Caution

- In cases of "atypical intraductal hyperplasia", excisional biopsies need to be performed.
- Core biopsies showing papillary neoplasms of the breast should lead to complete excision in order to be evaluated entirely. A final diagnosis of papilloma, intraductal papillary carcinoma, or atypical papilloma can often be made only on the excisional biopsies of papillary breast tumors.
- Frozen section of core biopsies or small incisional biopsies should never be done!
- Benign sclerosing lesions with pseudoinfiltrative patterns (radial scar, sclerosing adenosis) can be mistaken for invasive carcinomas. The recognition of a myoepithelial cell layer in such conditions helps avoid overdiagnosis.
- The grading of invasive carcinoma in CNB (Nottingham grading system), particularly the assessment of mitotic activity, can be problematic and should better be applied in excisional biopsies.

2.2.1 Additional Comments

Currently, there are no well-established guidelines for managing patients with lobular intraepithelial neoplasia (LIN, or atypical lobular hyperplasia/lobular carcinoma in situ) diagnosed in CNB. However, some recent studies [3, 6] have indicated that subsequent surgical excision is warranted in patients with CNB diagnoses of LIN in order to exclude the presence of DIN (DCIS) or invasive carcinoma.

Fibroepithelial lesions with cellular stroma in breast CNB specimens may result in either fibroadenoma or phylloides tumor at excision. Assessment of stromal cellularity and mitoses as well as degree of cytological atypia may help determine the probability of phylloides tumor and may guide management in these cases [8].

Several recent reports have shown that routine use of touch imprint cytology of CNB can provide an immediate and reliable cytological diagnosis of symptomatic breast lesions. The potential use of this technique in a breast clinic setting may help relieve patient anxiety and expedite the planning of further surgical management [9, 10, 11].

Fine needle aspiration (FNA) for palpable masses, coupled with a physical and mammographic examination (triple test) is highly accurate for a diagnosis of breast cancer when all three modalities indicate malignancy and for a benign lesion when all three are negative. The accuracy of FNA for nonpalpable breast lesions is relatively low [13].

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2.3 Excisional Biopsy

The pathologist should record the shape, three-dimensional size in centimeters, and any unusual features. The biopsy should have sutures on different locations to allow exact topographic orientation [3, 8, 14].

An assessment of size of the invasive carcinoma and an estimation of the extent ("size") of DIN (DCIS) is important for the management and prognosis of breast carcinomas. Orientation, sectioning, and processing of biopsy specimens toward the nipple is one of the best ways to estimate the extent of DIN (DCIS). It should be emphasized that although an exact size determination of DIN (DCIS) is, in most cases, not possible, an estimation of its distribution or extent can and should be performed. This information should be an integral part of the pathology report [8, 17].

Optimally, the excisional biopsy should be conical in shape; the tip of such a sample would point toward the nipple, and its base toward the periphery of the breast. The sample should have sutures identifying the direction of the nipple, superior (inferior), and anterior margins [10, 11, 17].

The surface of the specimen should be marked by the pathologist, using either India ink or a variety of colors that adhere to the tissue surface [1, 2, 6, 7, 12].

Before any dyes are applied, the surface of the resected specimen should be blotted with a paper towel to remove excess moisture and blood. Various colors can be used to designate specific surfaces or margins. The surface of the specimen should be dried before slicing.

Serial sectioning and embedding of the sample sequentially from the periphery to the nipple can help identify the distribution of the lesion [11, 17].

Samples designated as inked margins are taken perpendicular to the six surfaces (two samples of each margin).

Tumors that grossly appear to be carcinomas 3 cm or smaller in diameter should be entirely submitted for histological examination. Adjacent tissue must be examined histologically in order to be evaluated for lymphatic invasion and intraepithelial neoplasia outside the lesion. For large carcinomas (>3 cm in diameter), one section per 1–2 cm of the tumor should be submitted for evaluation [3, 5, 8, 14, 15].

Biopsies of mammographically detected lesions suggestive of malignancy that are less than or equal to 5 cm in maximum dimension should be processed in their entirety. For larger specimens, at least 10 blocks from fibrous tissue should be evaluated histologically [3, 8, 9, 14, 15]. To avoid false-negative results, however, some laboratories (including academic centers) advocate processing the entire fibrous breast tissue regardless of the size of the excisional biopsies.

Reexcisional biopsies obtained because a prior biopsy had microscopically positive or "close" margins usually do not show grossly apparent tumor. Either the entire tissue or at least 10 blocks should be submitted for histologic examination.

Caution

- Avoid using the terms "close" or "negative" margin; instead, specify the distance from the edge of the cancer or DIN (DCIS) to the closest margin in millimeters.
- Negative margins, variably defined, are associated with a lower recurrence rate. However, about 40% of samples with negative margins (defined as the presence of 1 mm or more of uninvolved tissue between the tumor and the inked margin) show residual DCIS on reexcision! For this reason, some investigators require a minimum of 5 mm (or even 10 mm) between the lesion and the margin before considering the margin negative.
- The margin assessment of lobular intraepithelial neoplasia (LIN; LCIS) is meaningless because this kind of breast lesion very often occurs multifocally or multicentrally.

- One has to be aware of pathologic alterations attributable to needling procedures: Displaced DIN (DCIS) has been observed in breast stroma and within vascular channels in breast specimens that are obtained subsequent to core needle biopsy procedures. The displaced neoplastic cells of DIN (DCIS) can mimic stromal invasion. Histologic features suggesting such displacement include the presence of isolated fragments of tumorous epithelial cells in artificial spaces within breast stroma, accompanied by hemorrhage, sometimes along a needle track; hemosiderin-laden macrophages; fat necrosis; inflammation; and granulation tissue. The clinical significance of epithelial displacement is unknown. The artificial location of epithelial clusters within the vascular spaces should be mentioned in the surgical pathology report, with a comment that the significance of such finding remains uncertain.

2.3.1 Additional Comments

Studies using intraoperative cytological examination (touch imprint cytology, scraping cytology) of the resected margins have shown reliable results; however, false-negative results may occur [4].

Definitions of positive and close margins have not been standardized. Tumor transected at an inked surface represents a positive margin. Carcinoma and DIN (DCIS) less than 2 mm from the margin can be regarded as being close to the margin [17].

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2.4 Mastectomy

The description of the specimen should include overall size, the dimension and appearance of the skin, appearance of the nipple and areola, the presence of muscle and axillary tissue, and the presence of any palpable lesion.

The deep margin should be inked before the specimen is sliced. The breast is dissected by a series of parallel incisions approximately 4–5 mm apart through the posterior surface up to the skin.

The size and gross appearance of a tumor and the biopsy site should be noted. The appearance of four quadrants should be described. The size, location, and appearance of any discrete lesions including cysts should be reported.

Samples for histologic examination are taken from the tumor and/or biopsy site, nipple, skin, four quadrants, and deep (basal) margin. Two sections are taken randomly from the breast per quadrant. More extensive sectioning of the quadrants is indicated by the gross findings or if the mastectomy were done for intraepithelial neoplasias (DCIS, LCIS). The nipple and subareolar complex should be extensively sampled in cases of Paget's disease [18, 20].

In patients who received radiation therapy or (neo)adjuvant chemotherapy, extensive sampling of the mastectomy specimen is needed to identify any residual carcinoma and assess the therapeutically induced alterations on the tumor.

2.5 Axillary Lymph Nodes

Despite the prognostic and therapeutic significance of node status, there is no agreement on whether the dissected lymph nodes should be sampled partially or completely. To reduce the rate of false-negative results, however, a complete sampling of grossly normal-appearing lymph nodes is advised [8, 16].

Careful palpation after proper formalin fixation is particularly useful in identifying lymph nodes.

The number, size, and appearance of lymph nodes should be recorded.

Small lymph nodes (5 mm or smaller) are bisected and submitted in their entirely. While some investigators examine only representative sections from large nodes, most authors recommend examining the entire lymph nodes regardless of size. But if a lymph node contains grossly apparent metastatic carcinoma, it is unnecessary to process the entire lymph node for histological examination [8, 16].

Although the current TNM (UICC) classification on breast carcinoma [22b] does not pay particular attention to extranodal extension of metastatic tumor, extranodal infiltration (extension) of tumor should be noted in the pathology report because, in some studies, this finding has been associated with significantly decreased overall and recurrence-free survival, [10, 13].

2.6 Sentinel Lymph Nodes

Intraoperative morphologic evaluation of sentinel lymph nodes (SLNs) is appropriate if management of the patients will be changed during the operation by the result of this procedure. Intraoperative diagnosis of SLNs can be performed by frozen section, imprint cytology, or a combination of the two [6, 12, 14, 23–25].

SLN biopsy is an appropriate initial alternative to routine staging axillary lymph node dissection for patients with early-stage breast cancer with clinically negative axillary nodes. SLN biopsy should not be considered standard management of patients with DIN (DCIS), but it should be considered in cases of DIN (DCIS) when there exists a strong doubt of invasion and in cases with large solid tumors or extensive (>3 cm) DIN (DCIS).

Metastatic carcinoma is readily detected in a single hematoxylin and eosin (H&E) section of a SLN if it is involved with a macrometastasis (>2 mm). Serial sectioning and/or CK immunostaining contribute largely to the finding of micrometastases (metastases >0.2 mm but ≤2 mm) or submicrometastases (isolated tumor cell or very small aggregates of cell clusters ≤0.2 mm). If the intraoperative examination of SLN does not detect metastatic carcinoma, more intensive studies including serial sectioning eventually with CK immunostaining of the SLN can be performed. Currently, however, it is not mandatory to perform serial sectioning with additional immunohistochemical (CK) examination of SLN [5, 29, 30].

Various protocols combining multiple (serial) sections and CK immunohistochemistry have been used to examine SLNs, but currently there is no consensus as to which is most cost-effective. According to the current TNM (UICC) classification of breast carcinoma, a SLN that shows a few isolated epithelial tumor cells or very small cell clusters of tumorous cells that are less than 0.2 mm in diameter should be regarded pN0 (i+) and needs to be separated from micrometastasis (pN mi). The clinical significance of micrometastasis (pN mi) and submicrometastasis or pN0 (i+) is, however, uncertain [5, 9, 29, 30].

The current size definition of micrometastasis (metastasis between 0.2 mm and 2 mm) and submicrometastasis or isolated tumor cells (size ≤0.2 mm) as defined by the TNM is arbitrary and not evidence-based [9, 22b].

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Fibrocystic Change and Duct Ectasia

Contents

CHAPTER 3 Fibrocystic Change and Duct Ectasia

3.1 Fibrocystic Change

3.1.1 Definition

A benign alteration of the breast consisting of cystic dilatation of intralobular glands (terminal duct-lobular unit) with or without stromal fibrosis. Fibrocystic changes include apocrine metaplasia, mild epithelial hyperplasia, and mild degrees of adenosis.

3.1.2 Synonyms

There are several designations for fibrocystic change (FCC), such as fibrocystic disease, fibrous (fibrocystic) mastopathy, mammary dysplasia, and fibroadenosis cystica. The term "fibrocystic change" is the most appropriate one because it underlines an exaggerated physiologic phenomenon rather than a disease [3, 6, 7, 11, 12].

3.1.3 Etiology

Hormonal imbalances with a predominance or relative excess of estrogens [8, 16].

3.1.4 Macroscopy

Several clear or blue-domed cysts with a diameter of 1–2 mm (microcysts). Occasionally, larger cysts of 1–2 cm in diameter (macrocysts). Greyish-white cut surface with firm consistency.

3.1.5 Microscopic Features (Fig. 2)

- Round to ovoid cystically dilated spaces lined by one or two cell layer(s) of epithelial cells and attenuated myoepithelial cells.
- Apocrine metaplasia is a common finding. The apocrine metaplastic cells show abundant eosinophilic granular cytoplasm and round nuclei with prominent nucleoli. The cells often show a columnar configuration and display luminal cytoplasmic projections or "apical snouts."
- Sclerotic changes of the intralobular stroma may be prominent. In contrast to duct ectasia, the cysts and sclerotic areas do not contain elastic tissue.
- Rupture of the cysts with inflammatory reaction may be present.
- Microcalcifications are present in the lumens of cysts or within the connective tissues.
- A mild degree of adenosis or microscopic expansion of the lobules by an increase in the number of acinar structures per lobule can be present [1, 2, 3, 16].

Caution

- Fibrocystic change (FCC) without hyperplasia is not associated with an increased cancer risk. The designation of FCC should be restricted to lesions not associated with moderate to severe epithelial hyperplasia [11, 12].
- FCC represents an alteration of terminal duct-lobular units or intralobular glands. This condition should be clearly distinguished from duct ectasia, which is a disease of larger (extralobular) ducts (see section on duct ectasia) [2].
- Migrations of foam cells into the epithelial cell layers of cysts may mimic a pagetoid appearance of lobular intraepithelial neoplasia (pseudopagetoid appearance).
- Cysts that contain cell debris with fragmented, inhomogeneous secretory material should be examined at higher magnifications to exclude the possibility of intraepithelial neoplasia of flat type (see section on DIN flat type) [2].
- Apocrine metaplasia can be associated with significant cytologic atypia. To qualify as atypical apocrine metaplasia, the nuclei should at least reveal a threefold variation in size often with irregular chromatin distribution. The presence of prominent nucleoli is a common finding in ordinary apocrine metaplasia and, therefore, should not be used as an indication of atypicality.

3.1.6 Additional Comments

About one-third of women between 20 and 45 years of age show some clinical evidence of FCC. Histologically, FCC can be identified in about 55% of autopsies of women with clinically normal breasts [3, 6, 7, 11, 12].

FCC is frequently a multifocal, bilateral mammary alteration. It can cause premenstrual breast swelling or tenderness of 1 week's duration or can be associated with multiple hard, tender nodules. Permanent breast pain and tenderness can be the prominent clinical features of FCC in women 40–50 years of age [7, 10, 16].

FCC with atypical apocrine metaplasia seems to be associated with significant increased risk for breast cancer in women older than 60 years (elevated relative risk of 5.5 within 5.6 years of follow-up) [14].

Apocrine metaplastic cells are characteristically negative for ER and PR. They, however, are typically immunopositive for androgen receptors [15].

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3.2 Duct Ectasia (Periductal Mastitis)

3.2.1 Definition

A relatively common disease of extralobular ducts with irregular dilatation, periductal fibrosis, and/or inflammation.

3.2.2 Synonyms

Periductal mastitis, plasma cell mastitis, comedo mastitis, mastitis obliterans.

3.2.3 Etiology and Pathogenesis

Three possibilities exist [1, 5, 6, 14]:

1. Ductal dilatation as the initial phase of the disease due to endocrine abnormalities (hyperprolactinemia?)
2. Periductal inflammation, not ductal dilatation, as the initial and essential pathological manifestation of the disorder
3. Secondary duct ectasia proximal to intraductal proliferations such as central papilloma

3.2.4 Macroscopy

A single cystic space or multiple dilated structures containing thick or creamy yellow to white material sometimes closely resembling "comedo" necrosis [19]. Thickening and irregularity of the skin and nipple inversion are not infrequent [12, 20, 21].

3.2.5 Microscopic Features (Fig. 3)

- Periductal (large duct) lymphoplasmacytic infiltration
- Periductal fibrosis
- Irregular dilatation and obliteration of ducts
- Lipid-filled foam cells (macrophages) in the ductal lumina; eosinophilic inspissated luminal contents
- Intense neutrophilic granulocyte infiltration by acute phase of duct ectasia
- Total obliteration of the ductal lumen by fibrous tissue, with complete disappearance of the epithelial lining (mastitis obliterans) at the end stage
- "Recanalization" of obliterative duct ectasia: epithelial regeneration of the occluded duct, forming a single channel or grouped channels with penetration longitudinally into the fibrous plug
- Cystic disease and duct ectasia in combination; in practice, cystic disease and duct ectasia are not infrequently seen together in the same breast [1, 6, 19]

Table 3.1. Major differences between (fibro)cystic change and duct ectasia, modified from Azzopardi [1] (*TDLU* terminal duct-lobular unit)

Cystic change	Duct ectasia
Mainly lobular (TDLU) alteration	Ductal disease
Affects any part of breast	Mainly affects major ducts and subareolar ducts
No nipple discharge	Nipple discharge in about 20% of those with clinical disease
No nipple retraction	Nipple retraction common due to periductal fibrosis
No inflammatory disease except ruptured cysts	Usually periductal chronic inflammation
Can be associated with epithelial hyperplasia	Usually no epithelial hyperplasia
Cysts rounded or ovoid with thin yellow to brown contents	Irregularly dilated ducts with thin contents initially, followed by creamy ("comedo" type) contents; other ducts obliterated partially or completely by fibrous plug
No elastic layers in cyst walls (TDLU)	Usually elastica in ductal wall (elastic tissue stains)
Epithelial lining usually apocrine	Apocrine metaplasia very rare
Mammographic calcification more amorphous, scattered and not in line of ducts	Calcification common in periductal fibrosis, producing tubular, annular, and linear shadows on mammogram

Caution

- Duct ectasia (periductal mastitis) differs from (fibro)cystic change clinically, histopathologically, pathogenetically, and probably also etiologically. Duct ectasia can be associated with nipple abnormalities and may clinically simulate carcinoma. Pathologists should not misinterpret duct ectasia as FCC [1, 7, 9, 10, 12, 16, 20] (see Table 3.1).

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Fig. 2: Apocrine metaplasia.

Fig. 2.1: A cyst lined by one layer of cells showing deeply eosinophilic cytoplasm and round nuclei.

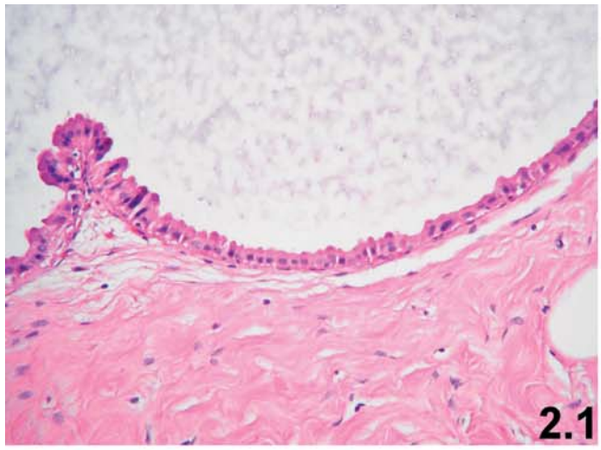
Fig. 2.2: Immunohistochemically, apocrine metaplastic cells are characteristically positive for androgen receptors. They are, however, almost always negative for estrogen receptors and progesterone receptors (not shown).

Fig. 2.3 and **2.4:** Imprint cytology showing clusters of apocrine metaplastic cells with abundant cytoplasm, round nuclei, and prominent nucleoli. Note the presence of numerous cytoplasmic granules (Diff-Quik stain).

Fig. 2.5 and **2.6:** Imprint cytology of a cyst shows cohesive clusters of apocrine metaplastic cells with eosinophilic or amphophilic cytoplasm and round, uniform nuclei (Papanicolaou stain).

Fig. 2.7: A cystically dilated duct lined by multiple layers of apocrine metaplastic cells. This is an example of intraductal apocrine hyperplasia.

Fig. 2.8: Higher magnification of apocrine metaplastic cells displays eosinophilic, granular cytoplasm.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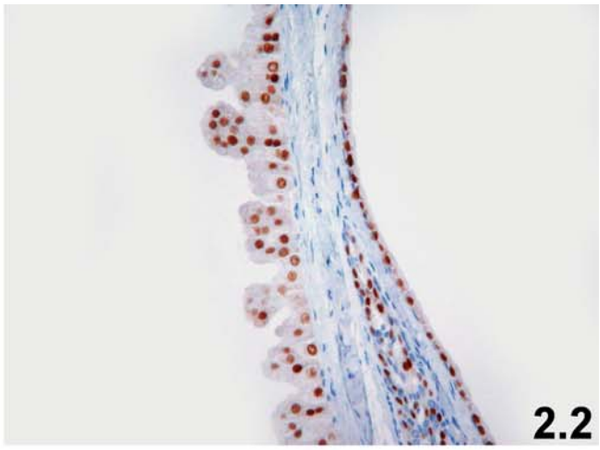
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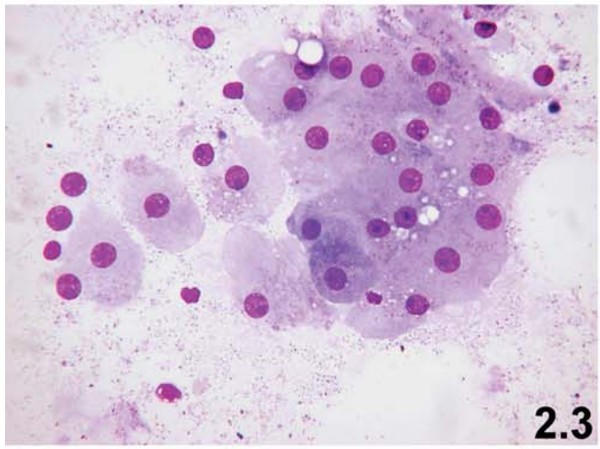
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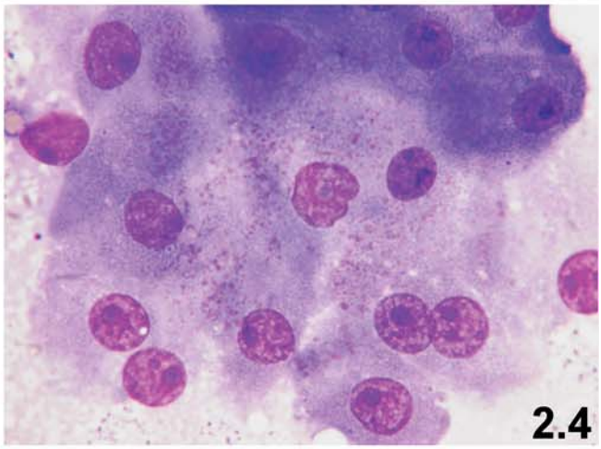
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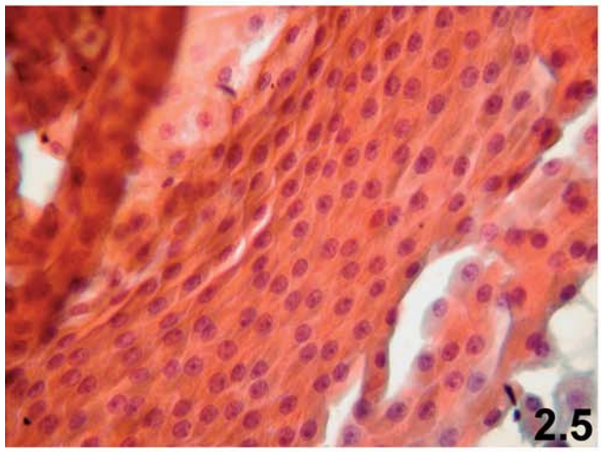
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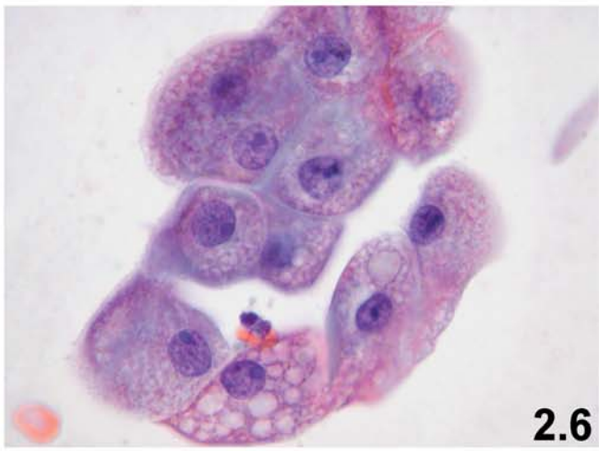
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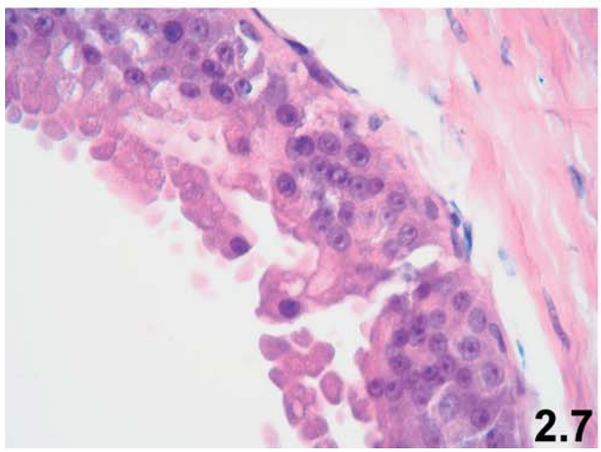
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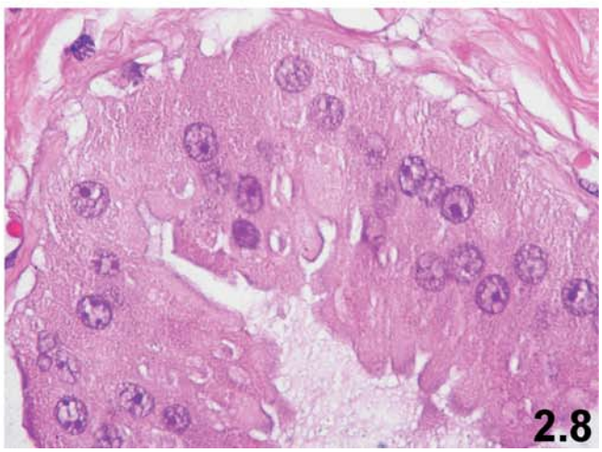
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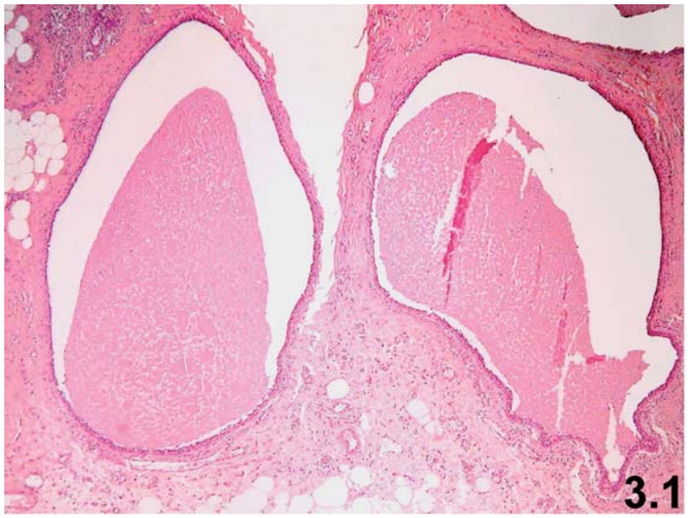
Fig. 3: Duct ectasia.

Case history: A 50-year-old woman presented with a hard and irregular mass in her left breast. She had a bloody nipple discharge and inflammatory skin changes. The clinical and mammographic findings were highly suspicious for malignancy (inflammatory breast carcinoma?). Excisional biopsy of the lesion was performed.

Fig. 3.1: Dilated ducts containing eosinophilic secretory material.

Fig. 3.2: While some ducts are irregularly dilated, others show marked periductal fibrosis and luminal obstruction.

Figs. 3.3 and **3.4:** Duct ectasia with marked periductal lymphoplasmacytic infiltration (chronic periductal mastitis).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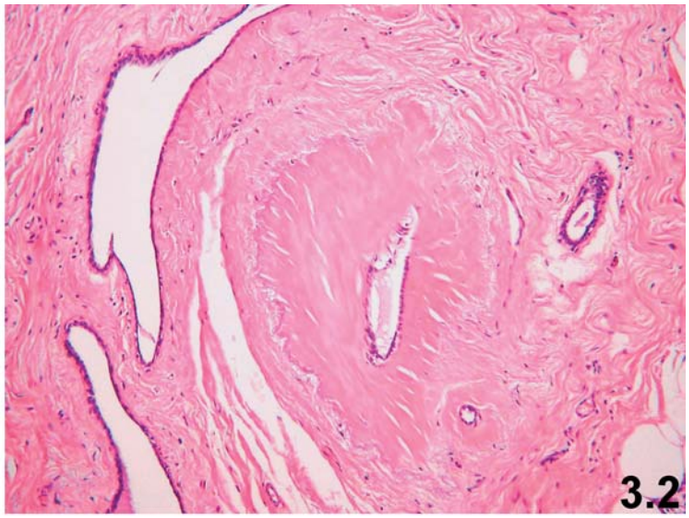
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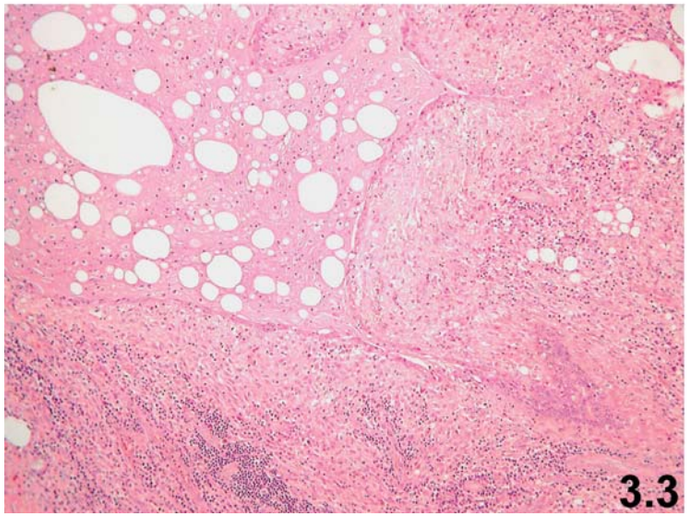
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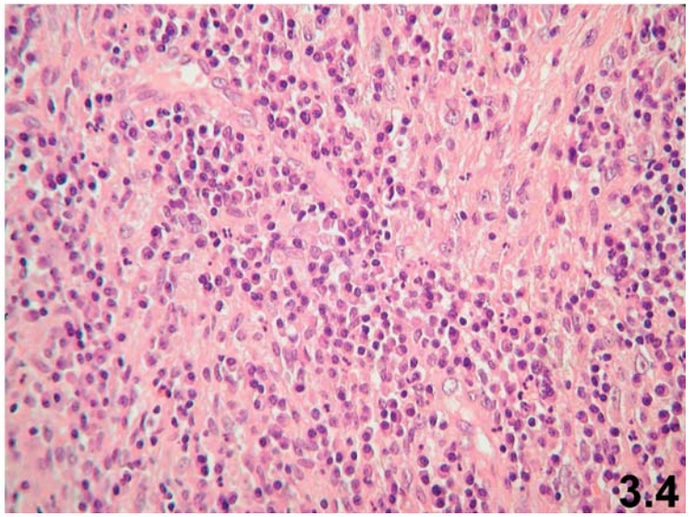
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Figs. 3.5 and **3.6:** Periductal histiocytic infiltration with numerous fibroblasts in duct ectasia causing obliteration of the involved ducts (obliterative phase of duct ectasia).

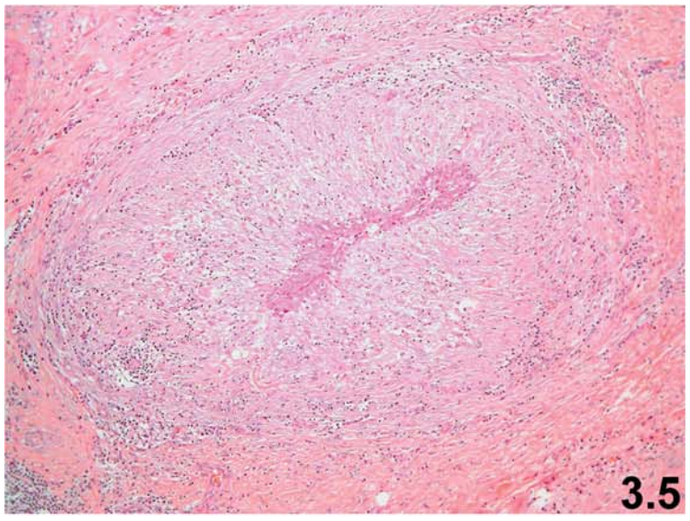
Fig. 3.7: An ectatic duct containing cellular debris combined with secretory material.

Fig. 3.8: Some of the involved ducts show reactive epithelial cell alterations characterized by enlargement of the nuclei, higher nuclear-cytoplasmic (N/C) ratio, and prominent nucleoli.

Figs. 3.9 and **3.10:** Van Gieson elastica stain in duct ectasia revealing either continuous or discontinuous elastic tissue in large (extralobular) ducts.

Fig. 3: Final remarks

- This case demonstrates that duct ectasia may appear clinically and mammographically as a tumor. Duct ectasia with inflammatory skin changes, nipple discharge, and nipple inversion can easily be mistaken for cancer, particularly inflammatory breast carcinoma.
- The involved ducts in duct ectasia may show epithelial cell alterations with significant reactive changes such as nuclear enlargement, higher N/C ratio, and prominent nucleoli. These alterations should not lead to misinterpretation as atypical ductal hyperplasia or ductal carcinoma in situ.
- Duct ectasia is a disease of large (extralobular) ducts. In contrast to fibrocystic change, which is an alteration of lobules lacking elastic tissue, the presence of elastic tissue is a hallmark of duct ectasia.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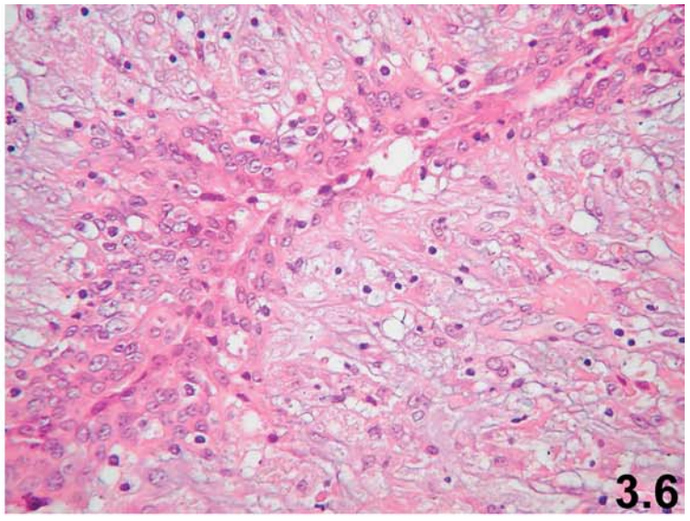
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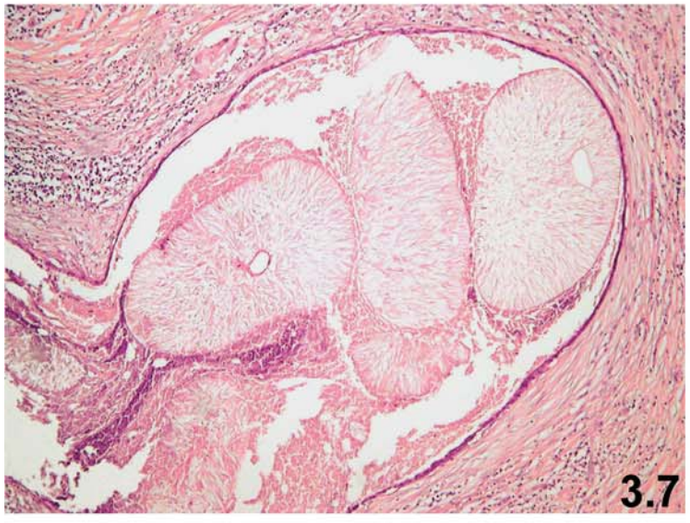
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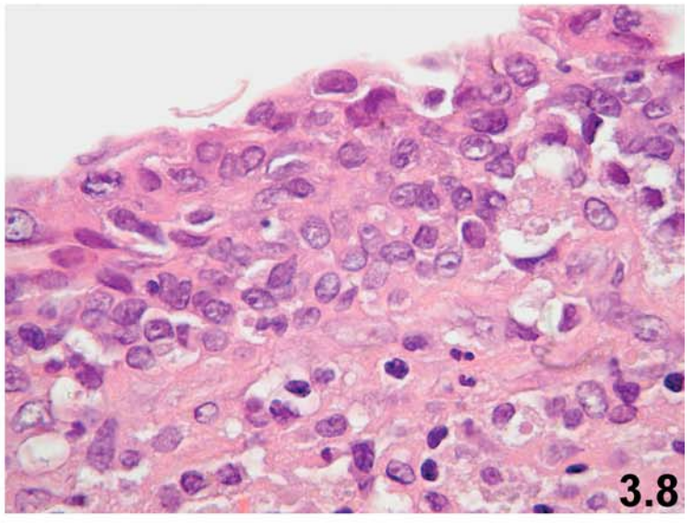
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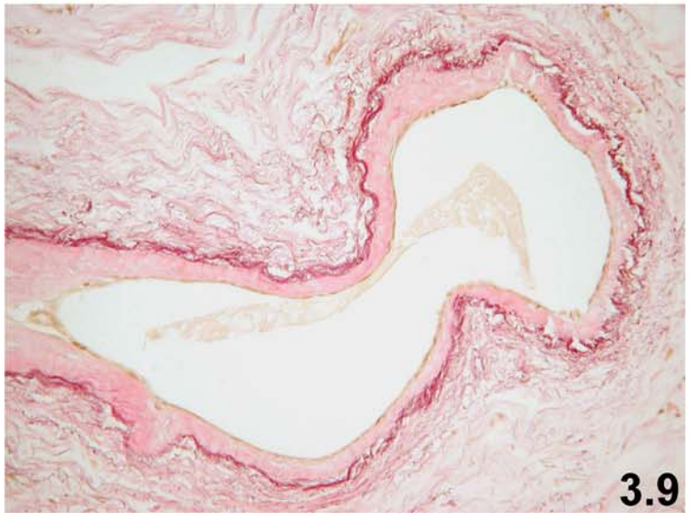
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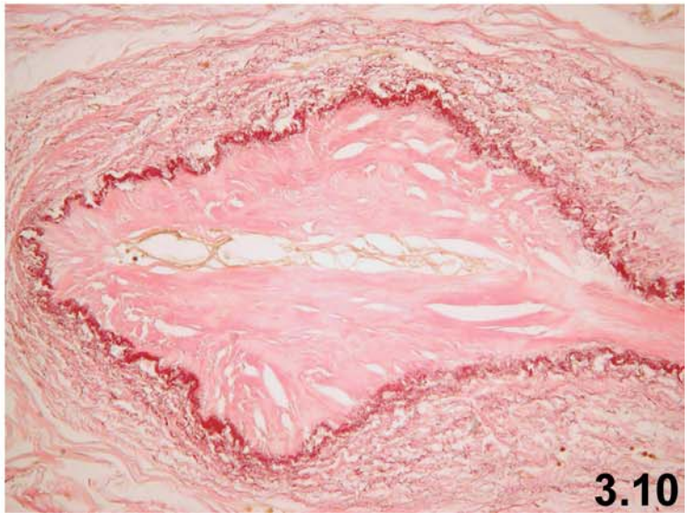
3.10

Adenosis

Contents

CHAPTER 4 Adenosis

4.1 Definition, Types, and Macroscopy of Adenosis

4.1.1 Definition

Enlargement of the lobules with an increased number of ductules or acini within them (hyperplasia of preexisting lobules). Adenosis per se, however, is not associated with intraluminal epithelial proliferation.

4.1.2 Types of Adenosis

Blunt duct, sclerosing, adenomyoepithelial, tubular, apocrine, secretory, and microglandular adenosis. It may form conspicuous nodules for which the designation of nodular adenosis is appropriate.

4.1.3 Macroscopy

Lesions with florid adenosis are often well-circumscribed nodules composed of grey or pale tan firm, homogeneous tissue. Lesions with prominent stromal sclerosing are likely to be less well defined grossly at the borders and more fibrous in appearance. Adenosis with prominent calcifications may seem gritty when cut. Gross cystic changes rarely occur. Adenosis without nodule formation is often indistinguishable from normal breast tissue. Rarely, fine granules can be palpated.

4.2 Blunt Duct Adenosis

4.2.1 Definition

A descriptive term for changes affecting the breast parenchyma, mostly with organoid hypertrophy of all lobular elements.

4.2.2 Synonyms

Columnar metaplasia, columnar alteration of lobules, columnar cell change (lesion), atypical lobules type A.

4.2.3 Microscopic Features (Fig. 4)

- Blunt duct adenosis (BDA) is characterized by an enlargement of lobular units showing elongated or dilated tubules, a simultaneous hypertrophy of epithelial and myoepithelial cells with blunt lateral outlines and blunt endings (curved structures), and often a simultaneous increase of intralobular ("specialized") connective tissue.
- The epithelium may be flattened, cuboidal, or columnar.
- Apical snouts or cytoplasmic blebs may be prominent.
- Luminal secretion and microcalcifications can be present.

Caution

- BDA, as defined here, should have no cytological or nuclear atypia and typically shows a simultaneous alteration of epithelial and myoepithelial cells. Changes with even mild nuclear atypia, and mild intraluminal epithelial proliferation of a monotonous (homogeneous) cell population should not be confused with simple BDA; these should be designated as intraepithelial neoplasia flat type (synonyms: flat epithelial atypia, columnar cell lesion with atypia). The acronym CAPSS, which stands for columnar cell alteration with prominent apical snouts and secretion, has been used by some authors for alterations similar to those of blunt duct adenosis, which also may include atypical epithelial cells forming bridges, tufts, and focal micropapillary structures. This condition should better be called ductal intraepithelial neoplasia, flat and/or micropapillary type, to emphasize the neoplastic nature of mildly atypical cells (see Chapter 5 on DIN flat type) [1, 3, 5, 6, 8, 9, 11–13].

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4.3 Sclerosing Adenosis

4.3.1 Definition

A benign lobulocentric lesion with significant sclerotic stromal changes. Occasionally, sclerosing adenosis (SA) forms either clinically palpable or grossly visible nodules (nodular SA, adenosis tumor).

4.3.2 Microscopic Features (Figs. 5 and 6)

- Low magnification: A lobulated, organoid proliferation of closely packed acini (ductules) with elongation and distortion of the involved structures due to compression by the stroma.
- High magnification: The normal bicellular lining (epithelial, myoepithelial) is retained in the ductules. The myoepithelial cell layer can be prominent (hypertrophic) or hyperplastic.

The central portion reflects the earlier stages and is more cellular. In the periphery of the lesion and in later stages, the cellularity is less, and the sclerosis dominates.

- The tubules of SA often proliferate parallel to the duct system, around the duct of origin, extending to the duct lumen, or both.
- Calcification is present in about 50% of cases.
- In less than 2% of cases, SA extends into perineural spaces. Very rarely, true vascular infiltration of benign glands of SA can occur.

Caution

- SA can mimic an infiltrating carcinoma mammographically, grossly, and even microscopically. The pathologist should not be influenced by suspicious clinical and radiological features. (See Table 4.1.)
- Frozen section (FS): The size of the sample must be sufficient (lesions should be at least ⩾5 mm in order to be examined by FS histology). In cases of doubtful diagnosis, one should wait for paraffin sections.
- Macroscopic appearances of SA sometimes suggest malignancy because of hardness or the presence of yellow streaks and flecks of elastosis.
- Paraffin sections: Examination on low-power magnification is absolutely crucial in order to identify a lobular and organoid pattern (nodular or whorled configuration).
- High-power magnification clearly reveals epithelial and basally located myoepithelial cells within the tubules of SA. In contrast, carcinomatous tubules are made up of a single cell type (lack of a myoepithelial cell component).
- Epithelial structures in sclerotic areas represent elongated and compressed tubules and strands as opposed to the rigid and angulated glandular structures of carcinoma.
- In some areas the outer cell type of the tubules of SA may show differentiation to myoid cells.
- The presence of basal lamina around the glands is typical for SA. In contrast, the malignant glands of infiltrating carcinoma do not form a continuous layer of basement membrane.
- SA in a pregnant woman can be extremely florid (cellular) and can look very alarming, especially on FS.
- Apocrine metaplasia with prominent nucleoli can be present within areas of SA. Therefore, areas of slightly pleomorphic epithelium with rounded, hyperchromatic nuclei, which are recognizably apocrine in type, should not be regarded with too much concern.

Table 4.1. Differential diagnosis of microglandular adenosis (MGA), tubular carcinoma (TC), and sclerosing adenosis (SA)

	MGA	TC	SA
Glandular distribution	Haphazard	Haphazard, stellate	Lobulated, rounded
Glandular shape	Round	Angulated	Round
Lumens	Open	Open	Small, compressed
Intraluminal secretions	Colloid-like +++	Colloid-like –	Colloid-like –
Number of cell layers	Epithelial only (one layer)	Epithelial only	Epithelial, myoepithelial (two cell layers)
Cytoplasmic protrusions (apical snouts)	Absent	Present	Mostly absent
Basement membrane	++(+)	–	++
Stroma	Mostly without reaction, hypocellular	Desmoplastic (reactive, hypercellular)	Zonal, sclerotic

- Neural and vascular infiltration: In rare cases (less than 2%), SA can be associated with (peri)neural and (peri)vascular invasion. The infiltrating tubules are cytologically benign and have an easily demonstrable two-cell type (epithelial/myoepithelial) structure. It is a true infiltrative process with no clinical consequences.
- Due to the irregularity of branching glands and extensive sclerosis, isolated epithelial cells may be present in some areas of SA. This should not mislead to the diagnosis of cancer!
- The lesion is not always well circumscribed or lobulated. A tubular, branching variant can occur that often mimics an infiltrating carcinoma. Lack of a lobulated outline and extension into adipose and sclerotic tissue is particularly noted in older patients with atrophic breasts.
- Lobular intraepithelial neoplasia (LIN) and ductal intraepithelial neoplasia (DIN; or ductal carcinoma in situ, DCIS) may also develop in SA and may be confined to SA; both LIN and DIN involving SA may be misinterpreted as invasive carcinoma. Immunostains for myoepithelial markers (such as SM actin, p63, and CD10) and laminin show positivity for myoepithelial cells and basal lamina, confirming the absence of invasion. In LIN the proliferating uniform cells are negative for E-cadherin (see Chapter 7 on LIN). The neoplastic cells of DIN in a background of SA are characteristically negative for high molecular weight cytokeratins (HMW-CK) such as CK5/6 (see Chapter 5 on DIN).
- In cases that display SA associated with DIN (DCIS), resection margins of the specimens should be evaluated carefully. If the margin is involved, reexcision needs to be done.

4.3.3 Additional Comments

SA without atypical intraepithelial proliferation (LIN or DIN) has a negligible relative risk of 1.7–2 (very similar to that of usual ductal hyperplasia) for the development of invasive breast carcinoma. In the presence of atypia (LIN, DIN), however, a relative risk of 4–10 has been reported [2, 9, 11].

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4.4 Apocrine Adenosis (Adenosis with Apocrine Metaplasia)

4.4.1 Definition

A variant of adenosis with a prominent (at least 50%) apocrine metaplasia within the involved glands.

4.4.2 Microscopic Features (Fig. 7)

- The apocrine cells have round nuclei, prominent nucleoli, and abundant eosinophilic granular or clear cytoplasm.
- Mild enlargement of nuclei and slight variation in nuclear size and shape are common in apocrine metaplasia and should not lead to overdiagnosis. In contrast, significant nuclear atypia (irregular chromatin distribution, irregular nuclear membrane, threefold variation in nuclear size, etc.) should lead to the diagnosis of atypical apocrine adenosis or apocrine adenosis with atypia.

Caution

- A few reports [1, 7, 12] suggest that apocrine adenosis with severe cytologic atypia, particularly in postmenopausal women, has a significantly increased relative risk (10 times) for subsequent development of invasive carcinoma; close follow-up is therefore prudent. Distinguishing between atypical apocrine adenosis and apocrine DCIS arising in the background of adenosis can be very difficult, if not impossible. Such lesions are best designated apocrine ductal intraepithelial neoplasia (mostly high-grade DIN) associated with adenosis.

4.4.3 Additional Comments

Apocrine adenosis of the breast has been shown to occasionally have HER2/neu (c-erbB2) overexpression and a possible premalignant potential. However, unequivocal HER2/neu gene amplification or chromosome 17 aneusomy is absent in apocrine adenosis without atypia [9].

Apocrine phenotype is characteristically associated with lack of estrogen and progesterone receptors. Androgen receptors, however, are typically immunopositive in apocrine metaplastic cells [4, 10, 12].

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4.5 Tubular Adenosis

4.5.1 Definition

A type of adenosis with prominent interlacing tubules.

4.5.2 Microscopic Features (Fig. 8)

- This pattern is characterized by numerous elongated and seemingly interdigitated ductules of relatively uniform size.
- The glandular structures lack the circumscribed whorled arrangement of more typical examples of adenosis.
- The tubular structures lack apical snouts and always contain a myoepithelial cell layer.
- Microcalcifications are common.

Caution

- Tubular adenosis differs from tubular carcinoma by showing a distinct layer of myoepithelial cells. The myoepithelial cells, however, can be attenuated and therefore may need to be confirmed immunohistochemically.
- Tubular adenosis can be confused with a well-differentiated infiltrating ductal carcinoma or tubular carcinoma, particularly in a needle core biopsy.

4.5.3 Additional Comments

In contrast to microglandular adenosis, a two-cell layer (epithelial/myoepithelial cells) is always present in tubular adenosis.

4.5.4 Further Reading

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4.6 Adenomyoepithelial Adenosis

4.6.1 Definition

A rare variant of adenosis with a prominent myoepithelial component within the involved glands (hypertrophy and/or hyperplasia of myoepithelial cells).

4.6.2 Microscopic Features (Fig. 9)

- Adenomyoepithelial adenosis can be well circumscribed or consist of multiple foci of haphazardly arranged ductules with luminal secretion, similar to microglandular adenosis (see next section).
- The tubules show a prominent myoepithelial cell component. The luminal epithelial cells and basally located myoepithelial cells not infrequently show enlarged nuclei and prominent nucleoli.
- Apocrine or squamous metaplasia may be present.
- Adenomyoepithelial adenosis cannot reliably be separated from a small (microscopic) adenomyoepithelioma.

4.6.3 Further Reading

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4.7 Microglandular Adenosis

4.7.1 Definition

A rare benign proliferative glandular lesion that may mimic carcinoma clinically and pathologically. It is a true infiltrative lesion composed of glands without a myoepithelial component.

4.7.2 Macroscopy

Grossly, an ill-defined infiltrative lesion (in most cases, 3–4 cm). In some cases, the gross appearance of microglandular adenosis (MGA) does not differ from the surrounding breast tissue.

4.7.3 Microscopic Features (Fig. 10)

- MGA is composed of round glands lined by a single layer of flat to cuboidal epithelial cells (no myoepithelial cell component!).
- It infiltrates into the adipose tissue.
- There is no cytologic atypia.
- The stroma is often unaltered (no desmoplastic stromal reaction).
- The bland-looking glands are surrounded by basal lamina. The basal lamina is usually thick.
- The tubules often contain deep eosinophilic colloid-like luminal secretion (PAS- and mucicarmine-positive).
- The tubules are intensely positive for cytokeratin and S100 protein.
- The lack of immunoreaction for ER, PR, GCDFP-15, and EMA is also characteristic for MGA.

Caution

- MGA is the only known benign breast lesion that lacks a myoepithelial cell layer. The lack of myoepithelial cells and the infiltrating pattern of MGA can easily lead to misinterpretation as carcinoma [2, 4, 9, 10].
- Atypical MGA is a rare variant with foci of complex structure (intraepithelial proliferation, epithelial bridging, back-to-back glandular arrangements) and/or cytologic atypia (Fig. 11). Atypical MGA probably represents a precancerous lesion and needs to be examined extensively. Nearly one-third of cases of atypical MGA harbor an invasive carcinoma [5–8].
- If the distinction between atypical MGA and invasive carcinoma is difficult, one should stay with a more conservative interpretation (atypical MGA). The resection margins, however, should be negative. In this setting, examination of sentinel lymph node and close follow-up of the patient are prudent.

4.7.4 Additional Comments

A recent study demonstrated MGA with transition into adenoid cystic carcinoma of the breast [1]. In this study, however, areas of typical and atypical MGA often showed myoepithelial cells. Because, by definition, MGA has no myoepithelial cell layer, the claimed transition from MGA into adenoid cystic carcinoma should be interpreted with caution.

It has been shown that in all cases in which carcinomas developed in the background of MGA, areas of atypical MGA were also present, characterized by cytologic atypia, epithelial bridging, and, often, a lack of intraluminal secretion. Carcinomas arising in the MGA can be intraductal (DCIS), invasive, or both. These carcinomas typically show a positive immunoreaction for S100 protein but are negative for estrogen receptors and progesterone receptors [3, 4, 6, 10, 11].

4.7.5 Further Reading

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4.8 Radial Scar/Complex Sclerosing Lesion

4.8 1 Definition

A distinct benign breast lesion consisting of a central fibroelastotic core surrounded by radiating ducts and lobules with or without intraluminal proliferation.

4.8.2 Synonyms

Sclerosing papillomatosis, sclerosing ductal proliferation, indurative mastopathy, nonencapsulated sclerosing lesion, infiltrating epitheliosis, radial sclerosing lesion.

4.8.3 Macroscopy

A majority of radial scars (RSs) are not grossly visible (incidental finding). Those that are apparent to the naked eye often mimic a carcinoma because of the stellate or nodular appearance, firmness of the lesion, and the presence of white to yellow streaks. Usually a few millimeters in size, rarely they can be larger than 1 cm. The term "radial scar" has been applied to small lesions and "complex sclerosing lesion" (CSL) to larger ones (>1 cm) that often are associated with ductal epithelial hyperplasia.

4.8.4 Microscopic Features (Figs. 12 and 13)

- At low magnification, the radial nature of the lesion is invariably evident.
- A stellate arrangement of ductules surrounds a central fibroelastic or fibrocollagenous zone.
- The central part of lesions with characteristic fibrosis and elastosis engulfs attenuated ducts. These ducts are haphazardly arranged and distorted, but they are consistently lined by epithelium and myoepithelium.
- The ductules around the central scarred zone can be associated with any type of intraluminal (intraductal) proliferation, such as usual ductal hyperplasia (UDH), DIN (ADH, DCIS), or even LIN. In rare cases, an invasive carcinoma (for example, tubular carcinoma) can be associated with a complex sclerotic lesion.
- Within a RS/CSL, areas of papilloma and sclerosing adenosis can be present.

Caution

- Two major types of RS should be distinguished: (1) simple RS with no intraepithelial proliferative lesion or cytologic atypia, usually associated with some cysts, and (2) RS/CSL associated with a variety of proliferative lesions, including UDH, DIN (ADH, DCIS), and LIN [1, 2, 5, 14, 15, 17].
- The reported increased risk of invasive carcinoma in patients with RS/CSL in a few studies most likely depends on the presence or absence and the nature of the associated intraepithelial proliferative lesions [10–12]. It is doubtful that, without epithelial proliferation or atypia, there is a significant risk of the subsequent development of invasive carcinoma. In the absence of any independent risk factor for carcinoma, no further follow-up of patients with RS/CSL is required.
- Very rarely, RS can be associated with neural or vascular infiltration, or both. This finding, however, is not clinically significant.
- Because of the lesion's complexity and the disorganized and infiltrating pattern of some glands, especially at low magnification, RS or CSL can easily be misinterpreted as infiltrating carcinoma. At higher magnifications, the presence of myoepithelial cells in the tubules and the strands of elongated cells confirm the lesion's benign nature [1–3, 8, 15].
- Mammographic findings and the gross appearance of the lesion are often highly suspicious for cancer. One needs to be aware of the risk of overdiagnosis when using frozen sections!
- The diagnosis of RS/CSL in a needle core biopsy should lead to complete excision of the lesion [6]. Because of sclerotic changes and irregular arrangements of the glands, core biopsies of RS/CSL may be misinterpreted as invasive carcinoma.
- Not infrequently, there is difficulty in diagnosing an early tubular carcinoma and in distinguishing florid intraductal hyperplasia from ductal carcinoma in situ within the complex lesions. In that setting, immunohistochemistry (myoepithelial markers, HMW-CK) can be very helpful.

4.8.5 Immunohistochemical Examination

Immunohistochemistry is used to identify myoepithelial cells: SM actin, SM myosin (heavy chain), calponin, CD10, p63, etc. One should not change the diagnosis if myoepithelial cells can be identified on the hematoxylin and eosin sections but the immunostain (for one of the myoepithelial markers) is negative in some areas of the lesion. One should try the immunostaining with other myoepithelial markers. It is important to note that the positive immunoreactivity of myoepithelial cells with certain antibodies is just a matter of cell function and differentiation. Therefore, the immunoreactions of myoepithelial cells can be weak or even negative for some of the markers, but intensely positive with others.

- In a difficult case of CSL associated with intraductal proliferations, examination with antibody against HMW-CK (CK34BE12 or CK5/6) can be very helpful; CSL associated with UDH (florid intraductal hyperplasia) shows an intense positive immunoreaction for HMW-CK. In cases with so-called atypical ductal hyperplasia or DCIS, however, the immunoreaction for HMW-CK is very often completely or predominantly negative in the proliferating luminal cells (see Chapter 5 on UDH).
- Lobular intraepithelial neoplasia (ALH, lobular carcinoma in situ) arising in a radial scar (CSL) is typically negative for E-cadherin but shows a positive immunoreaction for CK34BE12.

4.8.6 Differential Diagnosis

The differential diagnosis includes tubular carcinoma, microglandular adenosis, and SA (see Table 4.1). Radial scars have a characteristic stellate appearance at low magnification and a central zone of fibrocollagenous scar tissue, in contrast to the lobulated, organoid configuration of SA.

4.8.7 Further Reading

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4.9 Collagenous Spherulosis

4.9.1 Definition

An incidental histopathologic finding during examination of a breast biopsy showing a peculiar form of intraductal epithelial proliferation with numerous acellular spherules.

4.9.2 Macroscopy

Often has a normal gross appearance.

4.9.3 Microscopic Features (Fig. 14)

- Intraductal (intralobular) proliferation with several acellular 20–100-micron spherules surrounded by cords of bland round to ovoid cells.
- Predominantly basophilic and fibrillar spherules (basement membrane material positive for PAS and alcian blue).
- The cells immediately surrounding the spherules are immunoreactive for SM actin and p63 (myoepithelial cells).
- The constituent fibrils are usually arranged in a concentric or laminated fashion (positive immunoreactivity for laminin, collagen types III and IV).
- Not infrequently, it is associated with other conditions such as SA, peripheral intraductal papillomas, or RS. It can also be associated with LIN (Fig. 14).
- In some cases, the spaces contain only transparent mucoid material designated as mucinous spherulosis (Fig. 15). It is likely that mucinous spherulosis represents an earlier stage of collagenous spherulosis.

Caution

- Collagenous spherulosis simulates a cribriform growth pattern of low-grade DIN (DCIS). In contrast to DIN, however, HMW-CK (such as CK5/6) and SM actin are typically positive in the proliferating cells.
- Collagenous spherulosis can be misinterpreted as adenoid cystic carcinoma. But in contrast to adenoid cystic carcinoma, it is often an incidental (microscopic) finding and shows no infiltration into the surrounding tissues.
- Collagenous or mucinous spherulosis can be associated with LIN. The monotonous and small uniform epithelial cells of LIN can easily be overlooked.
- Rarely, it can be misdiagnosed as intraductal signet-ring cell carcinoma.

4.9.4 Additional Comments

There is no evidence to suggest that this lesion results in an increased risk of breast carcinoma. Because of a superficial resemblance to adenoid cystic carcinoma, an alternative term, adenoid cystic hyperplasia, has been used for this condition.

Collagenous and mucinous spherulosis are related lesions derived from a progressive accumulation of extracellular material (including mucopolysaccharides, collagen IV, and laminin) and transformation of the mucinous spherules of the early stage to the collagenous spherules of the end-stage lesion [7].

The close proximity of the myoepithelial cell to the spherules suggests that it is the source of the extracellular material, and this suggestion is supported by the identification of spherulosis in salivary gland tumors rich in myoepithelial cells [10].

A recent study has shown that collagenous spherulosis can rarely present as a mammographically suspicious mass or density and can be associated with microcalcifications [8].

4.9.5 Further Reading

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Fig. 4: Blunt duct adenosis.

Case history: Mammographic examination of a 43-year-old woman revealed multiple small cysts (up to 0.6 cm) in her right breast. Clinically, a few mobile and nodular areas with firm consistency were palpable. Histologic examination of the surgical specimen displayed multiple cysts associated with marked stromal fibrosis (fibrocystic changes, not illustrated). In addition, there were multiple areas with organoid lobular alterations as illustrated here.

Figs. 4.1 and **4.2:** Blunt duct adenosis (BDA) showing a characteristic organoid lobular arrangement of the involved acini (ductules). Note the presence of dilated tubules with blunt lateral outlines and blunt endings (curved structures).

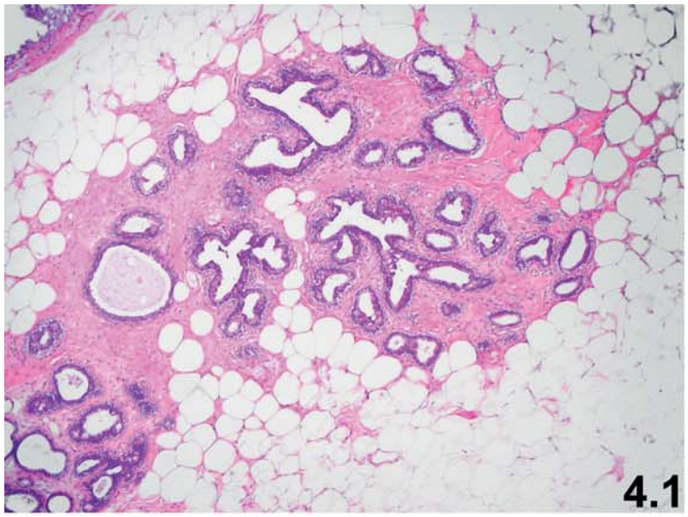
Fig. 4.3: A common feature of BDA is simultaneous alteration (hypertrophy) of epithelial, myoepithelial, and intralobular stromal cells.

Fig. 4.4: Higher magnification of BDA revealing simultaneous hypertrophy of epithelial and myoepithelial cells. This finding is in contrast to DIN flat type (flat epithelial atypia), which often affects the luminal epithelial cells at the expense of peripherally located myoepithelial cells. Note the presence of apical snouts.

Figs. 4.5 and **4.6:** Immunohistochemistry for CK5/6 in BDA shows a heterogeneous positive reaction of luminal cells. In contrast, CK5/6 is very often completely negative in DIN flat type (flat epithelial atypia). For more information with regard to separation between BDA and DIN flat type, see Chapter 5 on DIN flat type.

Fig. 4: Final remarks

- The simultaneous alteration or hypertrophy of epithelial and myoepithelial cells in this case is a characteristic feature of BDA and serves as a useful diagnostic criterion for distinguishing BDA from DIN flat type.
- As seen in this case, the luminal epithelial cells in some areas of BDA may show enlarged nuclei with prominent nucleoli. These cytologic features of epithelial cells that are accompanied by hypertrophy of myoepithelial cells should not lead to the diagnosis of flat epithelial atypia or DIN flat type.
- While CK5/6 is very often positive in BDA, the luminal cells of DIN flat type are typically negative for it.
- BDA can be associated with prominent apical snouts. One should keep in mind that the presence of apical snouts is common in both BDA and DIN flat type; therefore, it cannot be used as a discriminatory criterion.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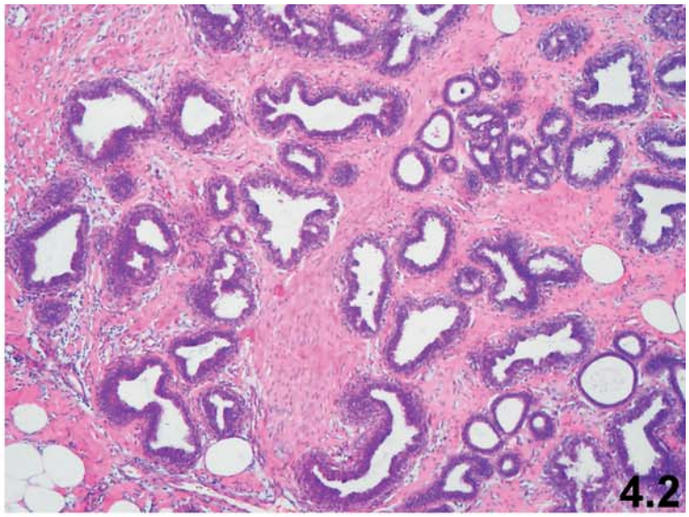
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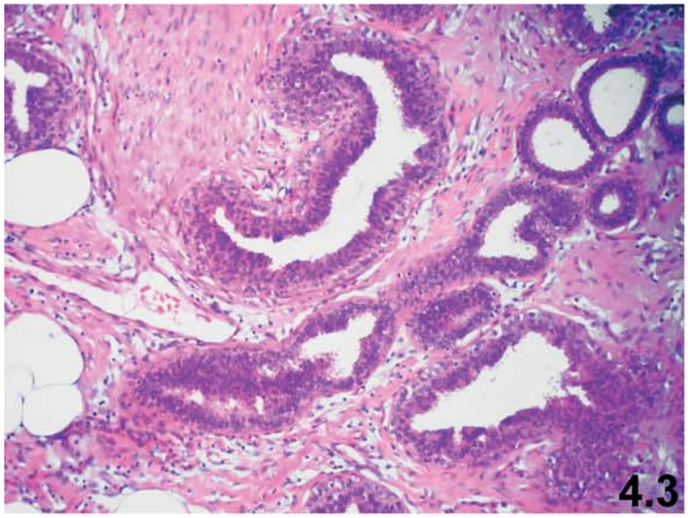
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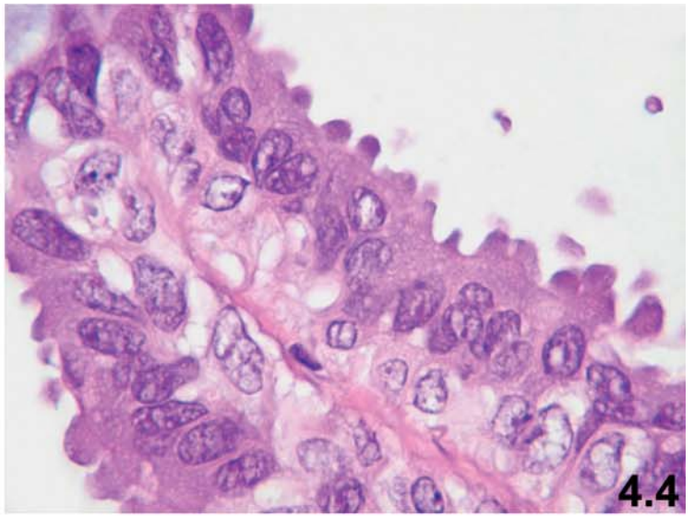
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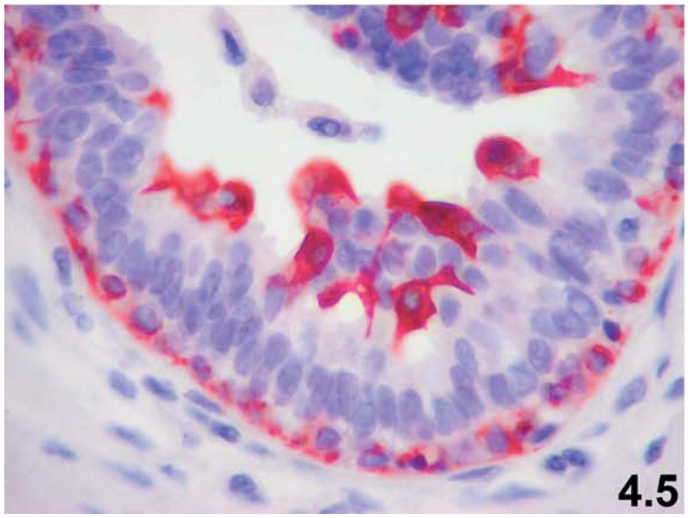
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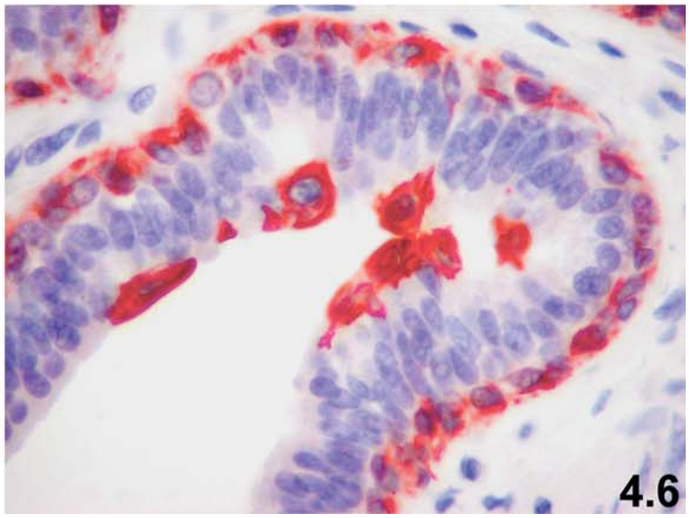
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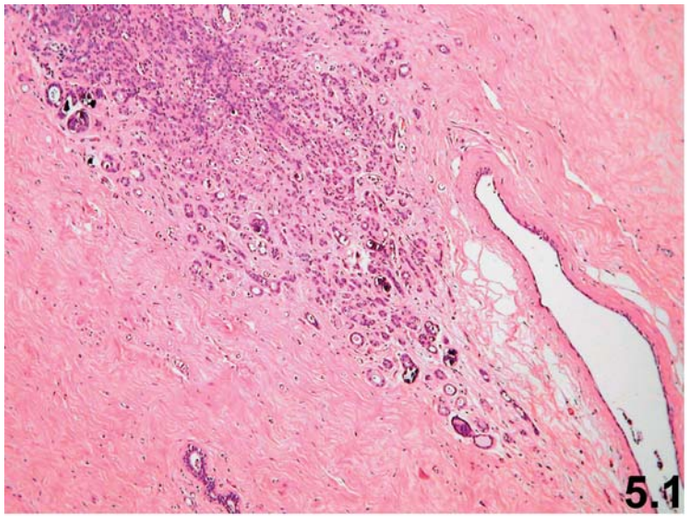
Fig. 5: Nodular sclerosing adenosis (adenosis tumor).

Case history: A 39-year-old woman presented with an irregular firm mass in her right breast (upper, outer quadrant). Mammography revealed a 2-cm nodule with partly irregular, suspicious borders. In addition, multiple areas with microcalcification were identified. The cut surface of the excisional biopsy showed a predominantly well-circumscribed firm nodule with focal marginal irregularity.

Figs. 5.1 and **5.2:** At low magnification, the nodule shows an organoid proliferation of closely packed acini (ductules). Multiple microcalcifications are present.

Figs. 5.3 and **5.4:** Several areas of the nodule display sclerotic stroma with elongation and distortion of the involved tubules (compression of the glands by the stroma). Note the irregular and pseudoinfiltrative pattern of the glands.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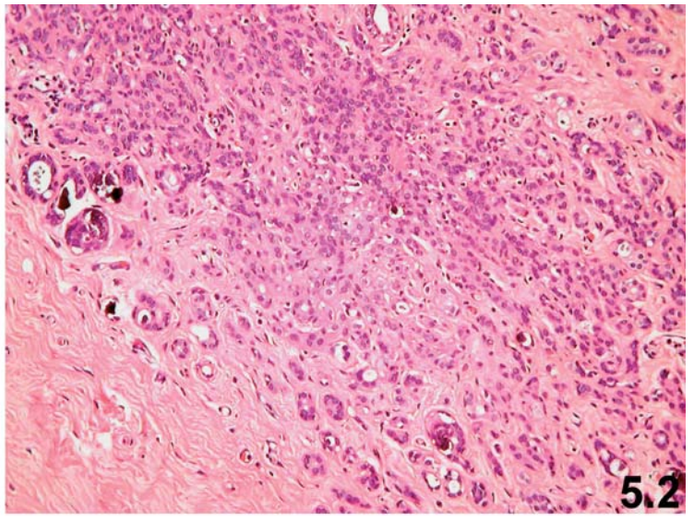
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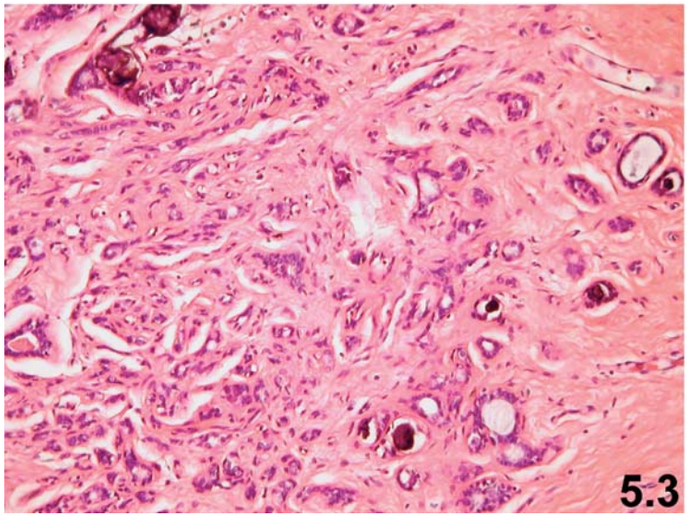
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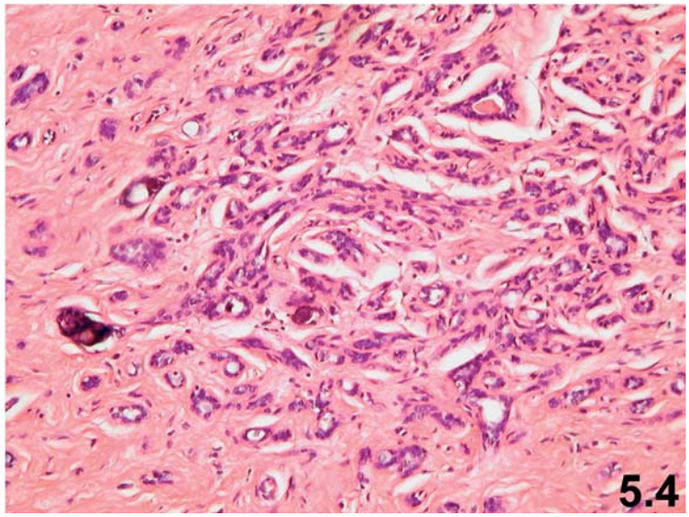

5.4

Fig. 5.5: Other areas of the lesion reveal well-circumscribed and organoid pattern of closely packed acini (micronodules).

Fig. 5.6: Elsewhere, the tubules not only proliferate around the duct, but also extend into the duct lumen (so-called ductal invagination).

Fig. 5.7: Sclerosing adenosis with extension into the duct lumen, resulting in a small peripheral papillary lesion (peripheral papilloma).

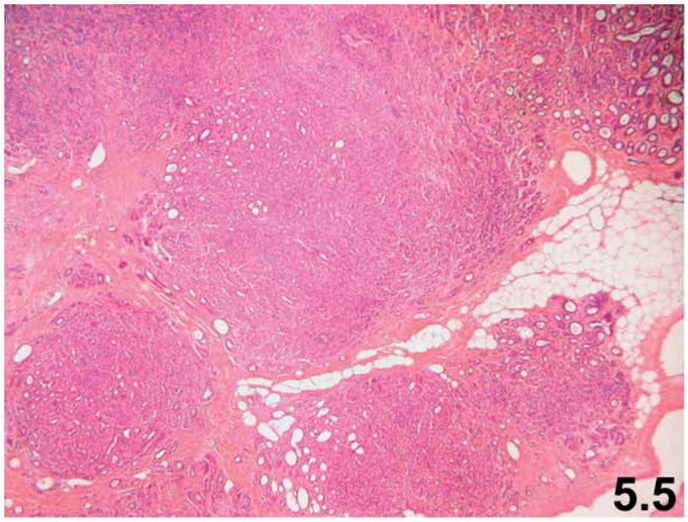
Fig. 5.8: Some of the closely packed tubules display apocrine metaplasia with prominent nucleoli and slightly pleomorphic nuclei.

Fig. 5.9: A portion of the nodule with an irregular, pseudoinfiltrative pattern simulates an invasive ductal carcinoma.

Fig. 5.10: Higher magnification of the glands, however, reveals the benign nature of the lesion, showing a clear-cut myoepithelial cell layer. Note the simultaneous alteration (hypertrophy) of luminal epithelial and peripheral myoepithelial cells.

Fig. 5: Final remarks

- The hallmark of this lesion is the presence of closely packed acini (ductules) with an organoid or micronodular growth pattern identifiable at low magnification. Some of the glands are irregularly distributed, which may mimic an infiltrating carcinoma. As identified at high magnification, the glands are composed of epithelial and myoepithelial cells.
- The luminal epithelial cells in sclerosing adenosis may show hyperchromatic or vesicular nuclei with a high nuclear-cytoplasmic ratio and prominent nucleoli. These cytologic alterations are relatively common in the florid phase of adenosis and should not be misinterpreted as atypia.
- This case demonstrates that peripheral papillomas may develop in a background of sclerosing adenosis through extension of the process into the duct lumen (ductal invagination).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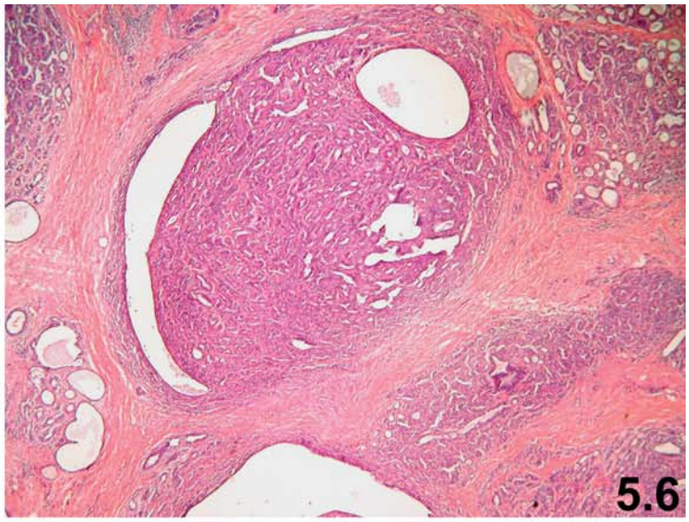
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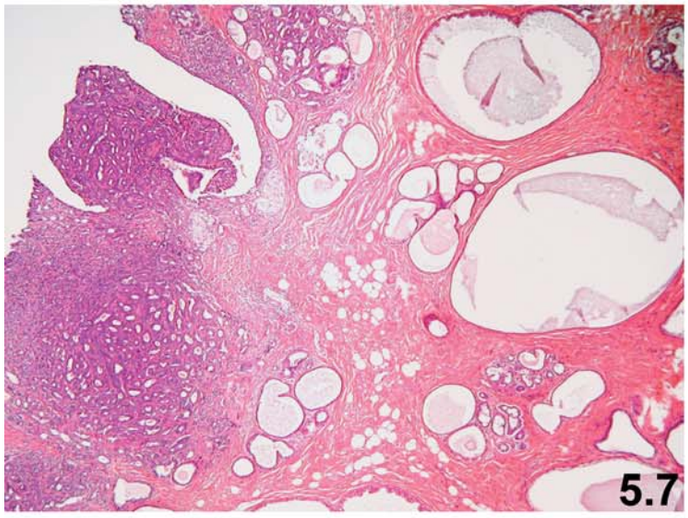
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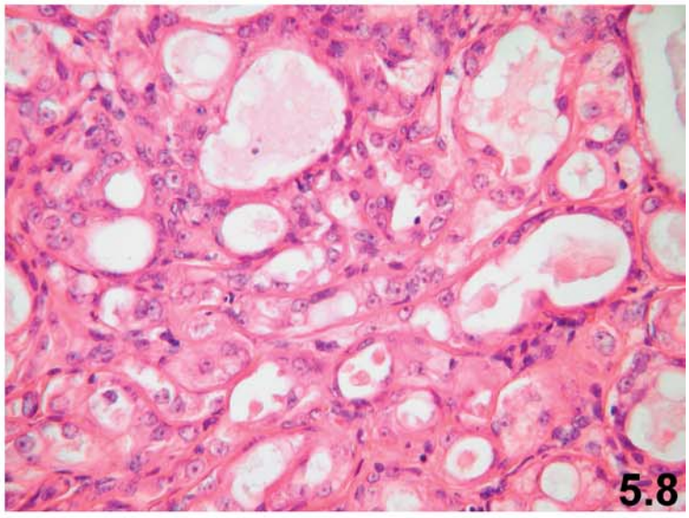
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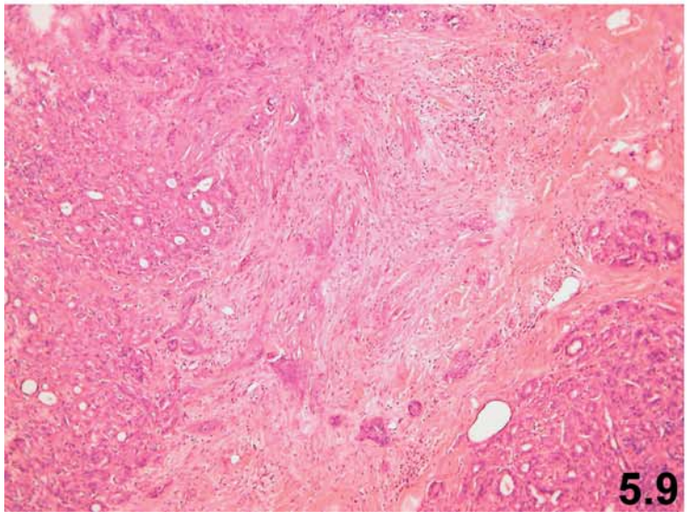
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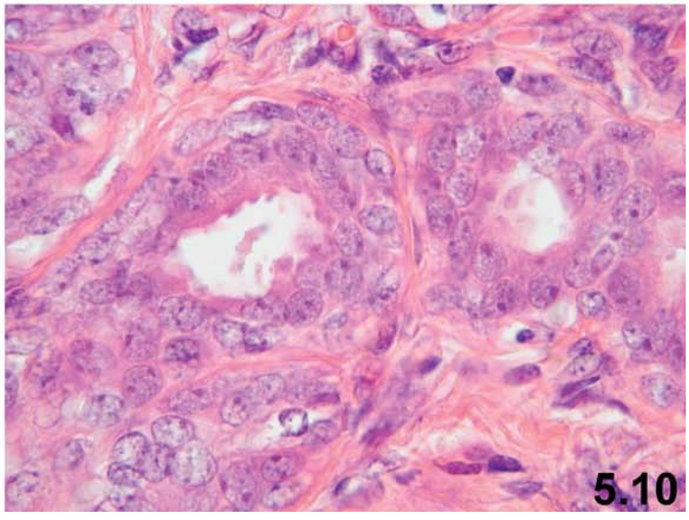
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Fig. 6: Sclerosing adenosis (with pseudoinvasion).

Case history: A 51-year-old woman had an abnormal mammogram of her left breast, showing an irregular mass (1.5 cm). A core needle biopsy of the lesion was performed.

Fig. 6.1: Core needle biopsy of the lesion shows a lobulated, organoid proliferation of closely packed glandular structures.

Fig. 6.2: Some areas of the lesion display intraductal proliferation with irregular secondary lumina (usual ductal hyperplasia).

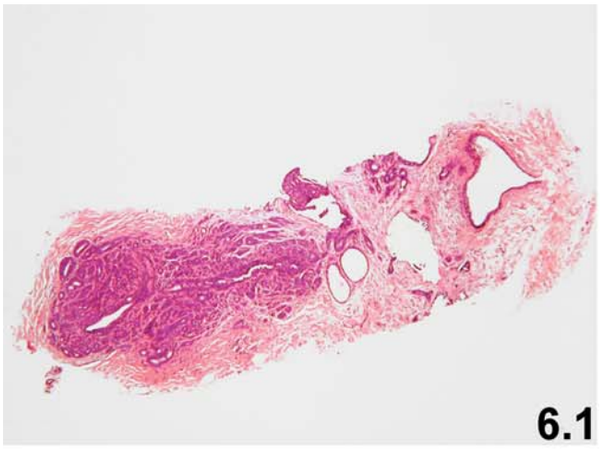
Figs. 6.3 and **6.4:** Some of the glands show irregular arrangements with an infiltrating growth pattern. Note the stromal alteration exhibiting granulation-tissue-like or desmoplastic stromal reaction adjacent to the irregular glands.

Fig. 6.5: Irregular and compressed glandular structures simulating an invasive carcinoma at low magnification.

Figs. 6.6, 6.7, and **6.8:** The glands and compressed epithelial structures with pseudoinfiltrative pattern show a clear-cut myoepithelial cell layer at higher magnification. The myoepithelial cells in these areas display elongated or spindle-shaped nuclei and scant cytoplasm.

Fig. 6: Final remarks

- This case created serious diagnostic problems for some pathologists mainly because of (1) a pseudoinvasive growth pattern simulating an infiltrating ductal carcinoma, (2) desmoplastic stromal alteration, and (3) the complexity of the lesion.
- One needs to keep in mind that the presence of desmoplastic stromal alteration in the breast by no means indicates malignancy. One should always examine glands with a (pseudo)invasive growth pattern at higher magnification in order to evaluate the presence or absence of myoepithelial cells within the glands.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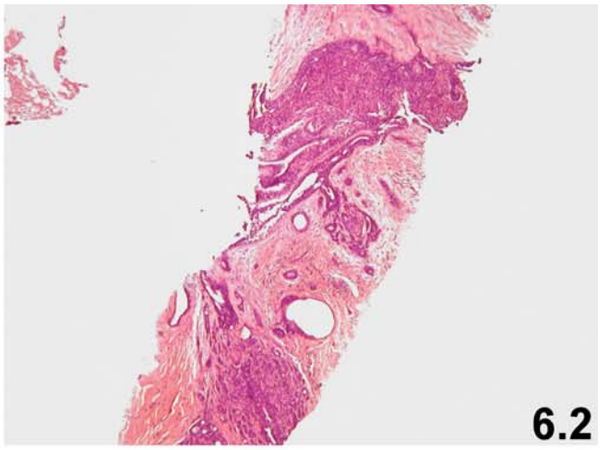
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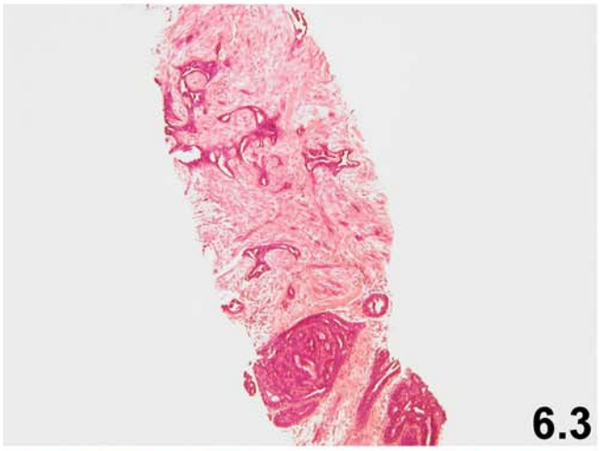
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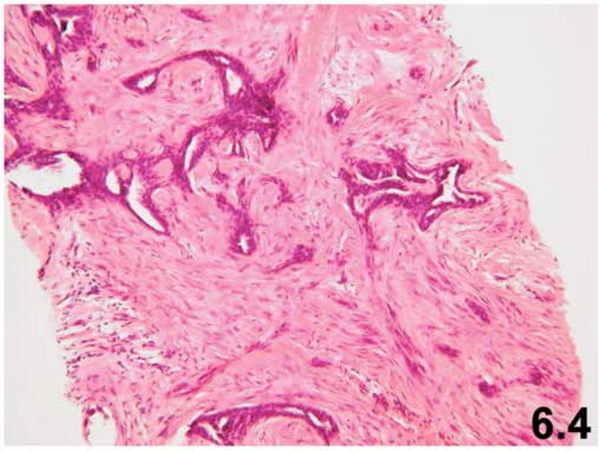
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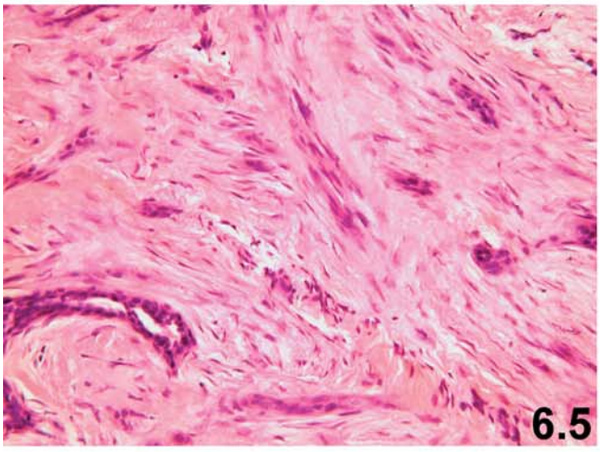
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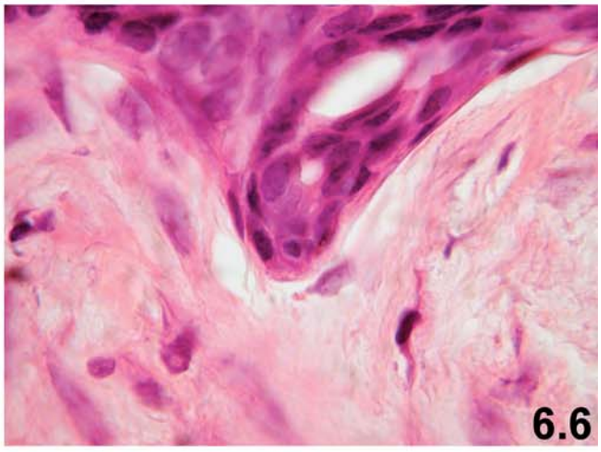
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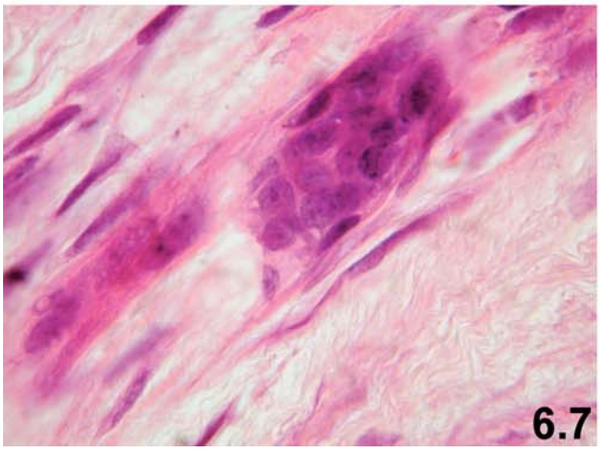
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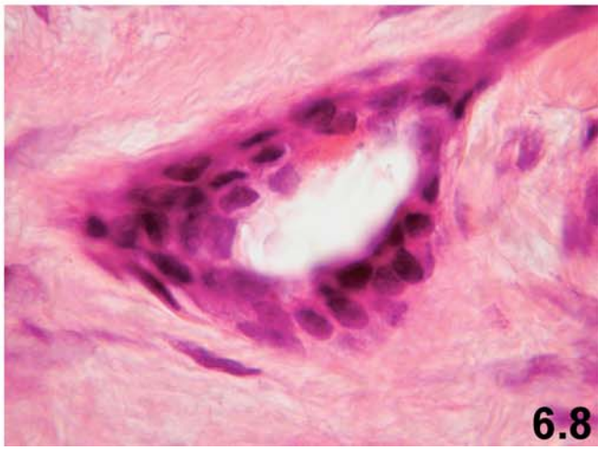
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Fig. 7: Apocrine adenosis (adenosis with prominent apocrine metaplasia).

Case history: Mammographic examination of a 36-year-old woman revealed a well-circumscribed mass (1.5 cm) in the upper outer quadrant of her left breast. The cut surface of the excisional biopsy showed a well-circumscribed, pale tan, firm nodule (1.5 cm).

Fig. 7.1: Low magnification of the lesion shows a nodular, organoid growth pattern of proliferating glands.

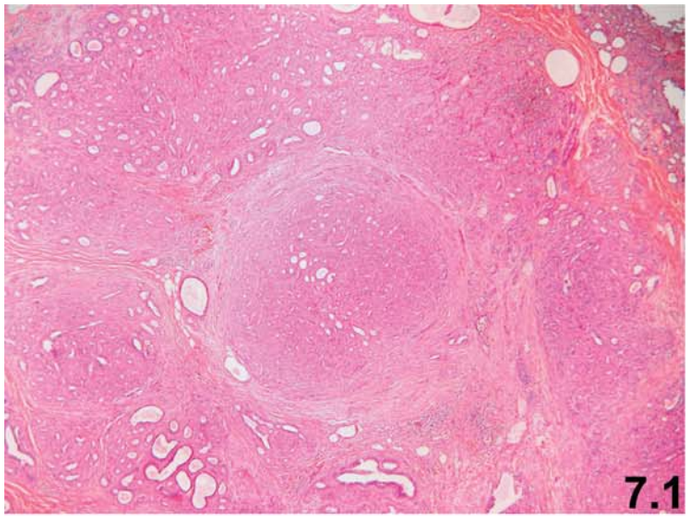
Fig.7.2: Some areas of the lesion display irregular arrangements of acini (ductules).

Figs. 7.3 and **7.4:** Several areas (more than 50%) of the lesion show apocrine metaplasia within the closely packed glands.

Figs. 7.5 and **7.6:** Apocrine metaplastic cells showing nucleoli and slight variation of nuclear size. Note the regularity of chromatin distribution in metaplastic apocrine cells.

Fig. 7: Final remarks

- A mild degree of nuclear size variation is common in apocrine metaplasia. Areas of apocrine metaplasia showing slightly pleomorphic epithelium with hyperchromatic nuclei and prominent nucleoli should not cause too much concern.
- Significant nuclear atypia, including irregular chromatin distribution, irregular nuclear membrane, and threefold variation in nuclear size, should, however, lead to the diagnosis of atypical apocrine adenosis (apocrine adenosis with atypia).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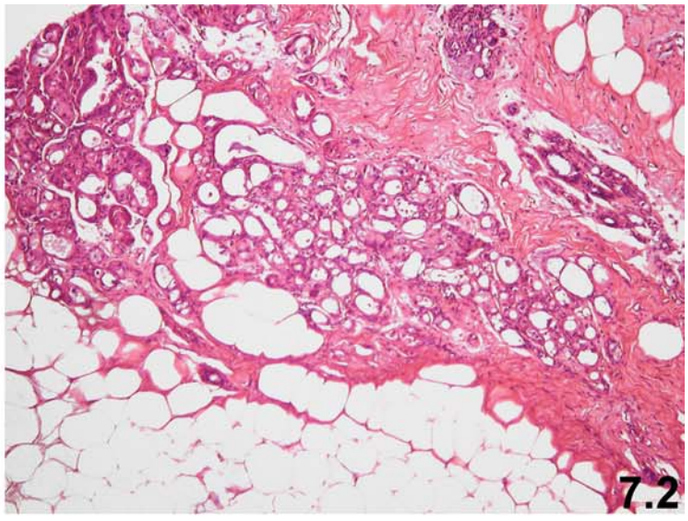
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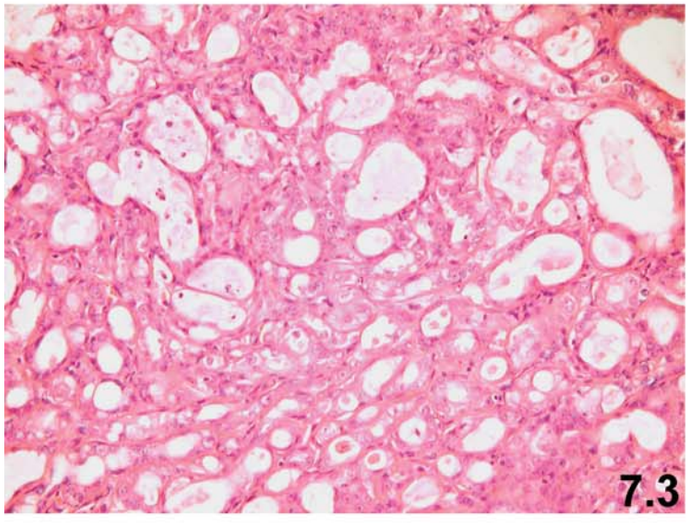
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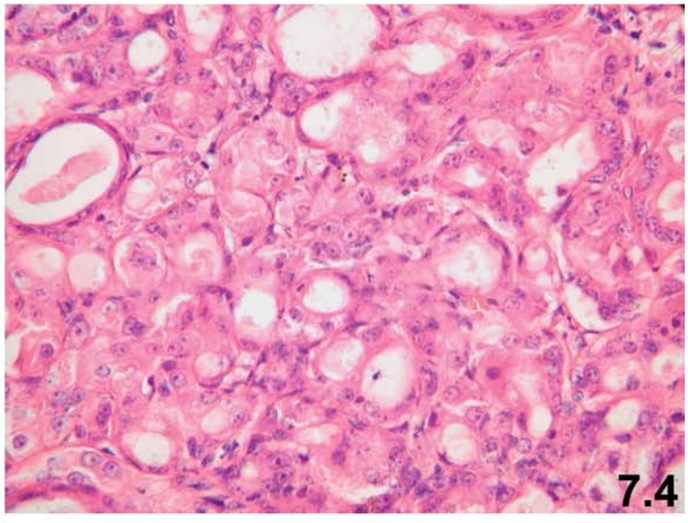
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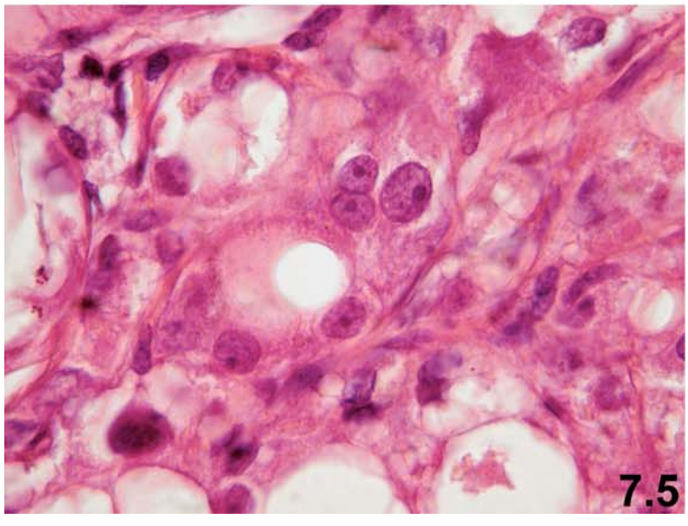
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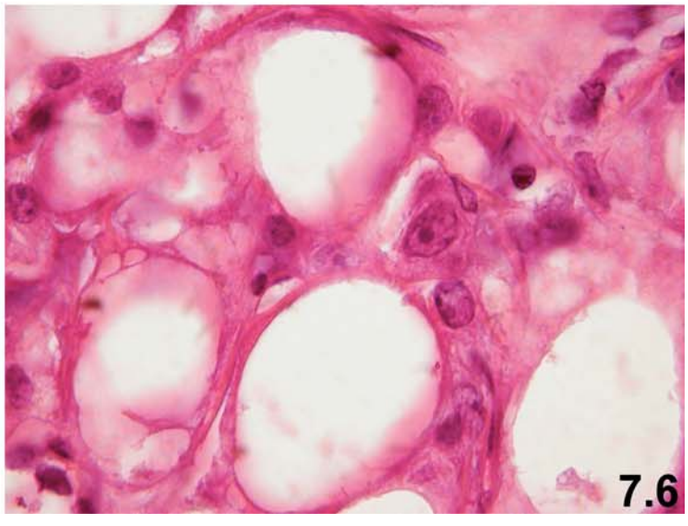
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Fig. 8: Tubular adenosis.

Case history: A 28-year-old woman presented with a mammographically suspicious lesion with irregular borders in the lower inner quadrant of her right breast. The lesion was clinically not palpable. She was very anxious due to a positive family history of breast cancer (her mother).

Fig. 8.1: Excisional biopsy shows a partly well-circumscribed lesion composed of tubular structures.

Fig. 8.2: Other areas of the lesion display tubules with infiltration of adipose tissue.

Fig. 8.3: Tubules of relatively uniform size showing luminal epithelial cells and basally located myoepithelial cells.

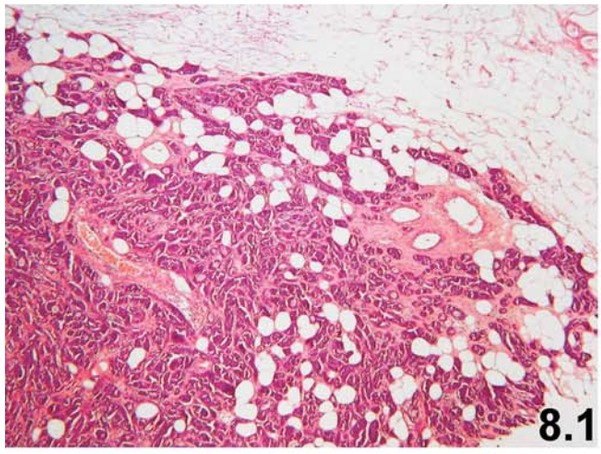
Fig. 8.4: Numerous elongated and seemingly interdigitated ductules. The tubules are surrounded by basement membrane.

Figs. 8.5 and **8.6:** Basally located myoepithelial cells are present at high magnification.

Figs. 8. 7 and **8.8:** Immunohistochemistry for myoepithelial cells using antibody against p63 showing nuclear positivity. Several other markers such as smooth muscle actin, smooth muscle myosin (heavy chain), and CD10 were also intensely positive (not illustrated).

Fig. 8: Final remark

- The presence of myoepithelial cells within the tubules in this case excludes the possibility of a tubular carcinoma.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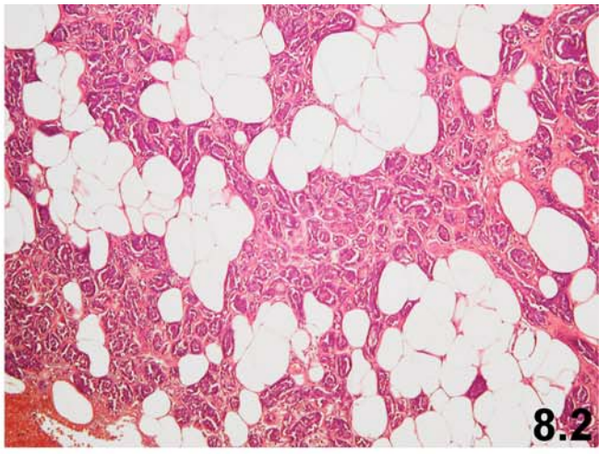
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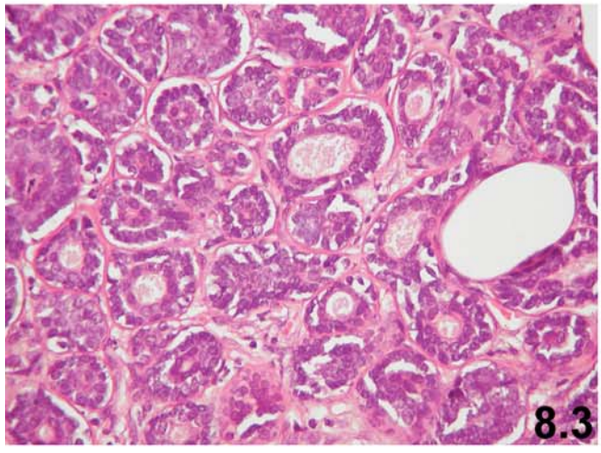
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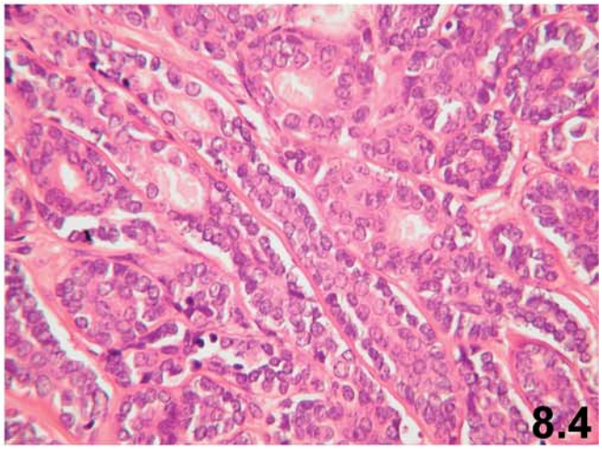
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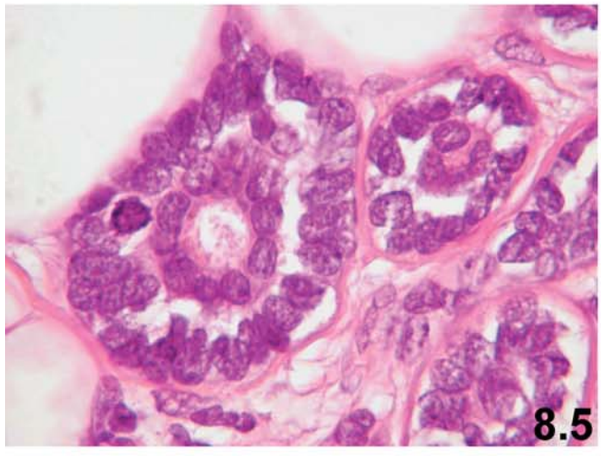
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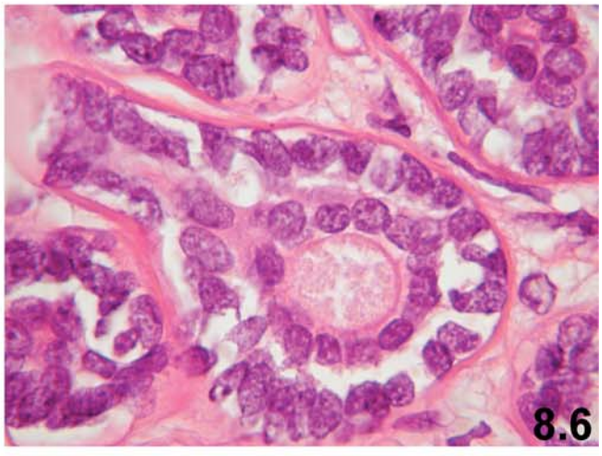
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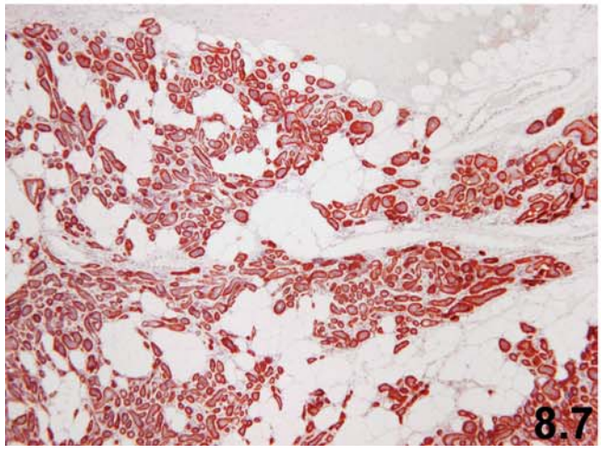
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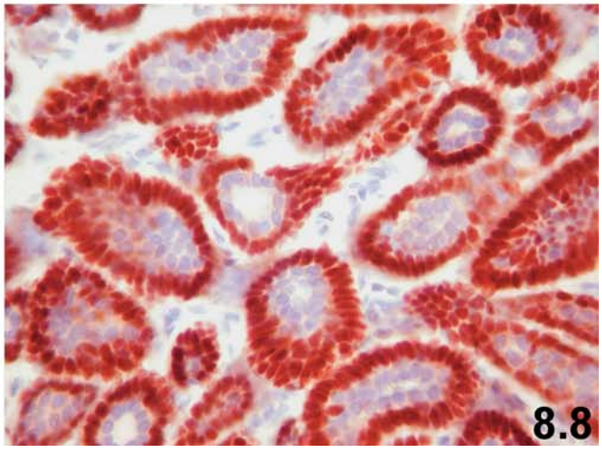
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Fig. 9: Adenomyoepithelial adenosis.

Case history: A 42-year-old woman presented with microcalcifications of her right breast that were suspicious for malignancy. The excisional biopsy revealed multiple areas of usual ductal hyperplasia as well as fibrocystic changes associated with microcalcifications (not illustrated). The following figures, however, represent an incidental microscopic finding.

Fig. 9.1: A well-circumscribed organoid lesion shows enlarged lobules with closely packed acinar structures.

Fig. 9.2: The glands show a prominent myoepithelial cell component.

Figs. 9.3 and **9.4:** The glands display simultaneous hypertrophy of epithelial and myoepithelial cells. Note myoepithelial cells with rare mitotic figures.

Fig. 9.5: The luminal epithelial cells show enlarged nuclei with an increased nuclear-cytoplasmic (N/C) ratio and multiple prominent nucleoli.

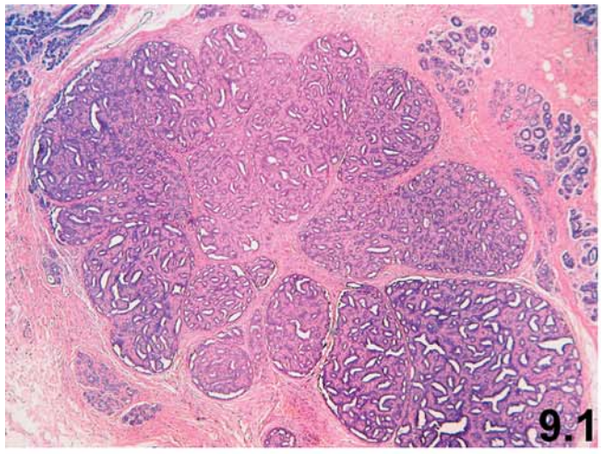
Fig. 9.6: Some of the glands show mitotic figures within the luminal epithelial cells.

Fig. 9.7: Immunohistochemistry for smooth muscle actin reveals a continuous myoepithelial cell layer.

Fig. 9.8: Immunohistochemistry for CD10 also shows a continuous layer of myoepithelial cells.

Fig. 9: Final remarks

- This case represents an adenosis of the breast that is associated with a prominent myoepithelial cell hypertrophy. The simultaneous alteration and hypertrophy of epithelial and myoepithelial cells is a hallmark of adenosis, particularly adenomyoepithelial adenosis.
- The luminal epithelial cells may show some atypical cytologic features, including nuclear enlargement, high N/C ratio, and multiple prominent nucleoli. These cytologic features of luminal epithelial cells may therefore cause diagnostic problems. It is important not to focus on the cytology of luminal cells without analyzing alterations in the basally located myoepithelial cells. The heterogeneous cell population with simultaneous hypertrophy of epithelial and myoepithelial cells in this case proves the lesion's benign nature.
- One cannot reliably separate adenomyoepithelial adenosis from a small or microscopic adenomyoepithelioma.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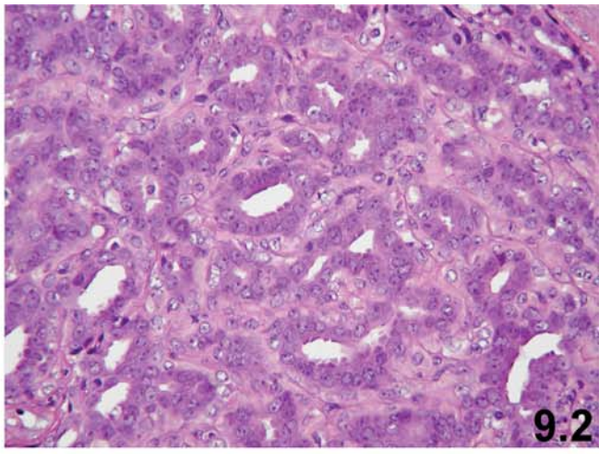
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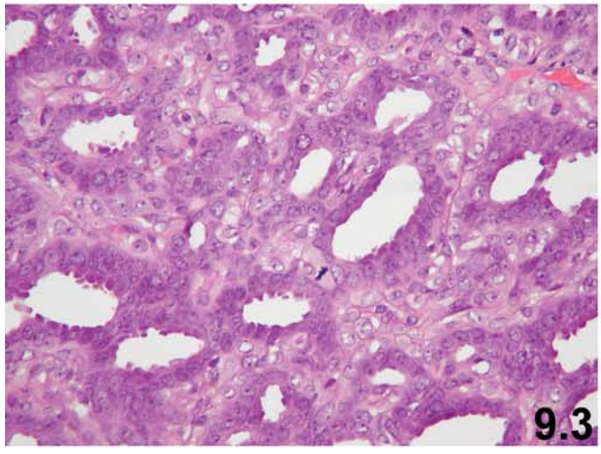
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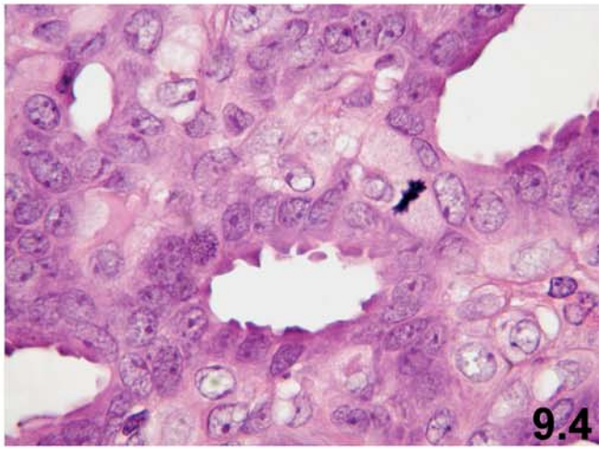
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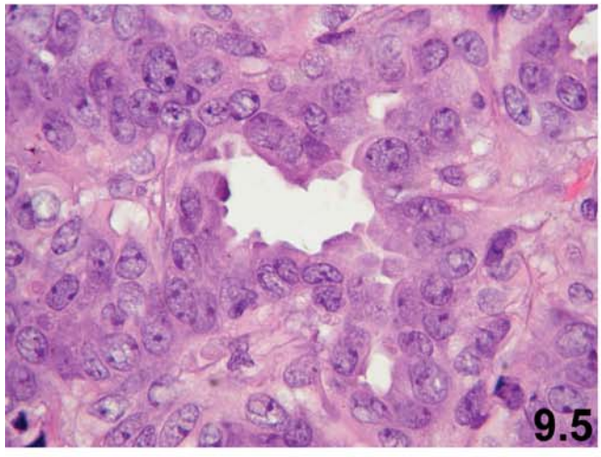
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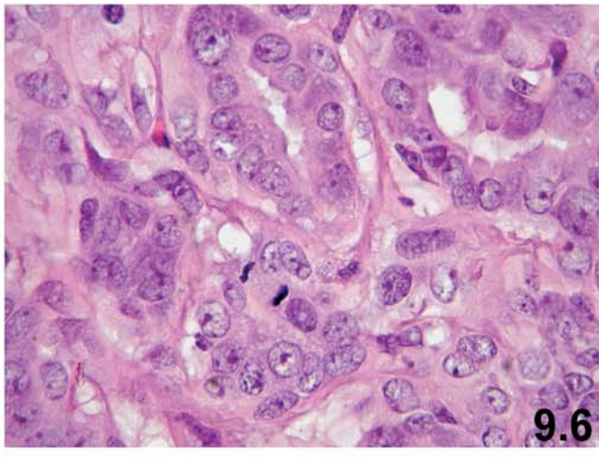
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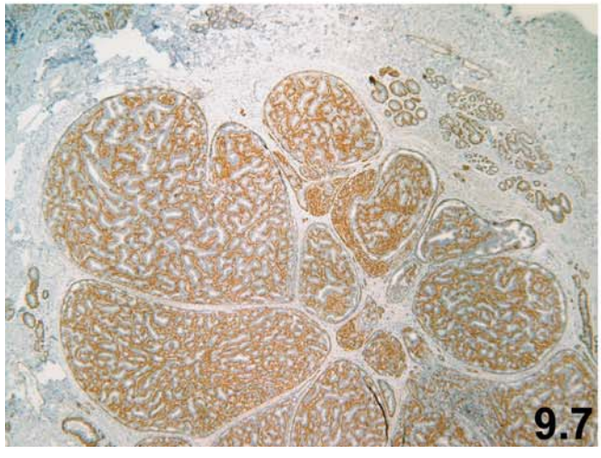
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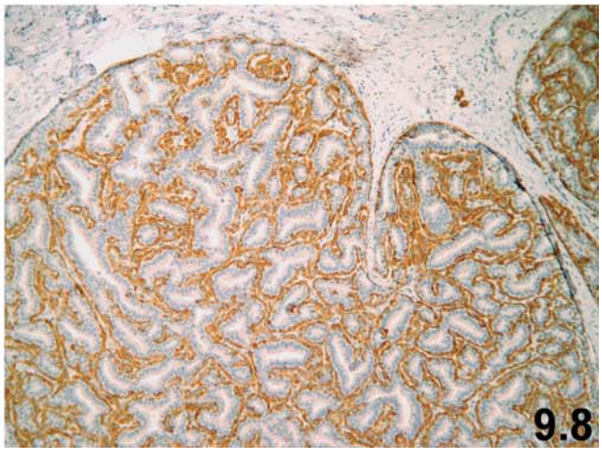
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Fig. 10: Microglandular adenosis.

Case history: A 45-year-old woman with an incidental microscopic finding of her right breast.

Figs. 10.1 and **10.2:** Low magnification of the lesion shows numerous round glands with infiltration into fat tissue.

Fig. 10.3: The glands contain deep eosinophilic colloid-like intraluminal secretion.

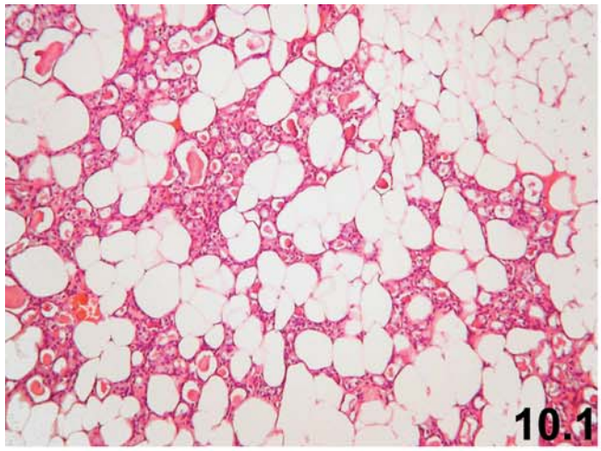
Fig. 10.4: Bland-looking glands containing eosinophilic secretion.

Figs. 10.5 and **10.6:** The tubular structures lack a myoepithelial cell layer. The epithelial cells do not show cytologic atypia.

Figs. 10.7 and **10.8:** Immunohistochemistry for S100 protein is positive in the infiltrating microglandular structures.

Fig. 10: Final remarks

- The lack of myoepithelial cells within the tubules and the infiltrating growth pattern in this case have caused diagnostic problems for some pathologists. Indeed, some pathologists misinterpret this lesion as a well-differentiated invasive ductal carcinoma.
- One should keep in mind that microglandular adenosis characteristically lacks a myoepithelial cell component. As a matter of fact, microglandular adenosis represents the only known benign breast lesion that lacks a myoepithelial cell layer.
- In contrast to other types of adenosis, microglandular adenosis often shows an infiltrative growth pattern.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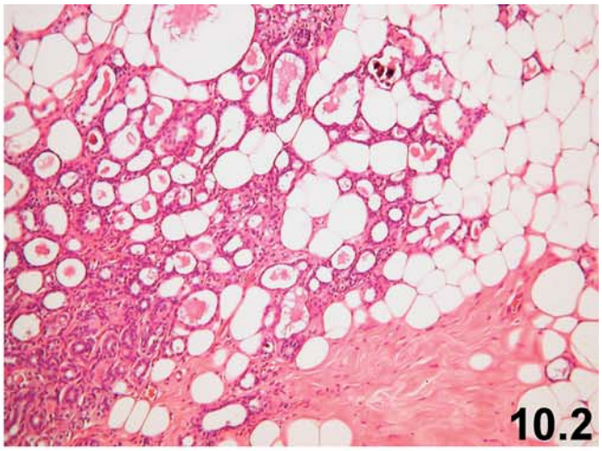
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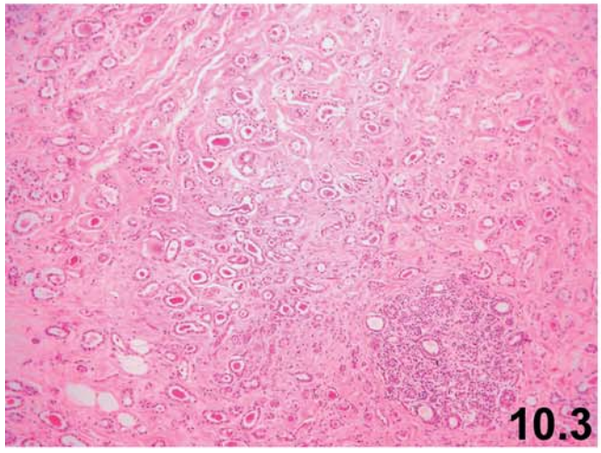
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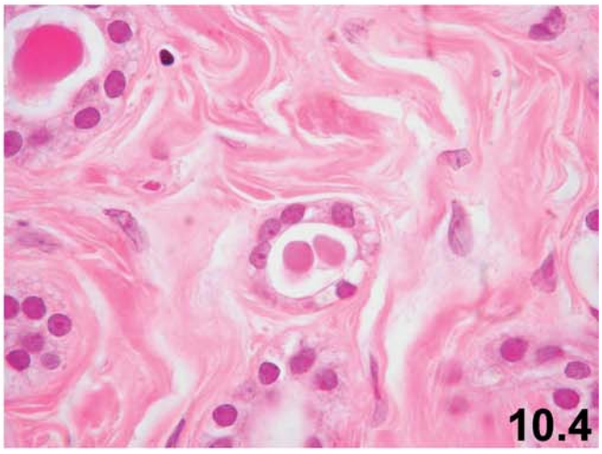
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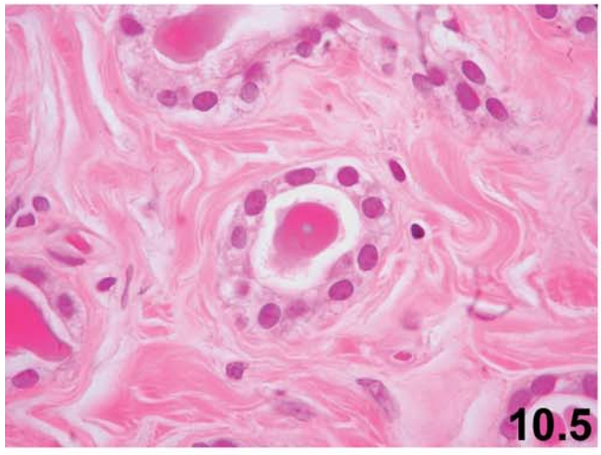
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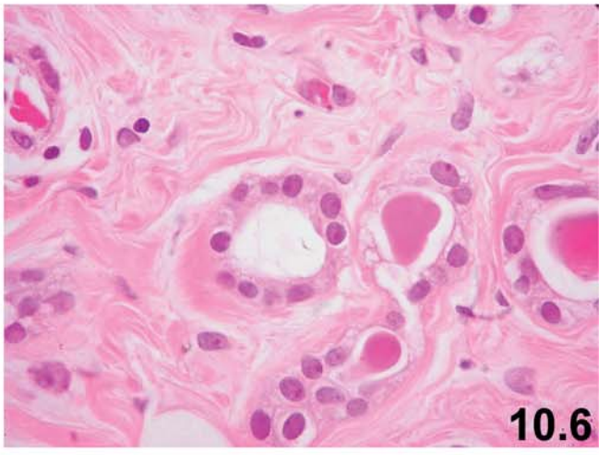
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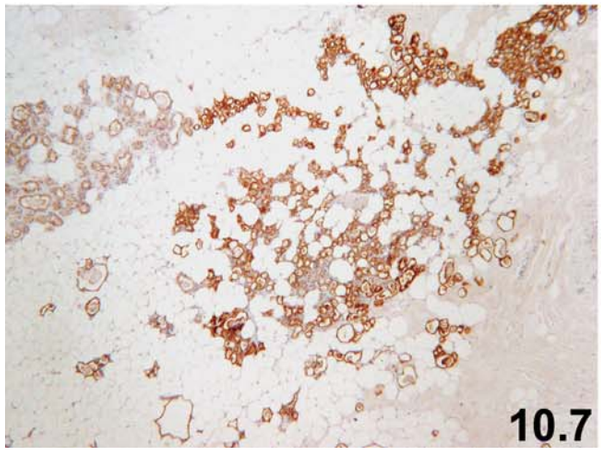
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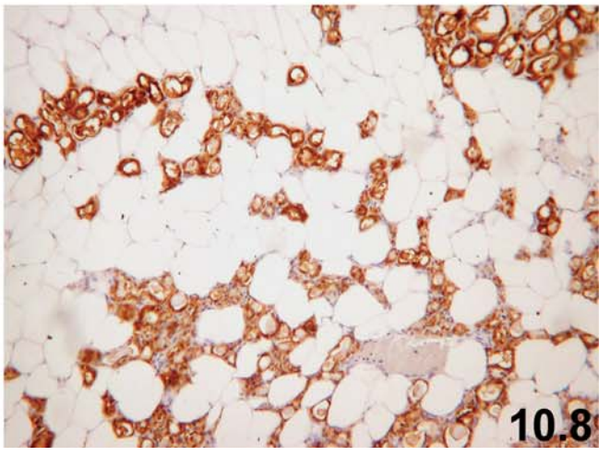
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Fig. 11: Atypical microglandular adenosis (microglandular adenosis with atypia).

Case history: A 52-year-old woman presented with clinical and mammographic signs of fibrocystic changes of her left breast. Although no palpable lesion could be identified, mammography showed an ill-defined area of about 1 cm in the lower inner quadrant. A core needle biopsy of the lesion was performed, which revealed a few atypical glands highly suspicious for an infiltrating ductal carcinoma. Excisional biopsy was finally done.

Fig. 11.1: Excisional biopsy of the lesion shows numerous small tubules with infiltration into adipose tissue. Several areas of the lesion also showed bland-looking microglandular structures containing deep eosinophilic secretion (typical microglandular adenosis; not shown).

Fig. 11.2: Other areas reveal back-to-back tubules with a complex growth pattern.

Fig. 11.3: Whereas some glands contain luminal secretion, others lack luminal colloid-like material.

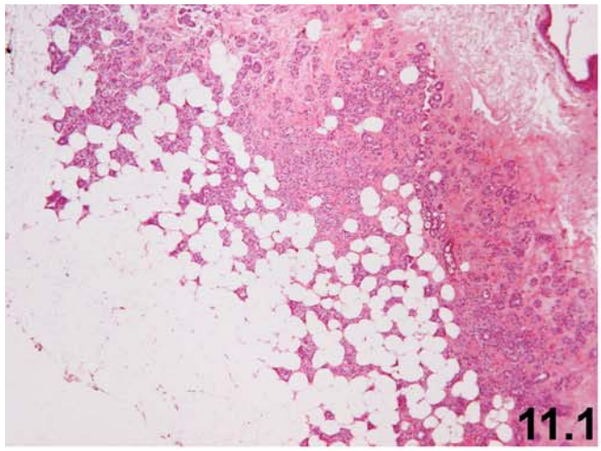
Fig. 11.4: At this magnification, the absence of colloid-like secretory material should alert the observer to the possibility of atypia.

Figs. 11.5 and **11.6:** In contrast to a typical microglandular adenosis, several foci of the lesion show atypical glands characterized by enlarged hyperchromatic nuclei with a high nuclear-cytoplasmic (N/C) ratio. Note also the absence of luminal eosinophilic secretion. The presence of circumferential basal lamina excludes an invasive carcinoma.

Figs. 11.7 and **11.8:** Immunohistochemistry for S100 protein revealing a diffuse and intense positive reaction of microglandular structures.

Fig. 11: Final remarks

- This case represents a rare variant of microglandular adenosis that is associated with architectural and cytological atypia. Such cases need to be examined extensively to exclude a clear-cut invasive carcinoma. The absence of myoepithelial cells within the glands and the infiltrative growth pattern in this case are insufficient for the diagnosis of infiltrating ductal carcinoma because all of these features are seen in typical and atypical microglandular adenosis.
- As a rule, carcinomas arising in the background of atypical microglandular adenosis are poorly differentiated and show high-grade nuclear atypia and numerous mitotic figures. In this case, the presence of microglandular adenosis without atypia (typical or classic pattern of microglandular adenosis) in some areas, the lack of grossly identifiable breast tumor, the lack of high-grade nuclear atypia, and the presence of circumferential basal lamina should lead to a more conservative interpretation such as atypical microglandular adenosis.
- As in this case, atypical microglandular adenosis often shows a combination of cytologic atypia, back-to-back arrangement, and lack of eosinophilic secretory material. In this setting, close follow-up of the patient is prudent.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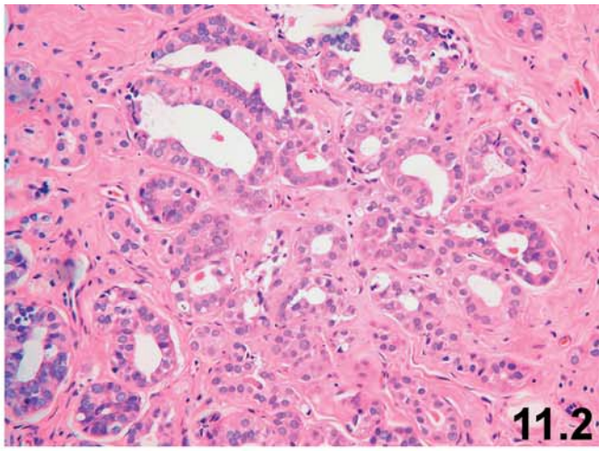
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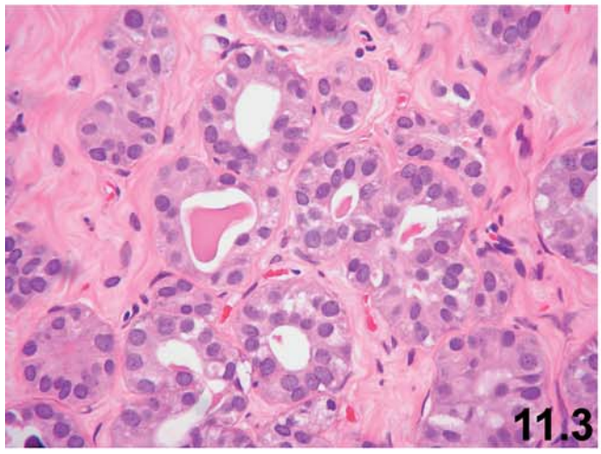
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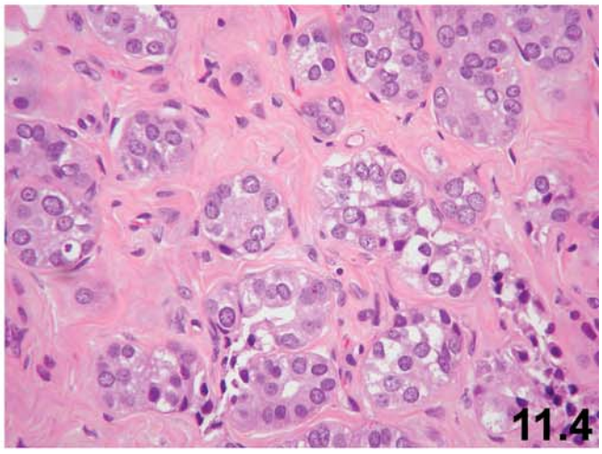
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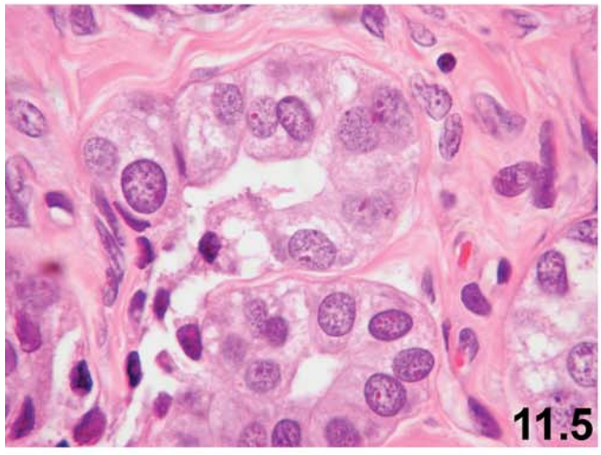
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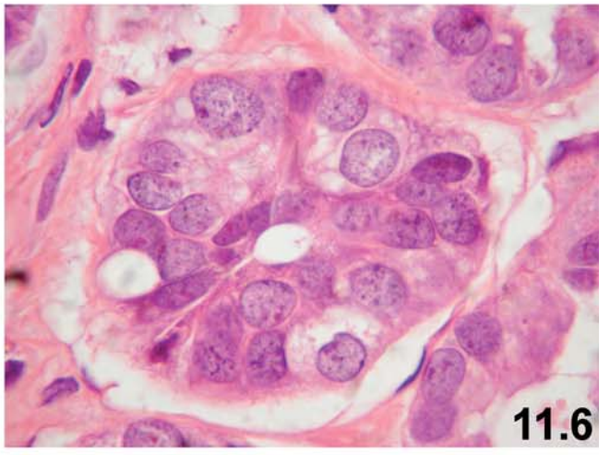
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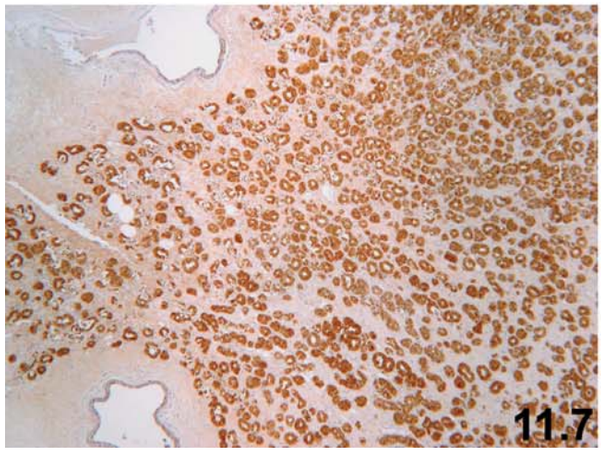
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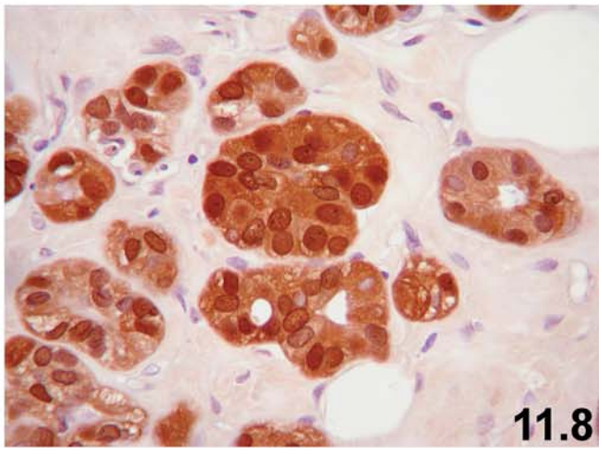
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Fig. 12: Radial scar/complex sclerosing lesion.

Case history: Routine mammographic examination of a 40-year-old woman showed a 1.5-cm left breast lesion (upper inner quadrant) with irregular and infiltrating margins. The lesion was regarded as highly suspicious for malignancy. Excisional biopsy was performed.

Fig. 12.1: The cut surface of the excisional biopsy shows a firm, greyish-white lesion with infiltrating or radiating borders. The gross appearance of the lesion is highly suspicious for malignancy.

Fig. 12.2: At low magnification, the radial nature of the lesion is evident. While the lesion shows a central hypocellular fibrocollagenous zone, a stellate arrangement of ductules is present at its periphery.

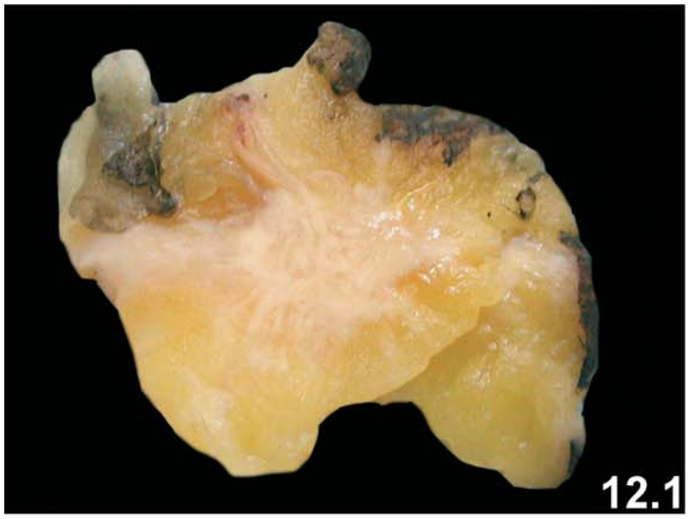
Fig. 12.3: At the periphery of the lesion, some small ducts show intraluminal epithelial proliferation with irregular, slit-like secondary lumina.

Fig. 12.4: Higher magnification reveals proliferation of a heterogeneous cell population consisting of epithelial and modified myoepithelial cells. The architectural and cytological alterations are typical for usual ductal hyperplasia, which occurs at the periphery of this lesion.

Figs. 12.5 and **12.6:** Another area of the same lesion (a different paraffin block) displays a stellate arrangement of ductules with a central fibroelastotic zone. The small ducts are haphazardly arranged and distorted. At the periphery of the lesion, closely packed glands with adenosis pattern are present.

Fig. 12: Final remarks

- The major differential diagnosis in this case is tubular carcinoma or well-differentiated infiltrating ductal carcinoma. The glands in this case are lined by epithelial and myoepithelial cells, proving the benign nature of the lesion.
- The designation of benign complex sclerosing lesion is appropriate in this case because of the size of the lesion (1.5 cm) and its association with ductal hyperplasia and sclerosing adenosis.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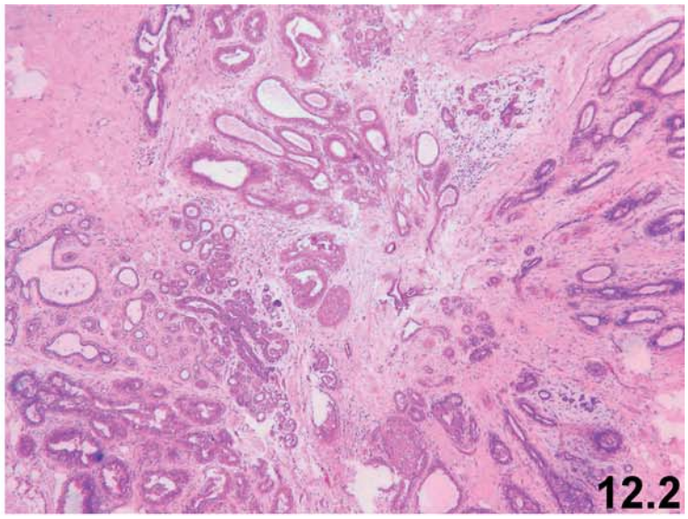
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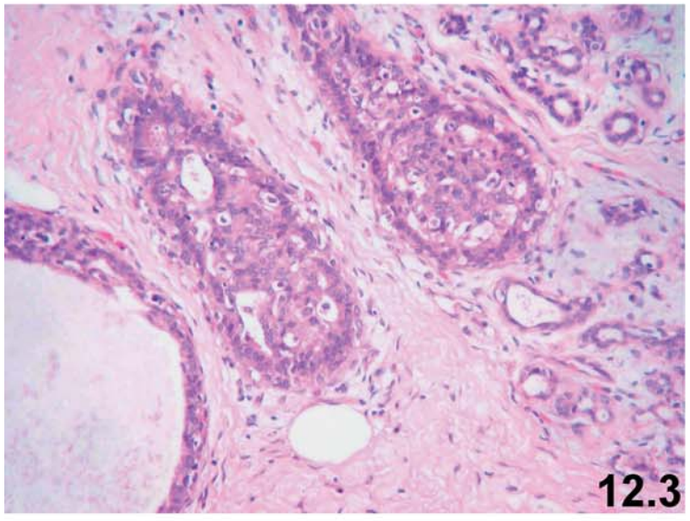
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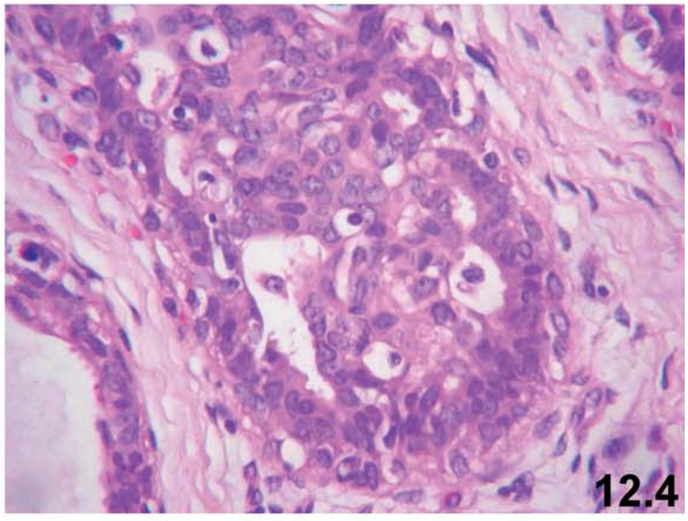
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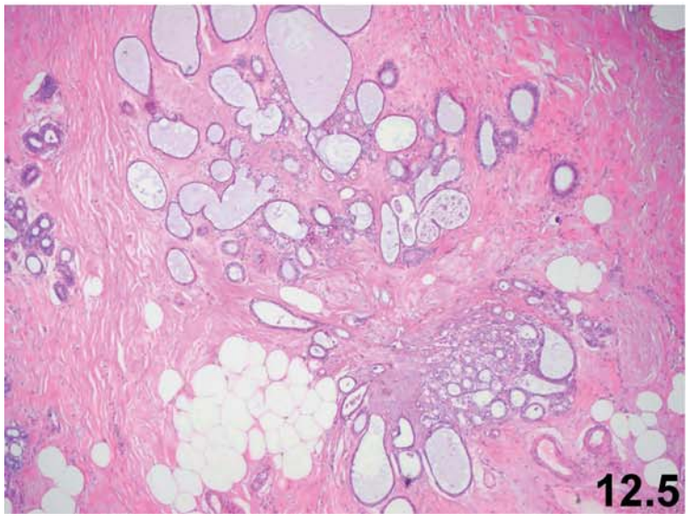
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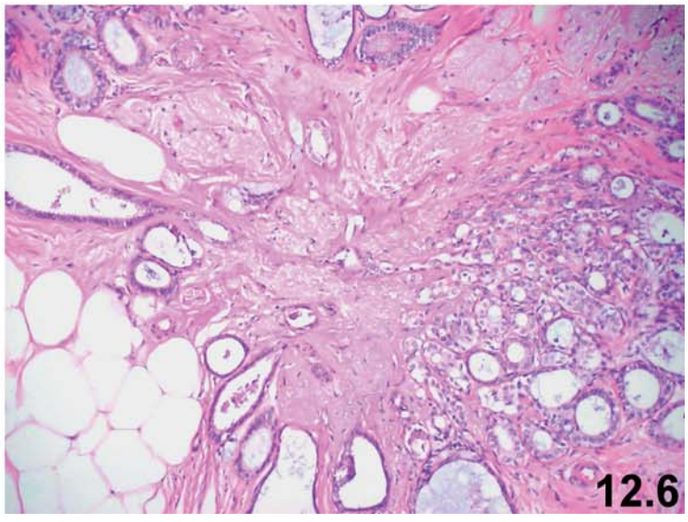
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Fig. 13: Benign complex sclerosing lesion associated with pseudoinvasion.

Case history: A 29-year-old woman presented with a clinically palpable tumor of her left breast (lower outer quadrant). Mammographic and ultrasonographic examinations revealed a 2.5-cm tumor with ill-defined borders suspicious for malignancy.

Fig. 13.1: At low magnification, a sclerosing lesion with several disorganized glands and infiltrative growth pattern is present.

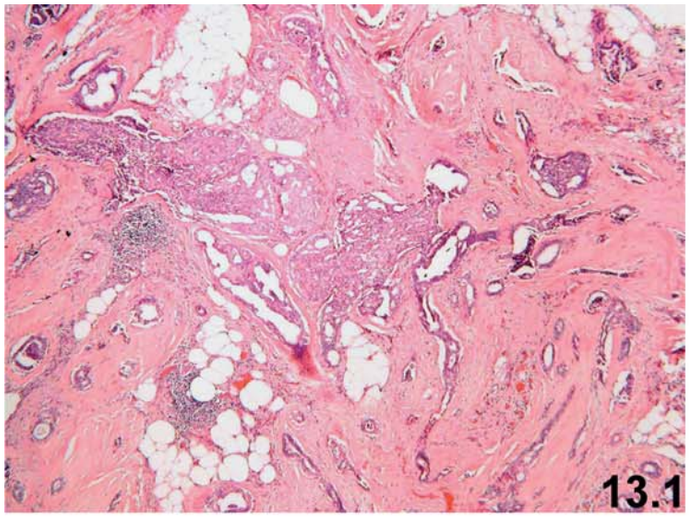
Fig. 13.2: Low magnification shows open glands in a fibrocollagenous background.

Fig. 13.3: The glands are haphazardly arranged and distorted.

Fig. 13.4: Several areas of the lesion show tubules with irregular arrangements. Several glands with sharp contours are seen.

Fig. 13.5: In addition, some tubules show a glandular confluence, a feature rather typical for an invasive carcinoma.

Fig. 13.6: Higher magnification displays glands with basally located myoepithelial cells.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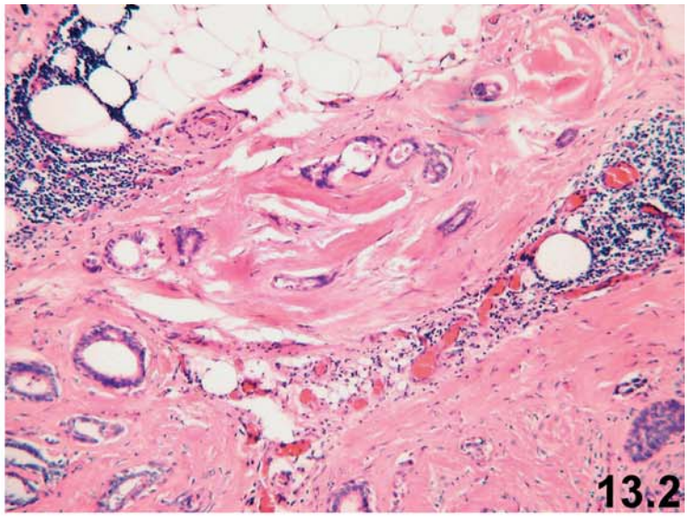
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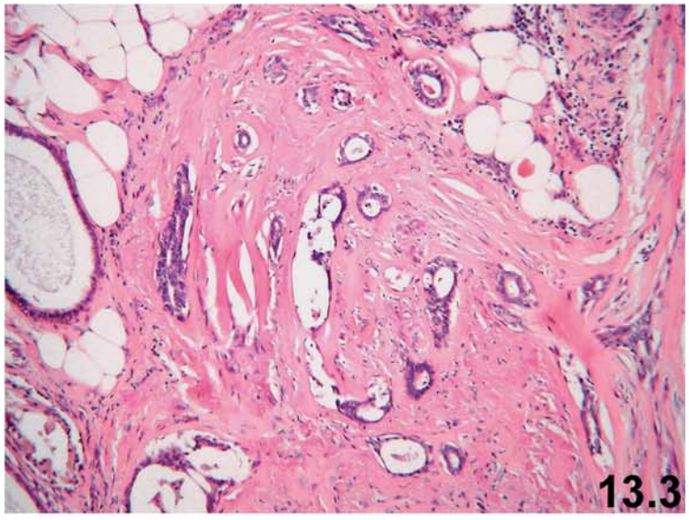
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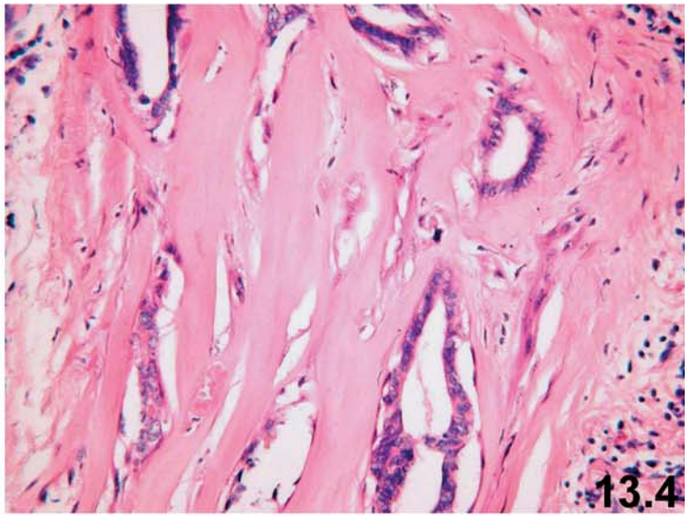
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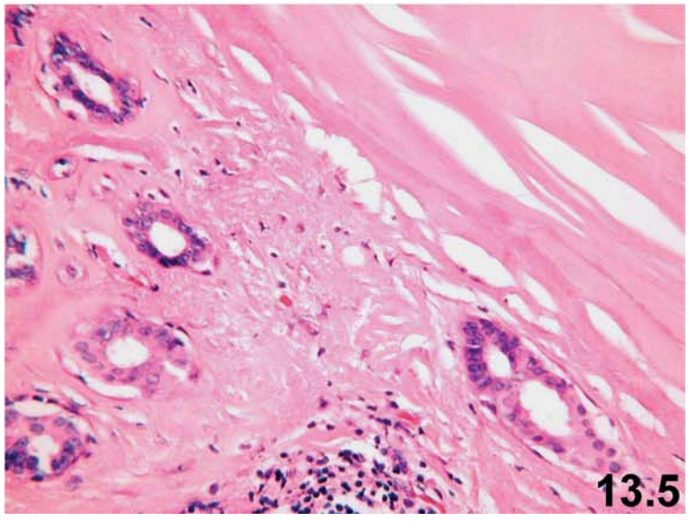
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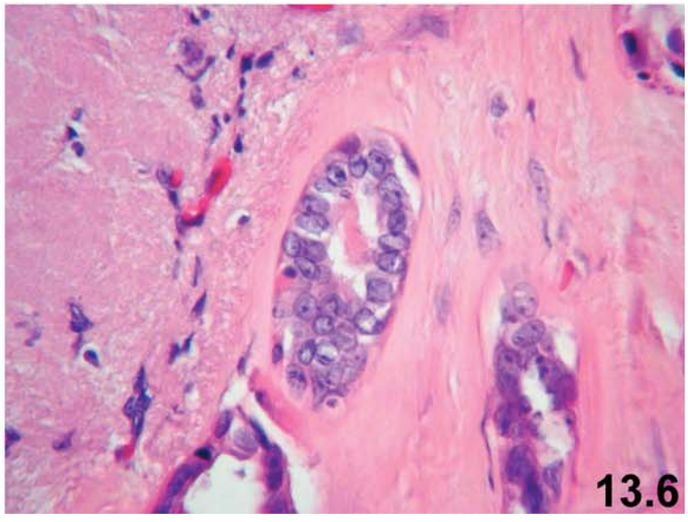
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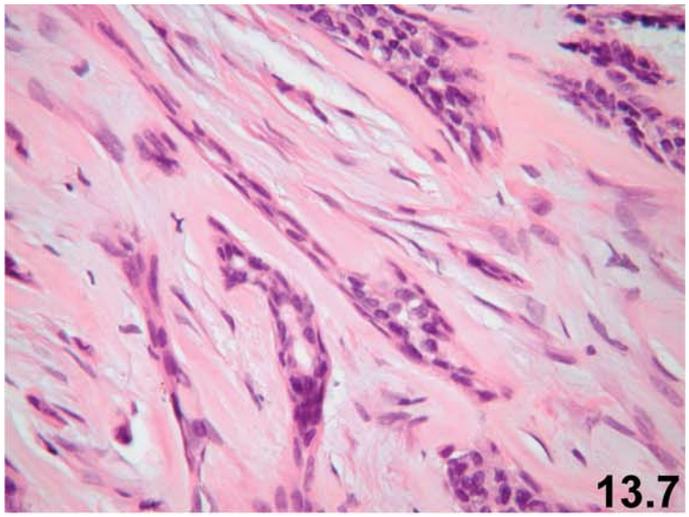
Figs. 13.7 and **13.8:** Irregular, solid, or trabecular epithelial structures simulate an invasive ductal carcinoma. The presence of (attenuated) myoepithelial cells, however, excludes malignancy.

Fig. 13.9: Small epithelial clusters and isolated cells closely mimic a malignant process.

Fig. 13.10: Central areas of the lesion with florid ductal hyperplasia lined by a discontinuous layer of myoepithelial cells as demonstrated by an antibody against smooth muscle actin.

Figs. 13.11 and **13.12:** Immunohistochemistry for smooth muscle actin and smooth muscle myosin (heavy chain; not shown) clearly shows that the glands with seemingly infiltrative pattern contain myoepithelial cells.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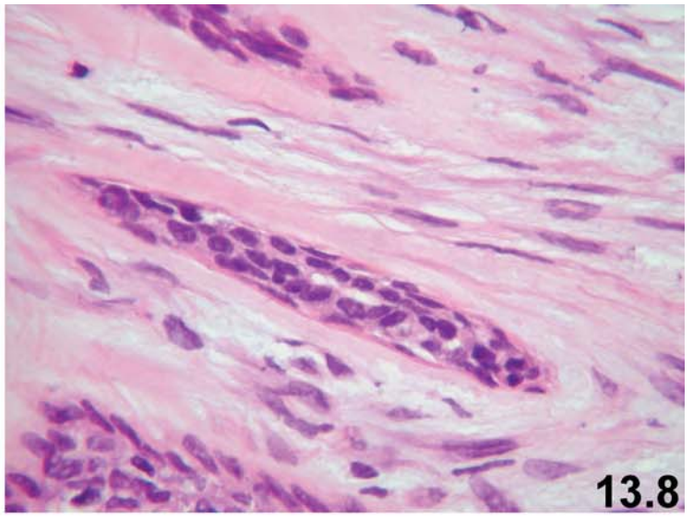
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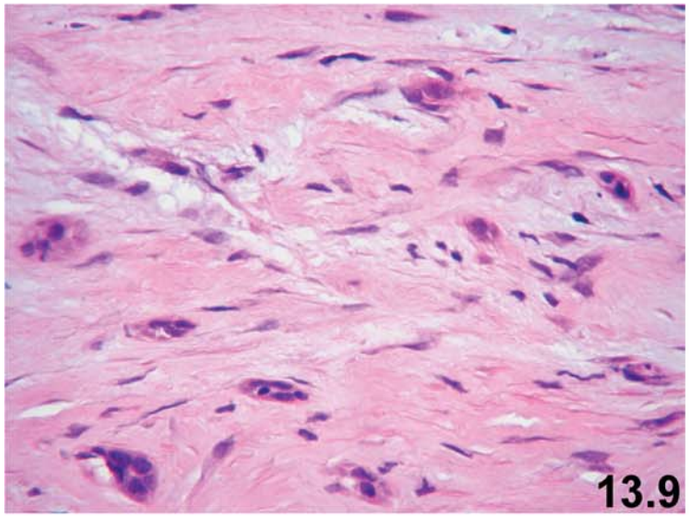
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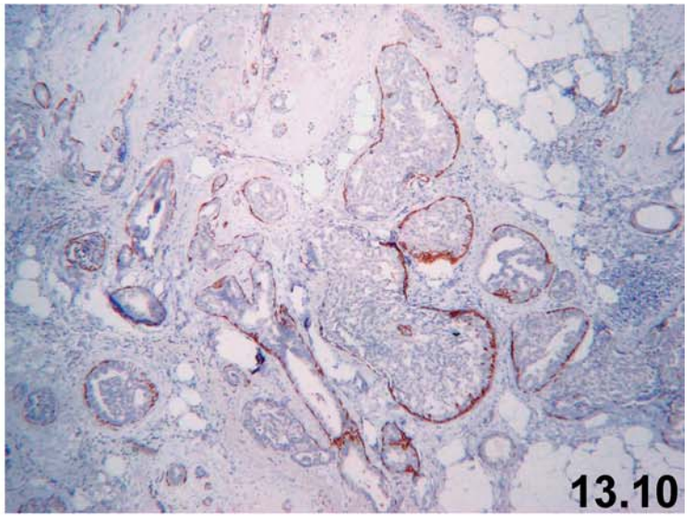
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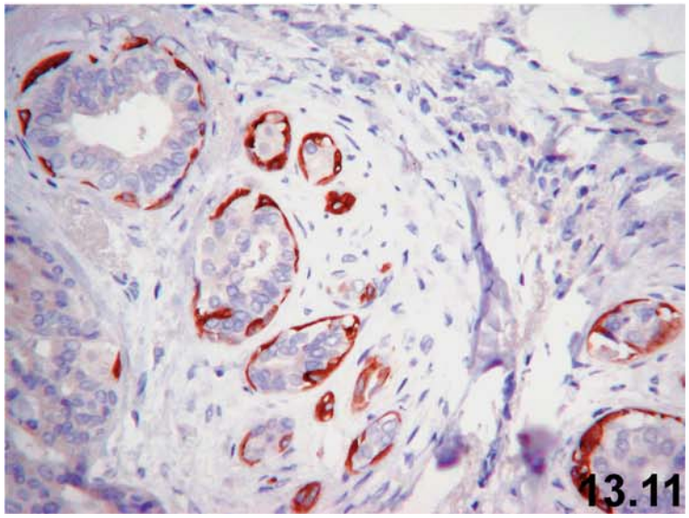
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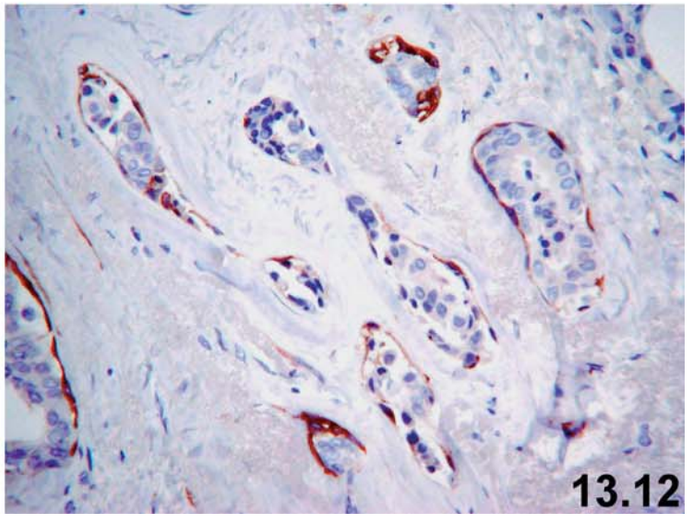
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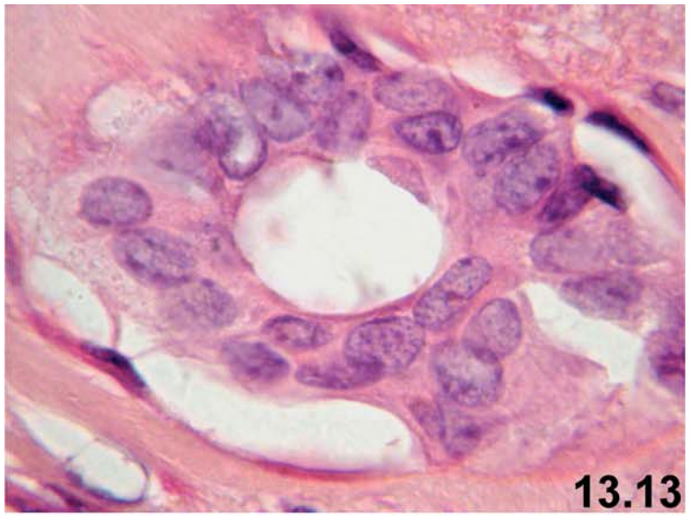
Figs. 13.13 and **13.14:** Even without immunohistochemistry, many areas of this complex lesion reveal a clear-cut myoepithelial cell component. At higher magnification, the glands show attenuated myoepithelial cells with spindle-shaped or bipolar nuclei.

Fig. 13.15: Immunohistochemistry for pancytokeratin showing small and irregular clusters of epithelial cells within the fibrocollagenous stroma – a feature that may easily lead to misinterpretation as carcinoma.

Figs. 13.16 and **13.17:** Immunohistochemistry for cytokeratin shows small epithelial clusters and isolated cells in this complex sclerosing lesion. The seemingly isolated epithelial cells and compressed clusters are, in fact, connected to the larger, branching ducts and contain myoepithelial cells.

Fig. 13: Final remarks

- The infiltrative growth pattern of some glands, particularly those with open lumina and sharp angular contours, and the presence of some isolated epithelial cells in the sclerotic stroma in this case created serious diagnostic problems for some pathologists. Indeed, even some experienced pathologists called this lesion an infiltrating ductal carcinoma.
- This case represents a typical example of pseudoinvasion in a benign complex sclerosing lesion that can easily be misinterpreted as invasive carcinoma. Identification of myoepithelial cells within the glands by using high magnification (and immunohistochemistry for myoepithelial markers) is crucial to avoid overdiagnosis in such cases.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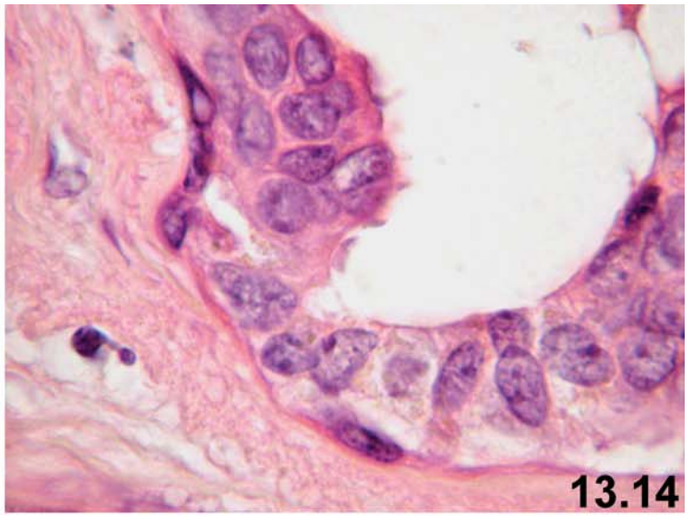
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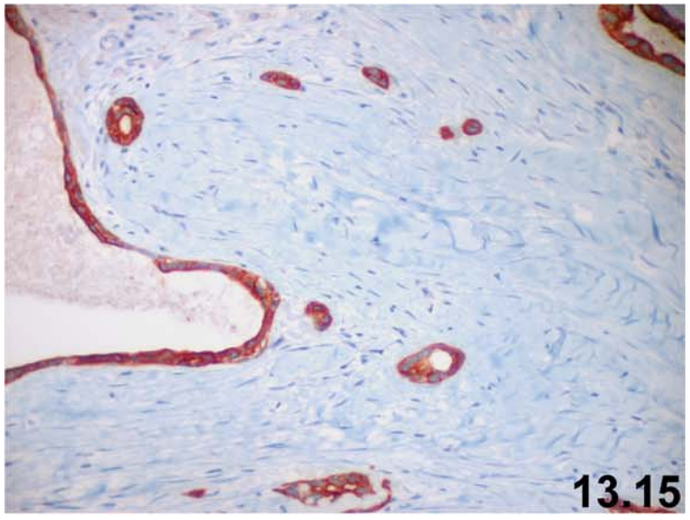
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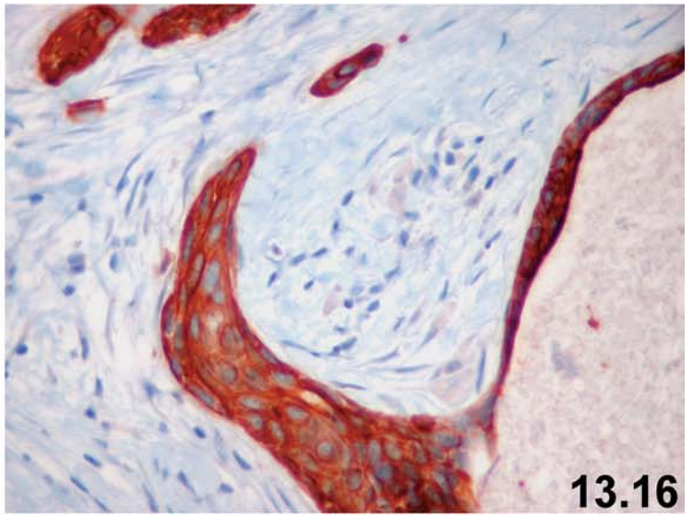
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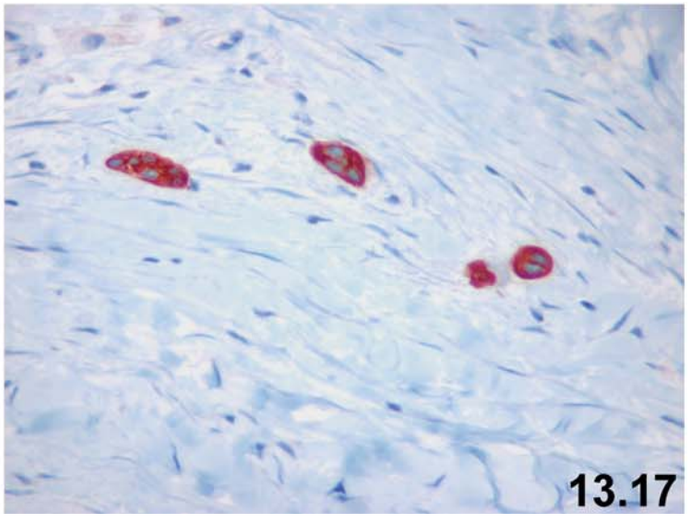
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Fig. 14: Radial scar associated with collagenous spherulosis and lobular intraepithelial neoplasia.

Case history: A 55-year-old woman presented with clinical and mammographic signs of fibrocystic changes of her left and right breasts. Mammographic examination of the left breast showed a well-defined tumor (0.8 cm in diameter) that histologically proved to be an intraductal papilloma (not shown). The excisional biopsy also revealed incidental histological findings as seen below.

Fig. 14.1: Low magnification shows a typical radial scar with a stellate arrangement of small ducts surrounding a central fibrocollagenous zone.

Fig. 14.2: The periphery of the incidental (microscopic) lesion shows haphazardly arranged and distorted tubules.

Fig. 14.3: At the periphery of the lesion, some ducts display an intraluminal proliferation with cribriform-like growth pattern.

Fig. 14.4: Elsewhere at the periphery, fibrillar spherules are evident admixed with monotonous and somewhat loosely cohesive epithelial cells.

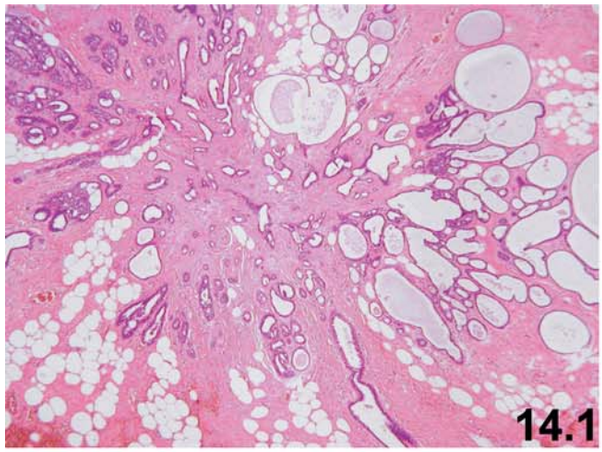
Fig. 14.5: Intraductal proliferation with several fibrillar spherules. Note the presence of a monotonous cell population of mildly atypical cells around the spherules.

Fig. 14.6: Typical collagenous spherulosis displaying acellular fibrillar structures surrounded by round to ovoid cells.

Figs. 14.7 and **14.8:** Intraductal proliferation with several spherules containing basement-membrane-like material showing a concentric or laminated arrangement. Note the simultaneous presence of loosely cohesive cells with a monotonous appearance and cells with pale cytoplasm. These monotonous cells are neoplastic and lobular in nature (lobular intraepithelial neoplasia), occurring in the same ducts with collagenous spherulosis.

Fig. 14: Final remarks

- The cribriform-like growth pattern in this case may easily be confused with a cribriform ductal carcinoma in situ (DCIS). In contrast to DCIS, collagenous spherulosis contains concentric or laminated fibrils (basement-membrane-like material) and intraluminal myoepithelial cells around the spherules.
- The monotonous and small uniform epithelial cells of lobular intraepithelial neoplasia in this case may easily be overlooked.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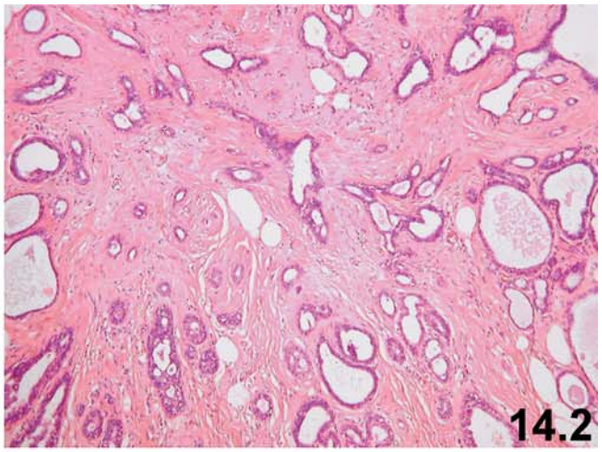
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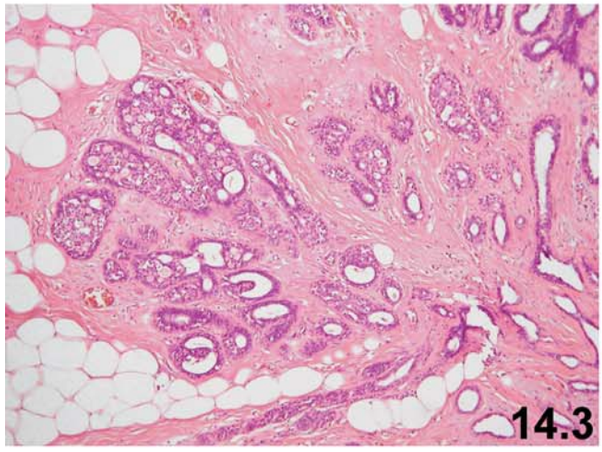
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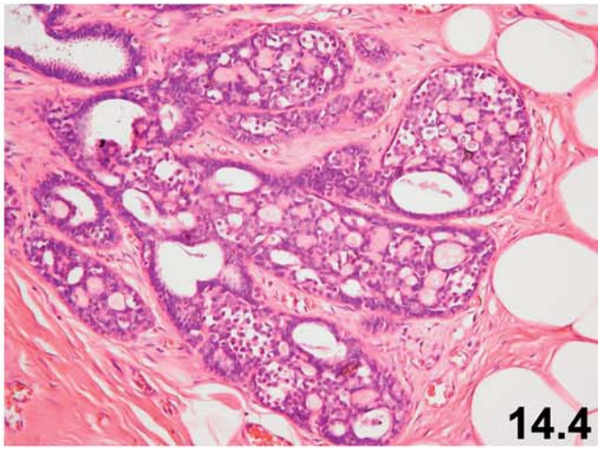
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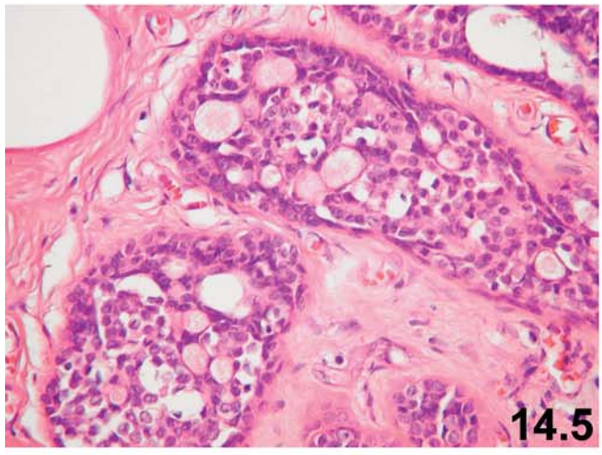
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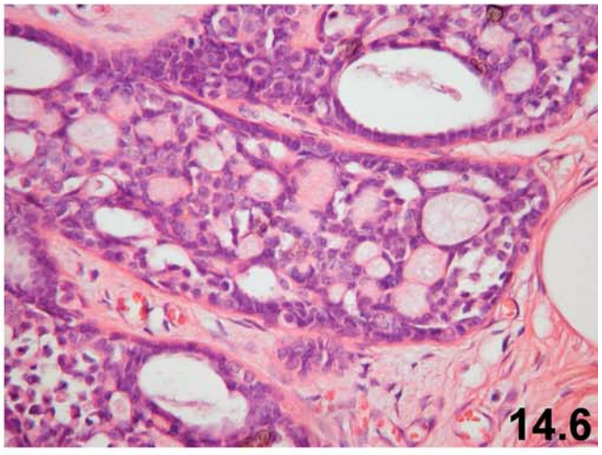
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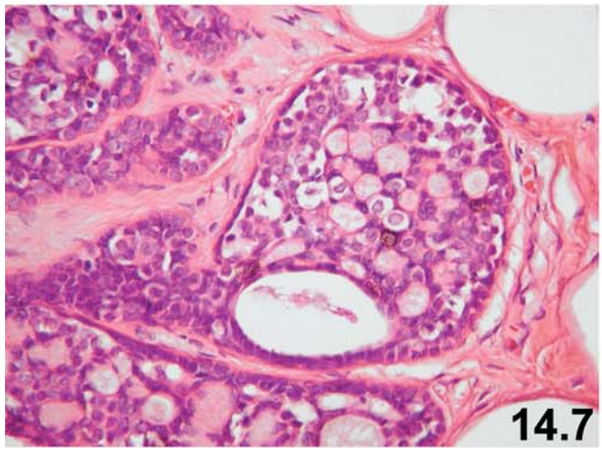
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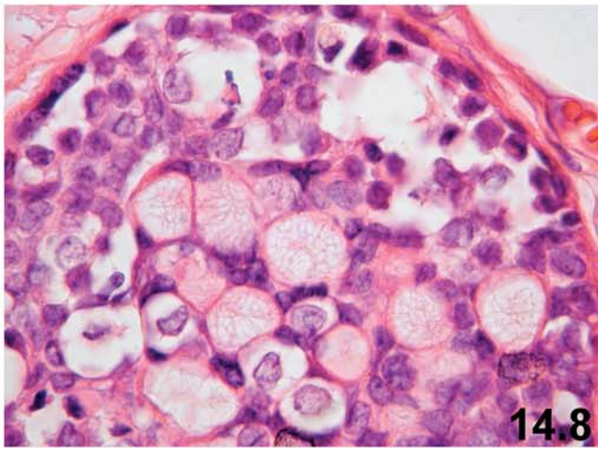
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Fig. 15: Mucinous spherulosis.

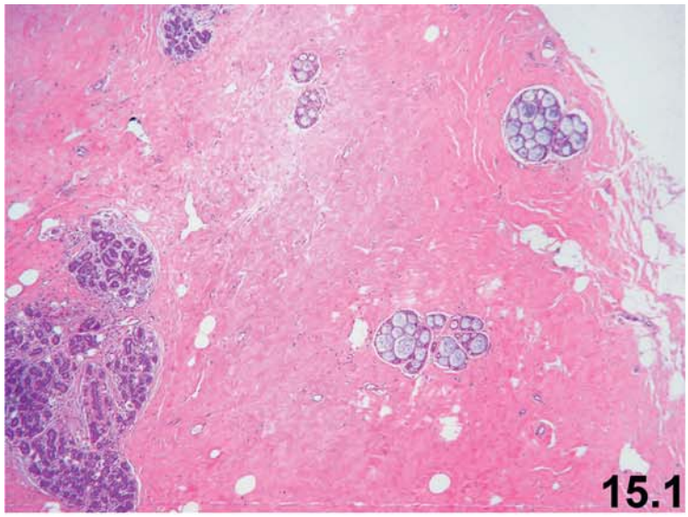
Case history: A 36-year-old woman presented with a fibroadenoma and sclerosing adenosis in her right breast (histology not shown). The excisional biopsy also revealed an incidental finding as described below.

Fig. 15.1: At low magnification, lobules with acellular spherules are present.

Fig. 15.2: Multiple small ducts showing a cribriform-like growth pattern associated with luminal basophilic mucoid material.

Figs. 15.3 and **15.4:** The spaces contain only mucoid material. These spherules represent an earlier stage of collagenous spherulosis.

Figs. 15.5 and **15.6:** Several rounded secondary spaces containing mucoid material. The spaces in Figs. 15.4, 15.5, and 15.6 are lined by smooth muscle actin positive myoepithelial cells (immunohistochemistry not shown).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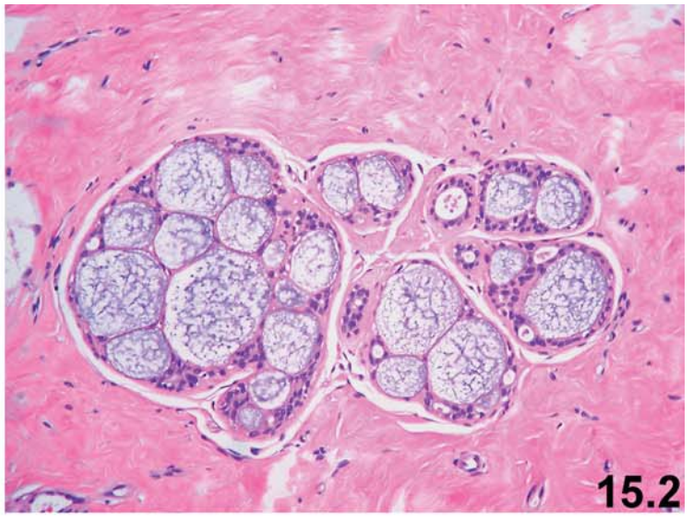
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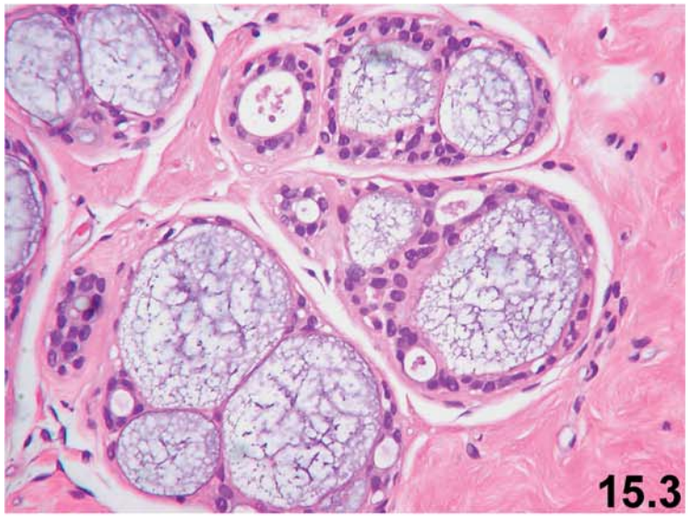
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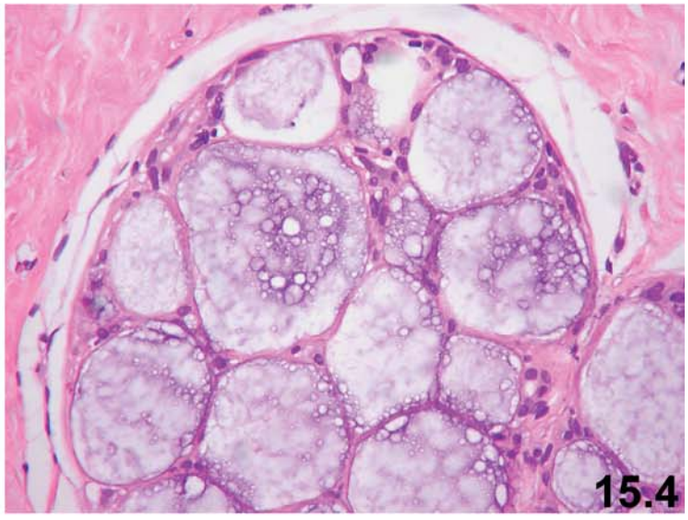
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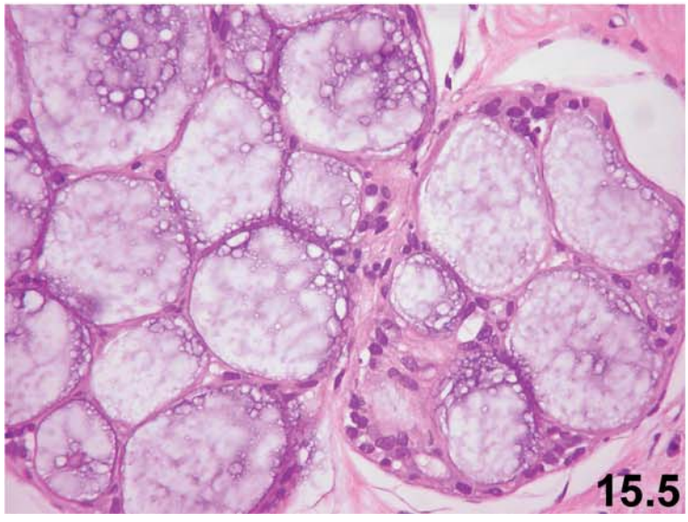
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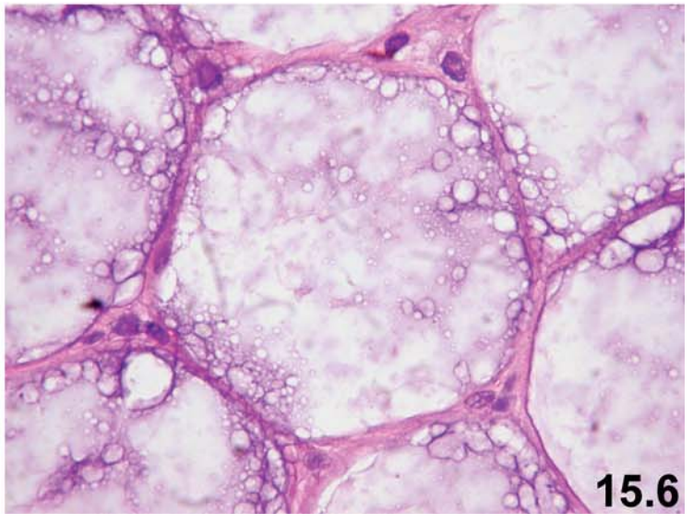
15.6

Intraductal Proliferative Lesions

Contents

CHAPTER 5 Intraductal Proliferative Lesions

Intraductal proliferative lesions are a group of cytologically and architecturally heterogeneous intraductal proliferations associated with an increased risk, albeit of different magnitudes, for subsequent development of infiltrating carcinoma.

Intraductal proliferative breast lesions have traditionally been divided into three categories: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS).

5.1 Usual Ductal Hyperplasia

5.1.1 Synonyms

Intraductal hyperplasia, ductal hyperplasia of usual type, ordinary intraductal hyperplasia, epitheliosis.

5.1.2 Macroscopy

There are no grossly apparent features specifically associated with UDH. However, it is often associated with fibrocystic changes.

5.1.3 Microscopic Features (Figs. 16–18)

5.1.3.1 Architectural Features

- There is often a characteristic streaming or swirling growth pattern, which can be distinct or subtle. Streaming means that the proliferating cells and their nuclei have a parallel orientation of their long axes.
- Secondary lumens are irregular in size and shape, angulated, slit-like, and sometimes peripheral in location.
- Epithelial bridges may occur, but they are stretched with elongation of the cells: fragile spindle cell bridging and tufting (no rigid "roman" bridge).
- The proliferating cells show uneven distribution of nuclei and overlapped nuclei.

5.1.3.2 Cytologic Features

- Characteristically, there is a heterogeneous cell population of intraluminal cells (mixed cell type, heterogeneity of divergent cell population consisting of epithelial, myoepithelial, and apocrine metaplastic cells).
- The appearance of nuclei is varied (angulated, spindled, oval, or rounded).
- The proliferating cells show numerous modified myoepithelial cells characterized by small pyknotic or elongated (bipolar), spindle-shaped nuclei.
- The cell margins are indistinct.

It is important to note that the most characteristic feature of UDH is the presence of a heterogeneous cell population consisting of epithelial and modified myoepithelial cells (pleomorphism of divergent cell population). It is highly likely that the cells with bipolar or spindle-shaped nuclei in UDH are closely related to myoepithelial cells. Based on morphological similarities of these cells with basally located myoepithelial cells and immunoexpression of some, but not all, myoepithelial markers (see the following section on immunohistochemistry), these cells can be regarded as "modified" myoepithelial cells. Other terms, such as poststem or progenitor cells, have also been used to describe the above-mentioned cell type in the breast [4, 5].

5.1.4 Immunohistochemistry

- Intense positive immunoreactions for both low (CK8, CK18, CK19) and high molecular weight cytokeratins (HMW-CK), such as CK5/6, CK14, and CK34betaE12, are characteristic for UDH.
- The use of high molecular weight cytokeratin (CK5/6, CK14, or CK34betaE12) in a problematic case with intraductal proliferation is highly recommended; an intense positive reaction of proliferating cells for HMW-CK is highly suggestive of UDH. In contrast, the vast majority of cases with DCIS (and atypical intraductal hyperplasia) are completely or predominantly negative for HMW-CK (CK5/6) [16, 20, 22].
- The heterogeneous cell population of UDH consists of epithelial and modified myoepithelial cells. While the modified myoepithelial cells in UDH often lack immunoexpression for typical myoepithelial markers such as SM actin, SM myosin (heavy chain), and calponin, they are almost always positive for S100 protein, CK5/6, and CK14. The modified myoepithelial cells may also be positive for nerve growth factor receptor (NGFR/p75), which is a recently recognized myoepithelial marker in the breast. Occasionally, the proliferating cells in UDH focally show a positive immunoreaction for more conventional myoepithelial markers such as p63, CD10, maspin, or even SM actin.

Caution

- The uncommon presence of prominent nucleoli in UDH does not change the diagnosis.
- Mitotic figures are usually rare in UDH. Increased mitotic figures, however, do not indicate malignancy. The presence of atypical mitotic figures, however, is a worrisome finding.
- In the vast majority of cases with UDH, necrosis is absent or very inconspicuous. But the presence of luminal necrosis in rare examples of UDH does not influence the ultimate diagnosis; the lesion should be interpreted on the basis of the proliferating cell type.
- In the florid type of intraductal hyperplasia, the proliferating cells may show large nuclei with an increased nuclear-cytoplasmic (N/C) ratio. The nuclei can be either vesicular (open chromatin) or slightly hyperchromatic. These changes should not automatically lead to the diagnosis of atypical hyperplasia or ductal intraepithelial neoplasia (DIN). One should always keep in mind that the most characteristic feature of UDH is the presence of a heterogeneous cell population consisting of epithelial and modified myoepithelial cells (pleomorphism of divergent cell population) with variation in nuclear size and shape.
- In difficult or complex intraductal proliferative breast lesions, immunohistochemistry with an antibody against HMW-CK (such as CK5/6) can be very helpful (see the previous section on immunohistochemistry).

5.1.5 Additional Comments

Recent molecular genetic studies on UDH have shown that at least some of these lesions are clonal or neoplastic (see section on DIN). Indeed, it is possible that many cases with UDH represent a benign neoplastic intraductal proliferation. However, because UDH differs morphologically, immunohistochemically, genetically, and, most importantly, clinically (with regard to the relative risk for invasive carcinoma) from ADH and DCIS, it is better to separate UDH from other intraepithelial neoplastic proliferations that are associated with significant increased risk for subsequent development of breast carcinoma [5, 9, 11, 14, 17, 21, 27].

Recent studies have shown that CK5/6 is more reliable than CK34BE12 for distinguishing UDH from DCIS [16, 22, 26].

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5.2 Ductal Intraepithelial Neoplasia (DIN)

5.2.1 Synonyms

Ductal carcinoma in situ (DCIS), intraductal carcinoma.

"One problem is in the very name of these things as cancer. It's a problem for intraductal carcinoma (DCIS) and a much bigger problem for LCIS, which we don't regard as cancer at all. But once patients hear that word 'cancer,' what they envision is metastatic disease, and it's difficult to get beyond that to the idea that you are talking about risk and future cancer."

M. Morrow
A 47-year-old woman with ductal carcinoma in situ.
JAMA 1996;275:61–66

"Given the fact that women experience the same level of anxiety and depression whether they receive a diagnosis of in situ or invasive carcinoma, it is time to abandon the designation of carcinoma in situ. It is time to unify the intraductal proliferations/alterations under the designation of ductal intraepithelial neoplasia (DIN) lesions that constitute risk factors (albeit of different magnitude) for subsequent development of invasive carcinoma…There is no justification in separating atypical intraductal hyperplasia (AIDH) from low-grade ductal carcinoma in situ (DCIS); their similarity at the cytologic, immunohistochemical and molecular level obviates their separation."

F.A. Tavassoli
Breast pathology: rationale for adopting
the ductal intraepithelial neoplasia (DIN) classification.
Nature Clin Pract Oncol 2005;2:116–117

5.2.2 Background (WHO, 2003)

- "Intraductal proliferative lesions of the breast have traditionally been divided into three categories: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS). The term 'DCIS' encompasses a highly heterogeneous group of lesions that differ with regard to their mode of presentation, histopathological features, biological markers, and subsequent relative or absolute risks for progression to invasive carcinoma. In most cases, the histopathologic distinction between UDH and DCIS can be made on morphological grounds alone, particularly with standardization of histopathological criteria. However, even the distinction between some of the lesions (particularly between ADH and some low-grade forms of DCIS) remains problematic. In addition, population-based mammography screening has resulted in increased detection of lesions that show cytological atypia with or without intraluminal proliferation but do not fulfill the diagnostic criteria for any of the existing categories" [27].
- "The risk for subsequent development of invasive breast carcinoma ranges from approximately 1.5 times that of the reference population for UDH, to 4–5-fold (range 2.4–13.0-fold) for ADH, and 8–10-fold for DCIS" [27].

Table 5.1. Classification of intraductal proliferative lesions according to traditional and alternative (DIN) terminologies; World Health Organization classification, 2003 [27]

Traditional terminology	Alternative terminology
Usual ductal hyperplasia	Usual ductal hyperplasia
Flat epithelial atypia	DIN grade 1a (DIN1a)
Atypical ductal hyperplasia	DIN grade 1b (DIN 1b)
DCIS, low grade (G1)	DIN grade 1c (DIN1c)
DCIS, intermediate grade (G2)	DIN grade 2 (DIN2)
DCIS, high grade (G3)	DIN grade 3 (DIN3)

- "Recent immunophenotypic and molecular genetic studies have provided new insights into intraductal proliferative lesions indicating that the long-held notion of a linear progression from normal epithelium through hyperplasia, atypical hyperplasia and carcinoma in situ to invasive carcinoma is overly simplistic; the interrelationship between these lesions and invasive carcinoma is far more complex" [27].
- "The current data suggest that (1) UDH shares few similarities with most ADH, DCIS, or invasive cancer; (2) ADH shares many similarities with low-grade DCIS; (3) low-grade DCIS and high-grade DCIS appear to represent genetically distinct disorders leading to distinct forms of invasive breast carcinoma, further emphasizing their heterogeneity; and (4) at least some lesions with flat epithelial atypia are neoplastic" [27].
- Although used by many pathology laboratories, the traditional classification system suffers from high interobserver variability, particularly in distinguishing between ADH and low-grade DCIS. This problem (ADH as noncancer versus DCIS as cancer) currently has a significant impact on patient management. Indeed, there is no justification for the designation of "cancer" for a neoplastic intraductal lesion that is not invasive and, therefore, merely represents a precancerous condition [6, 14, 22, 25, 26, 28]. To overcome several disadvantages of the traditional classification system and replace it with a more meaningful system, an alternative terminology of ductal intraepithelial neoplasia (DIN) has been proposed [22, 25, 26, 28]. The current *World Health Organization Classification of Tumours of the Breast* (2003) includes the DIN terminology in addition to the traditional system [27]. According to this, for purposes of clinical management and tumor registry coding, when the DIN terminology is used, the traditional terminology should be mentioned as well. *In the following discussion and in the entire book, the DIN terminology/concept is preferred and is used with minor modification, accompanied by the traditional terminology in parenthesis.* (See Table 5.1.)

5.2.3 Comments on the Current WHO Classification of Intraductal Proliferative Lesions

- Usual ductal hyperplasia (UDH) or intraductal hyperplasia without atypia is not included in the WHO DIN classification [27]. It is, however, most likely that UDH represents a benign intraepithelial neoplastic (monoclonal) proliferation [26, 28], a lesion with minimal increased risk for subsequent develop-

ment of invasive carcinoma [26–28]. It is of note that UDH differs from ADH and low-grade DCIS morphologically, immunohistochemically, genetically, and, most importantly, clinically (with regard to the relative risk for invasive cancer).

- The lack of interobserver reproducibility is a major flaw of the traditional classification, resulting in drastically different terms such as ADH (noncancer) and DCIS (cancer) being used for the same lesion by different observers [21, 22]. The DIN concept reduces the impact of these terminology variations, pure and simple.
- Currently, we use the term DCIS (low to high grades) to describe a heterogeneous group of preinvasive breast lesions with significant differences in terms of their malignant potentials or risks for subsequent development of infiltrating carcinoma. In other words, although the use of the term DCIS seems to be justified conceptually, biologically, and histomorphologically, all of these lesions clinically represent premalignant conditions with low or high malignant potentials. Therefore, there is no need to continue designating a breast lesion as cancer (DCIS) if the lesion is clinically considered premalignant [14].
- The classic and often cited studies of DCIS [4, 18, 19] that showed a relative risk 8–10 times that of the general population for subsequent invasive carcinoma have a major limitation: DCIS is considered a homogenous group and is not divided into low-grade (G1), intermediate-grade (G2), and high-grade (G3) lesions. Therefore, a specific correlation between different grades of DCIS and subsequent invasive carcinoma could not be assessed in those studies.
- The term flat epithelial atypia or DIN1a (DIN, low-grade, flat type) is applied to flat lesions with mild cytologic atypia. A flat lesion with high nuclear atypia, however, is classified as DIN 3 (DCIS, high-grade or polymorphous variant of clinging carcinoma in situ). This high-grade variant needs to be distinguished from a low-grade flat lesion [15]. Recent genetic studies have clearly demonstrated that DIN flat type (low and high grades) shows almost identical genetic alterations (loss of heterozygosity) as those identified in the more "conventional" types of DCIS [15, 27]. It represents one of the earliest morphologically recognizable neoplastic alterations of the breast. Although the epithelial cells in this flat type of breast lesion reveal definite cytologic atypia, sometimes evident only at high magnification, architectural abnormalities are characteristically absent or minimal, if present at all. Therefore, this flat lesion may be, and is, readily overlooked or misinterpreted as normal [15].
- According to the current WHO classification (2003), "ADH corresponds to low-grade DCIS, cytologically" [27]. Furthermore, "ADH is diagnosed when characteristic cells coexist with patterns of UDH, and/or there is partial involvement of [the terminal duct-lobular unit] by classic morphology (of DCIS). There is currently no general agreement on whether quantitative criteria should be applied to separate ADH from low-grade DCIS. Some define the upper limit of ADH as one or more completely involved duct/ductular cross-sections measuring less than or equal to 2 mm in aggregate, while others require that the characteristic cytology and architecture be present completely in two spaces" [27].
- The current WHO classification divides DIN1 into three subcategories: 1a, flat epithelial atypia; 1b, atypical ductal hyperplasia; and 1c, low-grade ductal carcinoma in situ [27]. In the author's opinion, a reliable separation between ADH and low-grade DCIS is not possible, and these low-grade neoplastic lesions should be grouped together as low-grade DIN or DIN1. Thus, a separation between DIN1b and DIN1c is not meaningful. Furthermore, flat epithelial atypia or DIN1a represents another variant of low-grade DCIS ("clinging carcinoma in situ") and therefore can and should simply be designated as low-grade DIN flat type or DIN1. The subdivision of low-grade DIN into DIN1a, DIN1b, and DIN1c, as indicated by the current WHO classification, needs to be changed.
- A criticism of the DIN numerical terminology (DIN1, DIN2, and DIN3) has been that it implies a continuum of changes or a linear progression of intraepithelial neoplasia that may or may not exist [23]. In other words, linking these conditions in a graded system that presupposes a nosologic unity might be unwarranted and misleading. However, one could say exactly the same thing about the current grading of DCIS (G1, G2, G3)! One needs to keep in mind that the grading of DIN or DCIS (or even of infiltrating breast carcinoma) does not mean a linear progression from G1 toward G3 neoplastic lesions. It merely shows the degree of differentiation as a reflection of malignant potential.
- Some members of the WHO Working Group, including the writer, proposed that the traditional terminology be replaced by DIN and strongly felt that the term "carcinoma" should be reserved for invasive tumors. The majority of participants in the WHO Working Group, however, were in favor of maintaining the traditional terminology (UDH, ADH, DCIS) [27].
- The classification of intraductal proliferative lesions should be viewed as an evolving concept that may be modified as additional molecular genetic and clinical data become available.

5.2.4 Advantages of DIN Terminology

Advantages of DIN terminology include the following:

- It does not use the term "cancer" for a precancerous (preinvasive) neoplastic proliferation. The term "carcinoma" is reserved for invasive epithelial tumors with clinical malignant behavior. While it does not dismiss the category of "carcinoma in situ" as a significant risk factor for the development of invasive carcinoma, it does not elevate it to the frightening status of "cancer." Thus, the danger of overdiagnosis and excessive treatment could be reduced. Also, the emotional stress of women suffering from "cancer in situ" will be reduced.
- It does not distinguish between ADH and low-grade DCIS as two separate entities. These are regarded as closely related, if not identical, neoplastic proliferations that should probably be managed in the same way based on the size (extension) of the lesions.
- It includes the category of flat lesion (Azzopardi's designation: clinging carcinoma) in addition to more conventional types such as cribriform, micropapillary, solid, and so on.
- The malignant potential (risk for subsequent development of invasive carcinoma) is reflected by a grading system (DIN1–3 or low- to high-grade DIN). Again, according to the DIN concept, these lesions are regarded as neoplasias with low to high malignant potentials but not yet malignant tumors.

- It uses the unifying concept of intraepithelial neoplasia for precancerous lesions as already used in several other organs such as the cervix (CIN), vagina (VAIN), vulva (VIN), prostate (PIN), gastrointestinal tract (pancreatic, colonic, or gastric intraepithelial neoplasias) or even within the breast (lobular neoplasia [LN]).

"In all fairness, most of the arguments that have been raised against the adoption of DIN terminology apply to other organ sites just as well, yet they have not prevented a terminology change taking place in those sites."

J. Rosai
Rosai and Ackerman's Surgical Pathology
9th edition, 2004

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5.3 Ductal Intraepithelial Neoplasia (DIN), Flat Type

5.3.1 Definition

A neoplastic ductal alteration characterized by replacement of the native epithelial cells by a single cell or a very few cell layers of atypical cells. The neoplastic cells are limited to the periphery of the containing structures (ducts, ductules) in the sense that they do not fill the lumen in a solid or cribriform fashion, nor do they show the numerous cell layers usually seen in comedo DCIS [1, 7, 10, 14].

5.3.2 Synonyms

Clinging carcinoma in situ (Azzopardi), atypical cystic lobules, atypical lobules type A, atypical columnar changes, columnar cell alteration with atypia, columnar cell hyperplasia with atypia, flat epithelial atypia.

5.3.3 Types of DIN Flat Type

High-grade flat lesion as a variant of comedo DCIS: Very few cell layers of highly atypical (anaplastic) epithelial cells without significant luminal debris. At low magnification the atypical focus can be easily missed. It represents a high-grade DIN flat type (DIN3, flat type; synonym: pleomorphic variant of clinging DCIS).

Low-grade flat lesion (WHO: DIN1a, flat epithelial atypia): Very few cell layers of mildly atypical epithelial cells replacing the native epithelial lining cells. Synonyms for low-grade DIN flat type include flat epithelial atypia, columnar cell lesion (hyperplasia) with atypia, and atypical cystic lobules.

5.3.4 Microscopic Features of DIN Flat Type (Figs. 19, 20, 27)

- Homogeneous (monotonous) cell population of atypical cells showing nuclear enlargement, higher N/C ratio, abnormal chromatin structure, nucleolar prominence, increased mitotic activity (including abnormal mitoses), and eventually a few necrotic epithelial cells in the lumen (apoptosis). A single cell or a few cell layers (two to five) of cytologically atypical cells is seen, often with apical snouts [1, 14].
- The main changes affect epithelial cells as opposed to myoepithelial cells (no simultaneous epithelial/myoepithelial alterations as seen in adenosis) [1].
- Changes in cytoplasmic staining include "cytoplasmic pallor." The round or ovoid hyperchromatic nuclei stand out against a nearly colorless cytoplasmic background (similar to that of LCIS or lobular neoplasia). As emphasized by Azzapardi, "cytoplasmic pallor is a danger signal" that should alert one to make a closer study of a particular focus [1].
- There is often some degree of loss of the normal orientation.
- Regarding luminal contents, any deviation from the normal, usually eosinophilic, uniformly staining, thin-looking secretion of the lobular-ductal system must be examined carefully. As indicated by Azzopardi, "Inspissated, densely staining material, variations in staining intensity and texture of the material in a given lumen, granular and fragmented products sometimes associated with calcification, and the presence of even small amounts of nuclear debris (apoptosis) or a remote hint of the ghosts of dead cell outlines all need careful evaluation" [1].
- At low magnification, the altered structures often show rigid cystic dilatation.
- Although arcades and micropapillary formations are absent or rare, some of the dilated ducts with flat lesion can be focally associated with micropapillary or "early" rigid (roman) bridges.

5.3.5 Additional Comments

As emphasized by Azzopardi, "at low magnification, the lesion can be missed entirely since the alteration is cytological rather than architectural" [1]. Pathologists should more frequently use the high-power objective in combination with low-power magnification.

The diagnosis of low-grade DIN flat type (DIN1 flat type, flat epithelial atypia) can be difficult. To gain more experience with this type of breast lesion, one should examine tubular carcinomas of the breast, which very often show areas of DIN flat type adjacent to and at the periphery of the invasion. The similarity of cytologic atypia of tumor cells in tubular carcinoma and low-grade DIN flat type is striking.

Low-grade DIN flat type (DIN1 flat type, flat epithelial atypia) is not infrequently associated with lobular intraepithelial neoplasia (LIN; LCIS) [2, 7, 9].

HMW-CK, particularly CK5/6, is often negative in DIN flat type.

Recent genetic studies revealed that atypical cells of DIN flat type showed very similar or identical molecular alterations (loss of heterozygosity) to those observed in adjacent in situ and infiltrating ductal carcinoma. It seems that the DIN flat type represents one of the earliest morphologically recognizable neoplastic alterations of the breast. Recognition of the DIN flat type is important not only for early detection of (intra)ductal neoplasia but also to prevent misinterpretation and utilization of this lesion as a normal control in molecular and genetic studies [3, 7, 14].

The management of low-grade DIN flat type (DIN1 flat type or flat epithelial atypia) is currently a controversial issue. Follow-up data of this distinctive breast lesion are very limited. In the author's opinion, breast biopsy specimens with DIN flat type (flat epithelial atypia) should be embedded and worked up in toto and carefully searched for more advanced or "conventional" intraepithelial neoplasias (DCIS, cribriform, or micropapillary type as well as LIN) or invasive carcinomas (tubular carcinoma, invasive lobular carcinoma, etc.). Low-grade DIN flat type is, like LIN, often multifocal, if not multicentric. Similar to the situation with LIN, evaluation of the resection margins for low-grade DIN flat type (flat epithelial atypia) is not meaningful.

Caution

- Intraepithelial neoplasia flat type should not be confused with blunt duct adenosis (BDA). In contrast to DIN flat type, BDA shows simultaneous alteration (hypertrophy) of epithelial and myoepithelial cells with increased intralobular ("specialized") connective tissue. As opposed to rigid dilatation of DIN flat type, the dilated tubules of BDA show curved structures (blunt lateral outlines, blunt endings). Whereas in DIN flat type high-power magnification reveals mild to moderate nuclear atypia, no cytologic atypia should be found in simple BDA. In contrast to BDA, which is not associated with any intraluminal proliferations, the involved ducts in DIN flat type, low-grade often display a slight proliferation of luminal cells (two to four cell layers) showing a monotonous epithelial appearance. Also in contrast to BDA, the alterations in DIN flat type concern only one cell type, namely luminal epithelial cells. While the neoplastic cells of DIN flat type are negative for CK5/6, luminal cells in BDA often show a heterogeneous positive reaction for CK5/6.
- Like LIN, DIN flat type (particularly low-grade lesion) is often multifocal or multicentric. As with LIN, evaluation of resection margins in low-grade DIN flat type is not meaningful.

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5.4 Low-Grade Ductal Intraepithelial Neoplasia (WHO: DIN1b; Atypical Ductal Hyperplasia)

5.4.1 Definition

A neoplastic intraductal lesion characterized by proliferation of evenly distributed monomorphic cells and associated with a moderately elevated risk for progression to invasive breast cancer [27].

5.4.2 Risk of Progression

Relative risk of 4–5 times for subsequent development of infiltrating breast carcinoma. However, drastically different relative risk (RR) estimations have been reported for ADH, ranging from a low of 2.4 to a high of 13 (the upper values are even higher than the RR of 8–10 suggested for DCIS!) [27].

5.4.3 Microscopic Features

According to WHO (2003) [27], microscopic features include the following (Fig. 21):

- "Proliferation of evenly distributed, monomorphic cells with generally ovoid to rounded nuclei."
- "The atypical cells may grow in arcades, micro papillae, tufts, rigid bridges, solid and cribriform patterns."
- "Cytologically, ADH corresponds to low-grade DCIS."
- "ADH is diagnosed when characteristic cells coexist with patterns of UDH, and/or there is partial involvement of terminal duct-lobular unit (TDLU) by classic morphology of low-grade DCIS."
- "There is currently no general agreement on whether quantitative criteria should be applied to separate ADH from low-grade DCIS. Some (Tavassoli et al.) define the upper limit of ADH as one or more completely involved duct/ductular cross sections measuring less than or equal to 2 mm in aggregate, while others (Page et al.) require that the characteristic cytology and architecture be present completely in two spaces."

Caution

- *Diagnostic criteria for ADH remain subjective even among experienced pathologists*. Several studies have repeatedly shown that there is high interobserver (and intraobserver) variation among breast experts and community pathologists [1, 2, 14, 15, 19]. While pathologists can be "trained" to lower the level of their disagreement on the diagnosis of borderline breast lesions [23], a substantial level of interobserver variability has remained and will always remain.
- Recent immunohistochemical and molecular genetic studies show that ADH and low-grade DCIS are very close, if not identical, intraepithelial neoplastic lesions [5, 6a, 6c, 18].
- The current WHO classification (2003) considers ADH a low-grade intraepithelial neoplasia (DIN1b) [27].

5.4.4 Immunohistochemistry

In contrast to UDH and very similar to DCIS, most examples of ADH are negative for HMW-CKs such as CK5/6, CK14, and CK34BE12.

Caution

- According to the DIN concept, ADH and low-grade DCIS are qualitatively the same type of intraepithelial neoplastic proliferations (DIN, low-grade or DIN1). Indeed, the criteria for separation between ADH and low-grade DCIS are arbitrary and mostly subjective. It is time to admit that there is no scientific basis for separating ADH and low-grade DCIS. *Consistent and reproducible separation of ADH from low-grade DCIS is an impossible dream, and perhaps even an obsolete concept that should be put behind us.*

5.4.5 Additional Critical Comments on the Definitions and Criteria for ADH

The vast majority of criteria for distinguishing between ADH and low-grade DCIS are subjective, illogical, or imprecise [2, 8–16, 19]. To briefly review some of the commonly used criteria as proposed by Page et al. [8]:

1. "Atypical hyperplasia of ductal or no special type is diagnosed when either cytological or pattern criteria of ductal carcinoma in situ (DCIS) are met, but both are not present in full flower."

Comment: This kind of descriptive and subjective definition can hardly be applied to distinguish ADH from DCIS. Basically, it is a general statement that by no means helps pathologists to apply it objectively when they are dealing with a problematic intraductal proliferative lesion.

2. "Atypical hyperplasia is also diagnosed if criteria of DCIS are present, but not uniformly so throughout at least two spaces.… " Page et al. adopted an arbitrary rule for DCIS that two spaces have to be completely involved by a uniform population of cells demonstrating a diagnostic pattern. Therefore, "presence of a single space with diagnostic features of DCIS is diagnosed as ADH."

   Comment: There is no scientific justification for this semiquantitative and arbitrary "two spaces" rule. As accurately stated by Rosen [21], "there are a number of technical issues that hamper the application of (semi)quantitative criteria. What appear to be two contiguous cross sections may prove to be part of a single duct in serial sections, or deeper sections of a single duct lesion may detect more involved duct cross sections."

   Using the "two spaces" criterion, a single duct measuring 3 or 4 mm in diameter that reveals all of the cytological and architectural patterns of DCIS should be considered ADH. In contrast, two very small ductal spaces with atypical cytological and architectural features that hardly measure 1 mm in diameter must be designated DCIS! Indeed, the above statements by Page et al. clearly demonstrate that ADH and DCIS are qualitatively the same and do not represent two separate entities.

3. "DCIS is strongly suggested but is denied because the central cell population has a higher nuclear cytoplasmic ratio that is gradually lost towards the outer layer of proliferated cells."

   Comment: Why should all neoplastic intraductal cells display the same N/C ratios in order to be considered a part of DCIS? What is the rationale behind this statement? The neoplastic epithelial cells of DCIS can simply show some variation in their nuclear size. Therefore, it is not infrequent to see different N/C ratios among the neoplastic cells of DCIS. Besides, the neoplastic cells of low-grade DCIS usually show only a minor degree of nuclear enlargement (as opposed to intermediate and high grades DCIS) and do not necessarily display a high N/C ratio.

4. "A pattern recognized as ADH:…Occasionally, both pattern and cell population appear diagnostic (for DCIS), but portions of the spaces will be lined by cells maintaining a normal columnar layer of luminal cells."

   Comment: Why should the presence of some normal-appearing epithelial cells in a duct exclude the possibility of a neoplastic intraductal proliferation in the same duct that exhibits cytologic and architectural features of DCIS? The commonly used criterion of "partial involvement" (ADH) as opposed to complete involvement of a duct (DCIS) by the same type of atypical or neoplastic cells is not logical and is not based on any scientific studies. It is merely an arbitrary approach.

5.4.6 Comments on Quantitative Criterion of 2 mm (Tavassoli's Criterion)

In 1990, Tavassoli and Norris introduced the arbitrary quantitative criterion of 2 mm for separating ADH from DCIS and emphasized that if both the cytologic and architectural features of intraductal carcinoma (DCIS) are present partially within one or more ducts or completely involve one or more ducts that do not exceed 2 mm in aggregate cross-sectional diameter, then the lesion qualifies as ADH [24, 29]. However, they also emphasized that the latter group is qualitatively identical to low-grade DCIS. Currently, Tavassoli strongly favors and enthusiastically advocates the concept of DIN, believing that ADH and low-grade DCIS represent the same type of intraepithelial neoplastic proliferation that cannot be, and need not be, separated based on (semi)quantitative criteria [25, 26, 28].

It must be emphasized that the designation of ADH was promoted by Tavassoli at a time when mastectomy was the only treatment for DCIS regardless of size or grade, in order to prevent mastectomy for small lesions (Tavassoli, personal communication).

> *"I have submitted over 60 borderline cases to a number of pathologists, and have found that in not a single one has there been uniform agreement as to whether the lesion was benign or malignant.… This is no reflection on the diagnostic abilities of the pathologists; it is simply evidence that at the present time there are certain lesions of the breast about which we apparently do not agree from the microscopic appearance only."*
>
> *J.C. Bloodgood*
> Cancer of the breast. Figures which show that education can increase the number of cures. JAMA 1916;66:552–553

5.4.7 Comments on the Treatment of ADH

The diagnosis of ADH in a core needle biopsy should be followed by complete excision of the lesion. The size or distribution of ADH in an excisional biopsy should be provided. Because the nature of ADH and low-grade DCIS is basically the same, the therapeutic options, particularly in small lesions, should also be the same. Small areas of ADH and low-grade DCIS appear to be adequately treated with excision alone (without radiation therapy). Women with extensive low-grade DCIS may, however, benefit from mastectomy. The optimal management is evolving as data accumulate from a variety of prospective studies [7, 27, 30, 31].

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5.5 Ductal Intraepithelial Neoplasia (WHO: DIN1c–DIN3, DCIS)

5.5.1 Synonyms

Ductal carcinoma in situ (DCIS), intraductal carcinoma.

5.5.2 Information to be provided in the Surgical Pathology Report

- Grade of DIN (DCIS, nuclear grade, presence of necrosis)
- Type of DIN (DCIS, comedo, cribriform, micropapillary, solid, apocrine type, etc.)
- Extent of DIN (DCIS, estimation of size or distribution)
- Status of the margin (positive, specify where; specify distance from margin)
- Presence of microcalcifications (within or outside of DIN)

5.5.3 Macroscopy

When comedo DIN (DCIS) is extensive and necrotic debris is abundant in the duct lumens, these areas may be apparent to the naked eye. As a rule, however, other variants of intraductal carcinoma are not grossly detectable.

5.5.4 Types of DIN (DCIS)

- *Comedo type (comedo carcinoma)*: Characteristic features are the presence of abundant intraluminal necrosis (necrotic debris and numerous apoptotic bodies), severe nuclear atypia, and, often, loosely cohesive epithelial cells. Mitotic figures can be numerous. Periductal fibrosis or marked periductal lymphoplasmacytic infiltration may be present.

Caution

- In cases of comedo DCIS (DIN3, comedo type) with significant reactive or desmoplastic stromal changes (with or without lymphocytic infiltration), deeper levels should be ordered in order to exclude invasion.
- A variant or subtype of comedo carcinoma in situ is the pleomorphic variant of clinging DCIS or high-grade DIN flat type. This variant can easily be missed due to paucity of intraluminal proliferation!

- *Cribriform type* (Fig. 22): This type shows proliferation of a uniform epithelial cell population forming a sieve-like arrangement. The secondary lumens are more or less rounded. The epithelial bridges are rigid ("roman" bridges). A typical feature is formation of robust or rigid trabecular bars; a trabecula is defined by Azzopardi as a row of cells with their long axes arranged more or less perpendicular to the row's long axis. The nuclei are round to ovoid and evenly distributed with minimal overlapping. The cytoplasmic borders are often sharp. The nuclear atypia is often slight. Rare examples of cribriform DCIS can be associated with central necrosis or significant nuclear atypia (grade 2 or 3 DIN, DCIS). Calcification can be prominent in the secondary lumens [2, 22, 23, 34, 39].

- *Micropapillary type* (Fig. 23): This type is characterized by a homogeneous cell population of epithelial cells similar to that described for the cribriform variant, with formation of rigid epithelial tufts projecting into the lumens. These luminal projections do not contain fibrovascular cores. Frequent transitional forms of DIN (DCIS) occur whereby the micropapillary pattern appears to transform into the cribriform by forming arcades and bridges. Although micropapillary DIN usually is of low grade, sometimes it can be associated with central necrosis or significant nuclear atypia (G2 or G3) [2, 3, 23, 27, 33, 34, 39].

Micropapillary DIN (DCIS) is more frequently multifocal and even multicentric compared to other variants of DIN (DCIS).

Not infrequently, the proliferating cells of micropapillary DIN (DCIS) are so crowded and overlapping that their individual cell borders and cytoplasm cannot be identified. This should not lead to a misinterpretation of "micropapillary" intraductal hyperplasia.

- *Solid type*: This type displays a solid intraluminal proliferation of a homogeneous epithelial cell population with nuclear atypia ranging from mild to severe atypia. The remaining secondary lumens can be irregular and slit-like.

Caution

- The presence of irregular and slit-like secondary lumens in solid type of DIN (DCIS) may lead to the misinterpretation of UDH. One has to keep in mind that although the presence of irregular and slit-like secondary lumens or a streaming pattern of proliferating cells is more typical of UDH, these features by no means exclude DIN (DCIS). As mentioned before, it is the cell population (homogeneous versus heterogeneous) that basically distinguishes DIN (DCIS) from UDH.

- *Papillary type*: Refer to information on intraductal papilloma and intraductal papillary carcinoma.
- *Clear cell type* (Fig. 25): Neoplastic epithelial cells show optically clear cytoplasm and distinct cell margins forming any of the patterns (mostly cribriform, solid).
- *Spindle cell variant* (Fig. 26): This is a rare and difficult variant that can easily be misinterpreted as UDH. But in contrast to UDH, this variant is composed of a homogeneous cell population of spindled epithelial cells (there is no admixture of epithelial and modified myoepithelial cells). Therefore, the neoplastic cells in this variant are negative for HMW-CK (CK34BE12, CK5/6). The growth pattern is usually solid.

Caution

- The diagnosis of spindle cell variant of DIN (DCIS) requires proper immunohistochemical examination. The differential diagnosis includes UDH and florid proliferation of myoepithelial cells or myoepitheliosis. In contrast to UDH, spindle cell variant of DIN (DCIS) is negative for HMW-CK. The proliferating cells in myoepitheliosis intensely express myoepithelial markers such as SM actin, SM myosin, p63, and CD10.

"Clinging" type (Figs. 19, 20, 27): As described by Azzopardi, this variant shows very few layers of atypical epithelial cells lining the structure of the origin. "Clinging" means that the neoplastic cells are present peripherally while the lumen is almost empty. The alteration is predominantly cytological rather than architectural. This type often merges into other variants of DIN (DCIS), but when it is the dominant pattern, it is very easily missed. (For more details, see the section on DIN flat type) [2].)

- *Apocrine type* (Figs. 27, 28): To qualify as apocrine DIN (DCIS), the neoplastic cells should display abundant granular, eosinophilic cytoplasm and moderate to severe atypia, often with central necrosis. The neoplastic apocrine cells can show solid, micropapillary, or cribriform patterns [31, 45].

Caution

- Because of the high frequency of apocrine metaplasia and intraductal apocrine hyperplasia in association with fibrocystic changes, it is important to be particularly cautious in the diagnosis of apocrine DIN (DCIS). In the absence of necrosis and significant nuclear atypia, one has to be extremely careful about making the diagnosis of low-grade DCIS, apocrine type. The presence of prominent nucleoli is not a helpful diagnostic criterion.

The neoplastic apocrine cells can be positive for HMW-CK (CK34BE12, CK5/6)! The apocrine cells (metaplasia, hyperplasia, intraductal carcinoma) are typically negative for estrogen receptor (ER) and progesterone receptor (PR). The apocrine cells, however, are often intensely positive for androgen receptor (AR).

- *Cystic-hypersecretory variant* (Fig. 29): A rare variant of DIN (DCIS) that can easily be misinterpreted as fibrocystic change, duct ectasia, or ductal hyperplasia. The cysts contain deep eosinophilic, colloid-like secretory material and very often are lined by only a few cell layers of atypical cells. In contrast to cystic-hypersecretory ductal hyperplasia, the neoplastic cells are negative for HMW-CK (CK5/6, CK14, CK34BE12).

- *Signet-ring cell type* (Fig. 30): A very rare variant of DIN (DCIS) associated with solid or papillary growth pattern. Signet-ring cells may also occur in LIN.

5.5.5 Grading of DIN (DCIS; Figs. 23–28)

- Nuclear atypia (mild to severe)
- Presence of luminal necrosis

Both severe atypia and intraluminal necrosis: G3
Severe atypia without necrosis: G3
Mild atypia without necrosis: G1
Mild atypia with necrosis: G2
Moderate atypia with or without necrosis: G2

5.5.6 Extent (Distribution or Size) of DIN (DCIS)

Recommended approach: Measurements are obtained after the sample is serially sectioned at 2–3-mm intervals. The tissue sections are arranged and processed in sequence. The distribution of the lesion is based on direct measurement from the slide or estimation of the extension of the lesions in a sequential series of slides. Note that in practice, even direct measurements from the slide can vary significantly, depending on whether the intervening stroma between areas of DIN (DCIS) is included in the measurement.

Systematic orientation, sectioning, and processing of the biopsy specimen toward the nipple is one of the best ways to estimate the extent of DIN (DCIS).

5.5.7 Assessment of the Margins of Resected Tissues

A margin is positive when tumor is bisected at the time of resection or when tumor is covered by the ink painted over the resection margin.

The distance between the edge of DIN (DCIS) closest to the resection margin should be reported in millimeters (for example, "DIN within 2–3 mm of the inked margin"). One should also provide information on whether the proximity is focal (specify which margin) or whether much of the DIN (DCIS) is in the proximity of the margin [24, 26, 44].

Approximately 30% of samples with "negative" margins show residual DIN (DCIS)!

5.5.8 Further Reading

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Fig. 16: Usual ductal hyperplasia.

Case history: A 39-year-old woman presented with clinical and mammographic signs of fibrocystic changes of her right breast. She was very anxious and felt to have breast cancer. Fine needle aspiration cytology and subsequently excisional biopsy were performed.

Fig. 16.1: Fine needle aspiration cytology reveals numerous cohesive epithelial clusters. The clusters are composed of epithelial cells with round to oval nuclei and myoepithelial cells with elongated or bipolar nuclei.

Fig. 16.2: Some of the clusters show epithelial cells with enlarged nuclei and a high nuclear-cytoplasmic ratio (Diff-Quik stain). Note the presence of a second cell population showing small pyknotic or elongated nuclei. Although the presence of a heterogeneous cell population (epithelial and myoepithelial cells) is consistent with a benign proliferation, the fine needle aspiration was initially reported as suspicious for malignancy.

Fig. 16.3: Excisional biopsy of the lesion revealed an intraductal proliferation showing a heterogeneous cell population of epithelial cells (with round to oval nuclei) and modified myoepithelial cells (with elongated, dark, or bipolar nuclei). The secondary lumina are irregular and slitlike.

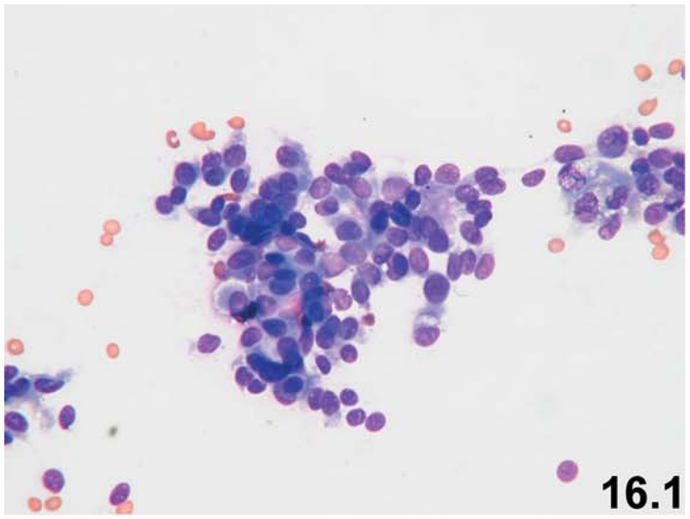
Fig. 16.4: A characteristic streaming growth pattern is present; the proliferating cells and their nuclei have a parallel orientation of their long axes. Note the heterogeneity of cell population and variation of size and shape of the secondary lumens. All of these features are characteristic of usual ductal hyperplasia (UDH).

Fig. 16.5: The proliferating cells of UDH are typically positive for high molecular weight cytokeratin such as CK5/6.

Fig. 16.6: The proliferating cells in UDH show an intense but heterogeneous positive immunoreaction for CK5/6.

Fig. 16: Final remarks

- The most important diagnostic feature of UDH is the heterogeneity of proliferating cells (pleomorphism of divergent cell population) that are composed of epithelial and modified myoepithelial cells (poststem or progenitor cells). The modified myoepithelial cells in UDH often show elongated or bipolar dark nuclei.
- Immunohistochemistry for high molecular weight cytokeratins (HMW-CKs) such as CK5/6, CK14 or CK34BE12 is always positive in UDH and shows an intense but heterogeneous immunoreaction of the proliferating cells. In contrast, in the vast majority of cases, the immunoreaction of proliferating cells in ductal intraepithelial neoplasia (ADH/DCIS) for HMW-CK is negative.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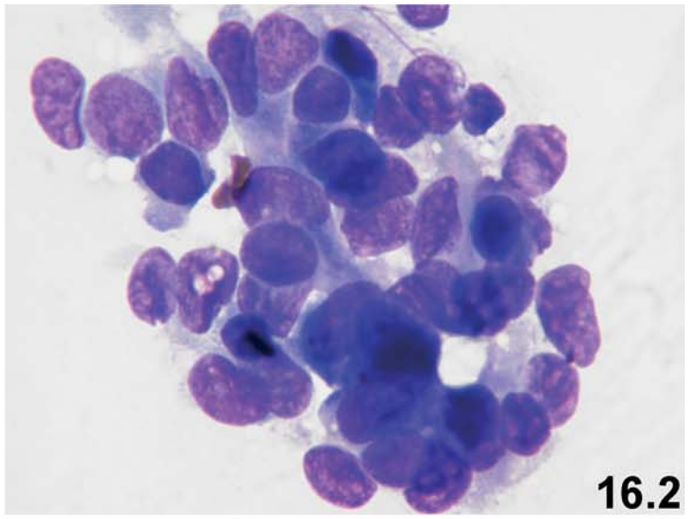
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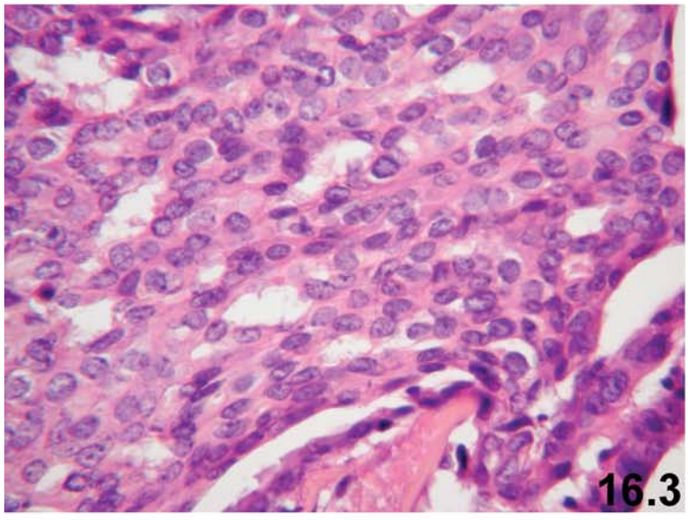
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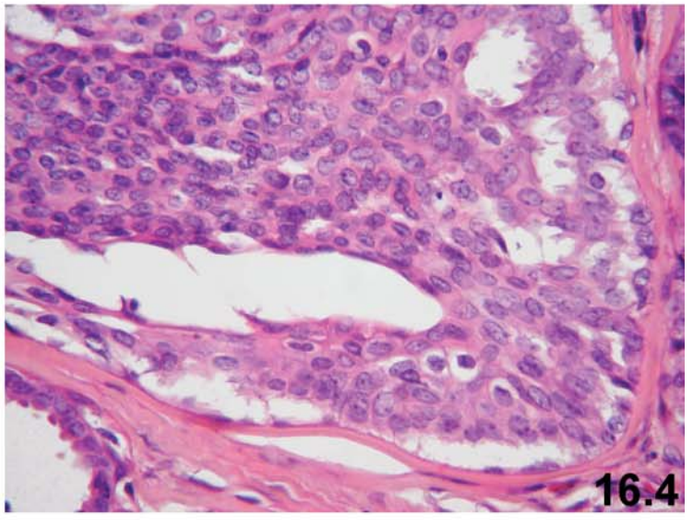
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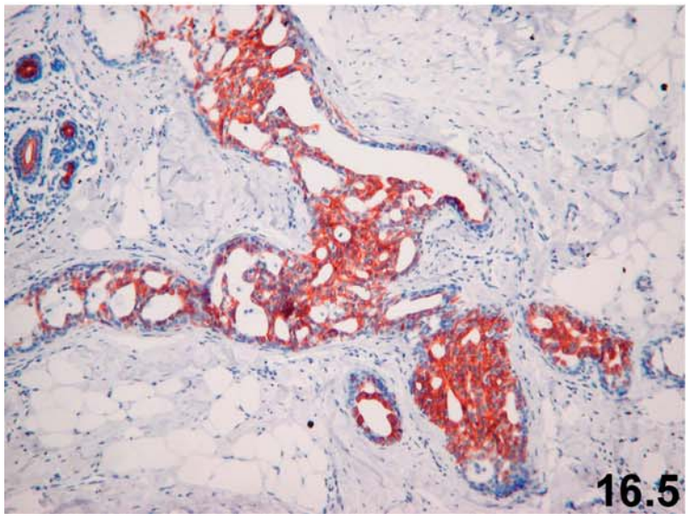
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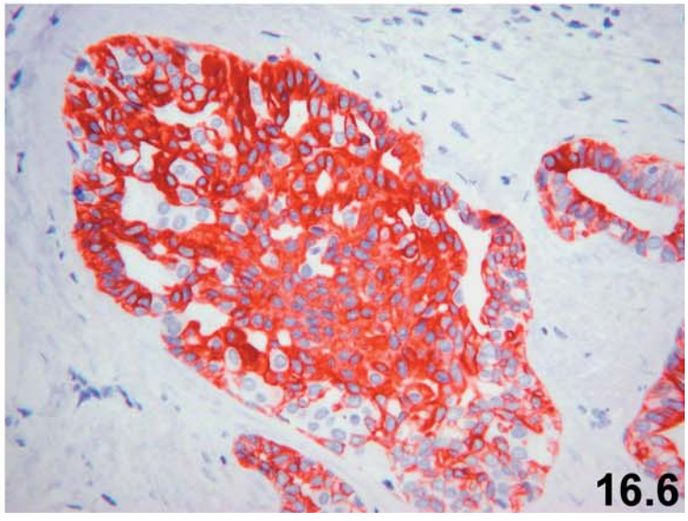
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Fig. 17: Usual ductal hyperplasia (associated with myoepithelial hyperplasia or myoepitheliosis).

Case history: Routine screening mammogram on a 52-year-old woman revealed multiple clusters of suspicious microcalcification in the upper outer quadrant of the right breast. There was no grossly apparent lesion on the cut surface of the excisional biopsy.

Figs. 17.1 and **17.2:** Sections show several ducts with intraluminal epithelial proliferation associated with microcalcification.

Fig. 17.3: Secondary lumens vary in size and shape. Many angulated or slit-like lumens are present.

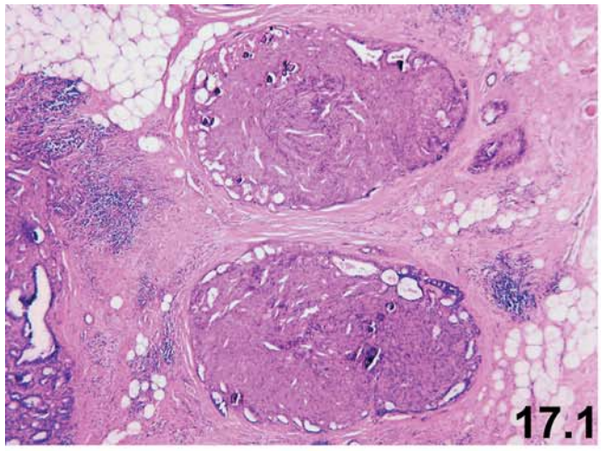
Fig. 17.4: The cell population of proliferating cells is quite heterogeneous, consisting of epithelial and modified myoepithelial cells. A very distinctive streaming or swirling growth pattern is present. Note the uneven distribution of nuclei and indistinct cytoplasmic borders.

Figs. 17.5 and **17.6:** Immunohistochemistry for high molecular weight cytokeratin (CK5/6) displays a heterogeneous (mosaic-like) positivity characteristic for usual ductal hyperplasia.

Figs. 17.7 and **17.8:** Immunohistochemistry for smooth muscle actin shows a positive reaction in some spindle cell areas with streaming or swirling pattern. Indeed, based on the morphology and immunohistochemistry for smooth muscle actin, these areas can be considered myoepitheliosis.

Fig. 17: Final remarks

- This case nicely demonstrates different cell populations of epithelial and myoepithelial cells in a florid ductal hyperplasia. The positive reaction for high molecular weight cytokeratins such as CK34BE12, CK5/6, or CK14 is a very characteristic feature of usual ductal hyperplasia (UDH). While the proliferating cells of UDH are usually negative for smooth muscle actin, S100 protein (another myoepithelial marker) is typically intensely positive in UDH. The CK5/6 and S100-protein-positive proliferating cells are closely related to myoepithelial cells. These cells have been designated as modified myoepithelial cells, poststem cells, or progenitor cells.
- The main differential diagnosis in this case is spindle cell variant of DIN (DCIS), which can closely mimic UDH. The neoplastic cells of spindle cell DIN (DCIS) are, however, negative for CK5/6.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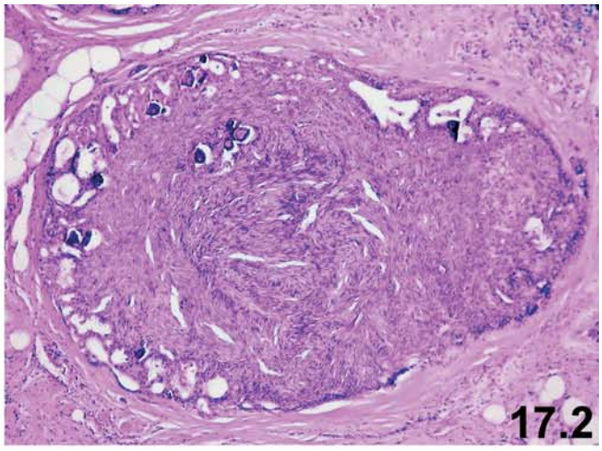
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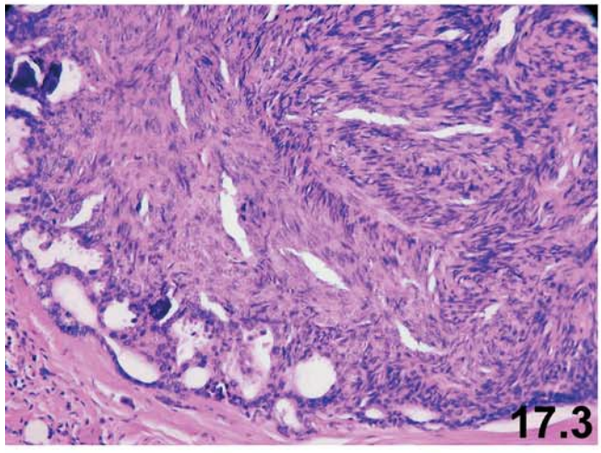
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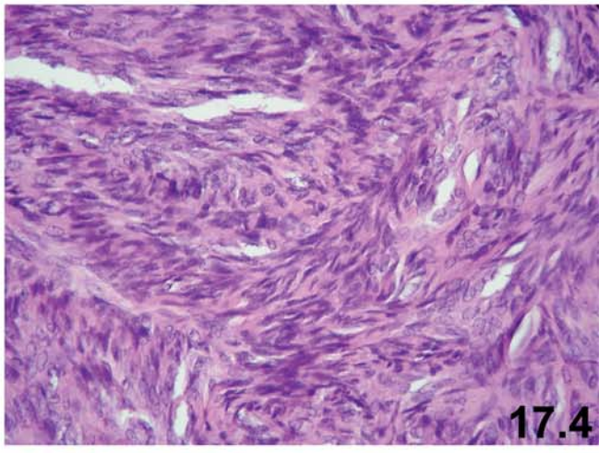
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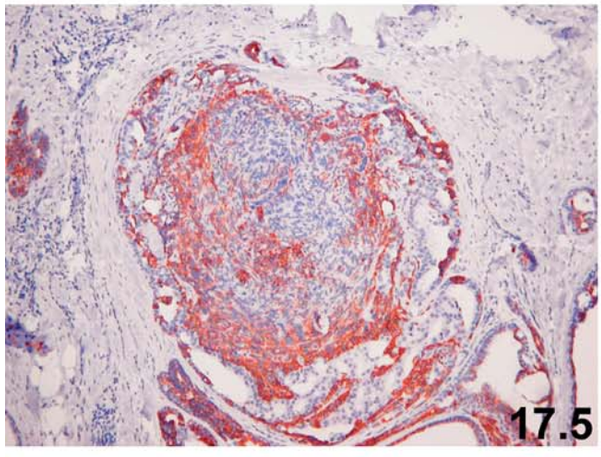
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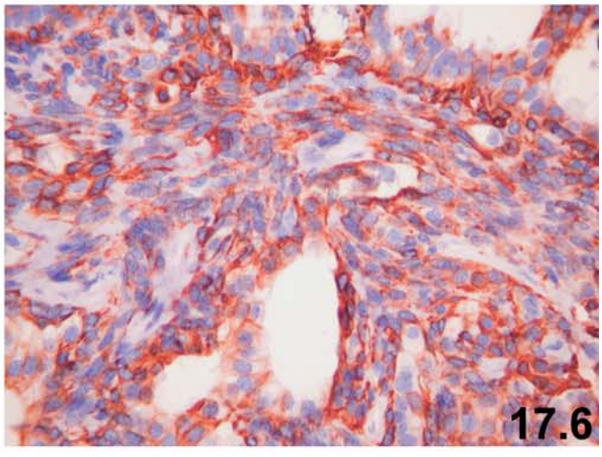
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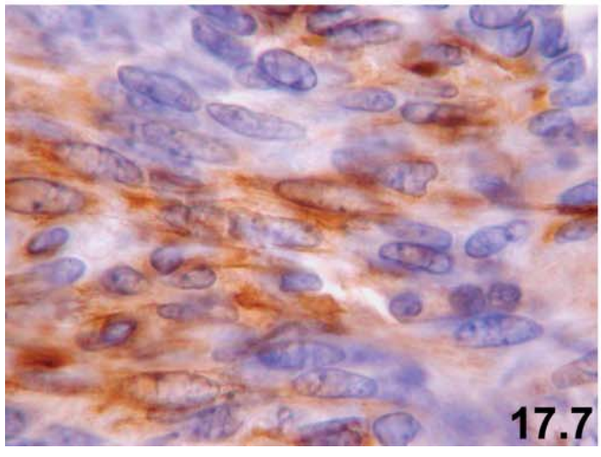
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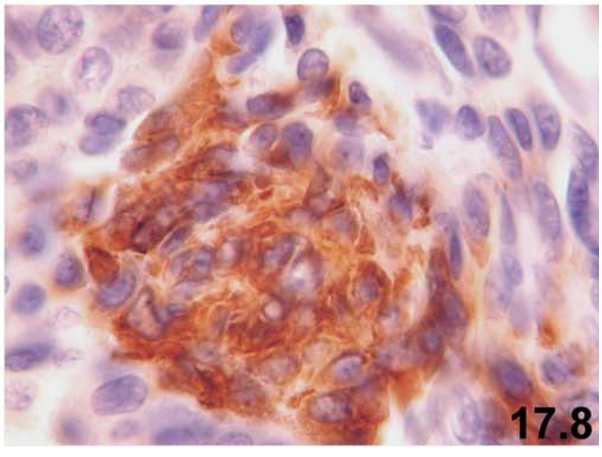
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Fig. 18: Usual ductal hyperplasia (UDH) associated with central necrosis and multiple foci of pseudoinvasion.

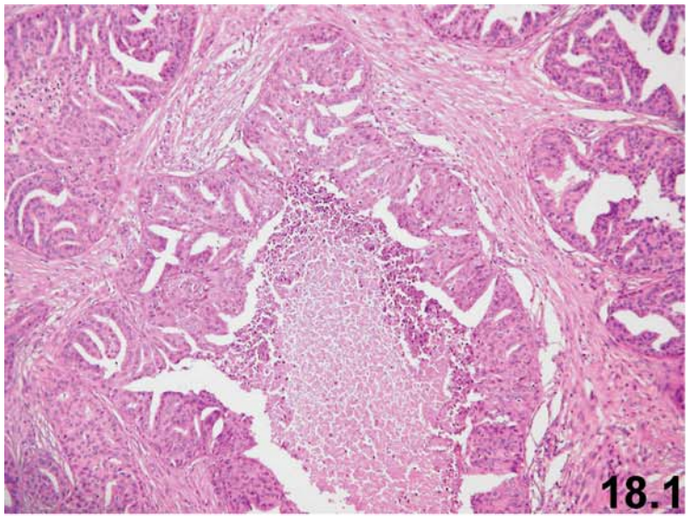
Case history: A 34-year-old woman had an abnormal mammogram of her left breast, showing a partly irregular lesion. It was interpreted as highly suspicious for cancer.

Figs. 18.1 and **18.2:** Low magnification of the lesion shows slit-like secondary lumens containing central necrosis.

Fig. 18.3: Intraductal proliferation associated with luminal necrotic cell debris.

Fig. 18.4: Higher magnification showing a mixed or heterogeneous cell population of proliferating cells with partly round to ovoid and partly spindle-shaped or bipolar nuclei. The heterogeneity of proliferating cells is characteristic of UDH. The presence of central necrosis in some areas of the lesion is, however, worrisome.

Figs. 18.5 and **18.6:** In addition, some areas of the lesion display small epithelial clusters and glands with irregular arrangement. The irregular and infiltrating growth pattern of the glands and solid structures is certainly another worrisome finding in this case.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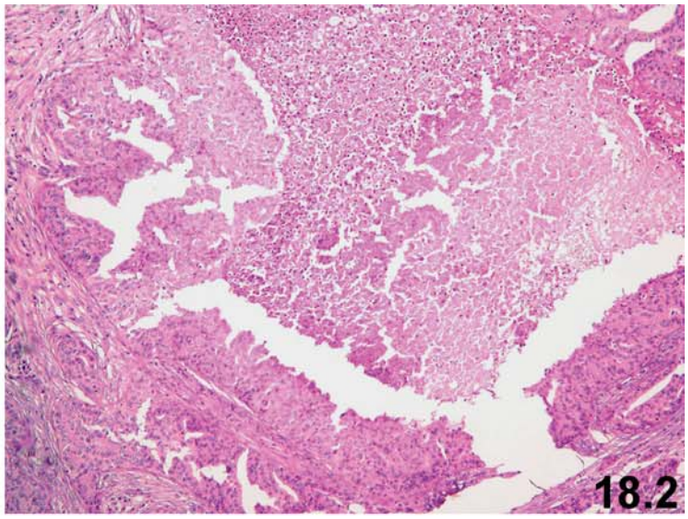
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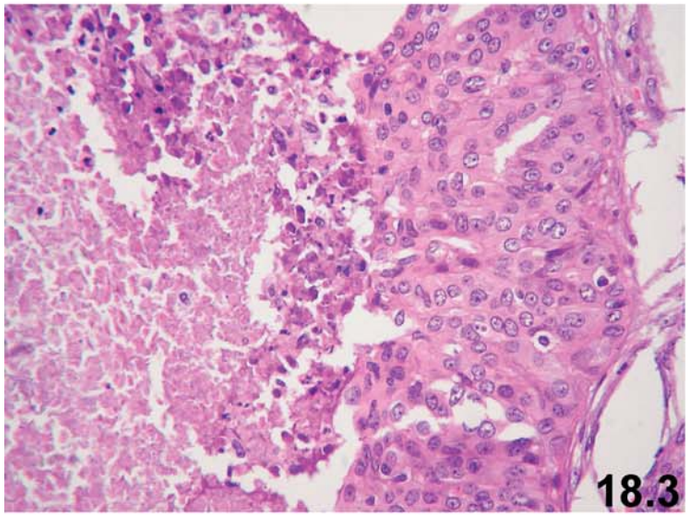
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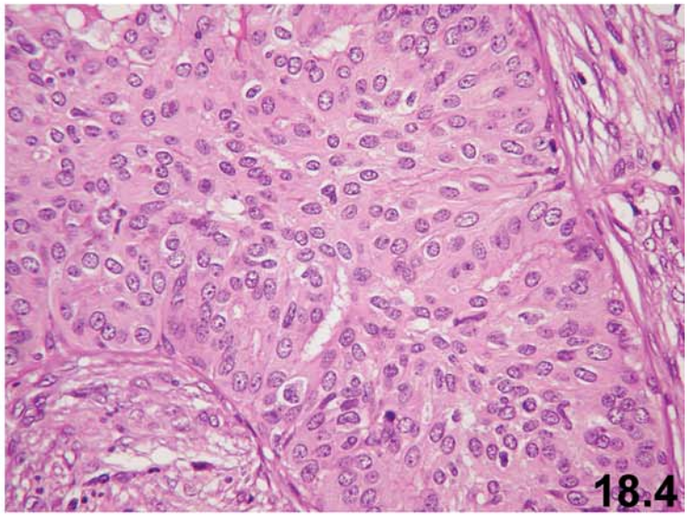
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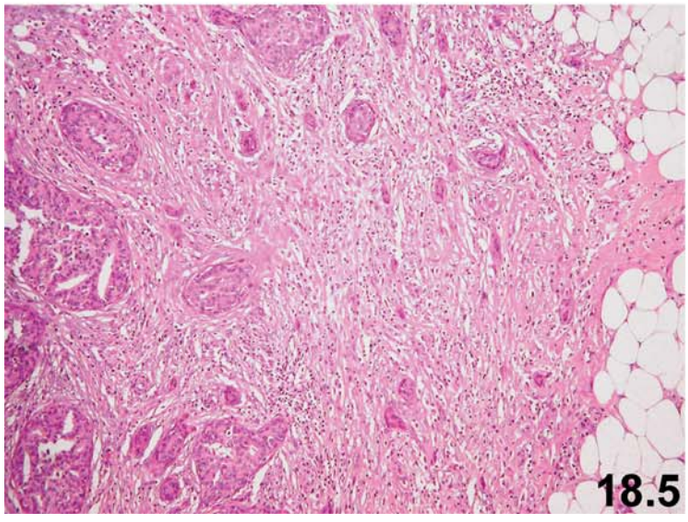
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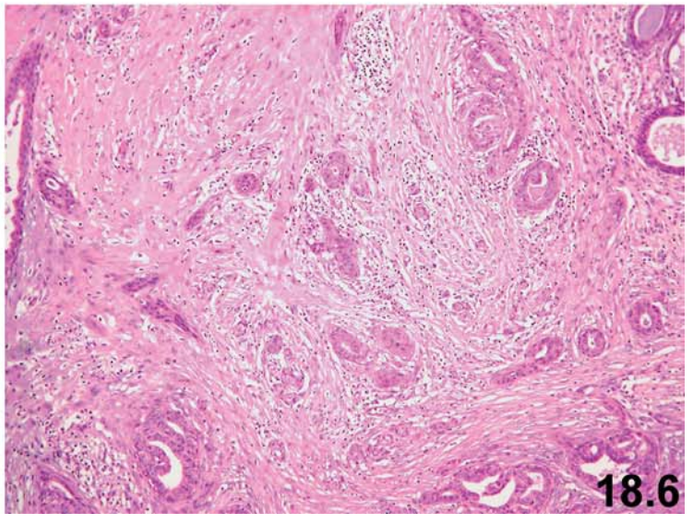
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Fig. 18.7: Small epithelial clusters in a background of altered stroma, which is infiltrated by lymphocytes and histiocytes.

Figs. 18.8 and **18.9:** Immunohistochemistry for CK5/6 shows an intense positive reaction that is typical for UDH.

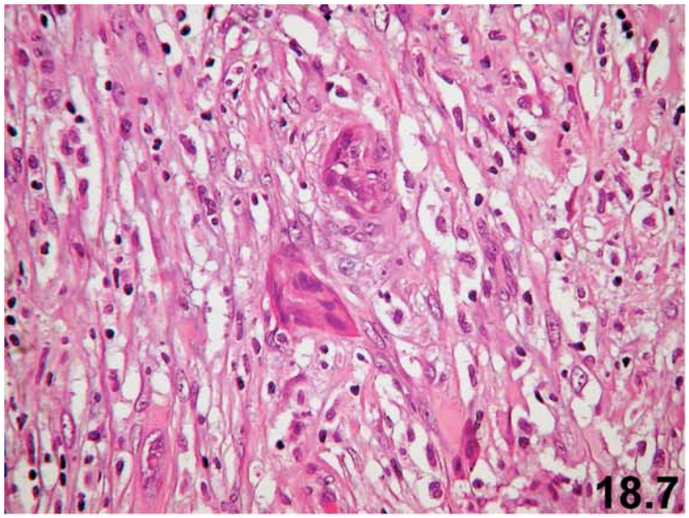
Fig. 18.10: In addition to the positive intraductal cells, CK5/6 shows positive glands and solid epithelial structures with irregular arrangement. Indeed, these glands are connected to the larger and branching ducts but appear to be separated and invasive due to tangential sectioning.

Fig. 18.11: Another area of the lesion that simulates an infiltrating ductal carcinoma.

Fig. 18.12: Immunohistochemistry for p63 clearly shows a myoepithelial cell component within the glands with infiltrating features. Several other myoepithelial markers such as CD10, smooth muscle actin, and calponin were also positive in these glands (not shown).

Fig. 18: Final remarks

- This challenging and very exceptional case caused serious diagnostic problems for several pathologists. Based on the hematoxylin and eosin sections, many pathologists called it invasive ductal carcinoma. The intraductal component of the lesion was also regarded as intraductal carcinoma with central necrosis (DCIS, G2) by several pathologists.
- Keep in mind that abundant central necrosis may rarely occur in florid ductal hyperplasia and should not be used as a single diagnostic criterion of malignancy. One should also be aware of the fact that usual ductal hyperplasia can also be associated with pseudoinvasion (synonym infiltrative epitheliosis). The identification of myoepithelial cells (use of high-power magnification and immunohistochemistry for myoepithelial markers) is crucial to avoid misinterpretation of such complex but benign breast lesions.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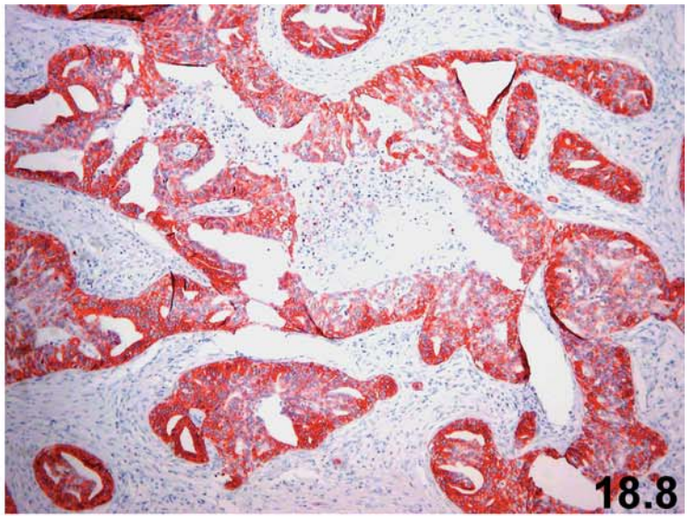
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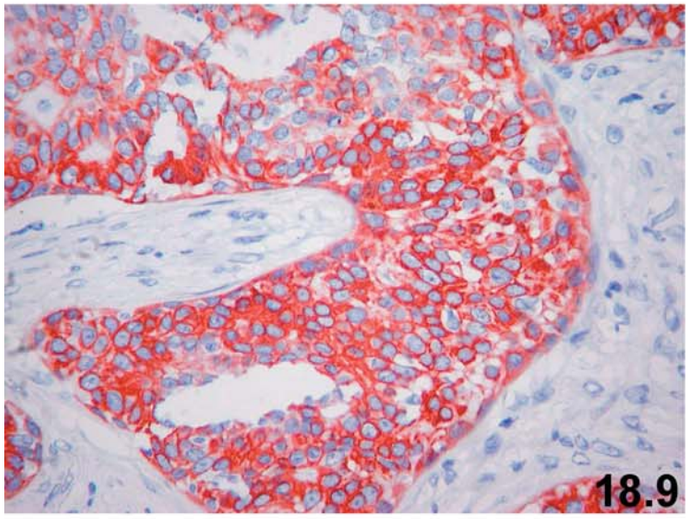
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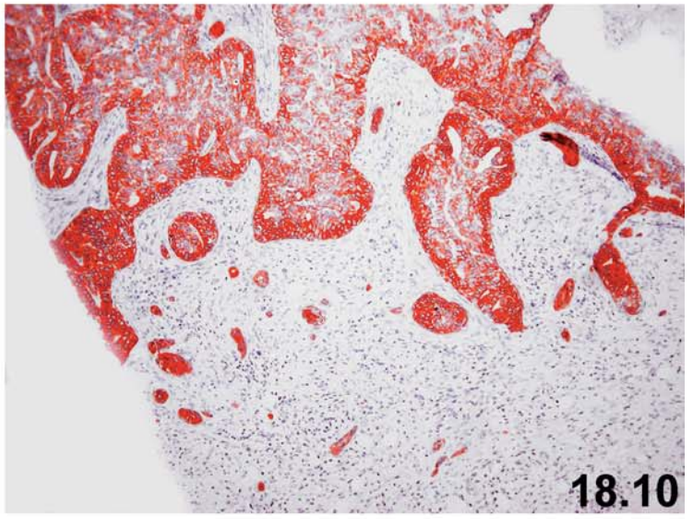
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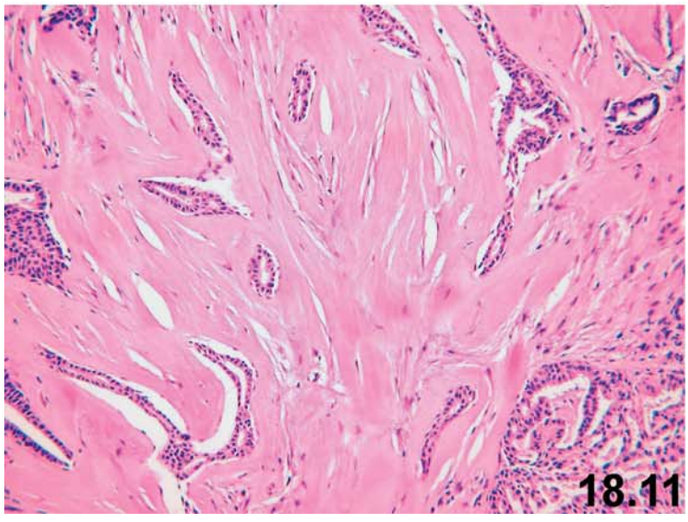
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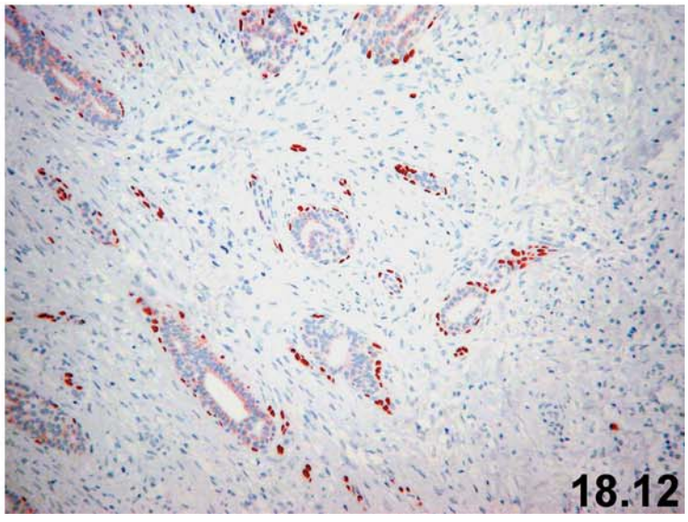
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Fig. 19: Low-grade ductal intraepithelial neoplasia (DIN) flat type (flat epithelial atypia).

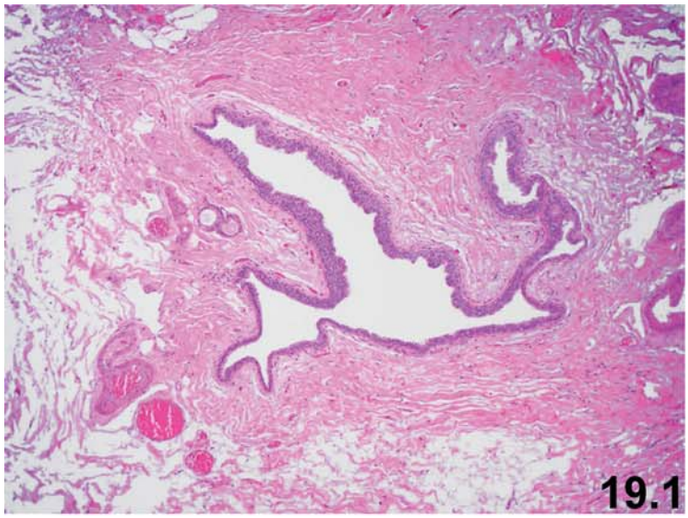
Fig. 19.1: Low magnification of a duct showing minimal epithelial cell proliferation.

Fig. 19.2: Another area of the same case revealing a large duct with prominent apical snouts.

Fig. 19.3: Rigid dilation of a small duct lined by two or three cell layers of monotonous epithelial cells.

Fig. 19.4: One or two cell layers of epithelial cells with apical snouts. Note the loss of polarity of luminal epithelial cells.

Figs. 19.5 and **19.6:** The ducts are lined by a homogeneous cell population of mildly atypical epithelial cells showing hyperchromatic nuclei. Note that the alteration mainly affects the luminal epithelial cells at the expense of the basally located myoepithelial cells. The myoepithelial cells are attenuated.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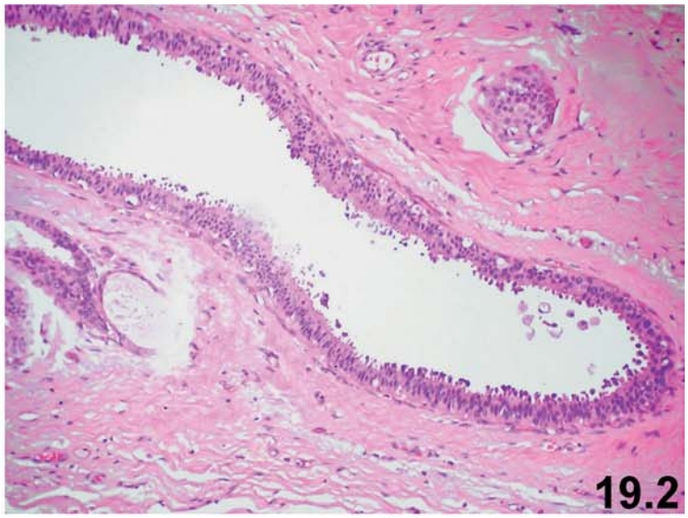
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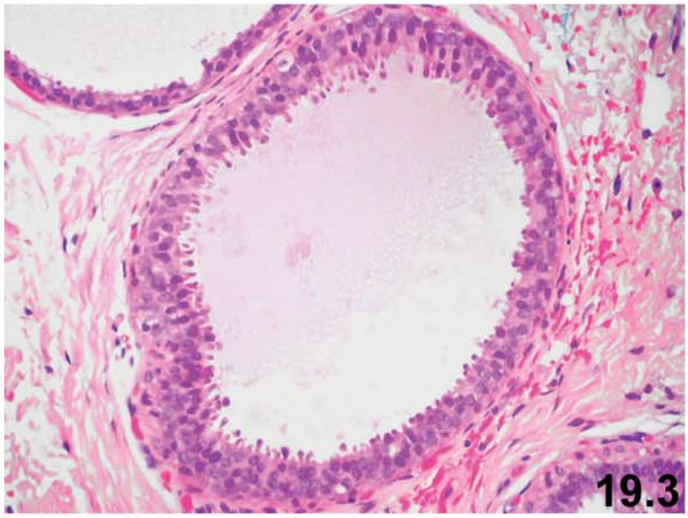
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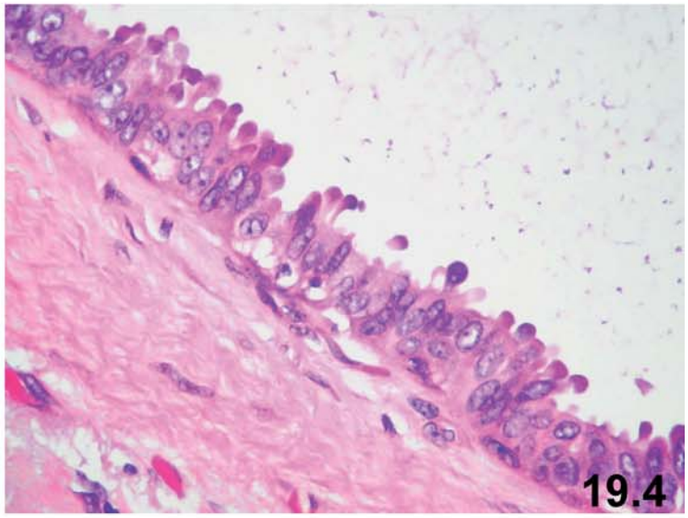
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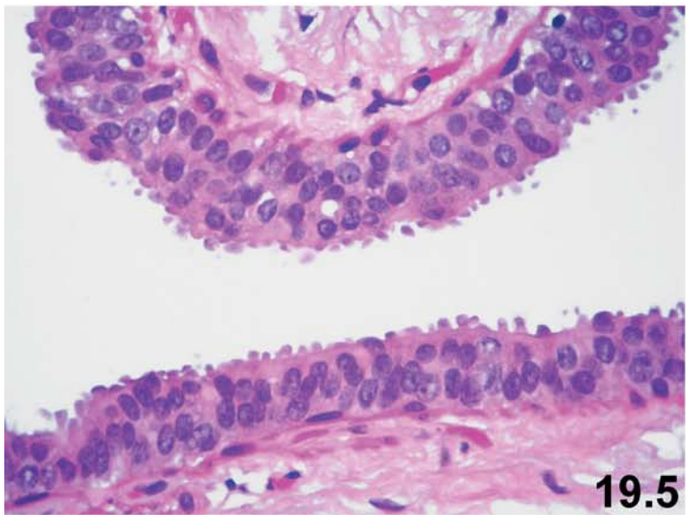
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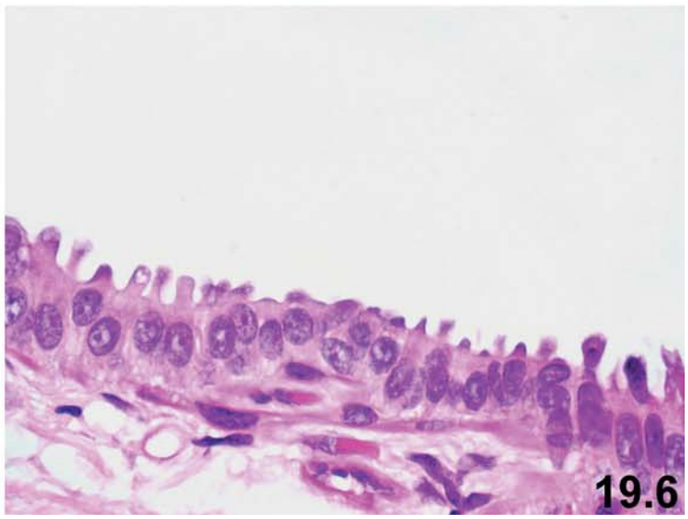
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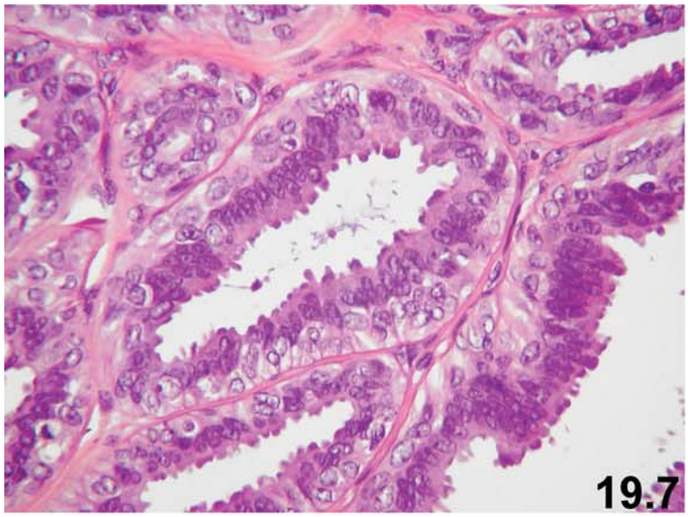
Figs. 19.7, 19.9, and **19.11: A case with blunt duct adenosis with typical simultaneous alteration (hypertrophy) of epithelial and myoepithelial cells.** The epithelial cells reveal numerous apical snouts.

Figs. 19.8, 19.10, and **19.12: A case with DIN flat type, low grade (flat epithelial atypia)** showing dilated ducts lined by very few cell layers of mildly atypical cells. Note that the alteration mainly affects the luminal epithelial cells and that the myoepithelial cells are attenuated. In other words, there is no simultaneous alteration or hypertrophy of myoepithelial and myoepithelial cells in DIN flat type. The luminal cells of low-grade DIN flat type are composed of monotonous (homogeneous) epithelial cells.

Fig. 19: Final remarks

- Apical snouts often occur in both blunt duct adenosis and low-grade DIN flat type. Therefore, the presence of apical snouts is not a helpful diagnostic feature for distinguishing between blunt duct adenosis and DIN flat type.
- To discriminate between BDA and DIN flat type, one should always pay particular attention to the cell population (homogeneous versus heterogeneous luminal cells) in the involved ducts and evaluate the accompanying myoepithelial cell alteration (hypertrophy versus attenuation).
- The luminal epithelial cells in blunt duct adenosis may show enlarged nuclei and prominent nucleoli. These features alone, however, should not lead to the diagnosis of DIN flat type (flat epithelial atypia).
- While the luminal cells in blunt duct adenosis show a heterogeneous positive reaction for CK5/6, the neoplastic cells of DIN flat type are characteristically negative for CK5/6.
- Like lobular intraepithelial neoplasia, low-grade DIN flat type is often multifocal. The evaluation of resection margins for low-grade DIN flat type is therefore meaningless. Regular (annual) clinical and mammographic examinations of patients with low-grade DIN flat type (flat epithelial atypia) are prudent.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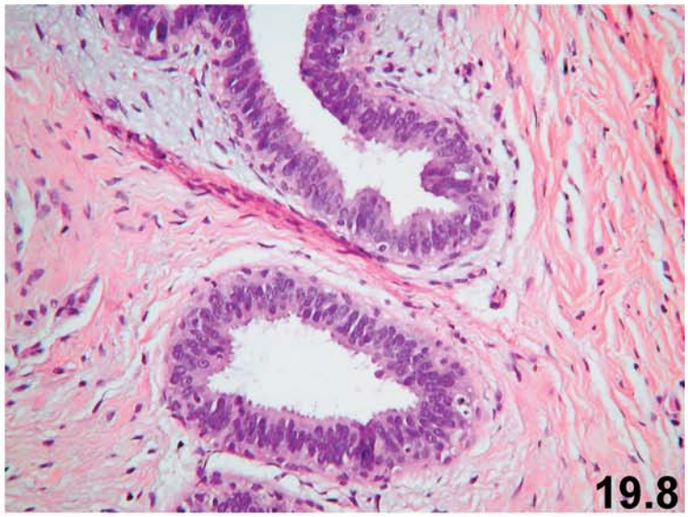
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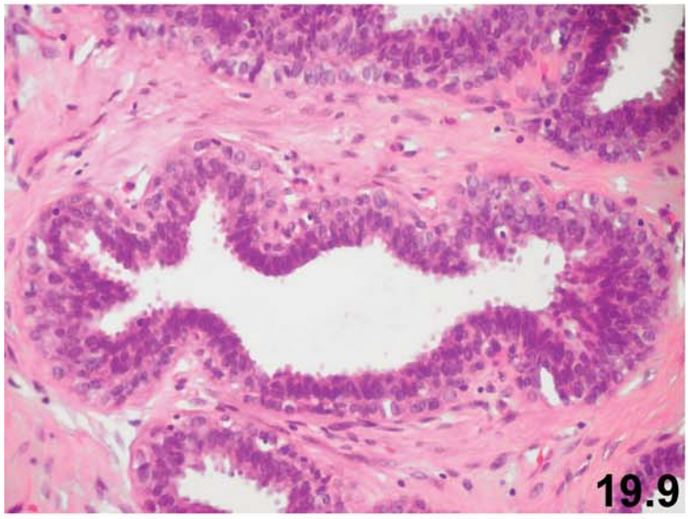
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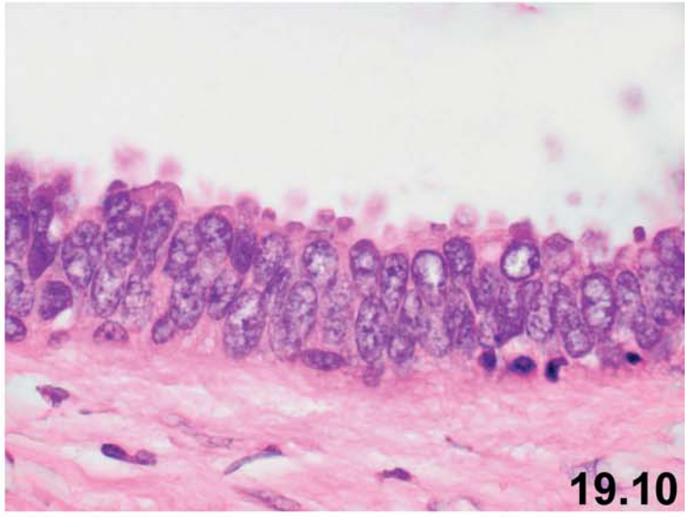
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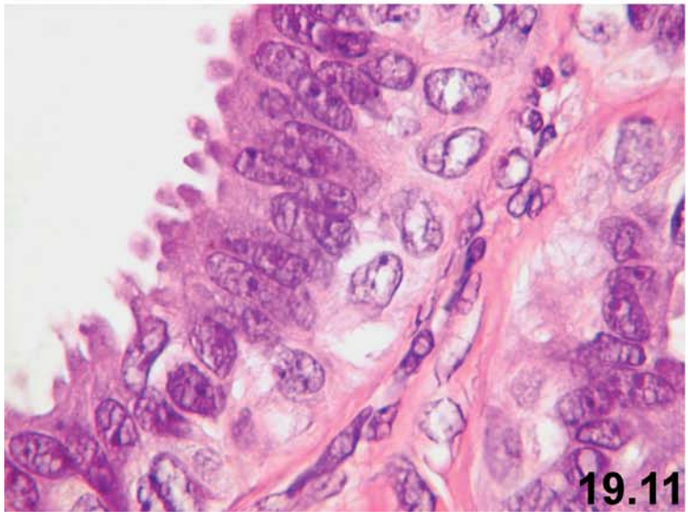
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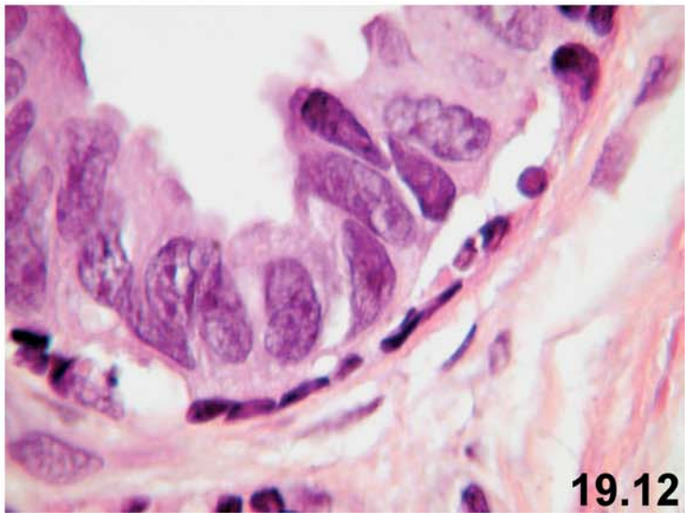
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Fig. 20: Low-grade ductal intraepithelial neoplasia (DIN1), predominantly of flat type.

Case history: A 38-year-old woman presented with an abnormal mammogram of her left breast, showing several clusters of suspicious microcalcifications (upper inner quadrant). There was no palpable breast mass.

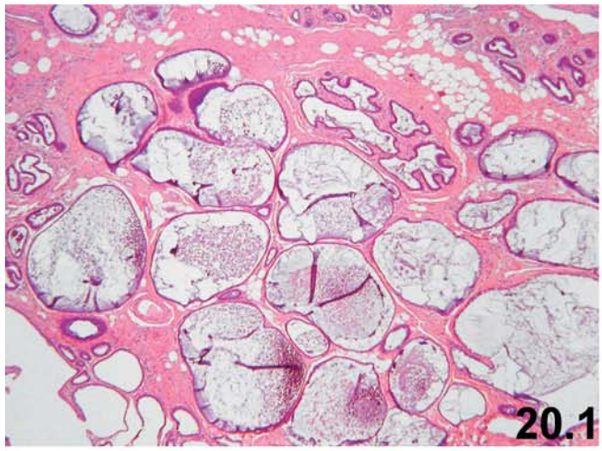
Fig. 20.1: At low magnification, several cysts with luminal secretions are present. Some cysts show luminal microcalcifications. This part of the lesion closely resembles fibrocystic changes.

Fig. 20.2: Another area of the lesion with adenosis-like pattern associated with microcalcifications.

Figs. 20.3 and **20.4:** Focally, the ducts display intraepithelial proliferation with cribriform or micropapillary growth pattern.

Figs. 20.5 and **20.6:** Several areas of the lesion reveal dilated ducts lined by a very few cell layers of epithelial cells showing apical snouts.

Figs. 20.7 and **20.8:** This particular focus of the lesion demonstrates a transition from DIN flat type (flat epithelial atypia) to a more solid luminal proliferation. Note the cytomorphological similarities between the cells in the flat and solid areas.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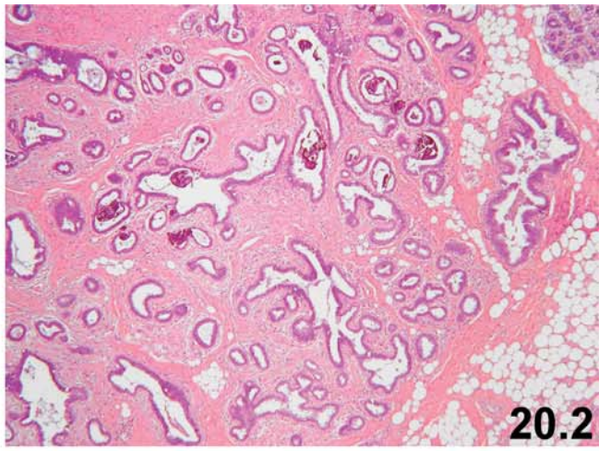
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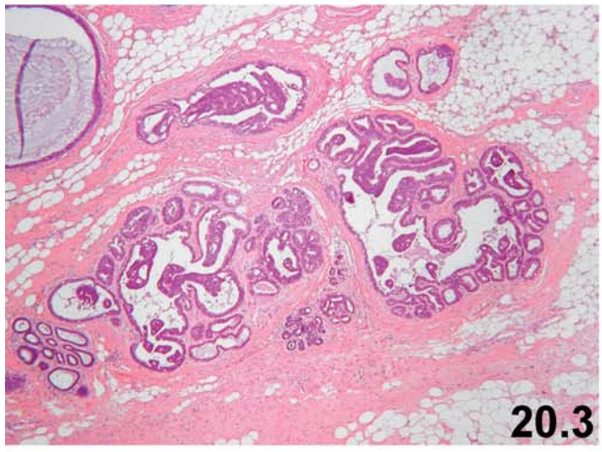
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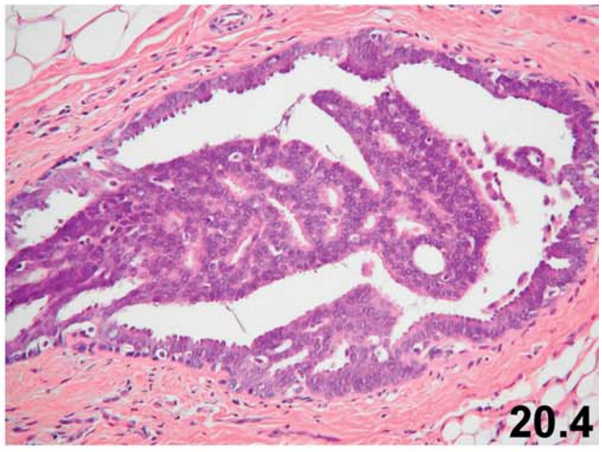
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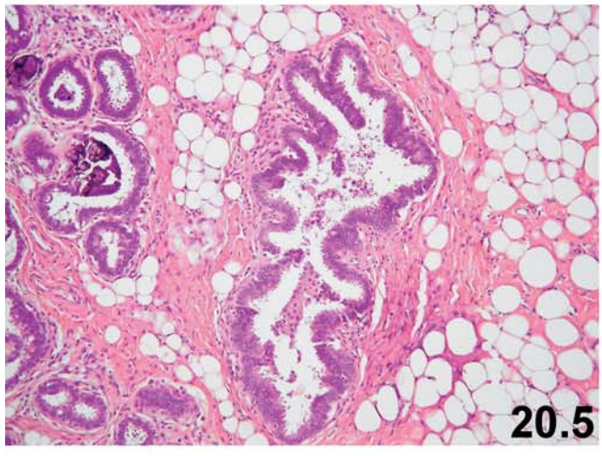
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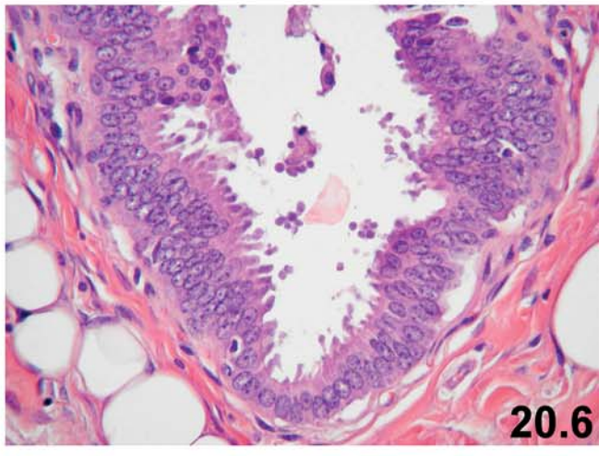
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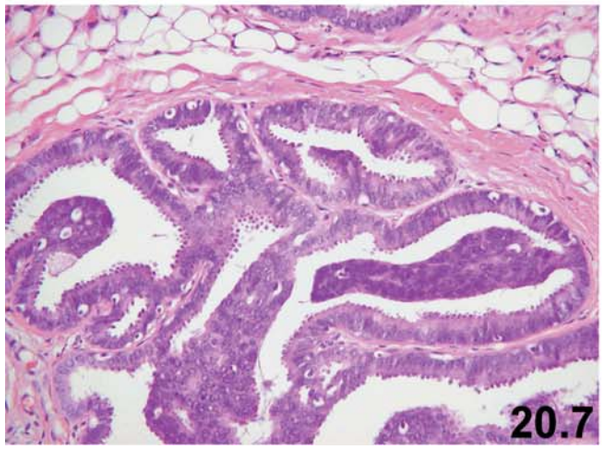
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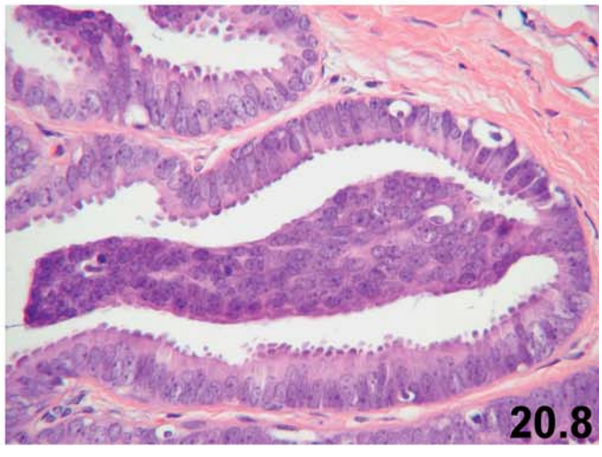
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Fig. 20.9: Higher magnification of Fig. 20.8, showing the same cell type with mild atypia in both flat and solid areas.

Fig. 20.10: Higher magnification showing the transition of a flat into a micropapillary proliferation. The morphological similarity of epithelial cells in areas with different growth pattern is striking.

Fig. 20.11: A small dilated duct containing basophilic, mucoid luminal material and a few apoptotic cells in the lumen.

Fig. 20.12: Cystically dilated ducts lined by one layer of epithelial cells. Note numerous small microcalcified structures admixed with luminal cell debris.

Fig. 20.13: Microcalcifications of laminated type in a duct lined by only one layer of atypical epithelial cells. The basally located myoepithelial cells are attenuated.

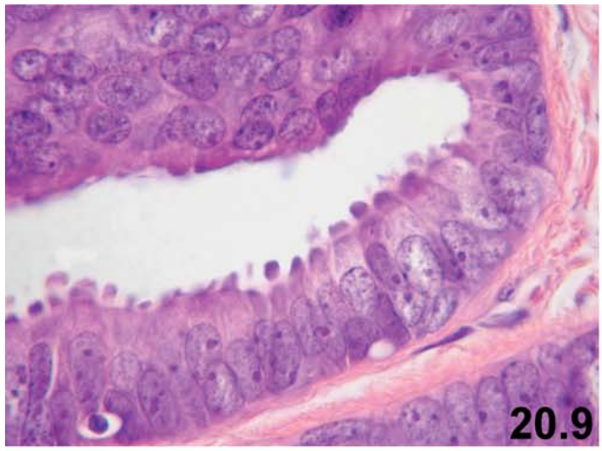
Fig. 20 14: Other cysts are lined by three to five layers of mildly atypical cells. The cells are homogeneous (monotonous) in appearance.

Fig. 20.15: One area with transition from a flat lesion into a solid fungus-like structure. The proliferating cells are homogeneous and lack a modified myoepithelial cell component.

Fig. 20.16: While there is no apparent mitotic activity or proliferation among the cells of DIN flat type, some areas show apoptotic bodies in the lumens. The lining epithelial cells show a mild degree of nuclear atypia. Note the attenuation of myoepithelial cells, which is a common feature of DIN flat type.

Fig. 20: Final remarks

- Many pathologists have reviewed this case. While many called it fibrocystic changes associated with microcalcifications and focal areas of atypical ductal hyperplasia, several others interpreted this lesion as a low-grade DCIS with a combination of clinging, cribriform, and micropapillary growth patterns.
- This case represents an example of a low-grade DIN that shows predominantly flat and only focal cribriform and micropapillary growth patterns.
- This type of breast lesion is often multifocal. Evaluation of resection margins in such cases is, therefore, not meaningful. Like lobular intraepithelial neoplasia, regular clinical and mammographic follow-up of patients with this type of low-grade neoplastic breast lesion is advised.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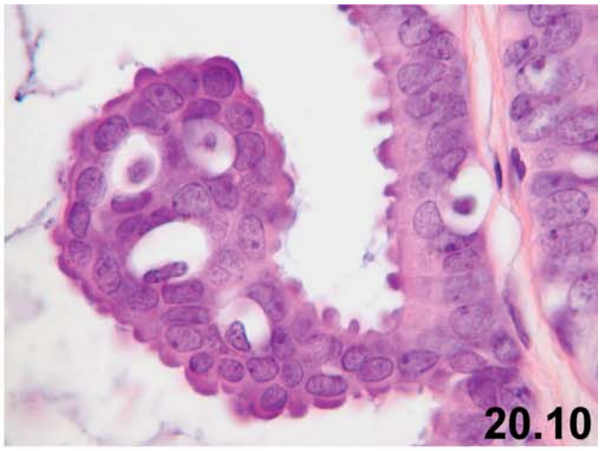
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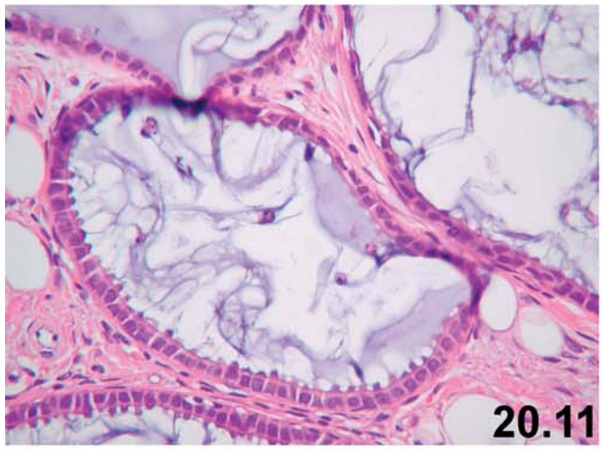
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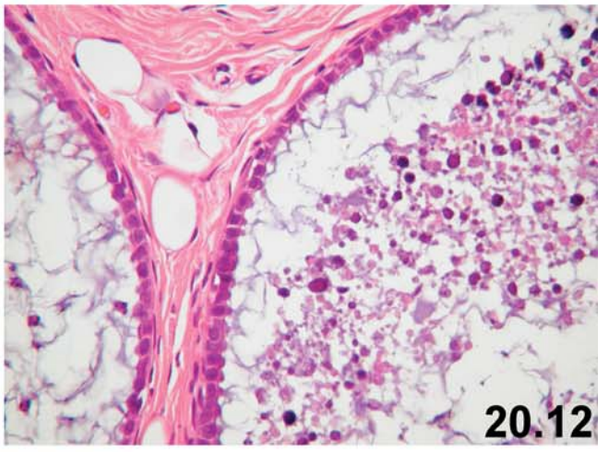
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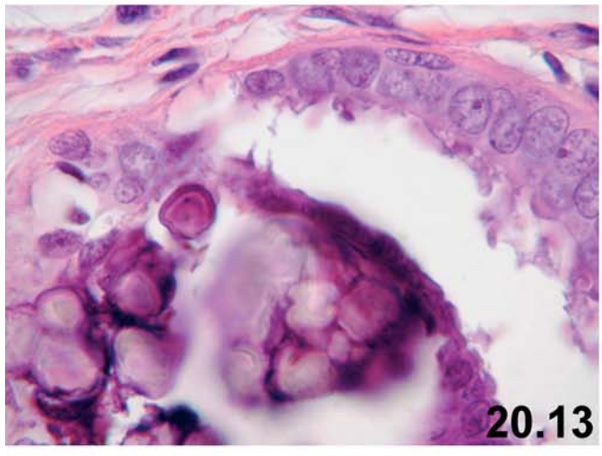
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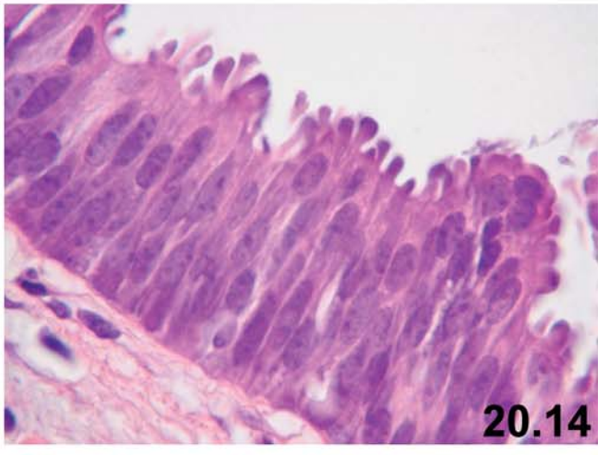
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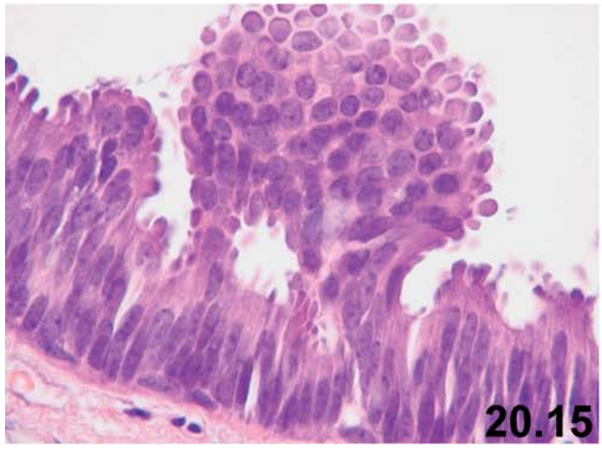
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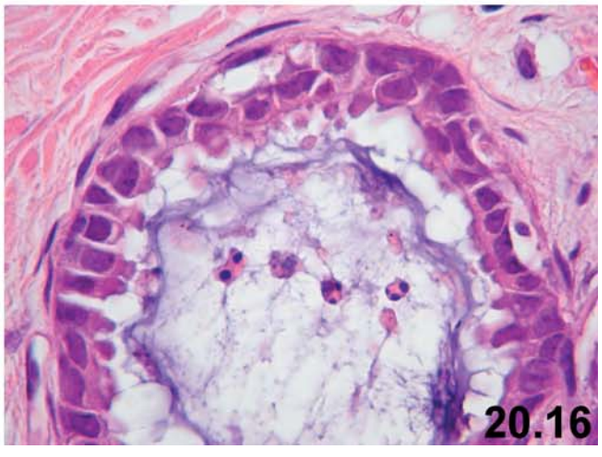
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Fig. 21: Low-grade ductal intraepithelial neoplasia (DIN1), cribriform type (atypical ductal hyperplasia).

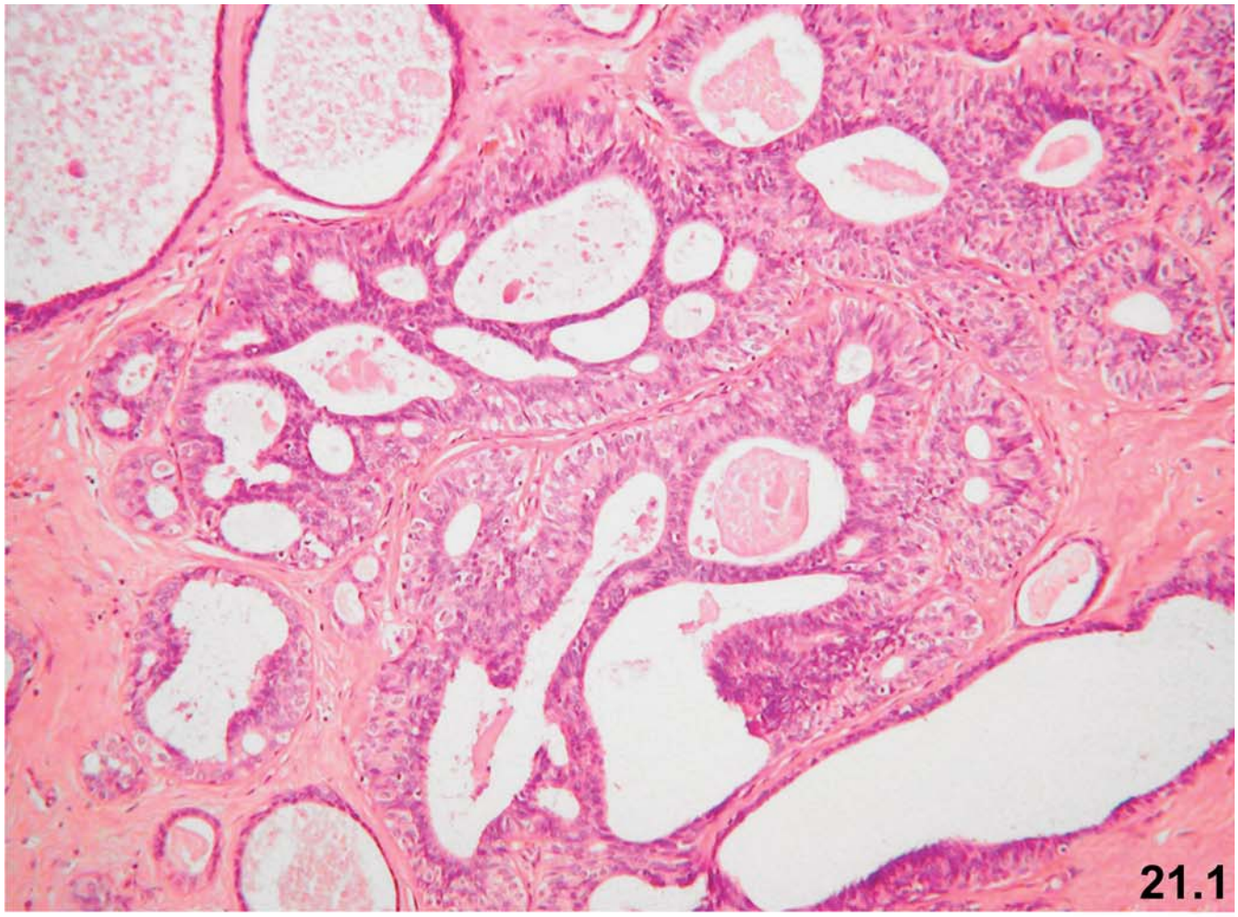
Case history: A routine screening mammogram was performed on a 48-year-old woman. It showed a well-circumscribed tumor (2 cm) that proved to be a fibroadenoma histologically. One section of the excisional biopsy showed an intraductal proliferative lesion 1 cm away from the fibroadenoma, as shown below.

Fig. 21.1: Multiple ducts show intraductal proliferation with several rounded rigid secondary lumens with a cribriform growth pattern.

Fig. 21.2: Proliferating epithelial cells in a duct forming rigid secondary lumens and cribriform structures that contain fragmented secretory-like luminal material. The proliferating cells are relatively monotonous in appearance. Immunohistochemistry for CK5/6 was negative in the proliferating ductal cells (not illustrated), which is a typical finding for atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS).

Fig. 21: Final remarks

- This case demonstrates a common diagnostic problem in breast pathology. The distinction between ADH and low-grade DCIS is difficult, if not impossible, in this case. Whereas several pathologists called this neoplastic lesion ADH, many others favored low-grade DCIS.
- There is no question that cells in ADH are neoplastic and do not differ qualitatively from those of low-grade DCIS. If one still wants to separate between ADH and low-grade DCIS in this case, the diagnosis of ADH would be more appropriate in order to avoid the term cancer. Using arbitrary criterion of 2 mm, this lesion would also be classified as ADH.
- It is important to keep in mind that ADH and low-grade DCIS represent morphologically, immunohistochemically, and genetically very close, if not identical, neoplastic breast lesions. The best designation for this type of breast lesion is, therefore, low-grade ductal intraepithelial neoplasia.



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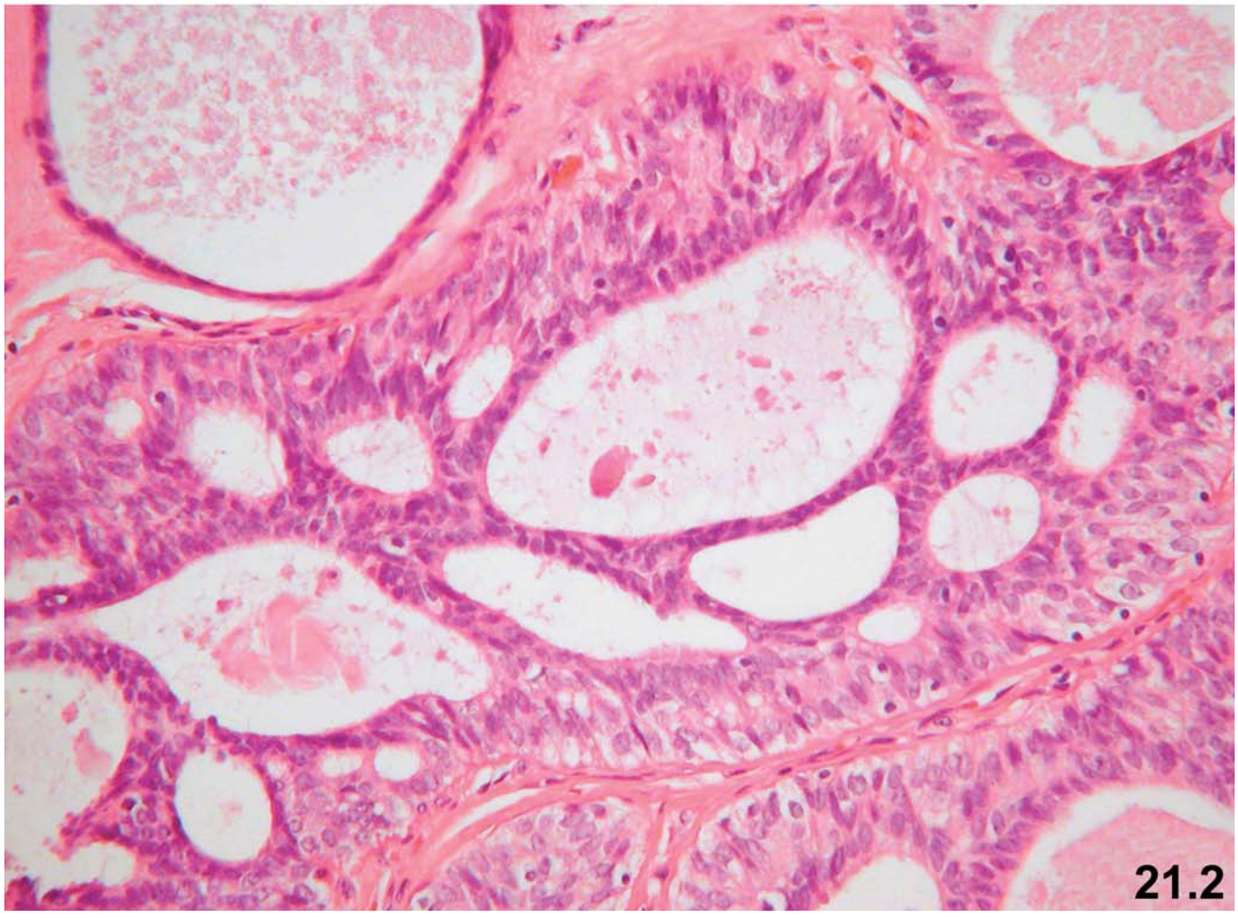

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Fig. 22: Low-grade ductal intraepithelial neoplasia (DIN) with trabecular (arcade) formation.

Case history: A 30-year-old woman presented with fibrocystic changes clinically and mammographically. Histology revealed several ducts with partial intraluminal proliferation. One duct with partial involvement is described below.

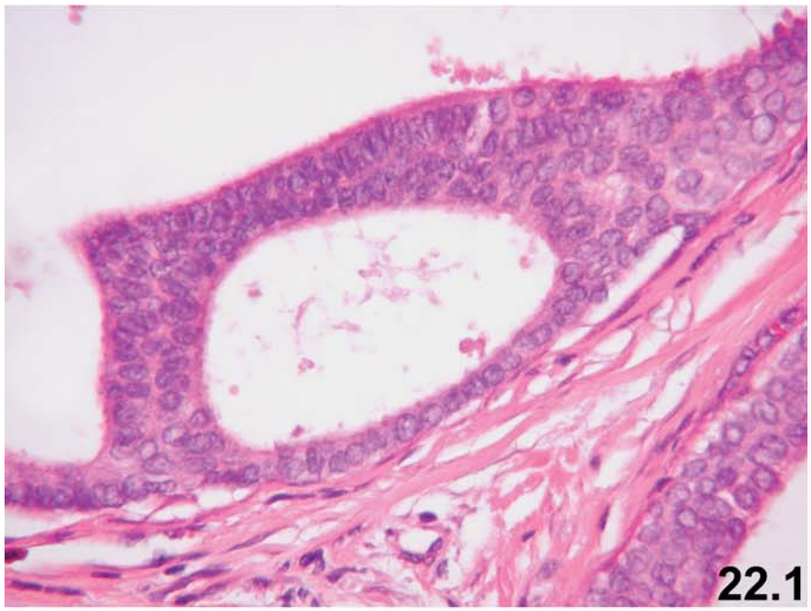
Fig. 22.1: An intraductal proliferative lesion characterized by a homogeneous cell population of mildly atypical epithelial cells forming a rigid (roman) bridge or a trabecula.

Fig. 22.2: At higher magnification, the trabecular (arcade) formation shows a row of epithelial cells (without a modified myoepithelial cell component) with their long axes arranged perpendicular to the long axis of the row.

Fig. 22.3: Another area of the robust trabecular bar or roman bridge showing one cell type (homogeneous cell population of mildly atypical epithelial cells). The cell population and nuclear orientation (perpendicular arrangement to the long axis of the row) are highly characteristic for DIN (DCIS).

Fig. 22: Final remarks

- Partial ductal involvement by atypical (neoplastic) cells is often considered a diagnostic criterion for separation between ADH and low-grade DCIS. This case is another example demonstrating that ADH and low-grade DCIS represent, cytologically and architecturally, the same low-grade neoplastic ductal lesion.
- A separation between ADH and low-grade DCIS based on the criterion of partial ductal involvement is not evidence-based. Cases with partial ductal involvement showing cribriform or micropapillary growth patterns and low-grade nuclear atypia should, therefore, be called low-grade DIN.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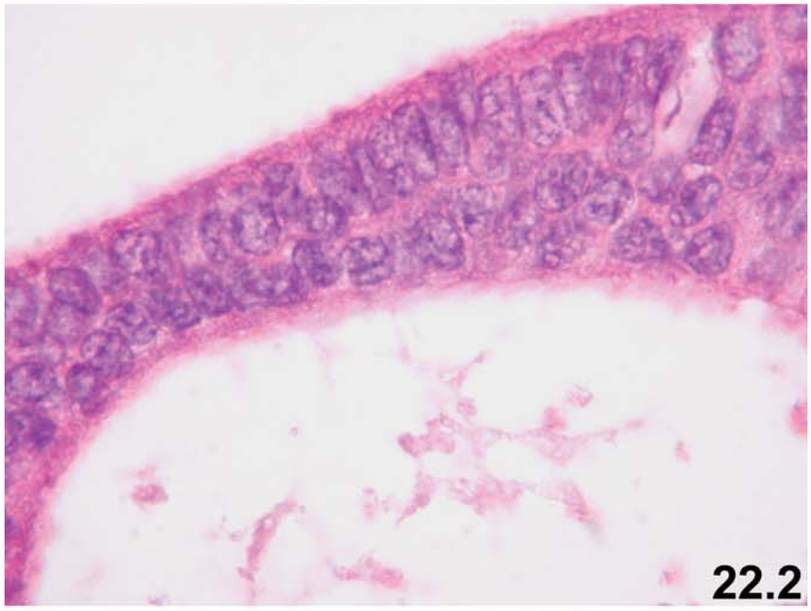
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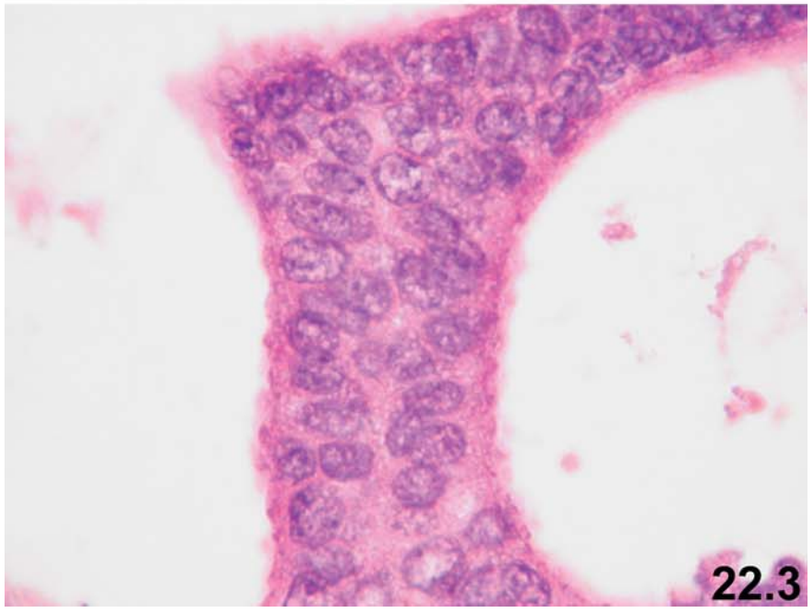
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Fig. 23: Ductal intraepithelial neoplasia (DIN, DCIS), predominantly of low-grade (DIN1) and focally of intermediate grade (DIN2).

Case history: A 35-year-old woman presented for evaluation of a palpable soft mass at the 9 o'clock position in the left breast. Mammography revealed some irregular areas with microcalcifications.

Fig. 23.1: Ducts with intraluminal proliferations showing micropapillary and cribriform structures. One duct displays intraluminal necrosis.

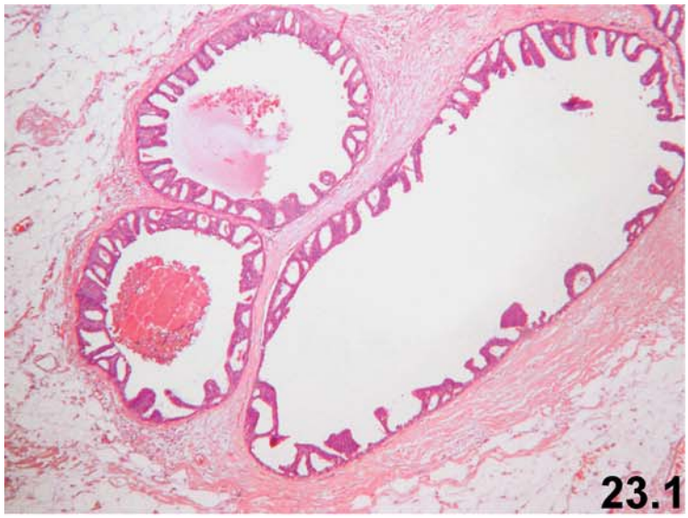
Fig. 23.2: A rigid bridge in a duct. The proliferating cells are uniform with subtle nuclear atypia.

Fig. 23.3: A rigid micropapillary structure in a duct showing homogeneous epithelial cells with mild nuclear atypia.

Fig. 23.4: Confluent micropapillary structures forming a cribriform growth pattern of atypical (neoplastic) epithelial cells.

Fig. 23.5: A homogeneous cell population of mildly atypical cells showing a cribriform growth pattern. Note the regular arrangement of the nuclei and the rounded secondary lumens.

Fig. 23.6: Immunohistochemistry for CK5/6 shows a typical negative reaction of the neoplastic ductal cells. Ducts with central necrosis are also negative for CK5/6.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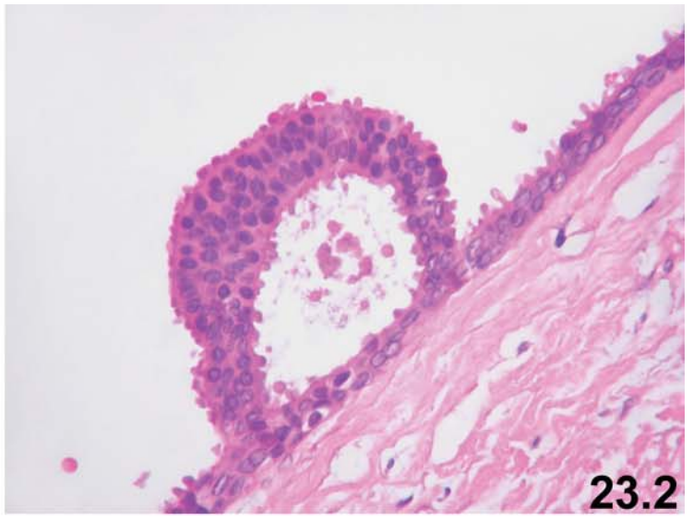
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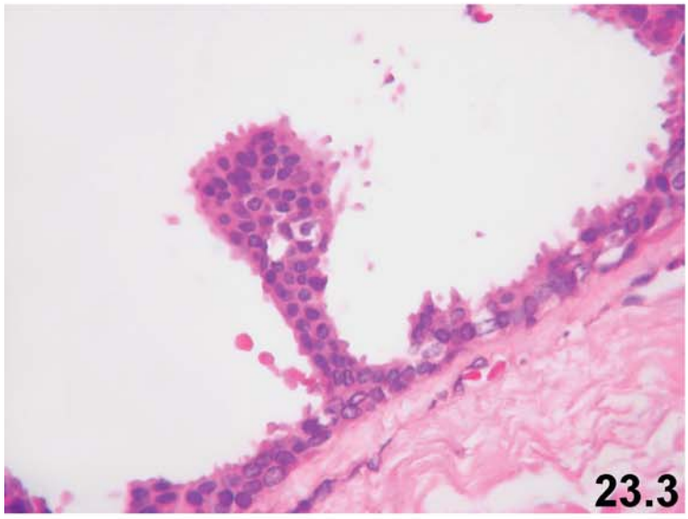
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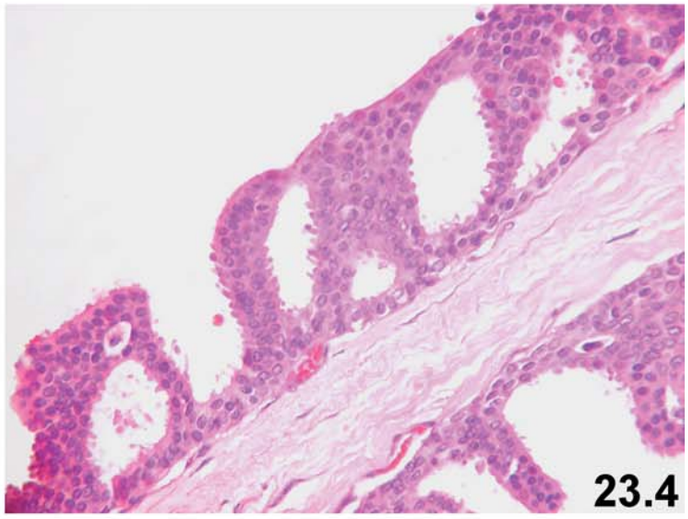
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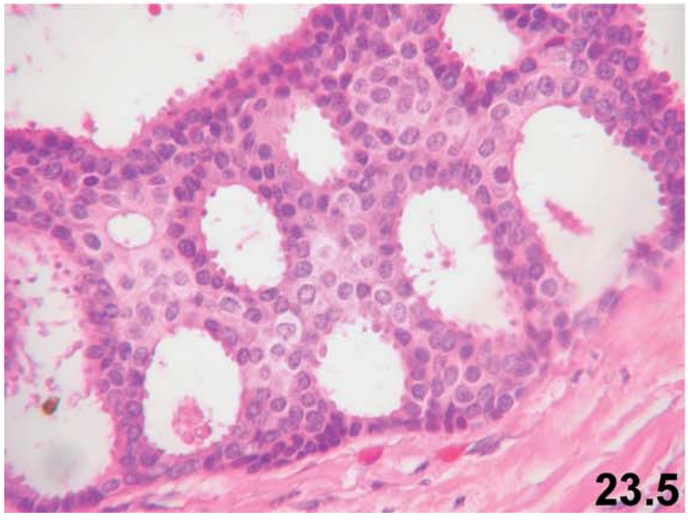
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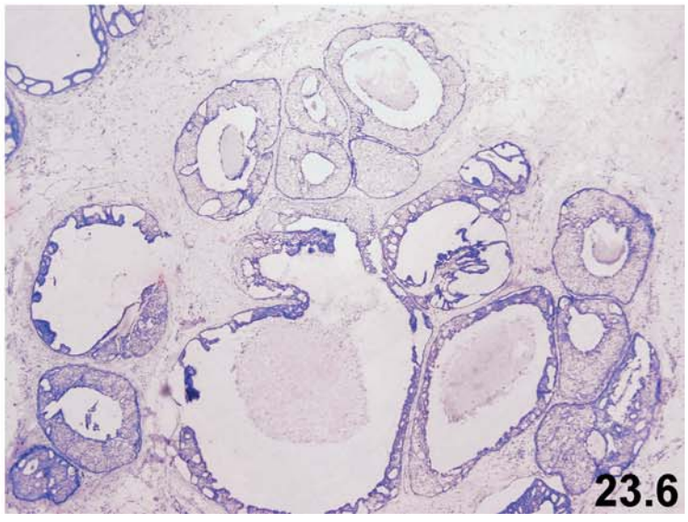
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Fig. 23.7: Negative immunoreaction of solid areas of DIN (DCIS) for CK5/6.

Fig. 23.8: Imprint cytology of the cut surface of the excisional biopsy (fresh material) in this case shows a cohesive cell cluster consisting of a homogeneous cell population with no myoepithelial component (Diff-Quik stain).

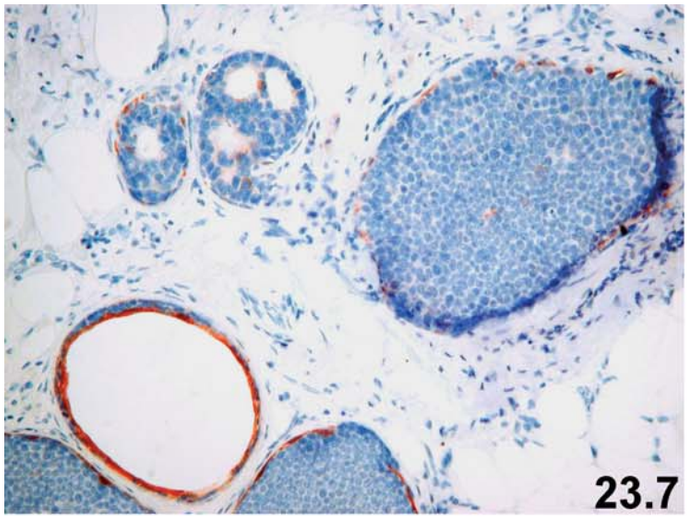
Fig. 23.9: Neoplastic ductal epithelial cells with micropapillary growth pattern. Note the similarity of atypical cells in the imprint cytology (Fig. 23.8) and the corresponding histology (Fig. 23.9).

Fig. 23.10: Neoplastic epithelial cells with hyperchromatic nuclei forming an early cribriform structure.

Fig. 23.11: While high molecular weight cytokeratin (CK5/6) shows a positive reaction in myoepithelial cells, the proliferating epithelial cells are negative for it.

Fig. 23: Final remarks

- This case demonstrates an example of DIN (DCIS) with cribriform and micropapillary growth patterns. While most areas of the lesion show low-grade nuclear atypia and lack luminal necrosis, a few areas reveal ducts with central necrosis.
- The presence of even focal necrosis in DIN justifies an upgrade from low to intermediate grade. This case, therefore, represents a combination of low-grade and intermediate-grade DIN (DIN 1 and DIN2 or DCIS G1 and G2).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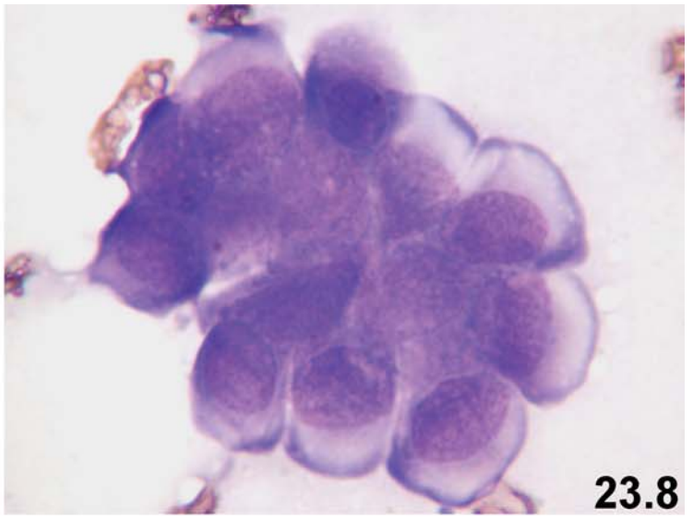
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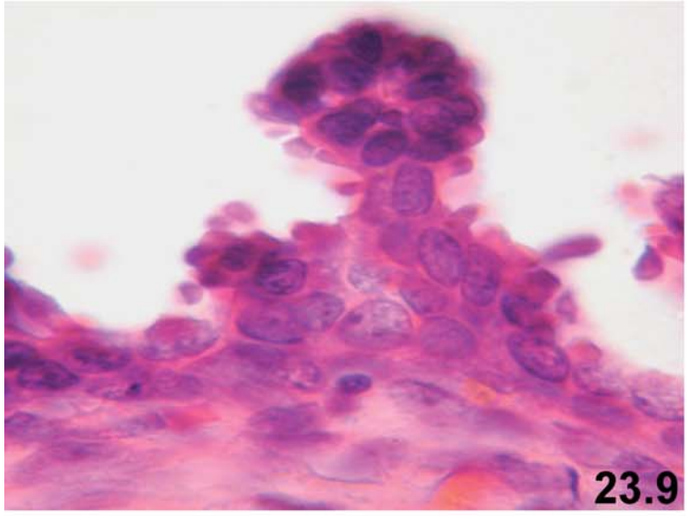
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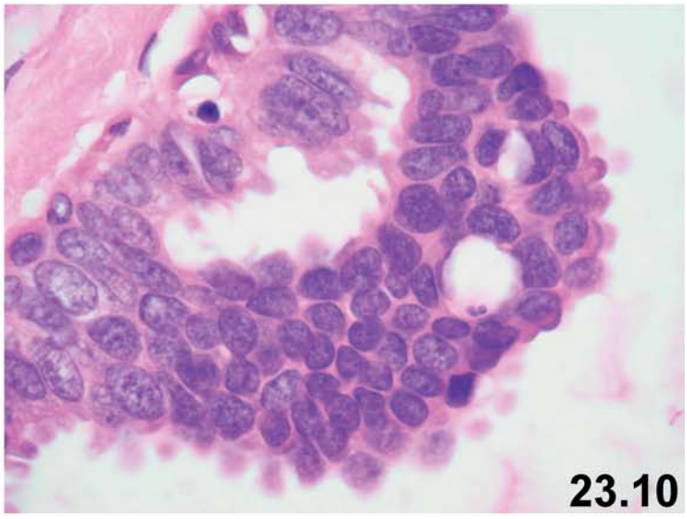
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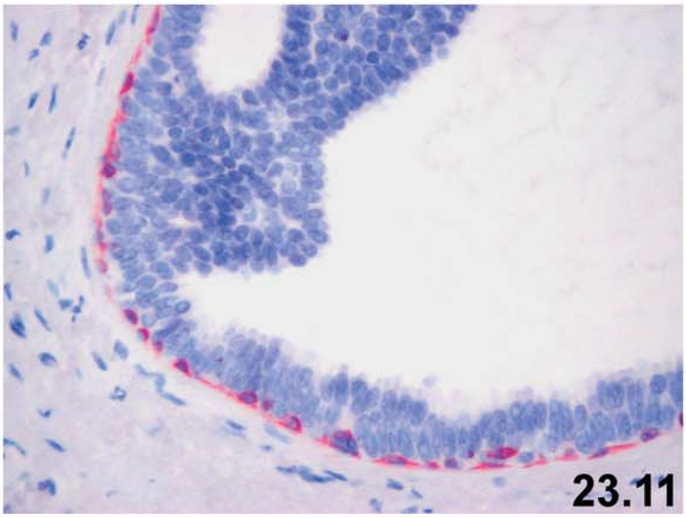
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Fig. 24: Ductal intraepithelial neoplasia (DIN), intermediate grade (DIN2, DCIS, G2).

Case history: Routine screening mammogram was performed on a 60-year-old woman in 1997. Follow-up was suggested because of asymmetric densities. Another mammogram was done in 1999 and revealed some areas with microcalcifications, which were interpreted as suspicious for malignancy.

Fig. 24.1: Imprint cytology of the cut surface of the excisional biopsy (fresh surgical specimen) shows at low magnification abundant necrotic background. In addition, there are isolated cells and clusters of epithelial cells (Diff-Quik stain).

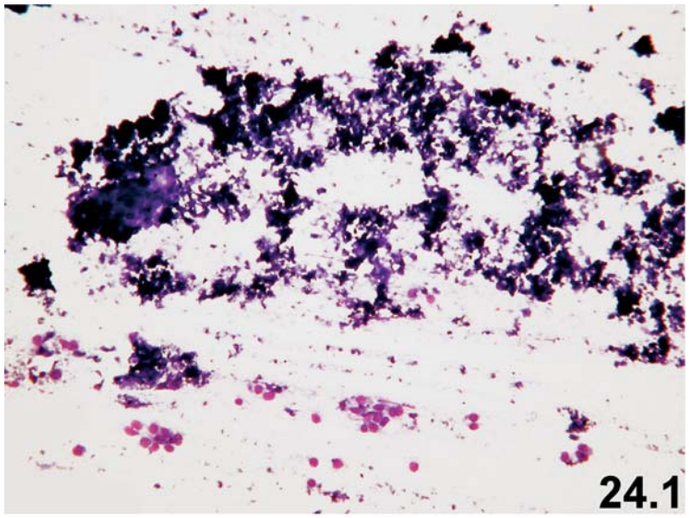
Fig. 24.2: Higher magnification of imprint cytology reveals cell debris admixed with cohesive atypical epithelial cells.

Fig. 24.3: Histology of the lesion shows a duct with intraepithelial neoplastic cells with micropapillary and cribriform growth patterns. The luminal secretory-like material is fragmented and shows several apoptotic bodies at its periphery.

Fig. 24.4: A duct with cribriform growth pattern and low-grade nuclear atypia. Note the presence of central necrosis or abundant aggregates of apoptotic bodies.

Fig. 24: Final remarks

- Although the neoplastic cells in this case show low-grade nuclear atypia, this lesion should be classified as intermediate-grade DIN (DIN2 or DCIS, G2) based on central necrosis.
- The presence of even abundant central necrosis in DIN without high-grade nuclear atypia does not justify designation of high-grade DIN (DIN3). A high-grade DIN (DIN3) must show high-grade nuclear atypia with or without central necrosis.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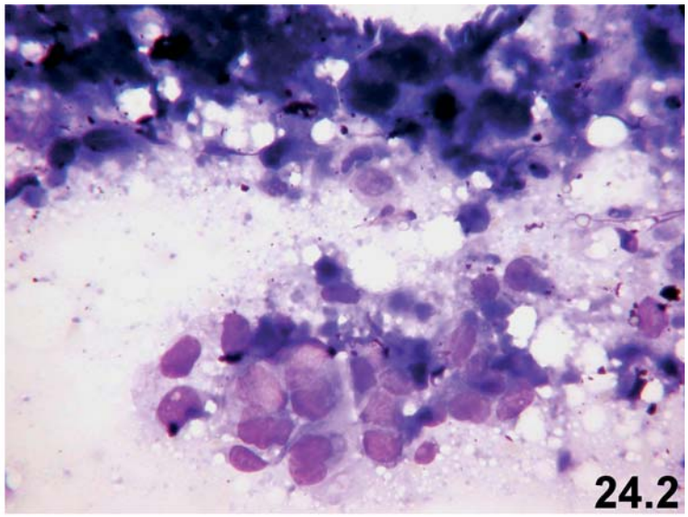
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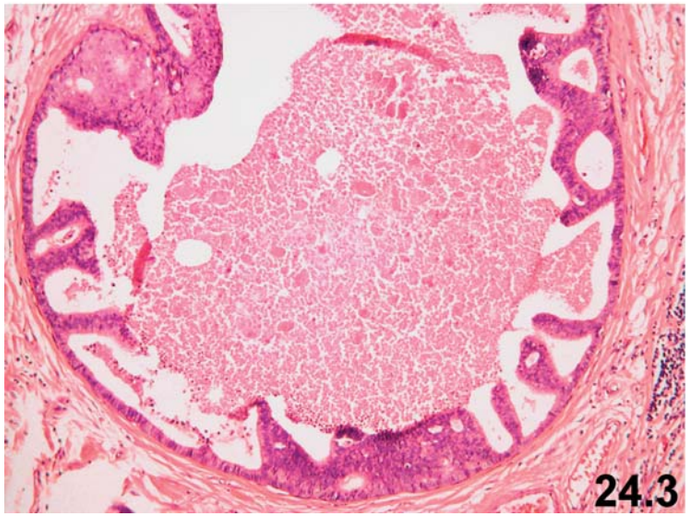
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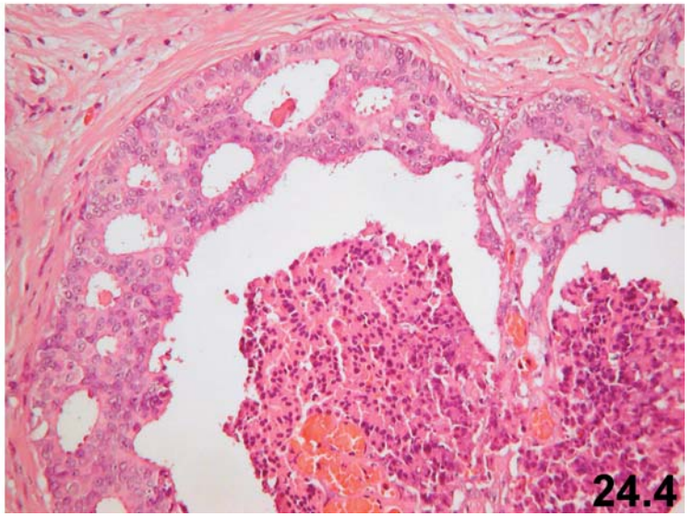

24.4

Fig. 25: Ductal intraepithelial neoplasia (DIN, DCIS), clear cell type.

Case history: A 66-year-old woman underwent a routine screening mammogram, which showed abnormal areas with microcalcifications of her right breast.

Figs. 25.1 and **25.2:** Several ducts show solid intraductal proliferation partly associated with central necrosis.

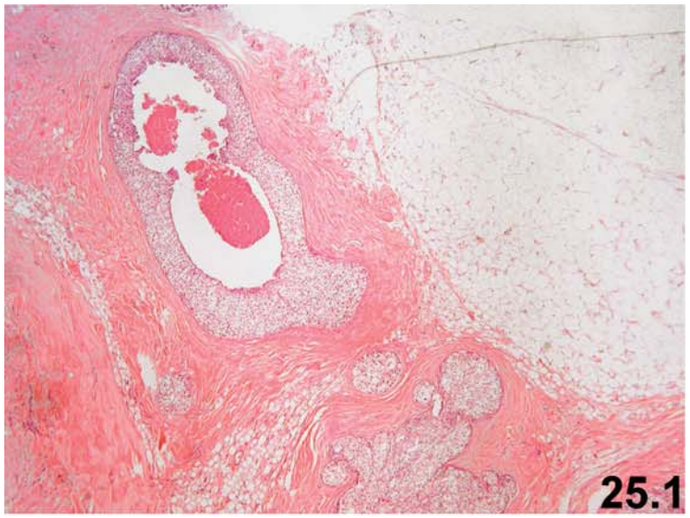
Fig. 25.3: The intraepithelial neoplastic cells show abundant clear cytoplasm.

Fig. 25.4: Neoplastic epithelial cells with clear cytoplasm. Note the presence of luminal necrosis.

Figs. 25.5 and **25.6:** At higher magnification the tumor cells display mild and focally moderate nuclear atypia. The tumor cells show abundant clear (glycogen-rich) cytoplasm and distinct cytoplasmic borders.

Fig. 25: Final remarks

- Clear cell variant of DIN (DCIS) is usually of grade 2 and shows moderate nuclear atypia with or without central necrosis.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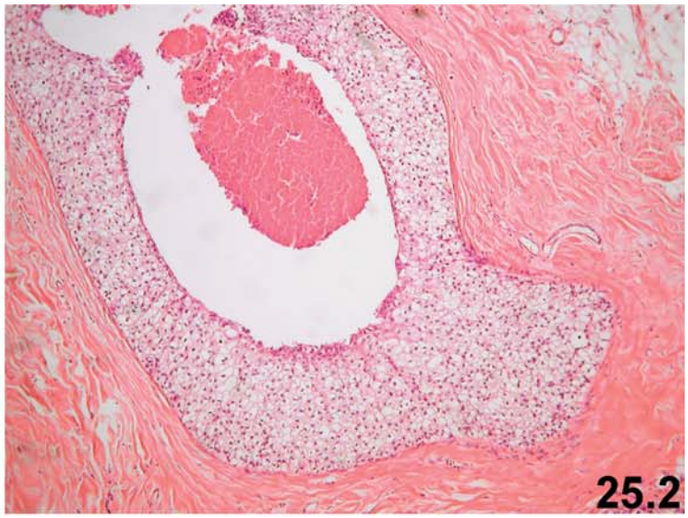
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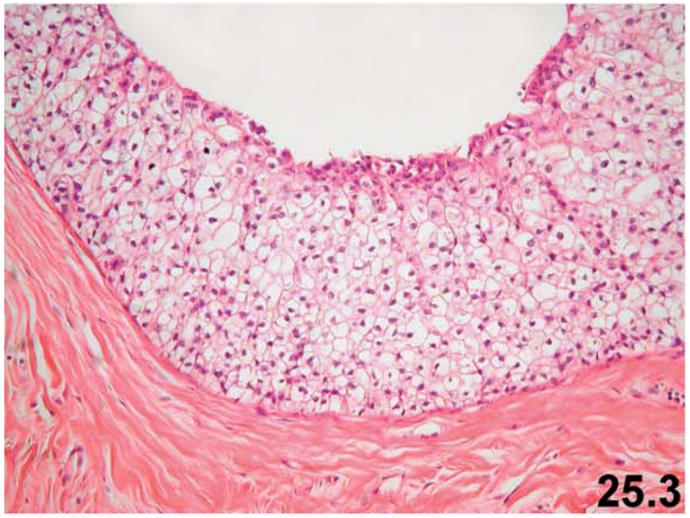
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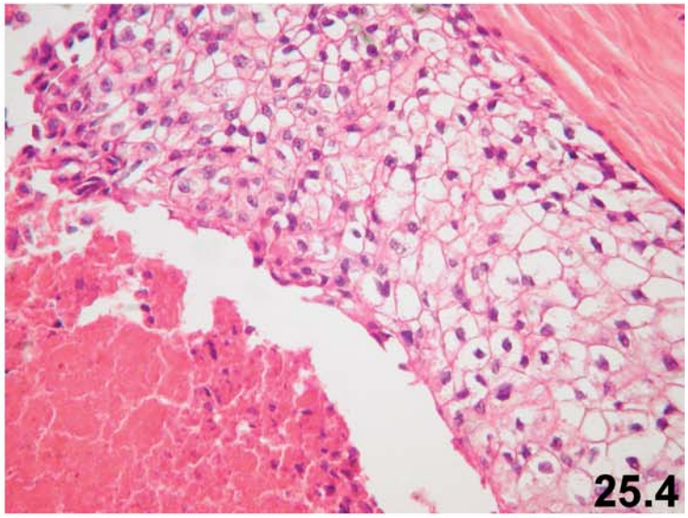
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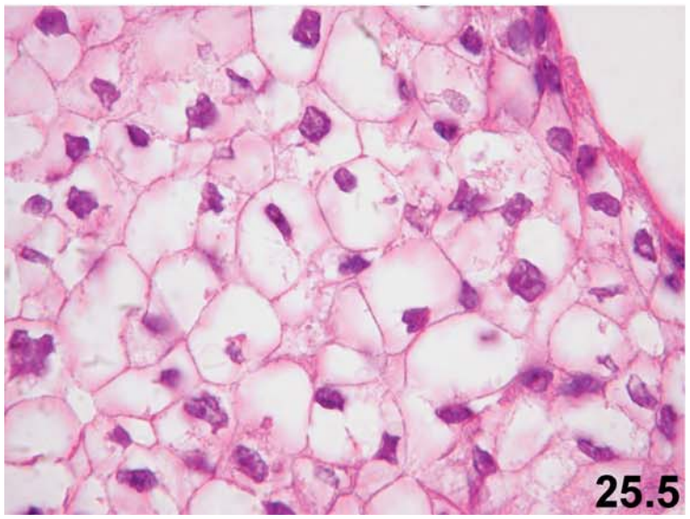
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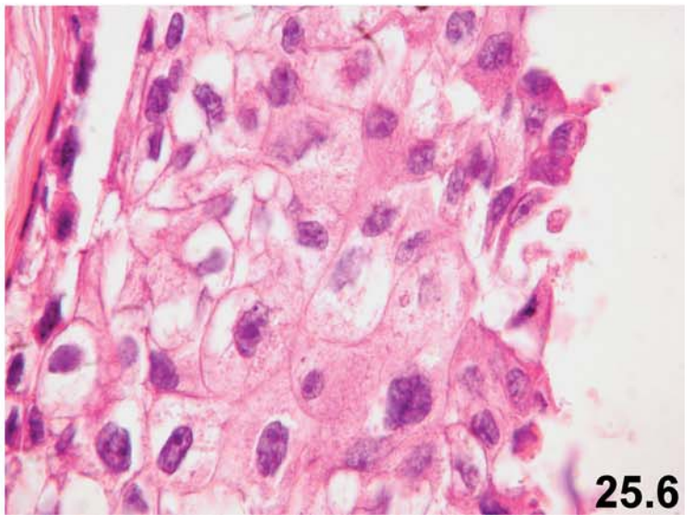
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Fig. 26: Ductal intraepithelial neoplasia (DIN, DCIS), spindle cell variant with neuroendocrine differentiation.

Case history: A 47-year-old woman presented for a routine screening mammogram. It showed small irregular areas without microcalcification in her left breast. Core needle biopsy revealed atypical ductal proliferation. Excisional biopsy of the lesion was subsequently performed. There was no grossly apparent lesion on the cut surface of the surgical specimen.

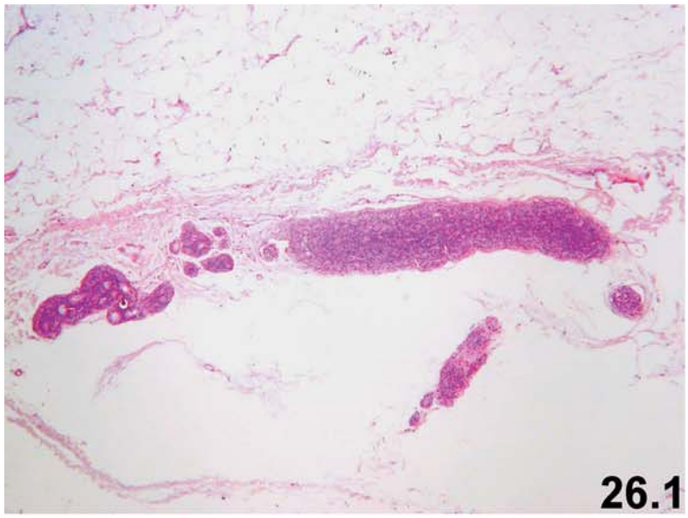
Figs. 26.1 and **26.2:** Low magnification of the lesion shows a predominantly solid intraductal proliferation.

Figs. 26.3 and **26.4:** Solid intraductal proliferation shows two cell types consisting of centrally located spindle cells with scant cytoplasm and peripherally located atypical cells with pale to eosinophilic and more cytoplasm.

Figs. 26.5 and **26.6:** Some ducts also display rounded secondary lumens and cribriform (or rosette-like) growth pattern. The neoplastic cells show hyperchromatic and enlarged nuclei.

Fig. 26: Final remarks

- The main differential diagnosis in this case is florid ductal hyperplasia or usual ductal hyperplasia (UDH). The presence of two cell types could easily be misinterpreted as an admixture of epithelial and modified myoepithelial cells (progenitor cells), which is characteristic for UDH. The presence of a cribriform growth pattern or rosette-like structures, however, is not consistent with the interpretation of UDH. One should keep in mind that the spindle cell variant of DIN (DCIS) often closely resembles UDH. In contrast to UDH, the neoplastic cells of DIN, spindle cell variant are negative for high molecular weight cytokeratins such as CK5/6 and CK14.
- Immunohistochemistry for CK5/6 was done in this case and revealed a completely negative reaction of the proliferating ductal cells (not shown).The neoplastic cells in this variant of DIN often show different epithelial cell types with neuroendocrine differentiation. Immunohistochemistry for synaptophysin and chromogranin were also performed in this case (not shown) and revealed a heterogeneous positive reaction of tumor cells.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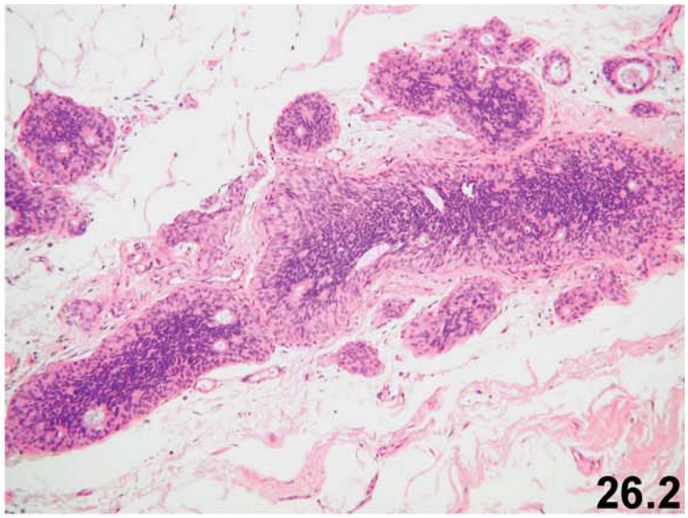
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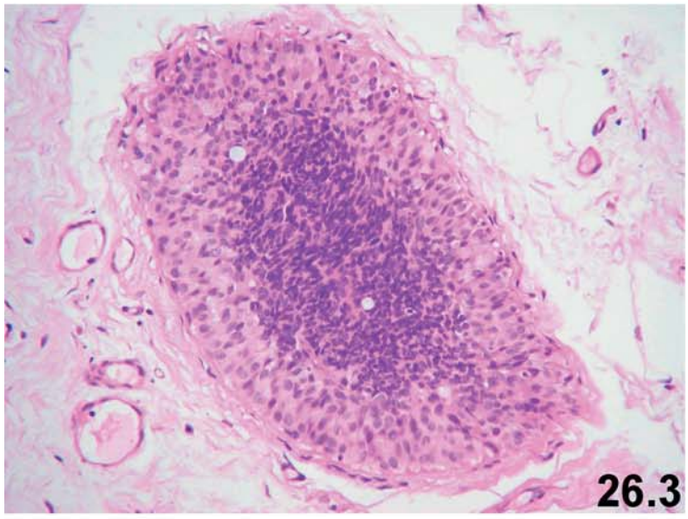
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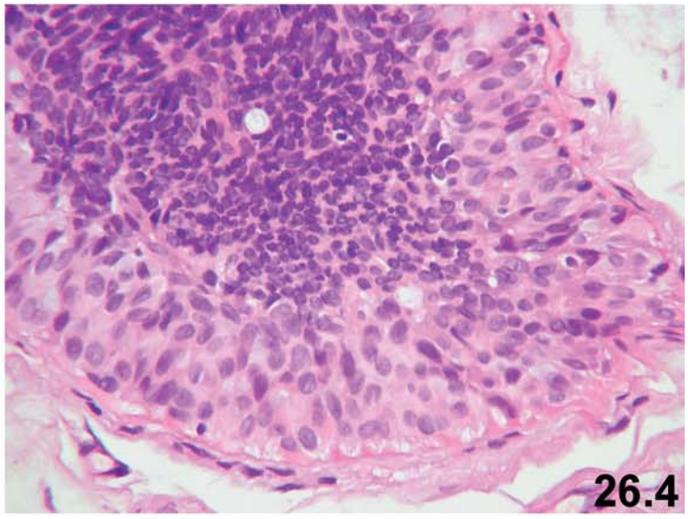
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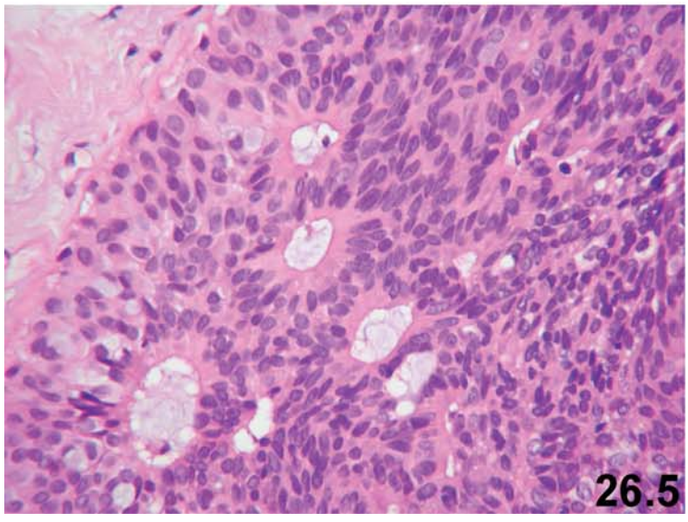
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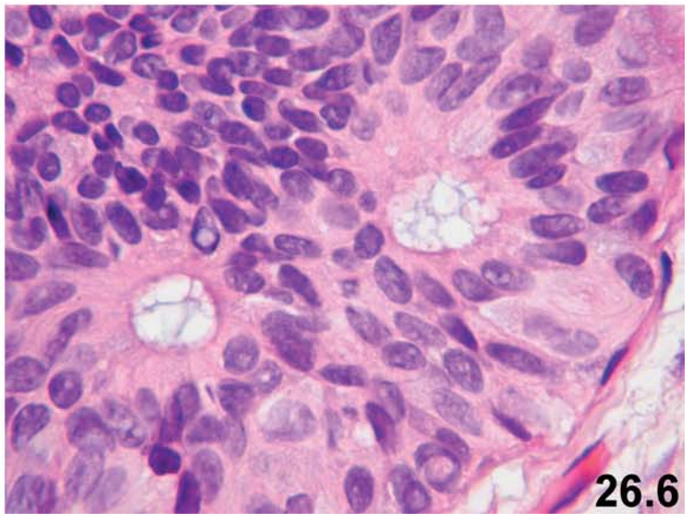
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Fig. 27: High-grade ductal intraepithelial neoplasia (DIN3)-flat type with apocrine features (pleomorphic variant of clinging carcinoma in situ or DCIS, G3).

Case history: A 34-year-old woman with a positive family history of breast cancer (sister) presented with an abnormal mammogram of the left breast. No palpable breast lesion was present.

Figs. 27.1 and **27.2:** Excisional biopsy of the lesion shows cystically dilated ducts lined by apocrine cells showing eosinophilic cytoplasm. Note the presence of luminal fragmented, not uniform, secretory-like material.

Figs. 27.3 and **27.4:** Higher magnification of the lesion demonstrates one or two layers of markedly atypical cells with hyperchromatic nuclei and irregular chromatin distribution. The atypical cells display eosinophilic cytoplasm. Note the attenuation of peripherally located myoepithelial cells.

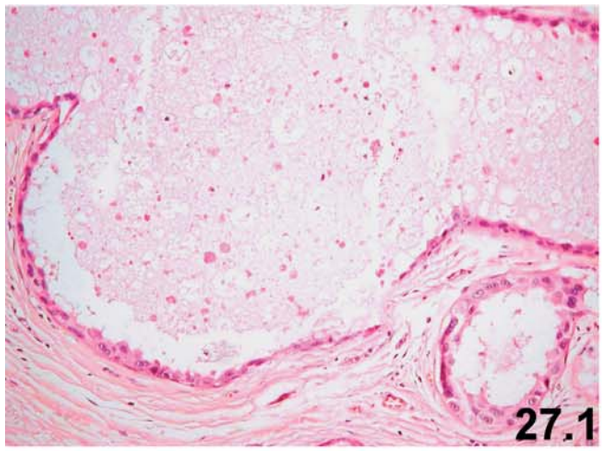
Fig. 27.5: High-power magnification reveals severe nuclear atypicality.

Figs. 27.6 and **27.7:** Immunohistochemistry for HER2/neu shows an intense (3+) and diffuse positive reaction of highly atypical epithelial cells.

Fig. 27.8: The highly atypical neoplastic cells display positive nuclear immunoreactivity for androgen receptor. The tumor cells, however, were negative for estrogen receptors and progesterone receptors (not shown).

Fig. 27: Final remarks

- This type of DIN (DCIS) can easily be overlooked or misinterpreted as fibrocystic changes with apocrine metaplasia. The presence of abnormal and fragmented luminal secretion, even in the absence of significant epithelial proliferation, should lead to examination of the lesion at higher magnification in order to recognize cytological atypia of the luminal cells.
- This case demonstrates that DIN flat type is not always of low grade and rarely can show high-grade nuclear atypia (with or without luminal necrosis). This high-grade variant of DIN flat type has been designated as pleomorphic variant of clinging carcinoma (in situ).
- The highly atypical cells in this variant of DIN flat type (DIN3-flat type) very often overexpress HER2/neu and are positive for androgen receptors. The tumor cells in DIN3 flat type are, however, typically negative for estrogen and progesterone receptors.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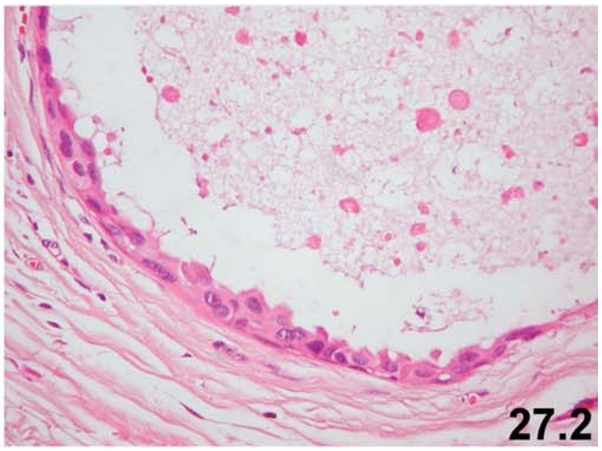
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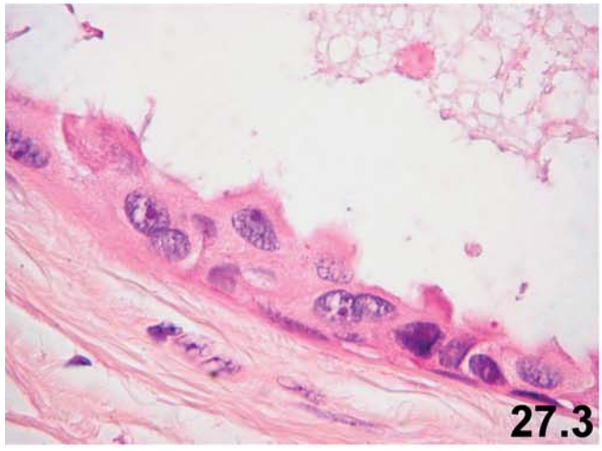
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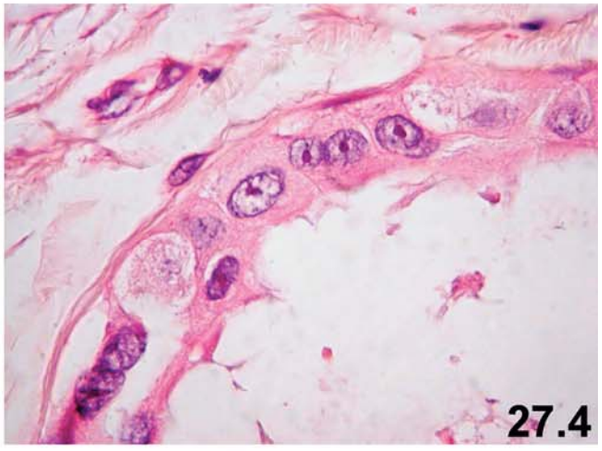
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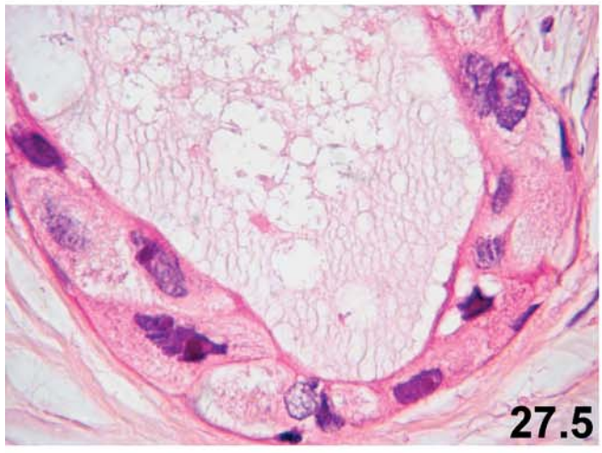
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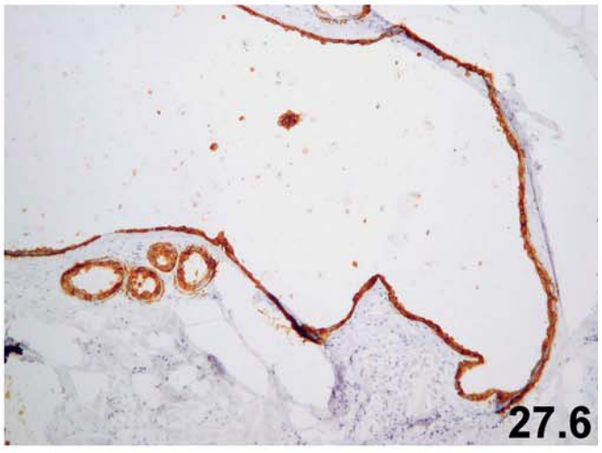
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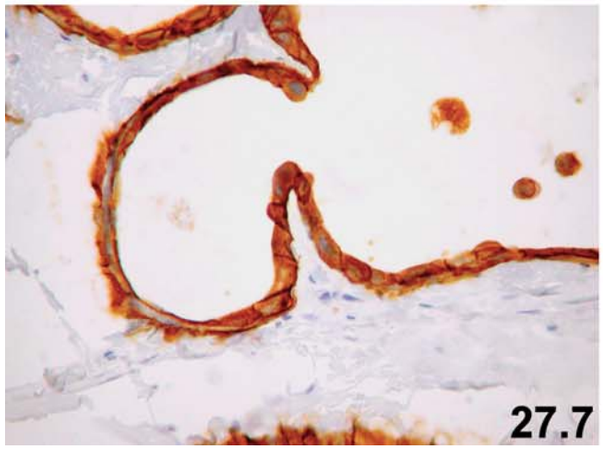
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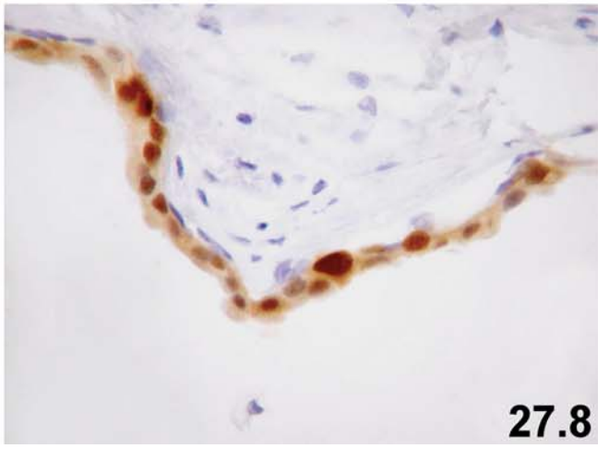
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Fig. 28: High-grade ductal intraepithelial neoplasia (DIN3, DCIS, G3) associated with sclerosing adenosis simulating invasive ductal carcinoma.

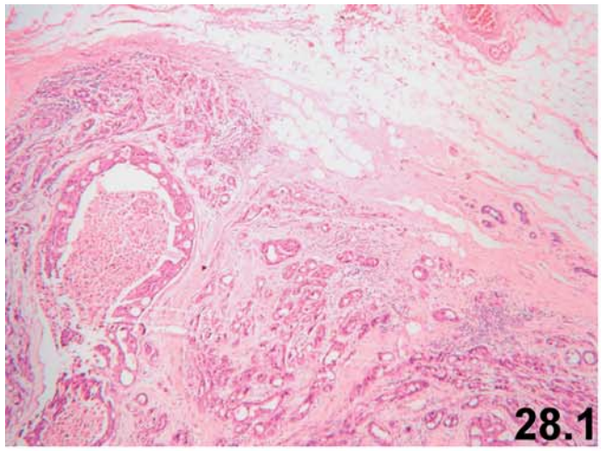
Case history: A 50-year-old woman presented with a palpable firm nodule of her right breast (upper outer quadrant). Her mammography revealed an ill-defined tumor, highly suspicious for breast cancer. Excisional biopsy of the lesion revealed a 1.4×1×0.6-cm greyish-white tumor with some irregular borders.

Figs. 28.1 and **28.2:** At low magnification, the lesion shows some areas with organoid, lobulated growth pattern. Several ducts also show cribriform intraluminal proliferation. Some of the ducts show luminal necrosis. In addition, there are several small glands with irregular outlines that appear suspicious for invasion at low magnification.

Figs. 28.3 and **28.4:** Areas with infiltrative growth pattern are adjacent to noninvasive or intraductal proliferation with cribriform pattern and central necrosis.

Figs. 28.5 and **28.6:** Higher magnification of small glands reveals irregular tubules and solid structures with severe nuclear atypia.

Figs. 28.7 and **28.8:** While the tubules with high-grade nuclear atypia seem to be invasive, they contain attenuated myoepithelial cells recognizable at higher magnification. The attenuated myoepithelial cells show bipolar or spindle-shaped dark nuclei and hardly visible cytoplasm.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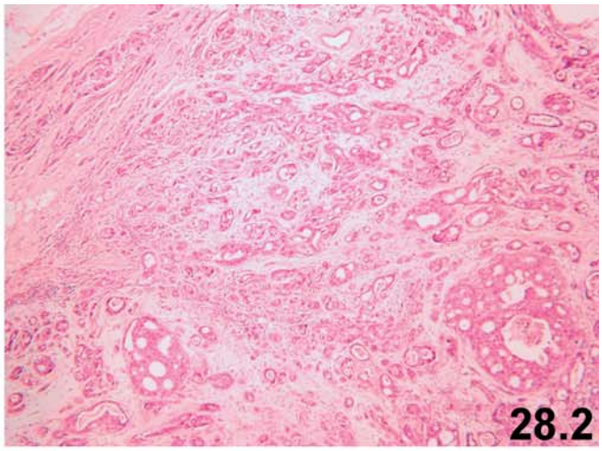
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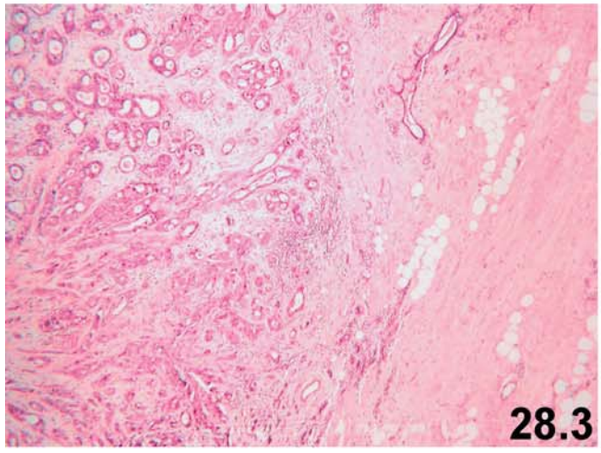
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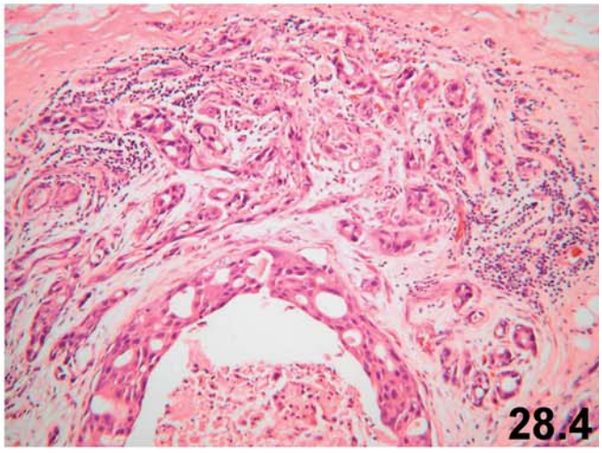
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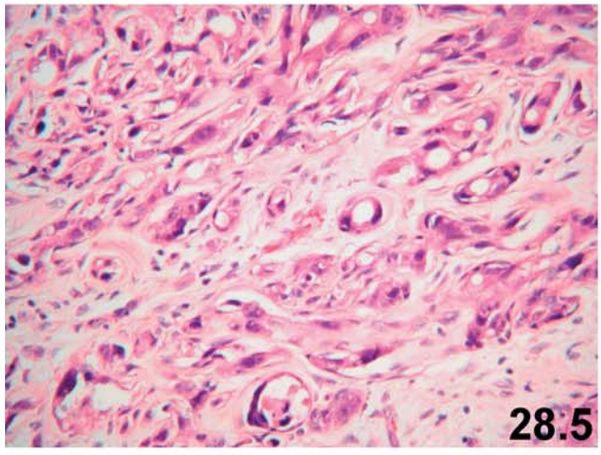
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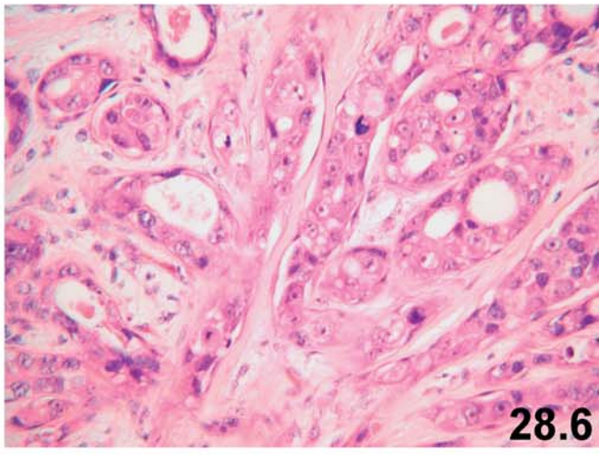
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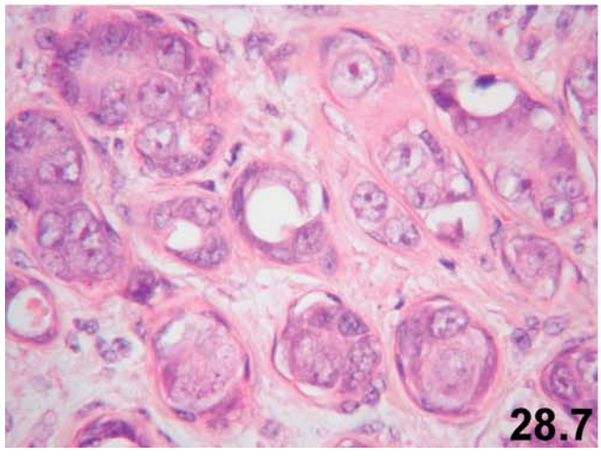
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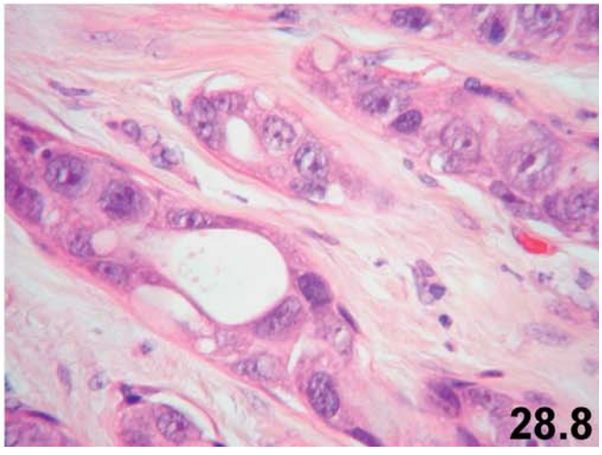
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Figs. 28.9 and **28.10:** Immunohistochemistry for smooth muscle actin reveals an attenuated cell layer of basally located myoepithelial cells.

Figs. 28.11 and **28.12:** Immunohistochemistry for calponin showing myoepithelial cells within the highly atypical glands.

Fig. 28.13: Immunohistochemistry for CD10, another myoepithelial marker, clearly demonstrates a positive reactivity of myoepithelial cells.

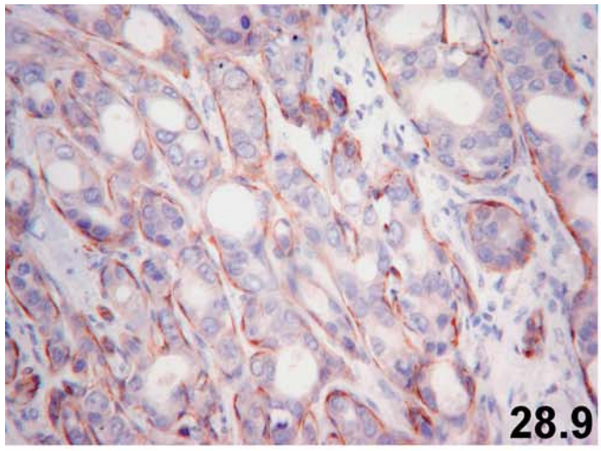
Fig. 28.14: Immunohistochemistry for HER2/neu showing an intense (3+) and diffuse reaction of glands with a pseudoinvasive pattern.

Fig. 28.15: Immunohistochemistry for HER2/neu reveals a strong reaction in an area with a cribriform growth pattern.

Fig. 28.16: Pseudoinvasive glands with highly atypical cells are positive for HER2/neu.

Fig. 28: Final remarks

- This challenging case has been reviewed by numerous pathologists. Because of the infiltrative growth pattern, complexity of the lesion, and presence of high-grade nuclear atypia, many reviewers made a definitive diagnosis of poorly differentiated invasive ductal carcinoma. The presence of myoepithelial cells within the highly atypical glands has been overlooked by several pathologists.
- The irregularity and pseudoinvasive glandular pattern in this case is due to the combination of DIN (DCIS) and sclerosing adenosis. Several areas outside of the nodule also revealed sclerosing adenosis (not shown). It is very likely that high-grade DIN (DIN3) in this case extends to areas of sclerosing adenosis or perhaps arises in areas of sclerosing adenosis closely mimicking an infiltrative process.
- In addition to low-power examination, one should always make use of high-power magnification in order to identify myoepithelial cells and evaluate cytological details.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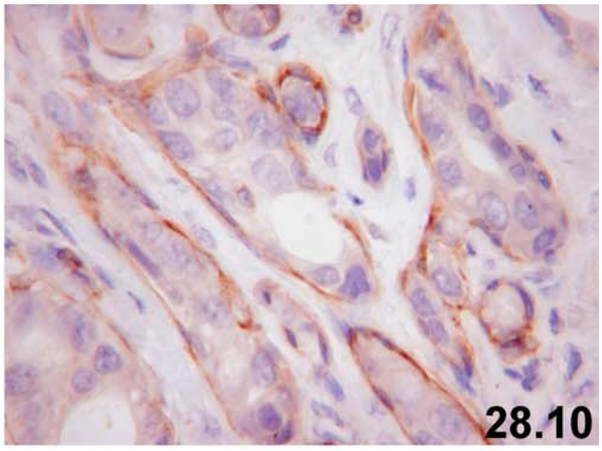
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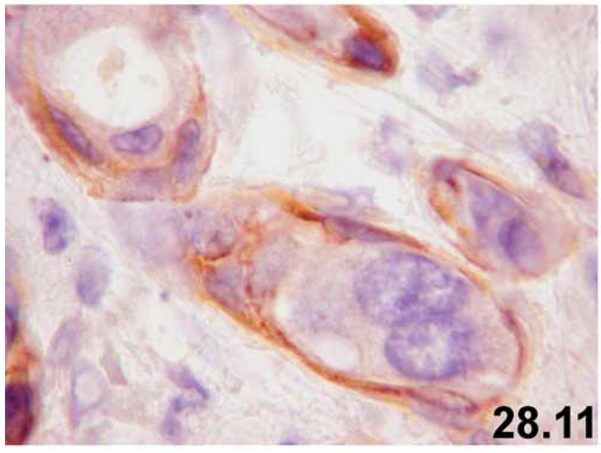
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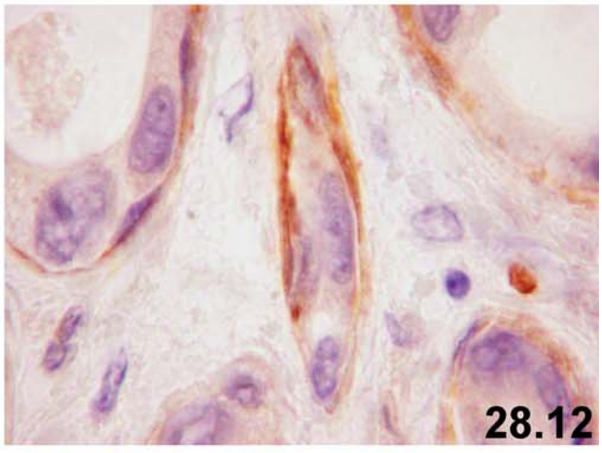
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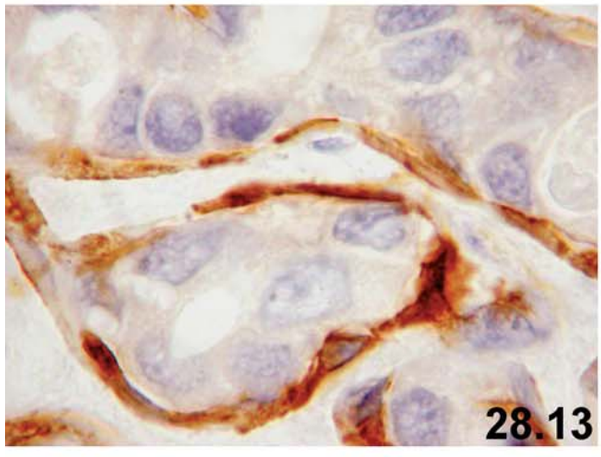
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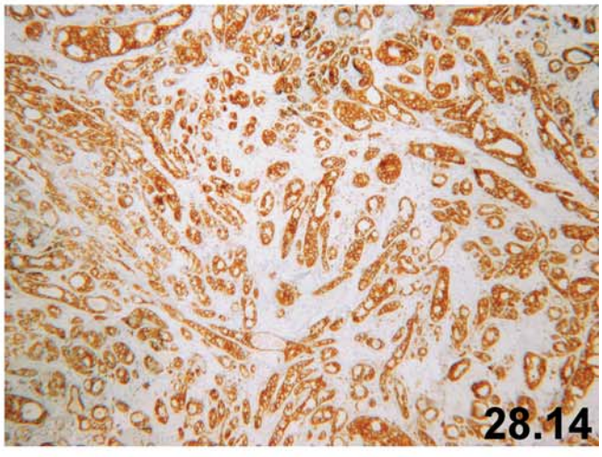
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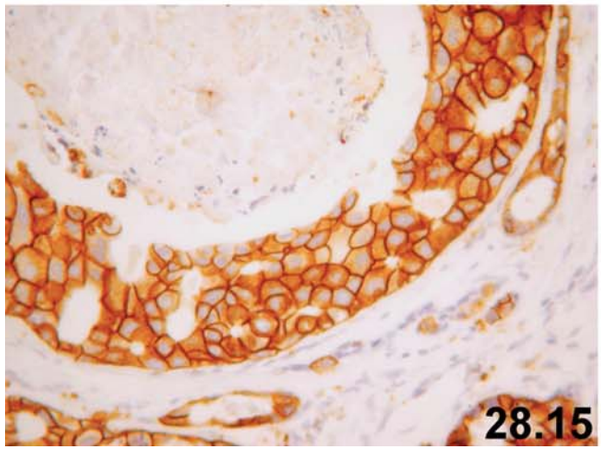
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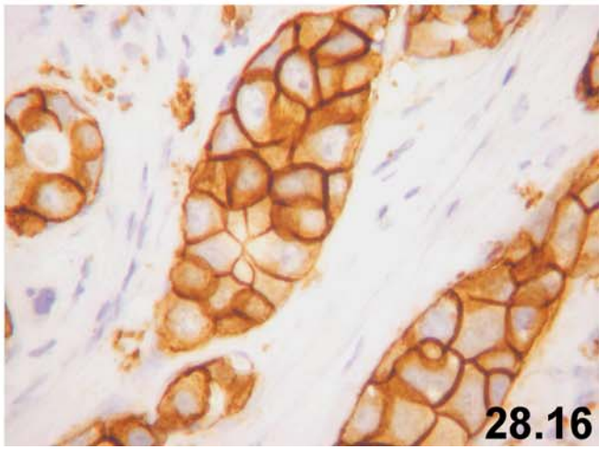

28.16

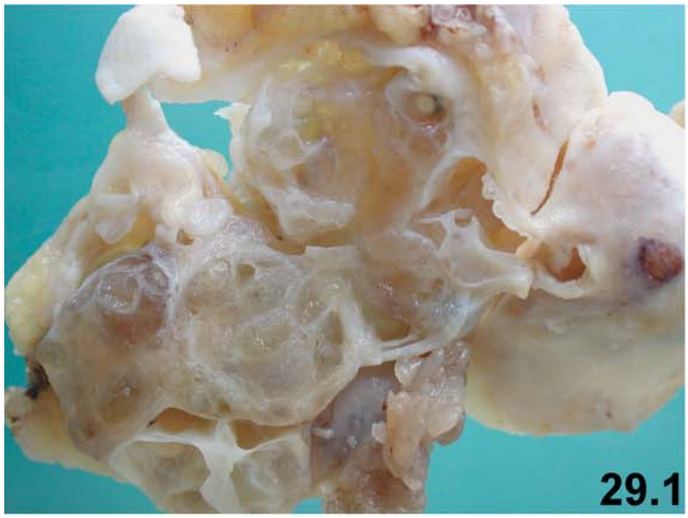
Fig. 29: Cystic-hypersecretory variant of ductal intraepithelial neoplasia (DIN, DCIS).

Case history: A 36-year-old woman presented with a palpable mass in the upper inner quadrant of her right breast. Ultrasonographic examination showed multiple cystic areas up to 3 cm in diameter.

Figs. 29.1 and **29.2:** Gross appearance of the lesion showing cysts containing thick yellow secretory material.

Figs. 29.3 and **29.4:** The lesion shows numerous cystically dilated ducts containing homogeneous, eosinophilic secretory material.

Figs. 29.5 and **29.6:** Deeply eosinophilic or colloid-like secretory material in the lumen of cystically dilated ducts. The overall appearance of the lesion closely resembles thyroid tissue.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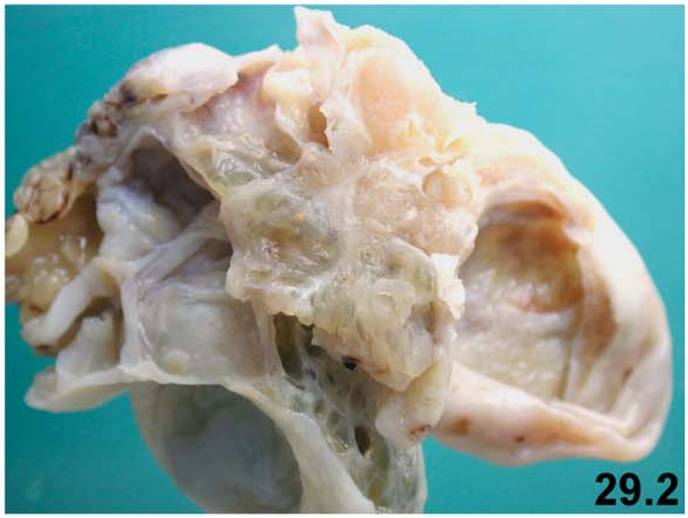
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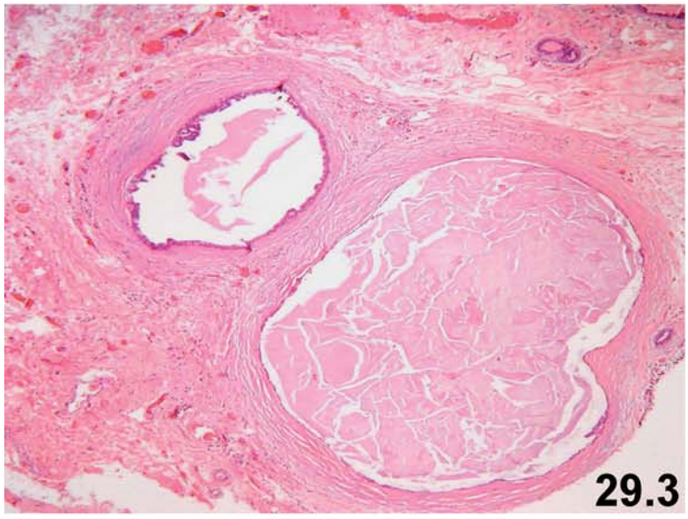
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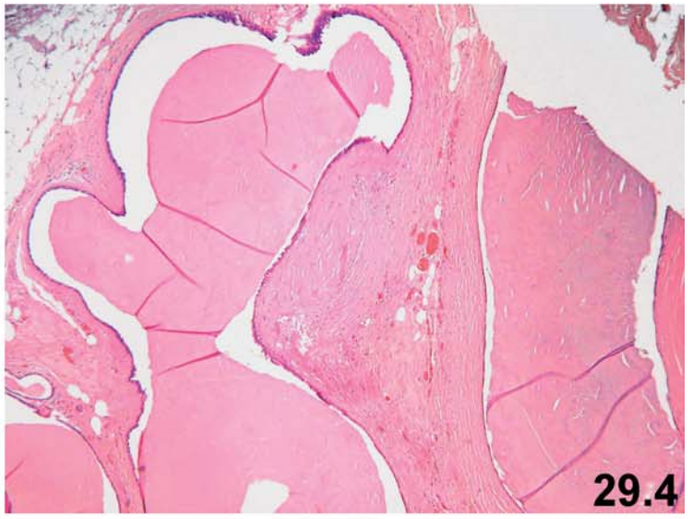
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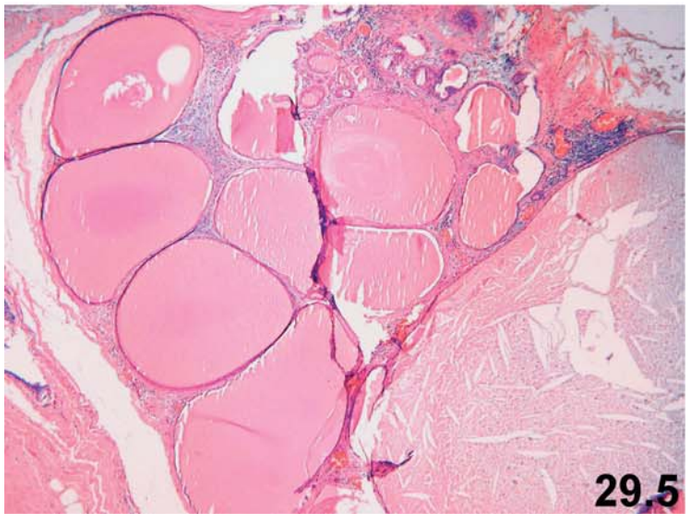
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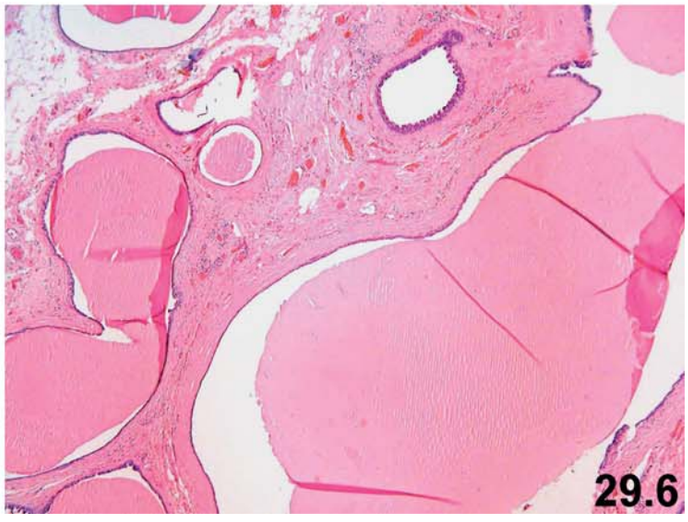

29.6

Fig. 29.7: A close examination of the cysts reveals that some are associated with intraepithelial proliferation.

Fig. 29.8: Higher magnification of Fig. 29.7, displaying epithelial proliferation with micropapillary growth pattern.

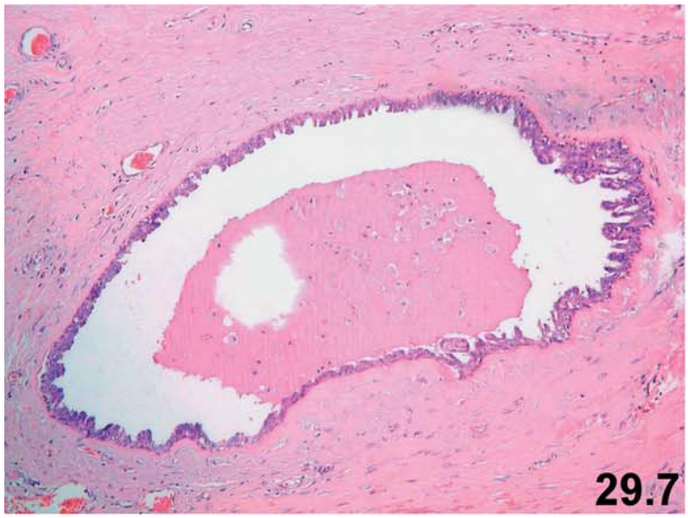
Figs. 29.9 and **29.10:** Another cystic area showing early cribriform structures at higher magnification. Note the cytological atypia and the monotony of the cell population.

Fig. 29.11: Some cysts are lined by few cell layers of mildly to moderately atypical epithelial cells. Note the irregularity of chromatin distribution.

Fig. 29.12: Rigid micropapillary structures consisting of a homogeneous cell population of atypical epithelial cells.

Fig. 29: Final remarks

- Cystic-hypersecretory variant of intraductal hyperplasia should be considered in the differential diagnosis in this case. The cell population in hyperplasia with cystic-hypersecretory features is always heterogeneous consisting of epithelial and modified myoepithelial cells. In contrast to hyperplasia, the proliferating epithelial cells in this case are homogenous and focally form cribriform or micropapillary structures. While the immunohistochemistry for CK5/6 is positive in hyperplasia, it is predominantly negative in DIN (DCIS), including its cystic-hypersecretory variant.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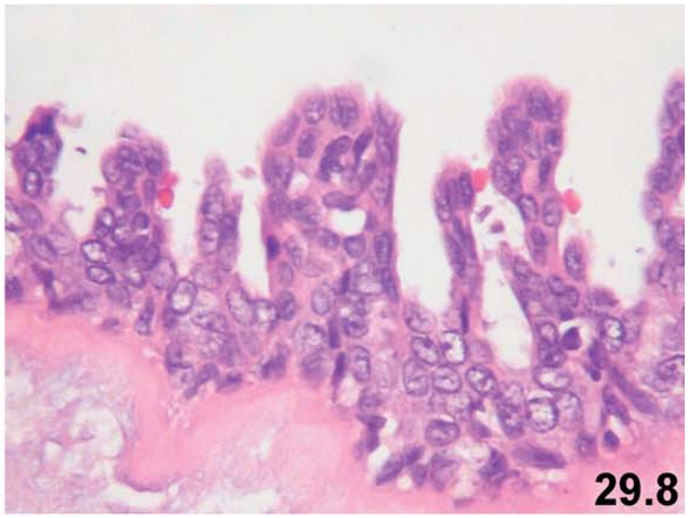
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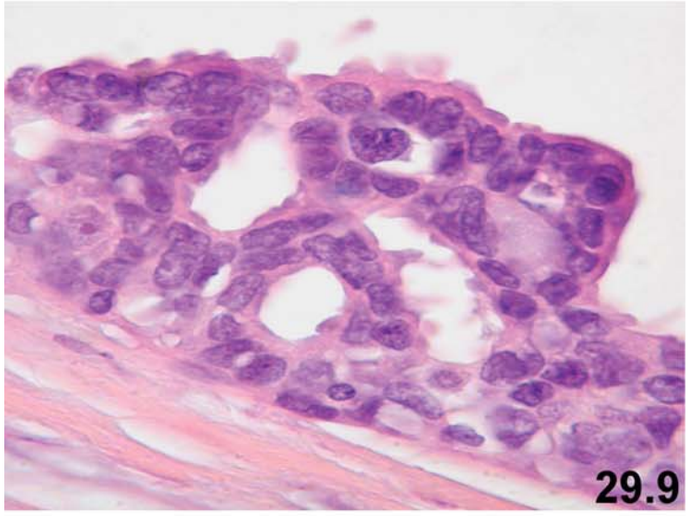
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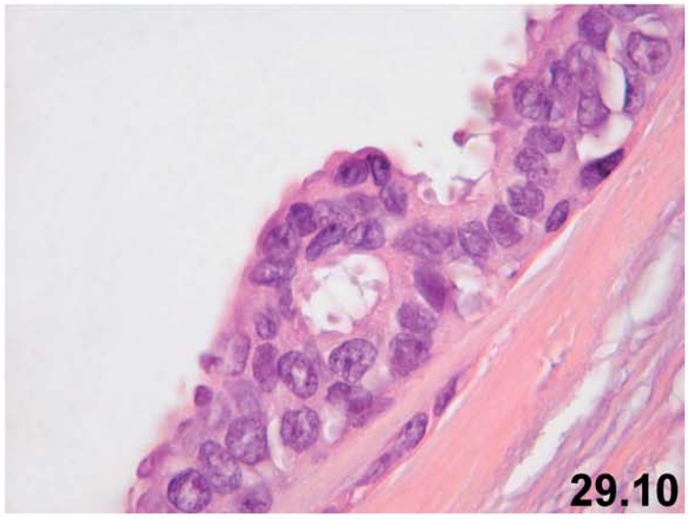
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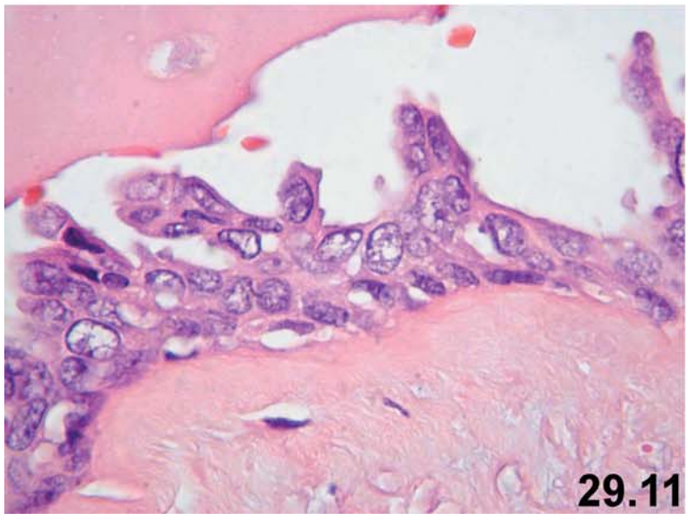
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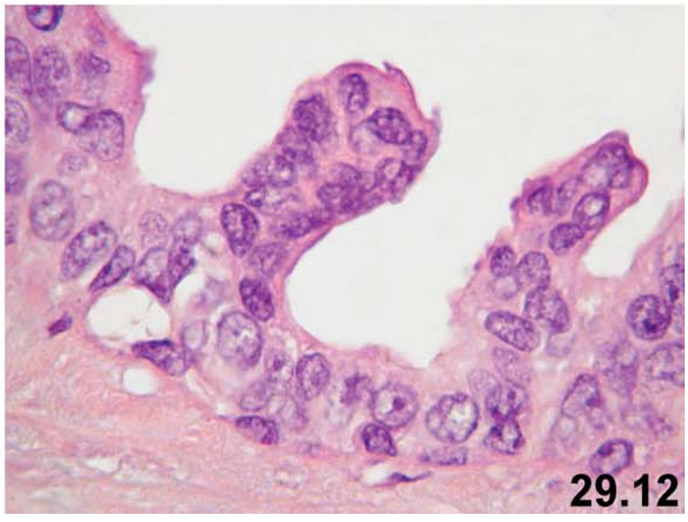
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Fig. 30: High-grade ductal intraepithelial neoplasia (DIN3, DCIS, G3) with signet-ring cells.

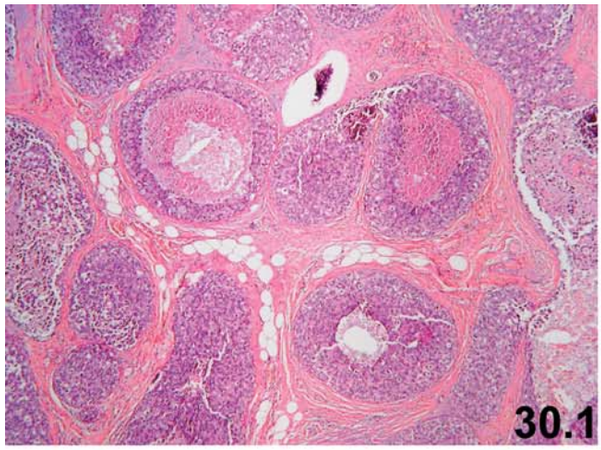
Case history: A 53-year-old woman had an abnormal mammogram of her left breast showing multiple clusters of suspicious microcalcifications. Core needle biopsy was done and showed several areas with high-grade DIN (DIN3 or DCIS, G3). An excisional biopsy was performed.

Figs. 30.1 and **30.2:** Several areas show solid intraepithelial proliferations associated with central necrosis and microcalcification.

Figs. 30.3 and **30.4:** Ductal intraepithelial neoplasia with solid growth pattern showing highly atypical cells associated with luminal cellular debris (apoptotic bodies).

Figs. 30.5, 30.6, and **30.7:** Several ducts display highly atypical and hyperchromatic, eccentric nuclei and abundant mucinous cytoplasm. These neoplastic cells fulfill the morphologic criteria for signet- ring cells. Special stains (PAS after diastase and alcian blue) were positive (not shown) in the signet-ring cell component of this high-grade DIN.

Fig. 30.8: Immunohistochemistry for HER2/neu shows a diffuse and 3+ reaction in the tumor cells with or without signet-ring cell differentiation.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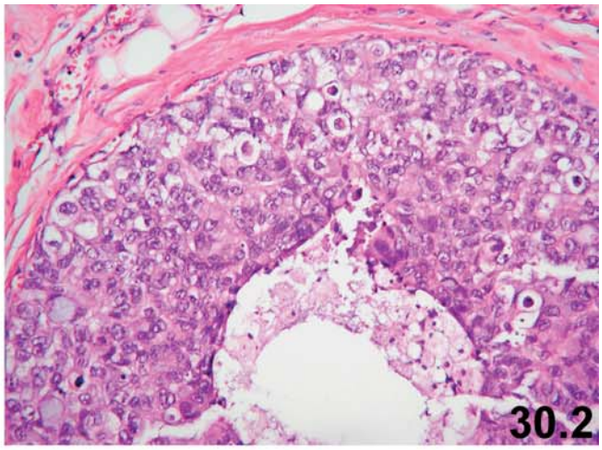
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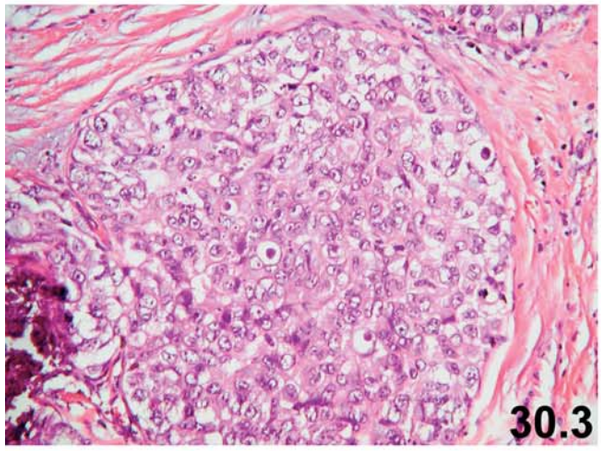
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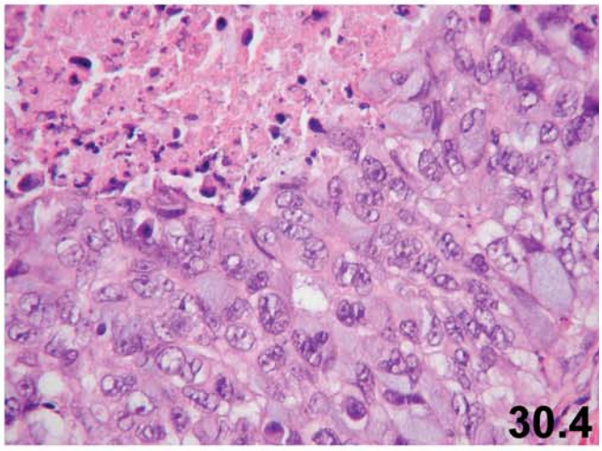
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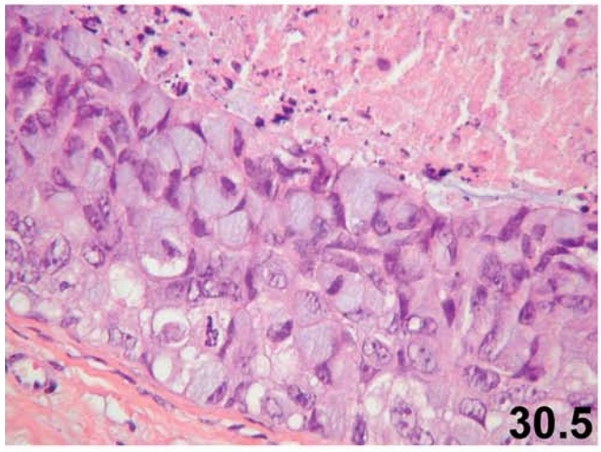
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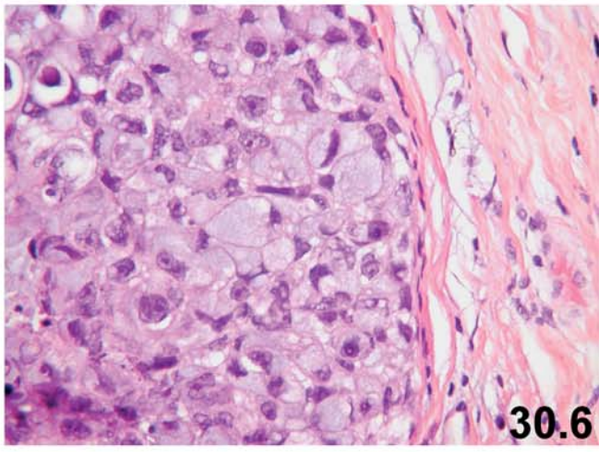
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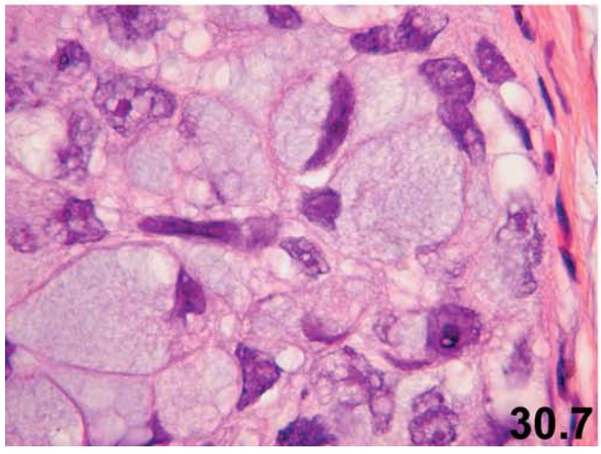
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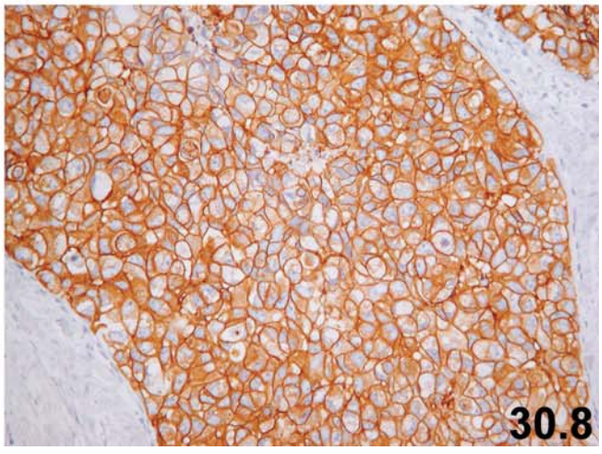
30.8

Intraductal Papillary Neoplasms

Contents

CHAPTER 6 Intraductal Papillary Neoplasms

6.1 Central Papilloma

Located in major ducts and the subareolar region.

6.1.1 Synonyms
Macroscopic papilloma, gross papilloma.

6.1.2 Macroscopy
May be grossly or only microscopically evident. Subareolar papilloma can cause cystic dilatation of the ducts (intracystic palpable tumor, 3–4 cm in diameter). Hemorrhage and necrosis may be present.

6.1.3 Microscopic Features (Figs. 31a and 31b)
- Epithelial fronds are supported by a fibrovascular stroma.
- Epithelial cells line the luminal aspect of the papillae, and a myoepithelial cell layer is invariably present between the epithelial cells and the basement membrane.
- Areas with apocrine metaplasia can be present.
- Solid and fenestrated epithelial hyperplasia, as well as stratification of the epithelial cells without cytologic atypia, can be present.
- Hemorrhagic infarction secondary to the torsion of some the fronds or the entire papilloma occurs occasionally.
- Squamous metaplasia is seen occasionally within papilloma, particularly in areas of infarction and around sites of needle core biopsy.
- Rarely, mucinous, clear cell, and sebaceous metaplasia can occur.
- Usually occurs as a solitary tumor. Rarely, it can be multiple.

Caution
- Central papilloma can be associated with florid intraductal hyperplasia (UDH). The proliferating cells may show large nuclei with increased nuclear-cytoplasmic (N/C) ratio and prominent nucleoli. In rare cases, papillomas associated with florid ductal hyperplasia may show central necrosis. These features should not be misinterpreted as atypia or carcinoma. The heterogeneity of proliferating cells (epithelial and modified myoepithelial cells) is a characteristic feature of usual ductal hyperplasia (UDH). If there is any doubt about the nature of the proliferating cells within the papilloma, immunohistochemistry with an antibody against high molecular weight cytokeratin (HMW-CK), such as CK5/6, needs to be performed [25].
- The diagnosis of papilloma in a core needle biopsy should lead to excisional biopsy of the breast lesion.
- Although the presence of myoepithelial cells is typical for papilloma, it does not invariably exclude the diagnosis of intraductal papillary carcinoma. The absence of a myoepithelial cell layer in a papillary neoplasm of the breast however, is highly indicative of an intraductal papillary carcinoma [3, 5, 12, 17, 22].
- Atypical intraductal papillomas (Fig. 35) are characterized by the presence of a focal atypical epithelial proliferation with low-grade nuclei (low-grade intraepithelial neoplasia). Such intraepithelial proliferations may be interpreted as either atypical intraductal hyperplasia or low-grade DCIS arising in the background of papillomas (Fig. 35). The significance of atypia within the papilloma is still not clear and is obscured by the frequent concurrent presence of atypia within the surrounding breast parenchyma [14]. It seems that if epithelial atypia is confined to the papilloma (no atypia in the surrounding breast tissue), the risk of subsequent invasive carcinoma is similar to that of non-atypical papilloma [14].

6.2 Peripheral Papilloma

6.2.1 Synonyms
Microscopic papilloma, multiple peripheral papillomas (papillomatosis).

6.2.2 Macroscopy
Often grossly normal cut surface. Occasionally, fine granular cut surface.

6.2.3 Microscopic Features (Figs. 32, 33)
- Multiple intraductal papillary projections within the terminal duct-lobular units (TDLUs) are present that show two cell layers of epithelial and myoepithelial cells.
- Can be associated with UDH: proliferation of a heterogeneous cell population with divergent cell differentiations (epithelial, modified myoepithelial cells with or without apocrine metaplasia), irregular secondary lumens, streaming pattern, and lack of rigid intraluminal bridges.
- Can be associated with ductal intraepithelial neoplasia (DIN; atypical ductal hyperplasia [ADH] or ductal carcinoma in situ [DCIS]).
- Can be very complex, associated with sclerosing adenosis with pseudoinfiltrating pattern.

Caution

- A peripheral papilloma with stromal sclerosis may simulate an invasive breast carcinoma, microscopically.

6.3 Sclerosing Papilloma

6.3.1 Definition

A variant of papilloma (central or peripheral type) with extensive stromal sclerosis, leading to prominent areas of hyalinization, distortion, and pseudoinvasive patterns [8].

6.3.2 Microscopic Features (Figs. 33 and 34)

- At low magnification, the papillary and intraductal nature is readily identified.
- Sometimes a stellate pattern of central fibrosis occurs, simulating a radial scar.
- The sclerotic areas usually displays distorted, entrapped tubules, mimicking an infiltrating carcinoma.
- At higher magnification, a layer of myoepithelial cells (even attenuated) is present within the papillary projections and the entrapped and distorted glands.
- In some planes of the section, the lesion may occasionally appear as solid intraductal proliferations (solid variant of intraductal papilloma). Deeper levels, however, often reveal a few papillary processes.
- Sclerosing papilloma can be associated with sclerosing adenosis. In fact, some papillomas reflect extension of sclerosing adenosis into the duct lumen (invagination of sclerosing adenosis into the duct wall).

Caution

- This lesion can easily be mistaken for infiltrating ductal carcinoma, particularly in core needle biopsies and frozen sections. As a rule, a definite diagnosis of papillary neoplasms of the breast should not be made based on frozen sections.
- Sclerosing papilloma with pseudoinfiltrative growth pattern can easily be misinterpreted as invasive carcinoma. In a difficult case of sclerosing papilloma, immunohistochemistry for myoepithelial cells (SM actin, p63, CD10, etc.) can be very helpful.

6.3.3 Further Reading

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6.4 Intraductal Papillary Carcinoma (Papillary Ductal Intraepithelial Neoplasia)

6.4.1 Synonyms

Noninvasive papillary carcinoma, papillary DCIS.

6.4.2 Macroscopy

A solid or intracystic well-circumscribed tumor with or without necrosis. Occasionally, the cut surface is fine granular.

6.4.3 Microscopic Features (Figs. 36 and 37)

- The hallmark of intraductal papillary carcinoma is the absence of a myoepithelial cell layer in the papillary processes proliferating into the distended duct lumen.
- The proliferating luminal cells are usually monotonous (homogeneous cell population), often with mild to moderate nuclear atypia.
- Intraluminal solid and/or cribriform patterns are often present.
- Sometimes a spindle cell-stratified pattern of atypical epithelial cells without significant intraluminal proliferation is identified.
- Mostly mild to moderate cytologic atypia is present, displaying hyperchromatic enlarged nuclei with a higher N/C ratio. Rarely, high-grade nuclear atypia can be present.

Caution

- Although the absence of a myoepithelial cell layer in the papillary projections is one of the most important diagnostic features of papillary carcinoma, the focal presence of myoepithelial cells does not exclude the possibility of carcinoma! More attention should be paid to the proliferating cell population: homogeneous versus heterogeneous cells [12]. (See Table 6.1.)
- Areas of focal or diffuse stromal fibrosis can be present, mimicking an invasive carcinoma. One needs to be extremely cautious not to call the lesion "invasive" if there is no clear-cut area with malignant glands infiltrating into the surrounding breast tissue [3, 12].
- Displacement of epithelium related to a preoperative core needle biopsy may occur (particularly in intracystic papillary carcinoma), causing diagnostic difficulty [7, 12].
- A variant of intraductal papillary carcinoma may show two or three different epithelial cell types closely resembling ductal hyperplasia within the papilloma. The neoplastic epithelial cells may be of spindle or mucinous type, and they often reveal fine eosinophilic cytoplasmic granules. This variant is often of neuroendocrine differentiation (focal positive immunoreaction for synaptophysin or chromogranin) [13]. It is important to keep in mind that the neoplastic cells in this variant are all of epithelial cell type without a modified myoepithelial cell component. In contrast to ductal hyperplasia, HMW-CK (such as CK5/6) is typically negative in the proliferating cells of this variant of intraductal papillary carcinoma.

6.5 Role of Immunohistochemistry in Diagnosing Intraductal Papillary Neoplasms

Myoepithelial cells can be decorated with antibodies against smooth muscle actin (SM actin), muscle-specific actin (HHF35), smooth muscle myosin (SM myosin, heavy chain), calponin, p63, CD10, etc. Usually one antibody (SM actin) is sufficient [6, 12, 16].

Caution

- Blood vessels (and occasionally fibroblasts/myofibroblasts) within the papillary structures are positive for SM actin (but not for p63). These cells could be misinterpreted as myoepithelial cells.

In complex cases with severe intraluminal proliferations associated with intraductal papillary neoplasms, immunohistochemical examination with antibody against HMW-CK (CK5/6 or CK34BE12) can be extremely helpful:

- HMW-CK (such as CK5/6) is intensely positive in florid ductal hyperplasia. In contrast, HMW-CK is completely or predominantly negative in intraductal papillary carcinoma. In areas with ADH or small areas of DCIS arising in the papilloma , the neoplastic epithelial cells are negative for HMW-CK.

6.6 Additional Comments

Frozen section: If the macroscopic examination reveals a tumor (solid or cystic) with "papillary" projections, frozen section should be refused (wait for final sections after formalin fixation). *If the frozen section of a lesion shows a papillary neoplasm, a definite intraoperative histologic diagnosis should not be made; one must wait for final sections in order to make the distinction between papilloma and intraductal papillary carcinoma.* Particularly complex papilloma associated with florid intraductal

Table 6.1. Morphologic differences between papilloma and intraductal papillary carcinoma

Papilloma	Papillary carcinoma
Papillary structures with two cell types of epithelial and myoepithelial cells; heterogeneous cell population	No myoepithelial cells; only a homogeneous cell population
Pleomorphism of divergent differentiation	Monotonous appearance; in rare cases, pleomorphism of anaplasia
Apocrine metaplasia frequent	Apocrine metaplasia absent
Nuclei often normochromatic	Nuclei hyperchromatic
Spindle cell bridging, streaming pattern, fragile bridges, irregular secondary lumens by usual ductal hyperplasia	Rigid ("roman") bridges or arcades, cribriform pattern by ductal carcinoma in situ

hyperplasia with or without pseudoinvasion can be misinterpreted as carcinoma. In that setting, the freezing artifacts often cause serious diagnostic problems!

Intracystic papilloma and intracystic papillary carcinoma: A solitary large (macroscopic) papilloma usually dilates the involved duct. The designation of "intracystic" should be reserved only for lesions that are associated with macroscopically cystic duct dilatation [3, 12].

Atypical papilloma and carcinoma in situ arising in papilloma (Fig. 35): Intraductal papilloma (central or peripheral type) can be associated with ADH or DCIS. If the areas with atypia are focal (usually less than one-third of papilloma), the designation of atypical papilloma would be appropriate (synonym: papilloma associated with ADH). By extensive involvement (more than one-third) of a papilloma by DCIS, the designation of DCIS arising in a papilloma has been used. The experiences at the Armed Forces Institute of Pathology, however, have shown that the prognosis of atypical papilloma and DCIS arising in a papilloma is the same. Therefore, all of these neoplasms could be considered and designated as atypical papilloma [12]. Indeed, the best designation for such papillary neoplasms that show atypical intraductal proliferations would be (low-grade) papillary ductal intraepithelial neoplasia.

Solitary atypical papilloma and intraductal papillary carcinoma (central type) do have an excellent prognosis (even lesions associated with high-grade nuclear atypia). One should pay attention to the margin: If the margin is clearly negative for tumor, no further treatment is needed. Follow-up of patients with central intraductal papillary carcinoma is advised [12]. In contrast, the peripheral type of papilloma associated with ADH or DCIS has a significant increased risk for subsequent development of infiltrating carcinoma (less favorable prognosis than that of central papillary neoplasms) [12]. These kinds of lesions are more often associated with DCIS or even invasive carcinoma in surrounding breast tissues. Therefore, in cases with peripheral papilloma associated with intraductal proliferations, one has to be more careful and review serial sections to exclude the possibility of ADH or DCIS within and outside of the papillary neoplasms. If the margin is close or positive, reexcision should be performed.

One should not misinterpret and overcall the pleomorphism of divergent differentiation in a papillary neoplasm. It is well known that the benign papilloma is frequently more pleomorphic in appearance than its malignant counterpart. As stated by Azzopardi, the pleomorphism of the papilloma is the pleomorphism of divergent cell differentiation, including epithelial and myoepithelial (and often apocrine) cell types (a heterogeneous cell population). In contrast, the intraductal papillary carcinoma usually has a monotonous appearance consisting of a homogeneous cell population (one cell type, only epithelial cells without a myoepithelial component). In rare examples of high-grade intraductal papillary carcinoma, the pleomorphism is present. This is, however, the pleomorphism of anaplasia (highly atypical or pleomorphic epithelial cells lacking a myoepithelial cell component) [1–4, 12].

Very rare variants of intraductal papillary carcinoma of the breast, such as transitional cell carcinoma and primary papillary tumor resembling the tall cell variant of papillary thyroid carcinoma, have been described [9, 15].

Using the DIN concept, an alternative designation for intraductal papillary carcinoma or papillary DCIS would be papillary ductal intraepithelial neoplasia (papillary DIN) to avoid the alarming term of "cancer" for this type of noninvasive neoplastic breast proliferation.

6.7 Further Reading

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Fig. 31a: Central intraductal papilloma.

Case history: A 48-year-old woman presented with a history of recurrent left nipple discharge. Mammography showed a well-circumscribed lesion with a diameter of 1.5 cm. Excisional biopsy was performed.

Fig. 31a.1: At low magnification, a dilated duct with a papillary neoplasm is present.

Fig. 31a.2: Irregularly dilated duct showing a papillary neoplasm associated with apocrine metaplasia.

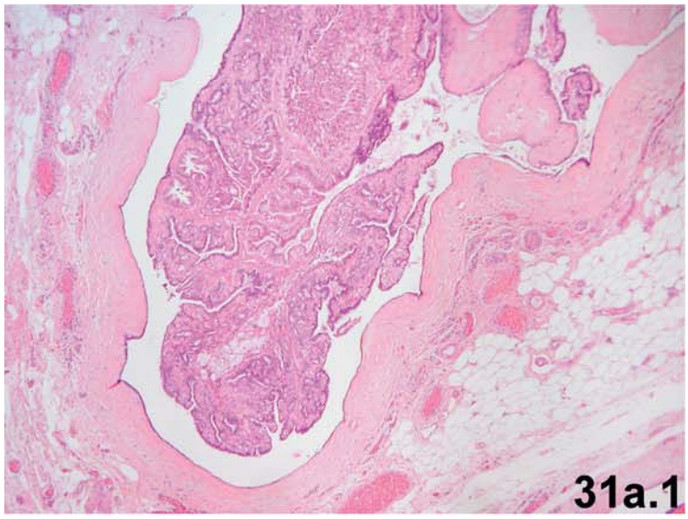
Fig. 31a.3 and **31a.4:** The papillary projections are lined by two cell types: luminal epithelial cells and basally located myoepithelial cells. The myoepithelial cells are hypertrophic and show abundant cytoplasm.

Fig. 31a.5: In some areas of the tumor, multiple layers of myoepithelial cells can be seen. Some of the basally located myoepithelial cells may show enlarged vesicular nuclei.

Fig. 31a.6: In addition to epithelial and myoepithelial cells, several areas of the lesion display apocrine metaplasia.

Fig. 31a: Final remarks

- The hallmark of intraductal papilloma is the presence of epithelial and myoepithelial cells within the papillary projections. Apocrine metaplasia is frequently present in papillomas. The presence of different cell types composed of epithelial, myoepithelial, and apocrine metaplastic cells has been regarded as pleomorphism of divergent cell population (Azzopardi). Pleomorphism of divergent cell population within benign papilloma should not be confused with pleomorphism of anaplasia (pleomorphic epithelial cells without myoepithelial cell component), which is a hallmark of high-grade neoplastic proliferation.
- Central intraductal papilloma not infrequently causes duct ectasia and nipple discharge.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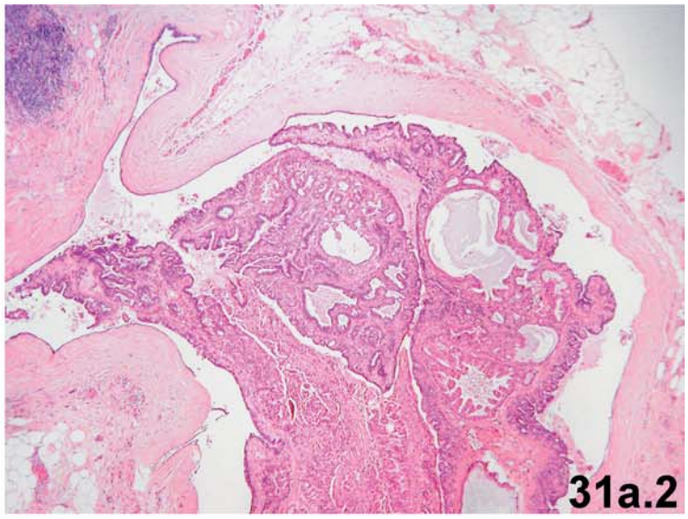
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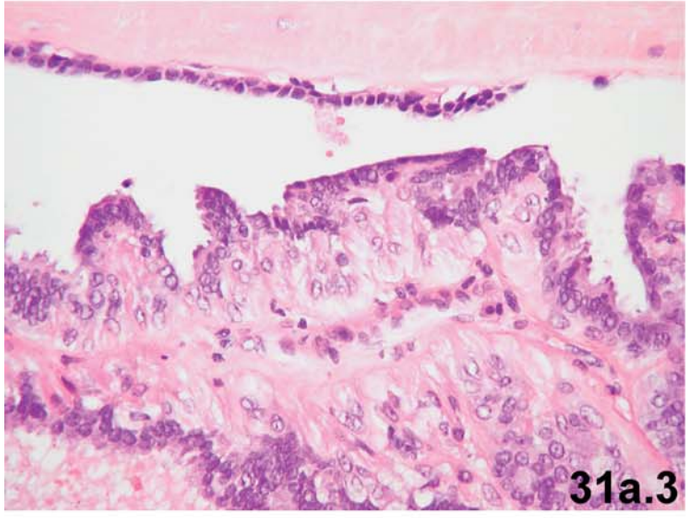
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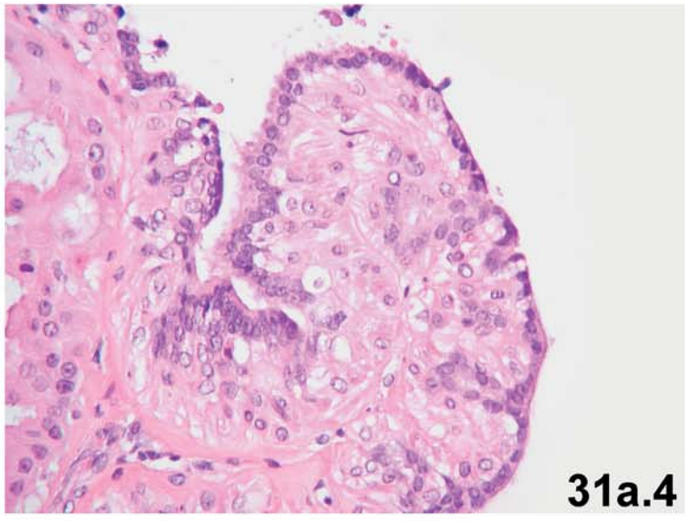
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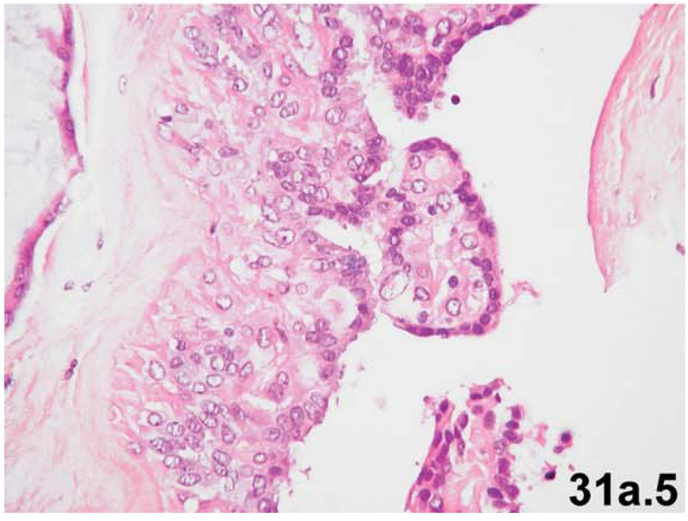
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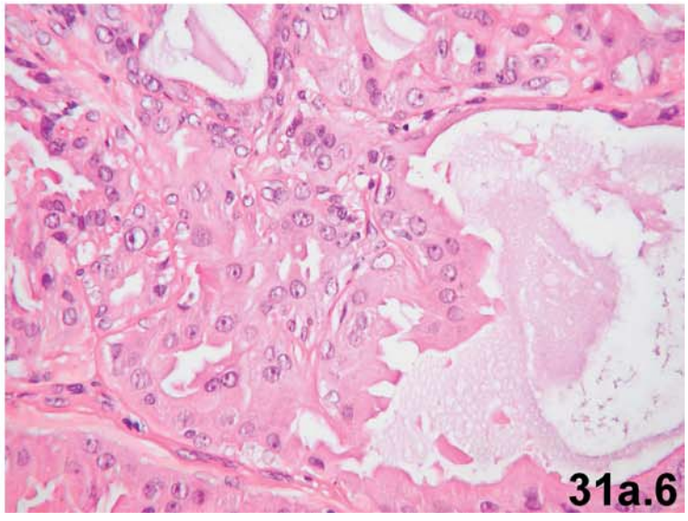

31a.6

Fig. 31b: Central intraductal papilloma associated with usual ductal hyperplasia and focal areas of necrosis.

Case history: A 36-year-old woman presented with a firm, centrally located, well-circumscribed tumor in her right breast.

Fig. 31b.1: Low magnification of the lesion shows a well-circumscribed papillary tumor with several fibrovascular cores.

Fig. 31b.2: Several intraepithelial proliferative areas are present within the papillary structures. The intraepithelial proliferations show irregular or slit-like secondary lumens.

Fig. 31b.3: Papillary structure showing basally located myoepithelial cells.

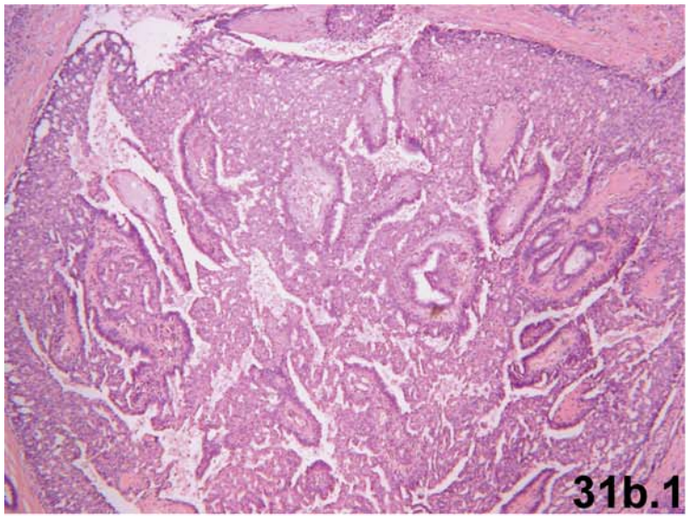
Fig. 31b.4: A solid proliferative area displaying a heterogeneous cell population of epithelial cells with rounded vesicular nuclei and modified myoepithelial cells with bipolar or spindle-shaped nuclei.

Fig. 31b.5: One area of the tumor shows luminal necrosis.

Fig. 31b.6: Usual ductal hyperplasia within the papilloma showing a streaming pattern. The cell population in Figs. 31b.5 and 31b.6 is clearly of the hyperplastic type.

Fig. 31b: Final remarks

- Intraductal papilloma, particularly the central type, can rarely be associated with luminal necrosis. One has to keep in mind that the presence of necrosis in papilloma or usual ductal hyperplasia by no means indicates malignancy.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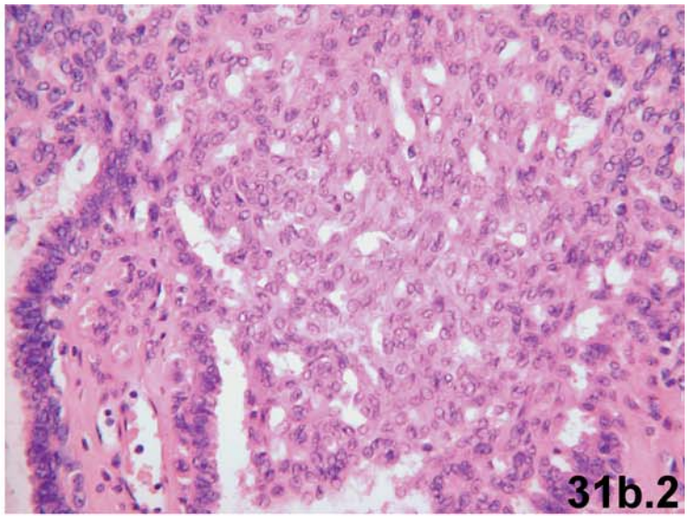
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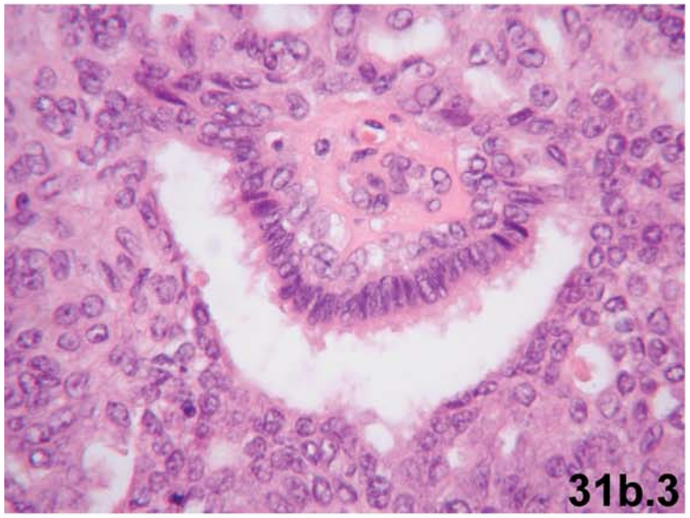
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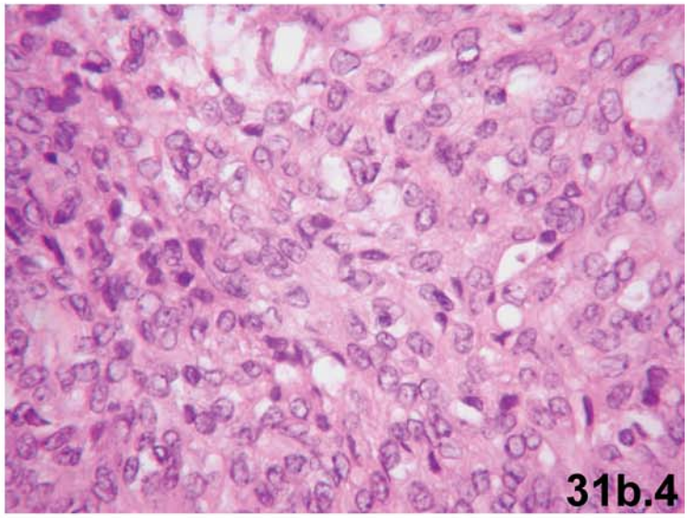
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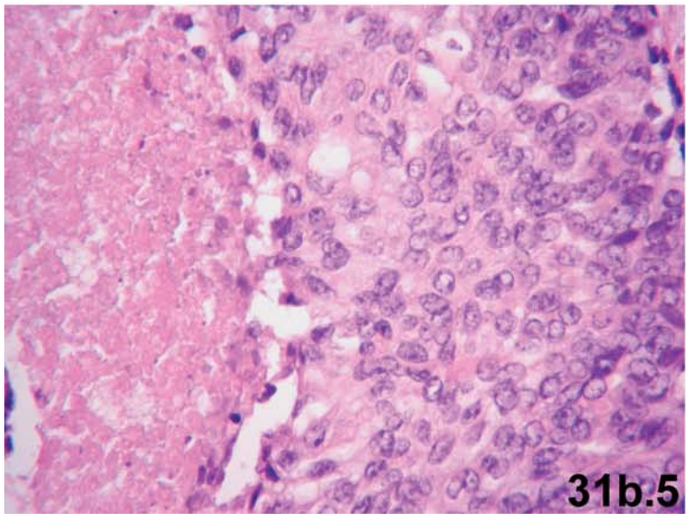
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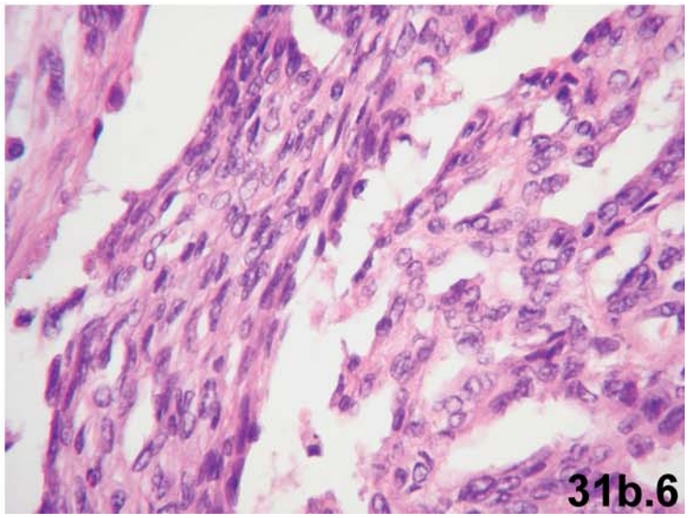

31b.6

Fig. 32: Multiple peripheral papillomas associated with usual ductal hyperplasia.

Case history: A 27-year-old woman presented with irregular areas identified in the mammogram of her left breast. There was no palpable breast tumor.

Figs. 32.1, 32.2: Low magnification shows several papillary proliferations associated with a marked intraepithelial proliferation.

Figs. 32.3 and **32.4:** Multiple areas of intraductal papillary proliferation combined with usual ductal hyperplasia showing slit-like secondary lumens.

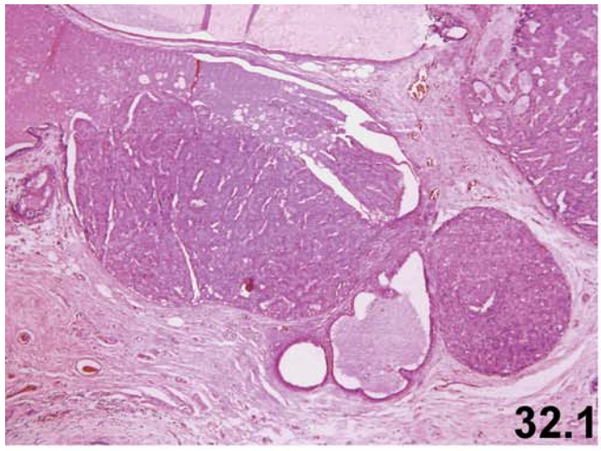
Figs. 32.5 and **32.6:** Areas of papillomas show a heterogeneous cell population of epithelial and apocrine metaplastic cells. These areas represent pleomorphism of divergent cell population, which is characteristic of benign papillomas.

Figs. 32.7: Immunohistochemistry for high molecular weight cytokeratin (CK5/6) shows a heterogeneous reaction of the proliferating cells within the papillomas.

Fig. 32.8: Immunohistochemistry for smooth muscle actin decorates a continuous cell layer of myoepithelial cells within the papillary structures.

Fig. 32: Final remarks

- The proliferating cells of usual ductal hyperplasia within papillomas may show enlarged nuclei, prominent nuclei, and increased mitotic activity. In the presence of a heterogeneous cell population, these features should not mislead to a diagnosis of atypical hyperplasia or atypical papilloma.
- Immunohistochemistry for high molecular weight cytokeratin (CK5/6, CK14, or CK34BE12) is often helpful for confirming the hyperplastic nature of the proliferating cells within a papilloma.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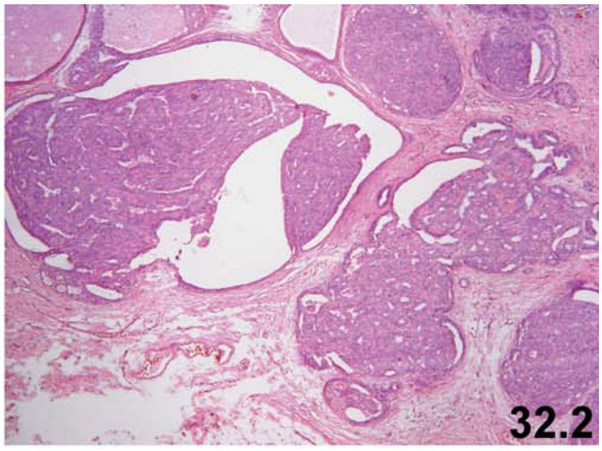
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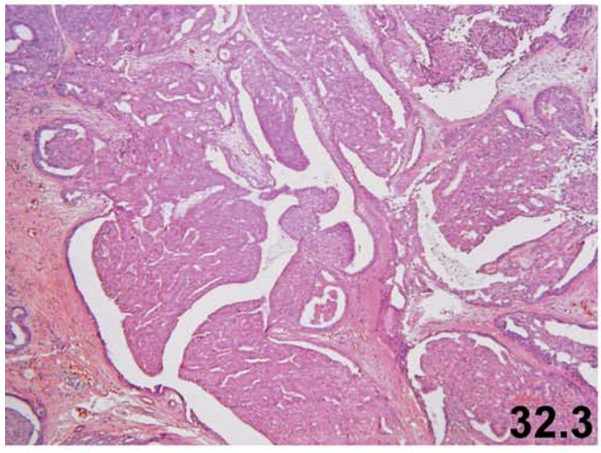
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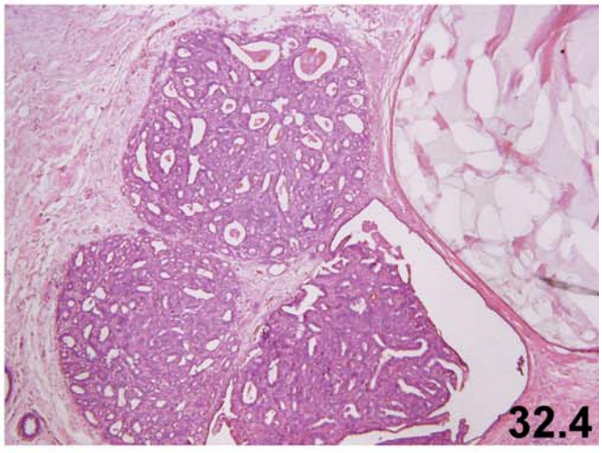
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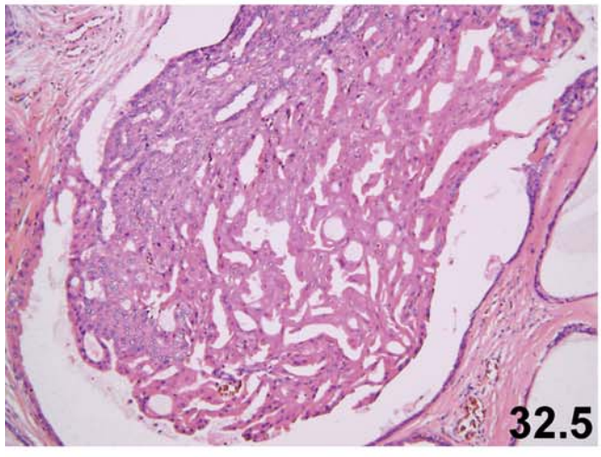
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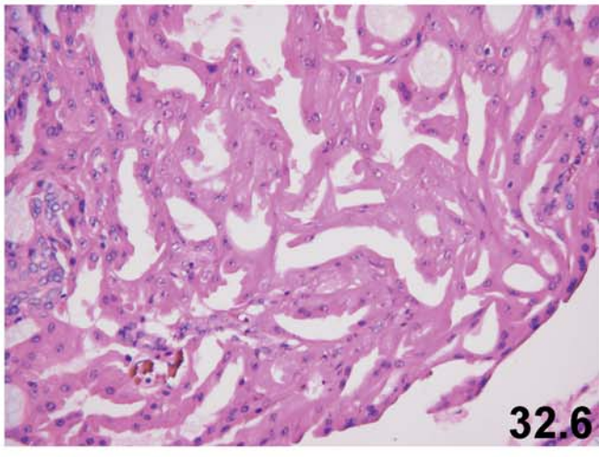
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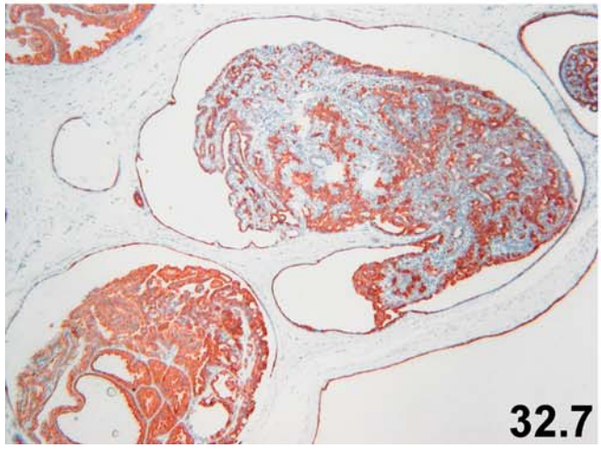
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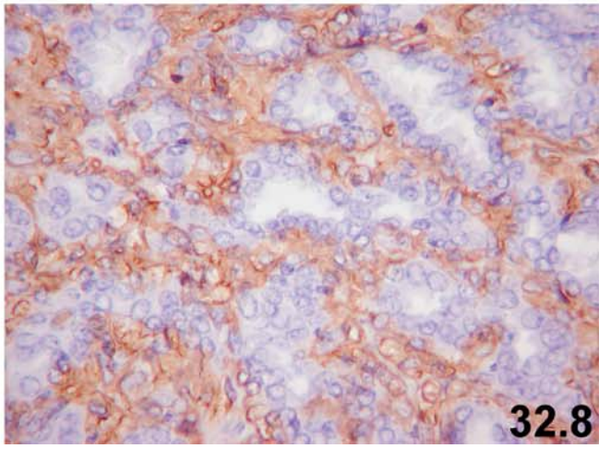
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Fig. 33: Juvenile papillomatosis with pseudoinvasion.

Case history: A 22-year-old woman presented with multiple small nodular or irregular areas in the mammogram of her left breast. Core needle biopsy revealed usual ductal hyperplasia and some irregular glands with an infiltrative growth pattern. Excisional biopsy of the lesion was performed.

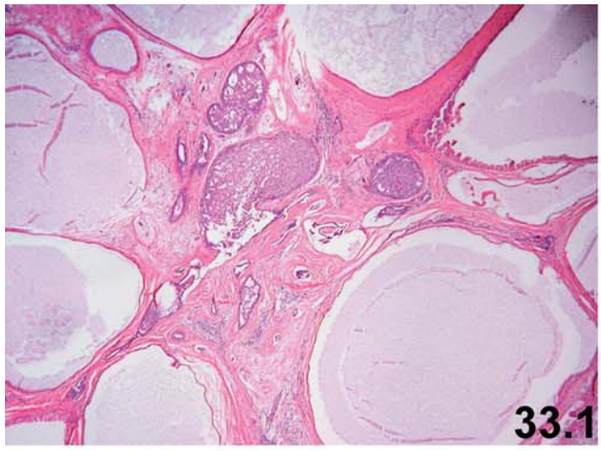
Figs. 33.1 and **33.2:** At low magnification, multiple cysts and several areas with marked intraductal proliferation are present.

Fig. 33.3: Multiple cysts are lined by apocrine metaplastic cells.

Fig. 33.4: Ducts with intraepithelial proliferation and some areas with apocrine metaplasia (apocrine hyperplasia) are present.

Figs. 33.5 and **33.6:** Intraductal hyperplasia showing typical irregular and slit-like secondary lumens.

Figs. 33.7 and **33.8:** Some areas of the lesion display glands or elongated tubules with distorted irregular configurations simulating an infiltrating carcinoma.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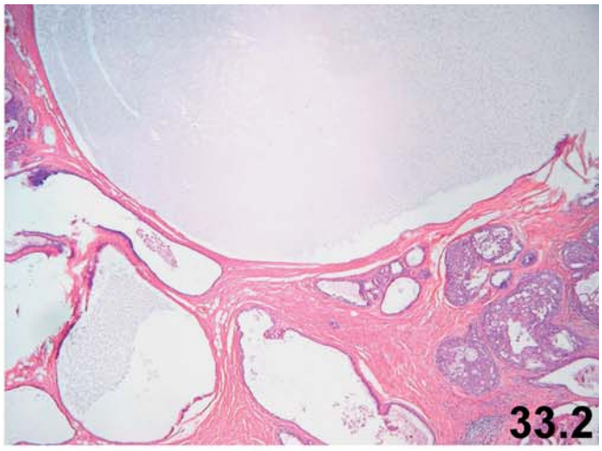
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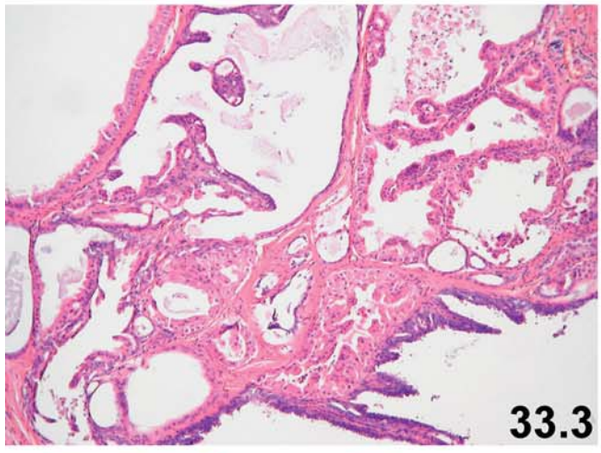
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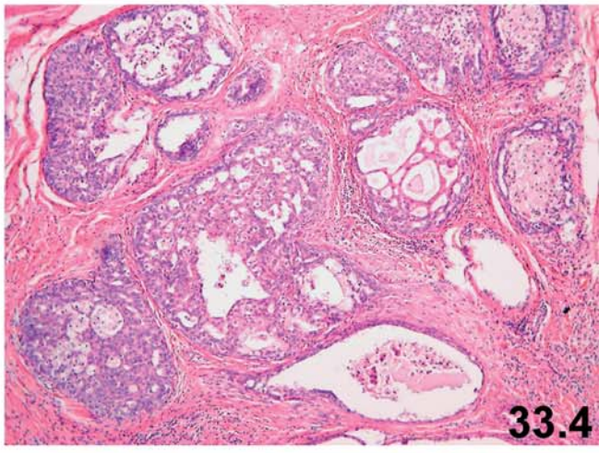
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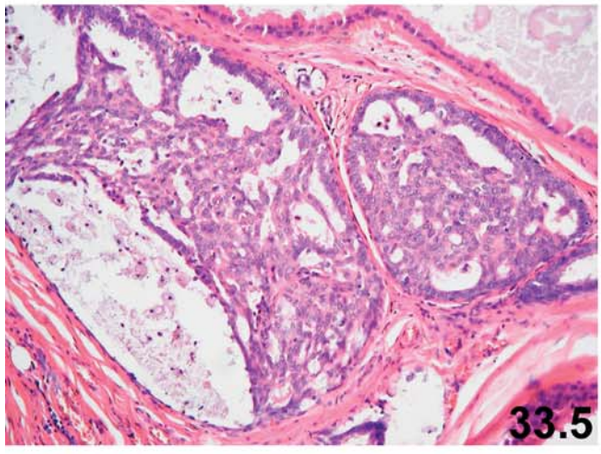
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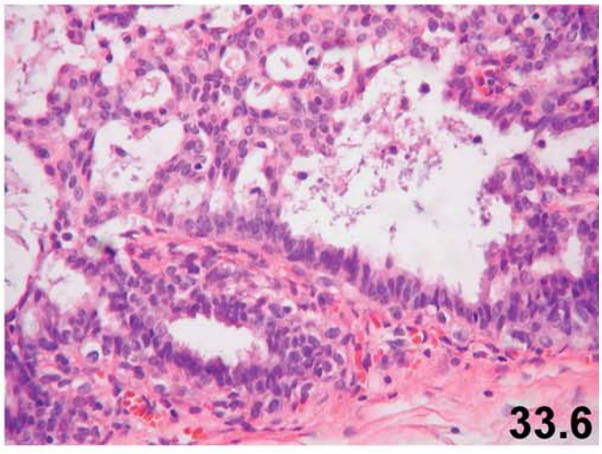
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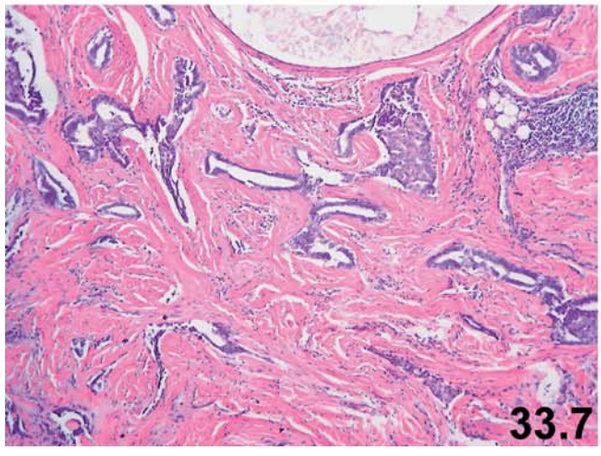
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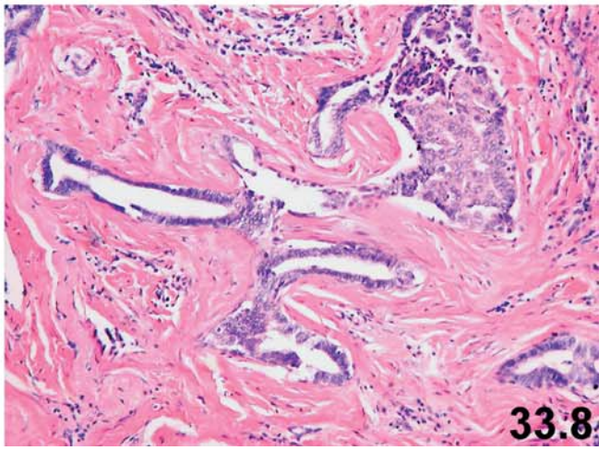
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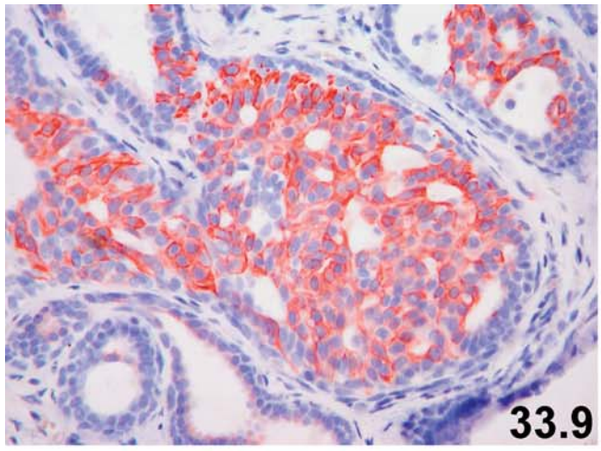
Figs. 33.9 and **33.10:** Immunohistochemistry for CK5/6 displays a positive reaction, which is typical for usual ductal hyperplasia.

Figs. 33.11 and **33.12:** Immunohistochemistry for smooth muscle actin shows a discontinuous layer of myoepithelial cells.

Figs. 33.13 and **33.14:** Immunohistochemistry for smooth muscle actin reveals a myoepithelial cell layer within the glands with seemingly infiltrating pattern.

Figs. 33.15 and **33.16:** Some areas of usual ductal hyperplasia within the papillomas showing enlarged nuclei with increased nuclear-cytoplasmic ratio. The cell population of proliferating cells is, however, heterogeneous, consisting of epithelial cells with round nuclei and modified myoepithelial cells (progenitor cells) with bipolar or spindle-shaped nuclei.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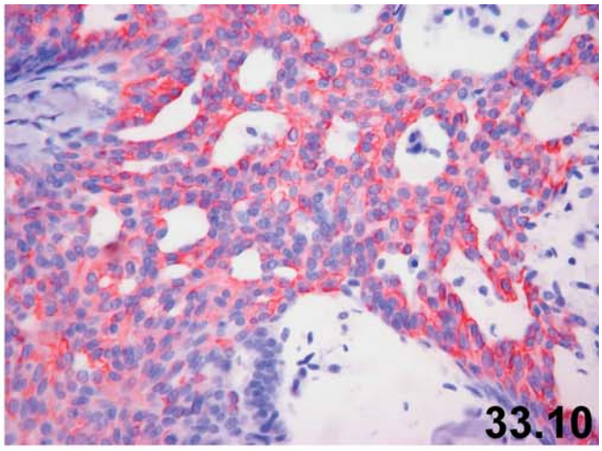
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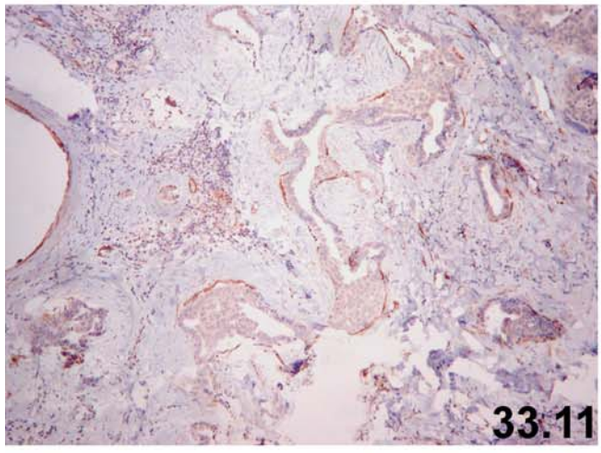
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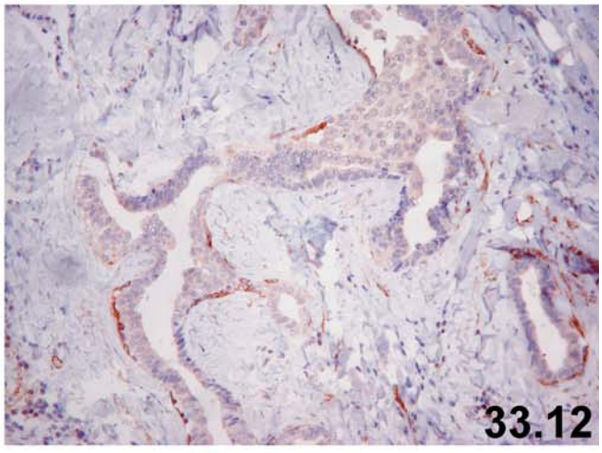
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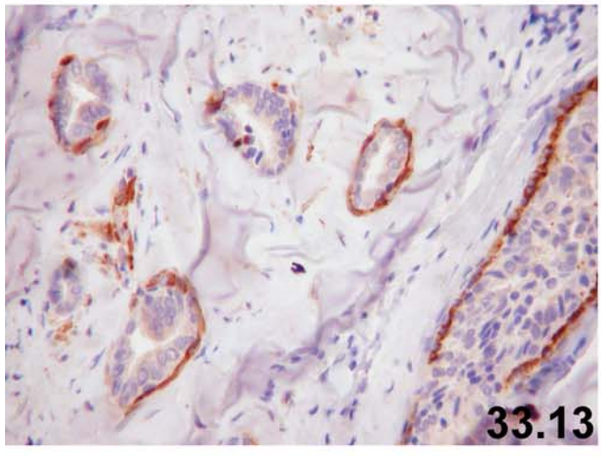
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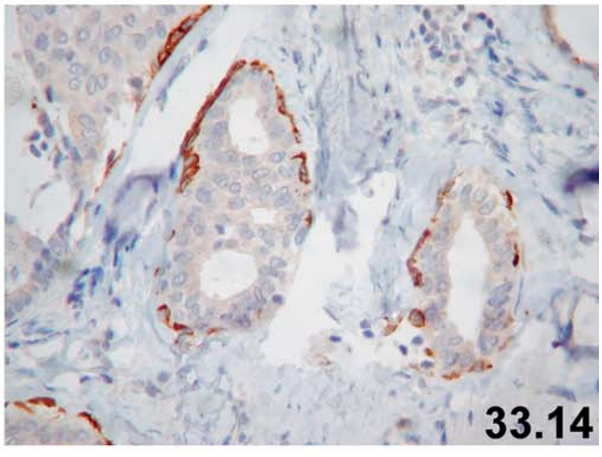
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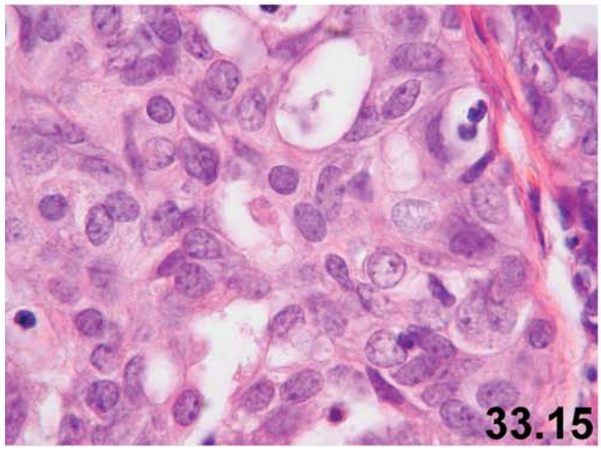
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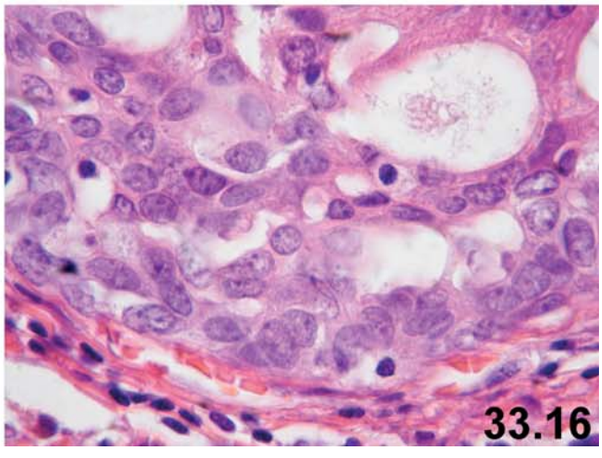
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Fig. 34: Intraductal papilloma associated with prominent myoepithelial hyperplasia and pseudoinvasion.

Case history: A 60-year-old woman presented with a centrally located palpable tumor in her left breast. The tumor was hard and measured 2.5 cm in maximum diameter. The excisional biopsy showed a predominantly well-circumscribed, greyish-white solid tumor with focally irregular borders.

Fig. 34.1: At low magnification, a papillary neoplasm is present. The tumor shows several fibrovascular cores and marked intraepithelial proliferation.

Fig. 34.2: Some areas of the papillary tumor display irregular tubular and solid structures closely mimicking an infiltrating ductal carcinoma. Note the sclerotic stromal change.

Fig. 34.3: Another area of the tumor exhibits an infiltrating growth pattern associated with sclerotic stroma.

Fig. 34.4: A central part of the tumor, showing solid and papillary structures. Note the prominent myoepithelial cell component of the tumor showing numerous bipolar or spindle-shaped dark nuclei.

Fig. 34.5: A heterogeneous cell population of epithelial and myoepithelial cells is recognizable in solid areas.

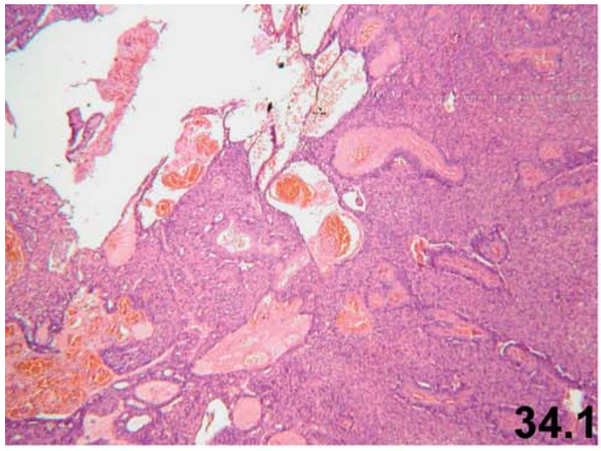
Fig. 34.6: Immunohistochemistry for smooth muscle actin shows a prominent myoepithelial cell component in solid and papillary areas.

Fig. 34.7: While immunohistochemistry for smooth muscle actin is intensely positive in solid areas of the tumor, it is weak in the glands with infiltrative growth pattern.

Fig. 34.8: At higher magnification, the tubules with infiltrative growth pattern clearly show basally located myoepithelial cells with positive reaction for smooth muscle actin.

Fig. 34: Final remarks

- This case represents a common diagnostic problem in breast pathology. The interpretation of such solid papillary neoplastic lesions can be very difficult, particularly in core needle biopsies or frozen sections. In this case, frozen section was performed and created serious diagnostic problems for the attending pathologist. Furthermore, the permanent sections of this lesion have been reviewed by numerous experienced pathologists. The diagnoses in this case varied significantly among them and ranged from intraductal papilloma with usual ductal hyperplasia (UDH) and atypical papilloma to intraductal papillary carcinoma associated with invasion.
- While the presence of irregular and infiltrative glands is a worrisome finding in this case, examination at higher magnification clearly reveals the myoepithelial cell component of the tubules excluding the possibility of an infiltrating carcinoma. The solid component of the tumor shows quite a heterogeneous cell population consistent with UDH. Immunohistochemistry for smooth muscle actin in solid areas of the tumor is a rather surprising finding which shows a very prominent myoepithelial cell proliferation (hyperplasia). Immunohistochemistry for high molecular weight cytokeratin (CK5/6 and CK34BE12) was also performed and revealed an intense positive reaction of the proliferating cells (not shown).
- While smooth muscle actin is negative in the proliferating cells in most cases of UDH, this case reveals a strong positive reaction for smooth muscle actin in many solid and papillary areas.
- Because of the significant myoepithelial proliferation, this case can also be regarded as an adenomyoepithelioma, papillary variant.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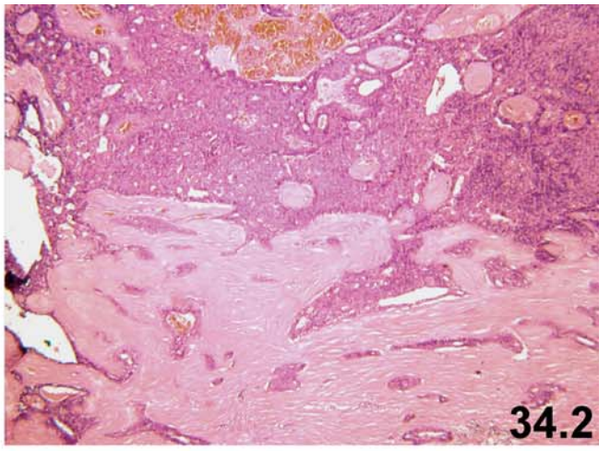
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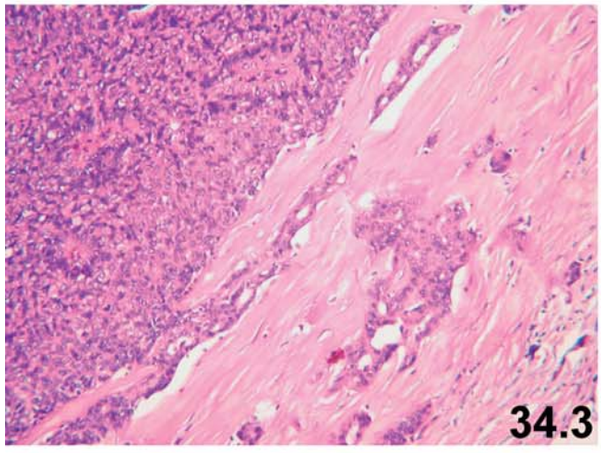
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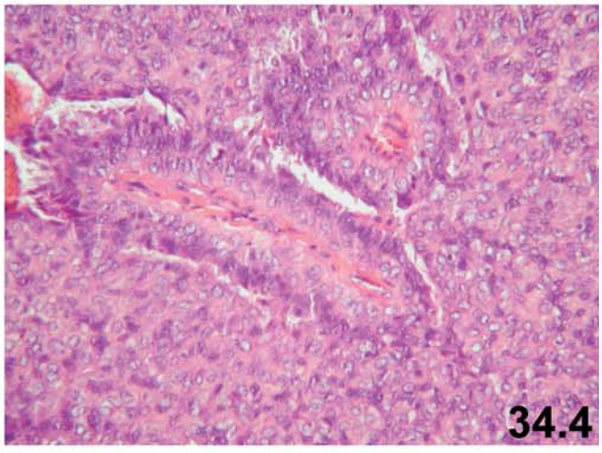
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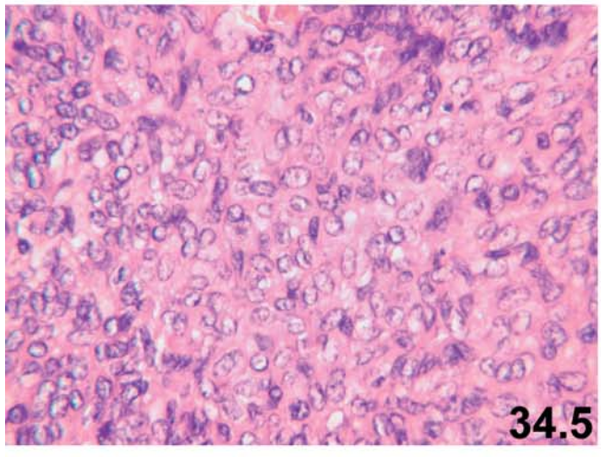
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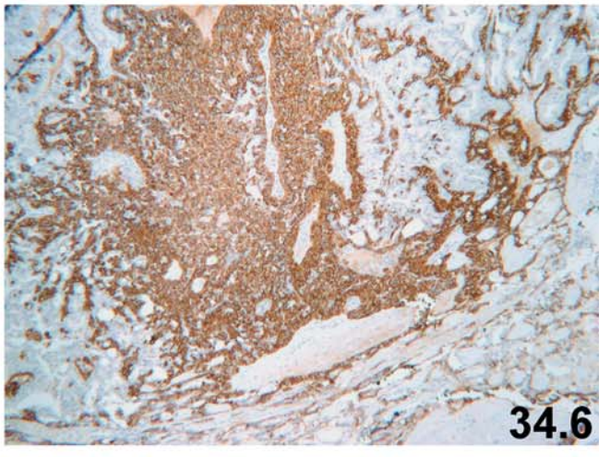
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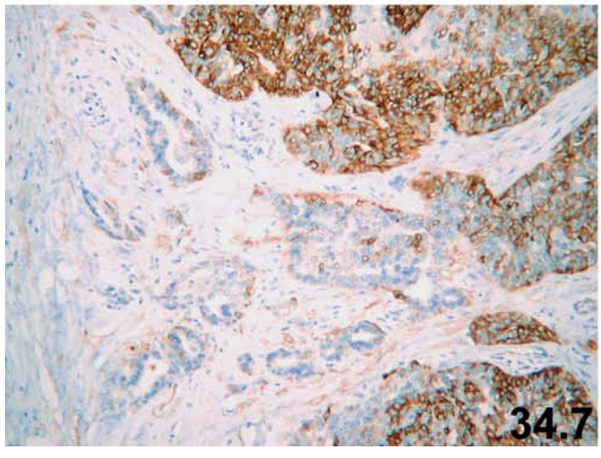
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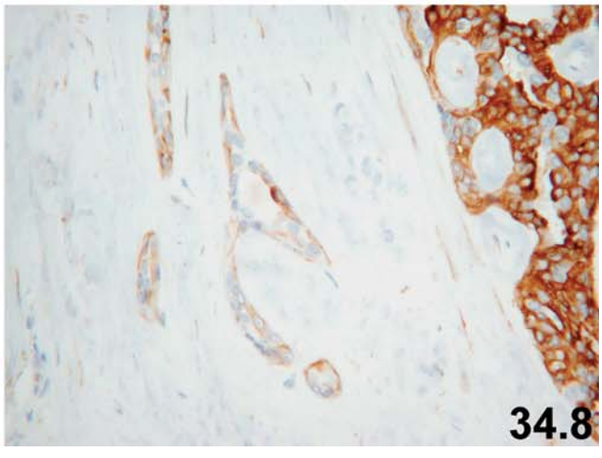
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Fig. 35: Atypical papilloma or low-grade papillary ductal intraepithelial neoplasia.

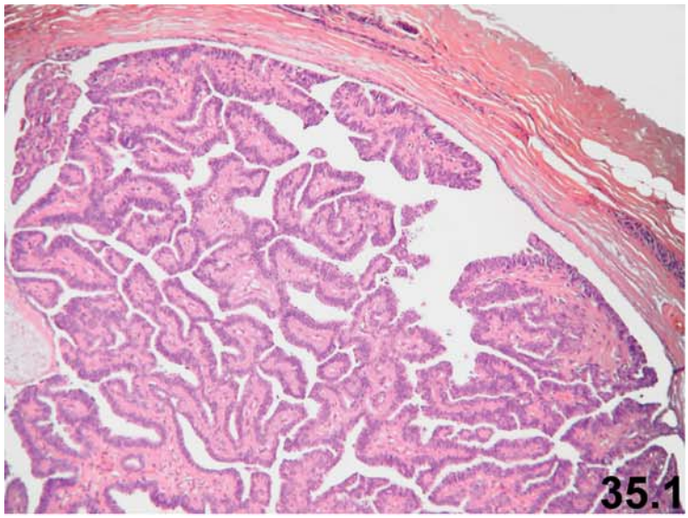
Case history: A 55-year-old woman presented with a centrally located, well-circumscribed firm mass in her left breast. The tumor was excised and measured 1.6×1×0.6 cm. The cut surface of the tumor showed granular, fine papillary structures.

Fig. 35.1: Low-power magnification of an intraductal papillary neoplasm shows several thin or finger-like projections.

Fig. 35.2: In several areas, a clear-cut myoepithelial cell layer is present. The recognition of myoepithelial cells within the papillary structures initially led to the diagnosis of intraductal papilloma (without atypia).

Figs. 35.3 and **35.4:** Some areas of the tumor show epithelial cells with enlarged hyperchromatic nuclei.

Figs. 35.5 and **35.6:** Other areas of the tumor reveal the absence of basally located myoepithelial cells – a finding more common in a papillary intraductal carcinoma. Note also the spindle-stratified atypical epithelial cells with hyperchromatic nuclei and increased nuclear-cytoplasmic ratio.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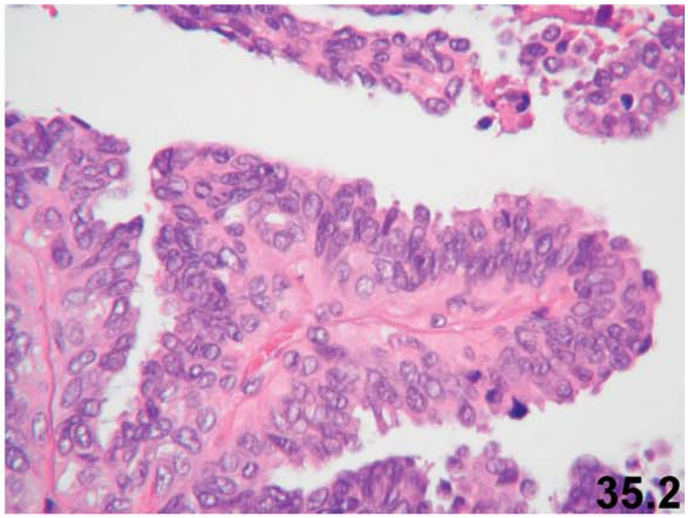
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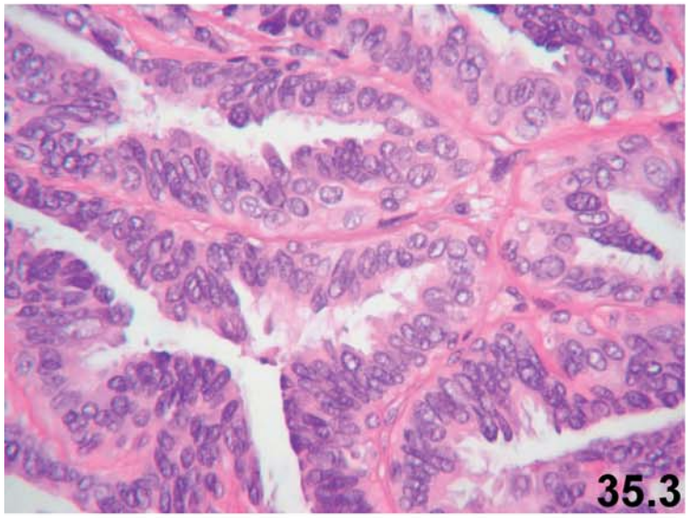
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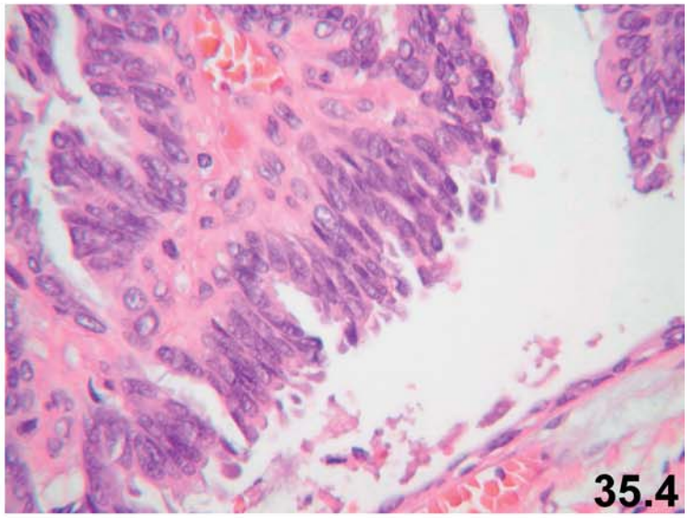
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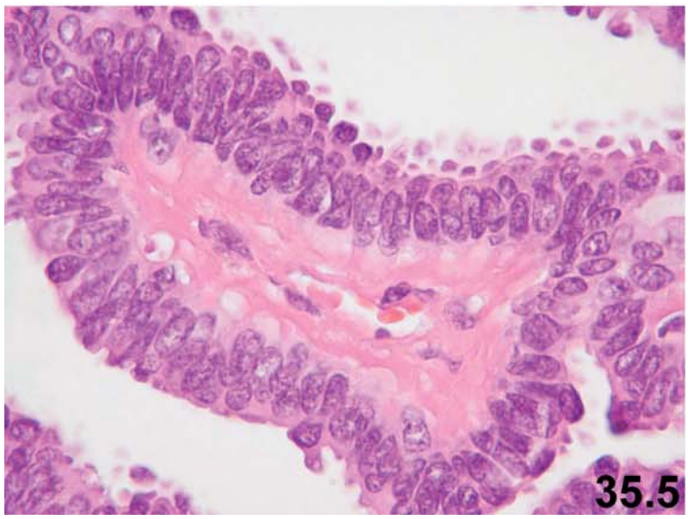
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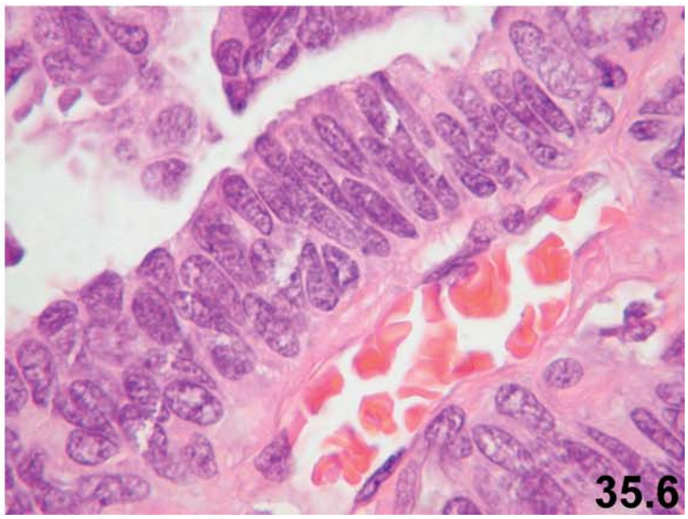
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Fig. 35.7: Spindle-shaped atypical epithelial cells showing hyperchromatic nuclei.

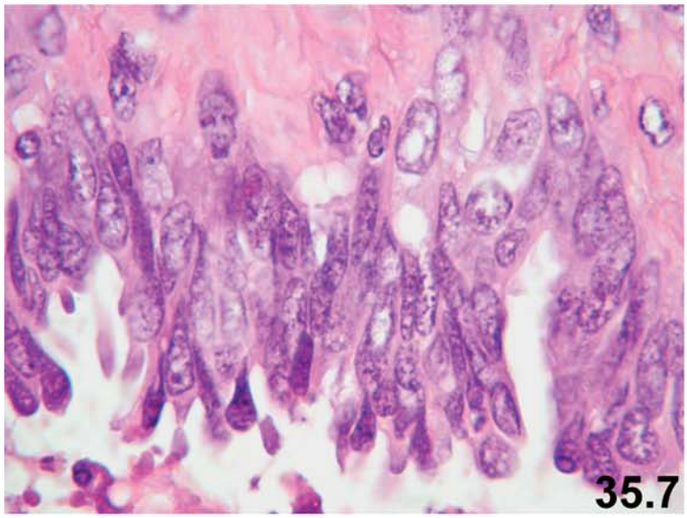
Fig. 35.8: Another area of the tumor with significant epithelial proliferation. The presence of a homogeneous cell population of epithelial cells is highly suspicious for an intraductal papillary carcinoma.

Figs. 35.9 and **35.10:** Immunohistochemistry for smooth muscle actin decorates a myoepithelial cell layer in several areas of the tumor.

Figs. 35.11 and **35.12:** Most areas of the papillary tumor with epithelial atypia show no positive immunoreaction for CK5/6. Note the positive CK5/6 reaction of the normal epithelium (Fig. 35.11).

Fig. 35: Final remarks

- The presence of myoepithelial cells within the papillary projections is typical for papillomas. While lack of myoepithelial cells is a characteristic feature of intraductal papillary carcinoma, the presence of myoepithelial cells in papillary projections does not exclude the possibility of papillary carcinoma. It is the type of proliferating cells (homogeneous versus heterogeneous cell population) that distinguishes papillomas from intraductal papillary carcinoma(papillary ductal carcinoma in situ).
- The morphology of the proliferating atypical cells (homogeneous epithelial cells) and the negative immunoreaction for CK5/6 in this case are consistent with an intraductal papillary carcinoma or a low-grade DCIS arising in the background of a papilloma. In order to avoid the term "carcinoma," a more appropriate term for this type of tumor would be atypical papilloma or low-grade DIN arising in papilloma.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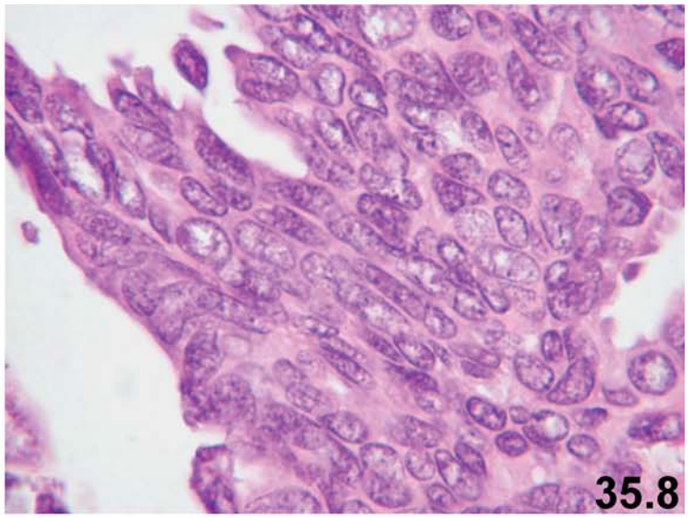
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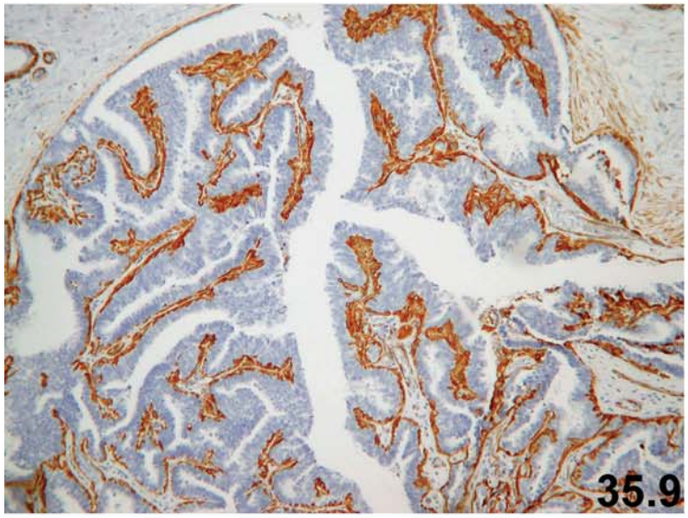
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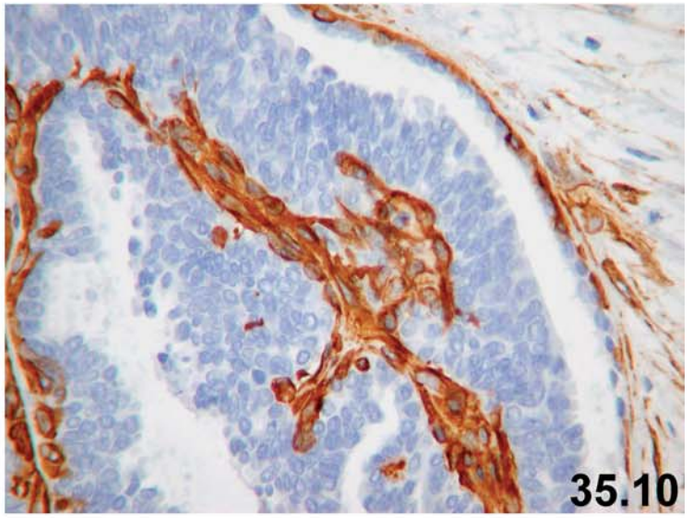
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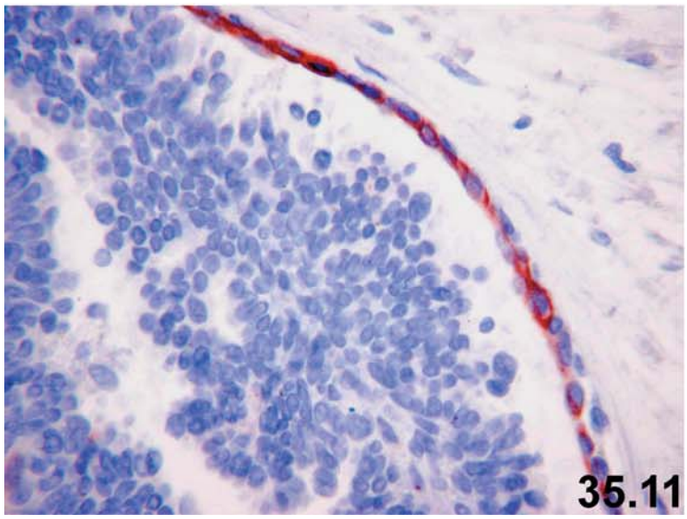
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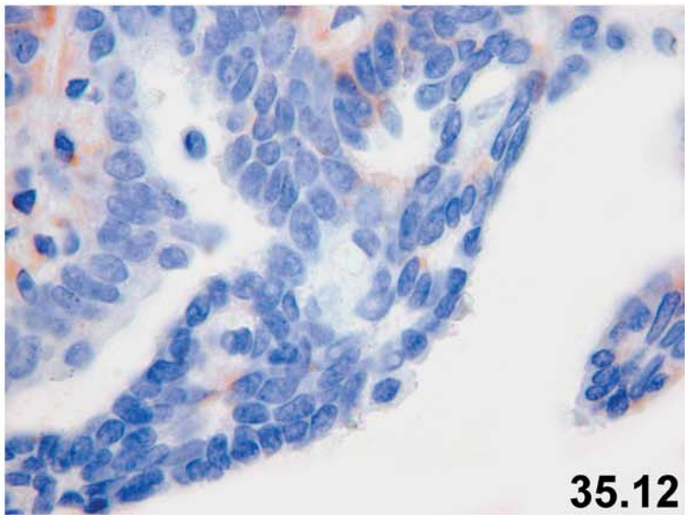
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Fig. 36: Low-grade intraductal papillary carcinoma, spindle cell variant (low-grade papillary ductal intraepithelial neoplasia).

Case history: A 73-year-old woman presented with a centrally located palpable tumor (2.5 cm) in her right breast. A core needle biopsy of the lesion was performed.

Figs. 36.1 and **36.2:** Core needle biopsy showing a tumor with several thin papillary structures.

Figs. 36.3 and **36.4:** Papillary structures of the tumor showing proliferating epithelial cells and fibrovascular cores.

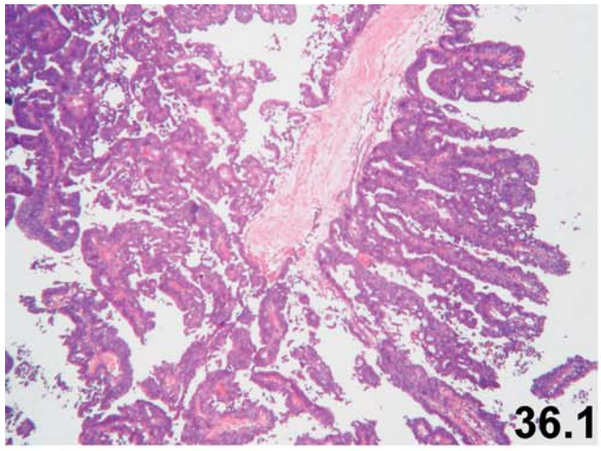
Figs. 36.5 and **36.6:** The lining epithelial cells are predominantly of spindle cell type and show stratified and enlarged hyperchromatic nuclei. Note the absence of myoepithelial cells within the papillary structures, which is highly characteristic of intraductal papillary carcinoma.

Fig. 36.7: Immunohistochemistry for CK5/6 is negative in the papillary tumor. Note the positive internal control (skin tissue).

Fig. 36.8: As is typical of the vast majority of papillary neoplasms, the tumor cells display an intense and diffuse positive immunoreaction for estrogen receptors.

Fig. 36: Final remarks

- The spindle cell (spindle cell-stratified) variant of intraductal papillary carcinoma can easily be mistaken for papilloma associated with usual ductal hyperplasia. The neoplastic spindle cells can also be confused with modified myoepithelial cells. Immunohistochemistry for myoepithelial markers (smooth muscle actin, p63, CD10, etc.) and high molecular weight cytokeratin (CK5/6 or CK34BE12) can be very helpful in such cases for distinguishing benign papillomas from intraductal papillary carcinomas.
- The tumor cells in this case reveal low-grade cytologic atypia. An alternative and more appropriate name for this papillary lesion would be low-grade papillary ductal intraepithelial neoplasia or papillary DIN.
- Excisional biopsy of the tumor was subsequently performed and showed an intracystic (intraductal) papillary carcinoma (low-grade papillary DIN).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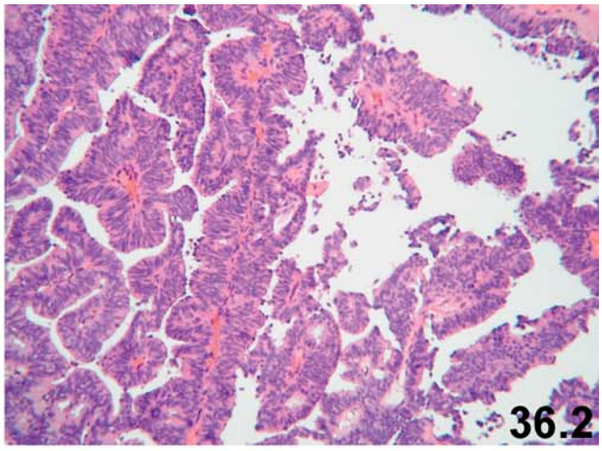
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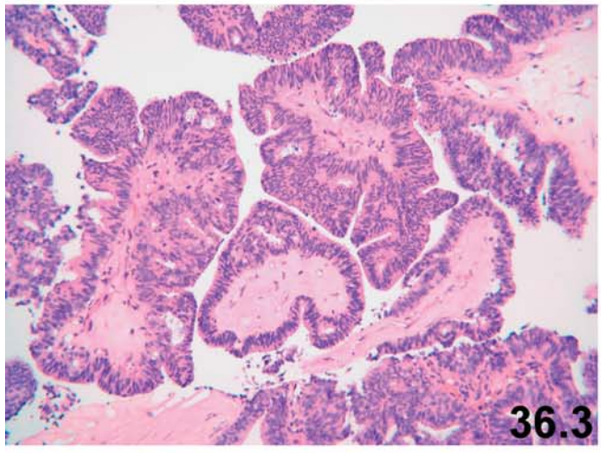
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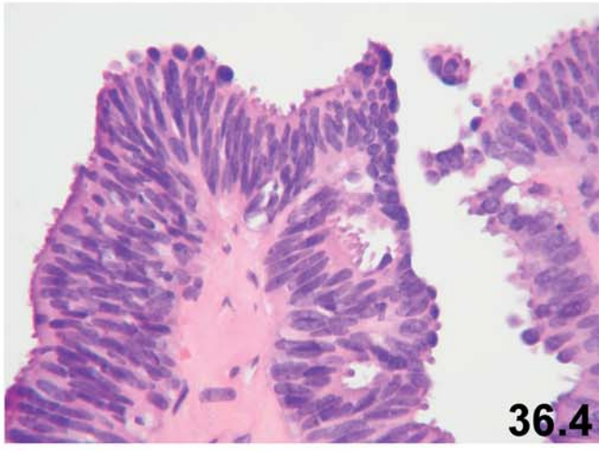
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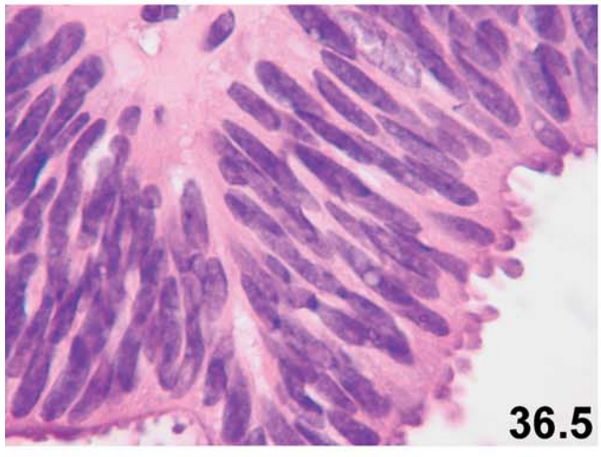
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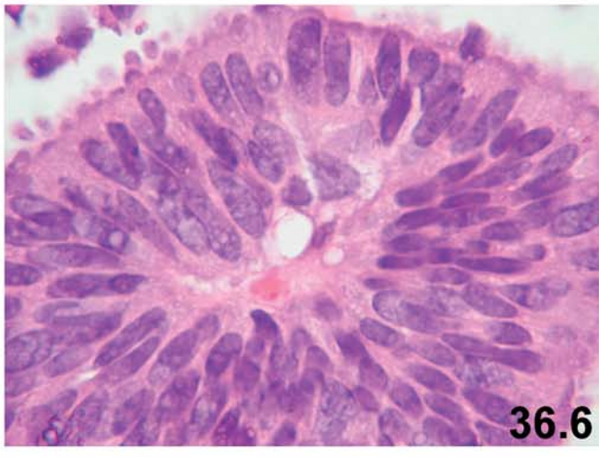
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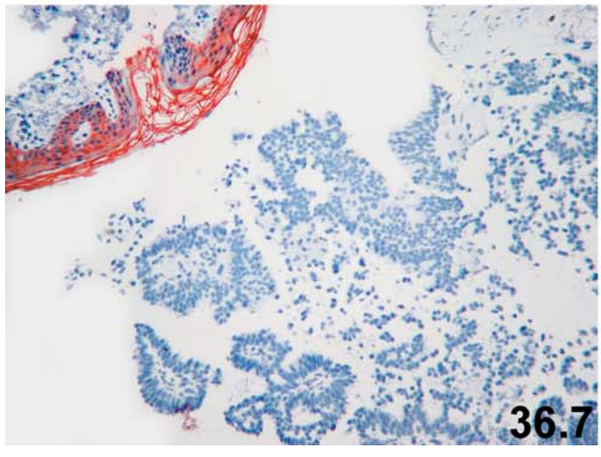
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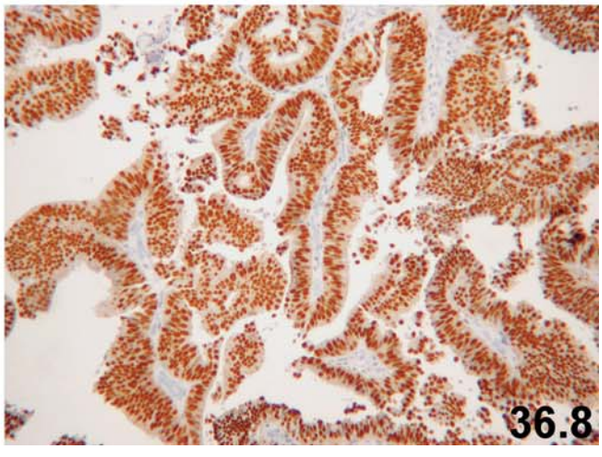
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Fig. 37a: Low-grade intraductal papillary carcinoma with neuroendocrine differentiation (low-grade papillary DIN with neuroendocrine differentiation).

Case history: A 74-year-old woman presented with a well-circumscribed firm mass in the upper outer quadrant of her left breast. Core needle biopsy of the lesion was performed and revealed a papillary carcinoma in situ. The tumor was excised and measured 2×1.3×0.7 cm.

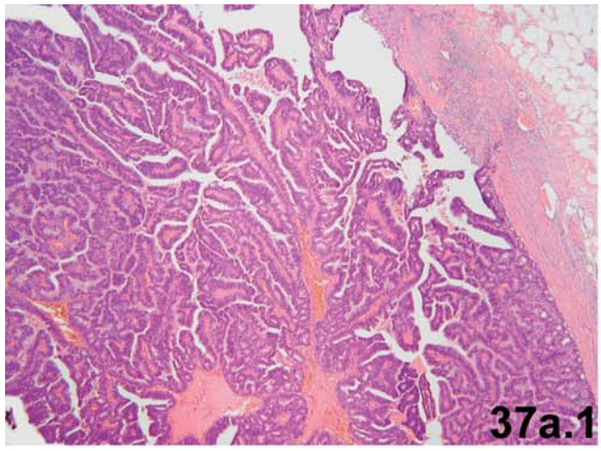
Figs. 37a.1 and **37a.2:** A well-circumscribed tumor showing numerous thin or fingerlike intraductal papillary projections.

Fig. 37a.3: Several areas with cribriform growth pattern are present within the papillary structures.

Figs. 37a.4 and **37a.5:** Other areas of the tumor reveal elongated or spindle-shaped epithelial cells.

Figs. 37a.6 and **37a.7:** While several areas of the tumor show rounded secondary lumens or a cribriform growth pattern, the proliferating cells display two different cell types. One cell type is smaller and shows cells with more hyperchromatic nuclei and scant eosinophilic cytoplasm. The second cell type displays larger cells with pale cytoplasm.

Fig. 37a.8: Some areas of the papillary tumor show two cell types closely mimicking epithelial and myoepithelial cells.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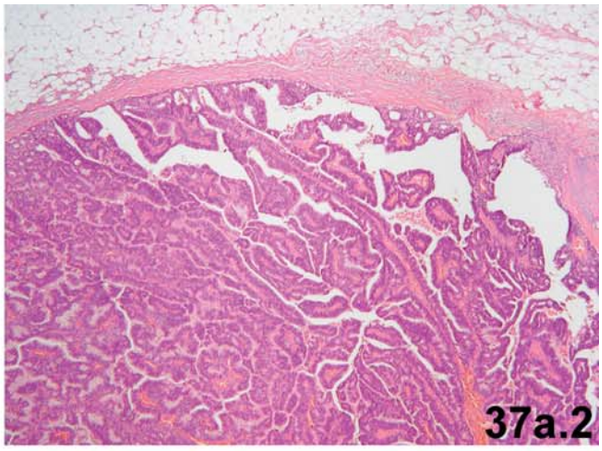
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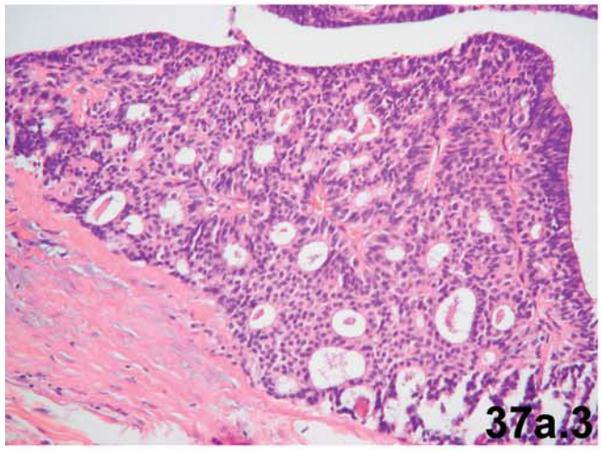
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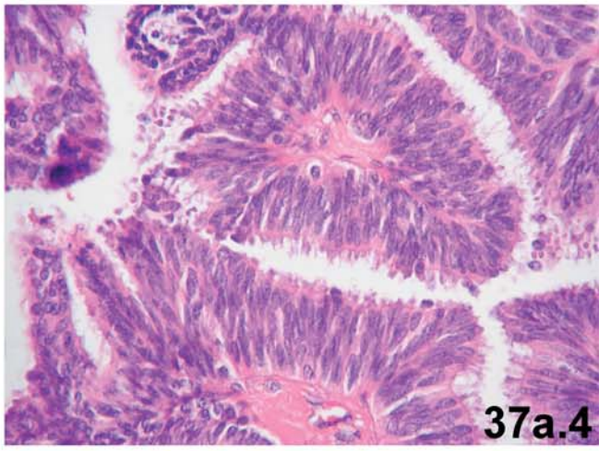
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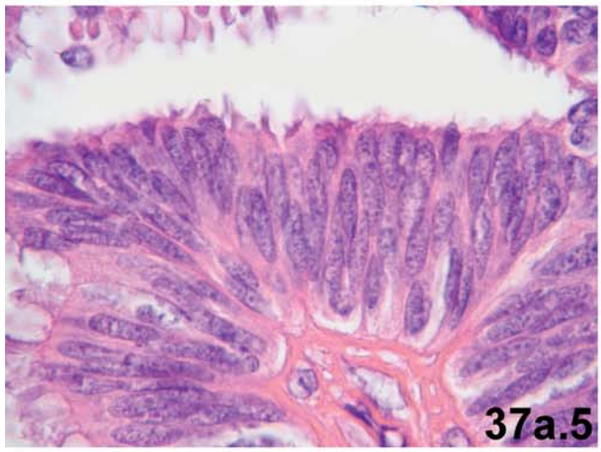
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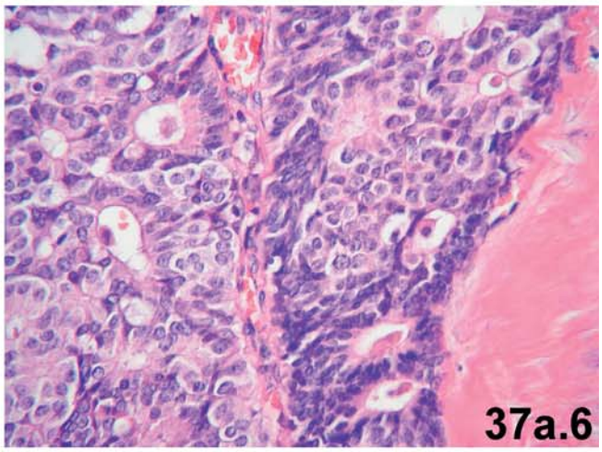
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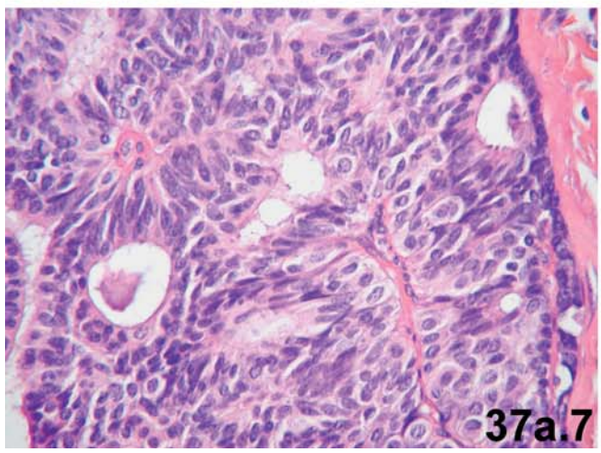
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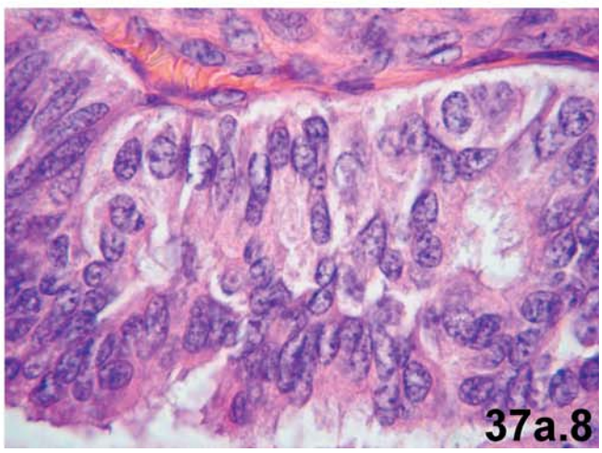
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Fig. 37a.9: Another area of the tumor with two different cell types. The luminal cells show scant cytoplasm and dense nuclei. The basally located cells are larger and show more vacuolated or fine granular, eosinophilic cytoplasm. These two cell types can easily be mistaken for epithelial and myoepithelial cells in a papillary neoplasm.

Fig. 37a.10: Immunohistochemistry for smooth muscle actin reveals no myoepithelial cells within the papillary tumor.

Fig. 37a.11: While the blood vessels display a positive reaction for smooth muscle actin, the tumor cells do not contain a myoepithelial cell component.

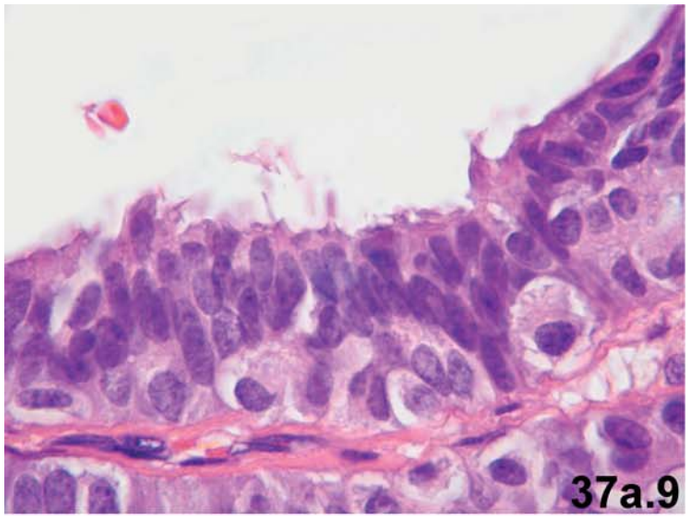
Fig. 37a.12: The tumor cells are negative for high molecular weight cytokeratin (CK34BE12). Note the positive internal control (normal duct).

Fig. 37a.13: Immunohistochemistry for high molecular weight cytokeratin (CK34BE12) shows no positive reaction in the proliferating cells.

Fig. 37a.14: Immunohistochemistry for synaptophysin reveals a heterogeneous positive reaction. The immunoreaction for chromogranin was also positive (not shown).

Fig. 37a: Final remarks

- Intraductal papillary carcinomas with neuroendocrine differentiation often show two or three different cell types. The presence of spindle cells, cells with fine eosinophilic granular cytoplasm, mucinous cells, or a rosette-like arrangement of the tumor cells should raise the possibility of neuroendocrine differentiation and, therefore, needs to be evaluated immunohistochemically (synaptophysin, chromogranin, etc.)
- Papillary neoplasms with neuroendocrine differentiation often display two or three different cell types closely mimicking a heterogeneous cell population of usual ductal hyperplasia. In that setting, immunohistochemistry for high molecular weight cytokeratin (HMW-CK) such as CK5/6, CK14 or CK34BE12 can be a very useful adjunct. While HMW-CK is always positive in usual ductal hyperplasia, it is very often negative in ductal intraepithelial neoplasia (DIN), including one with neuroendocrine features (differentiation).
- To avoid the designation of cancer for a neoplastic lesion that is not invasive, the more appropriate diagnosis in this case would be low-grade papillary DIN.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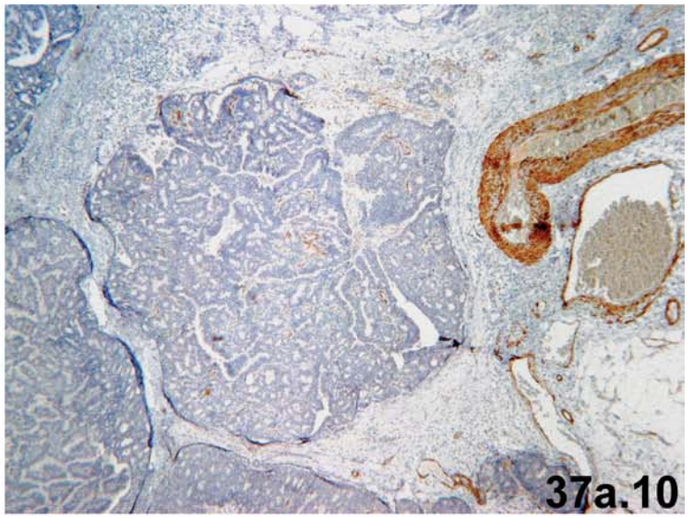
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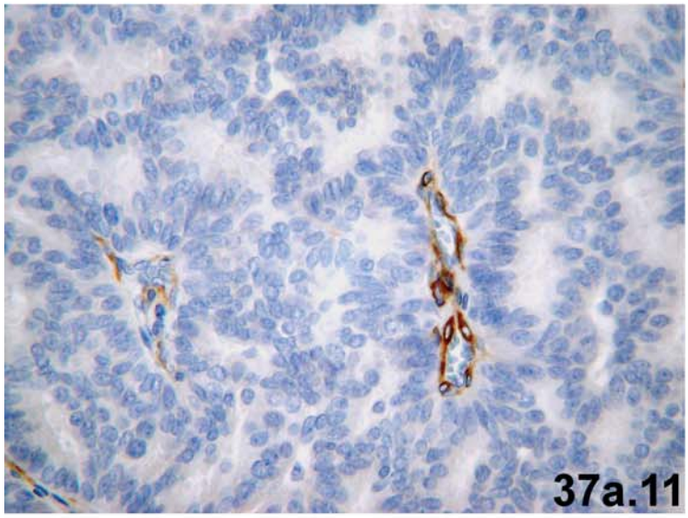
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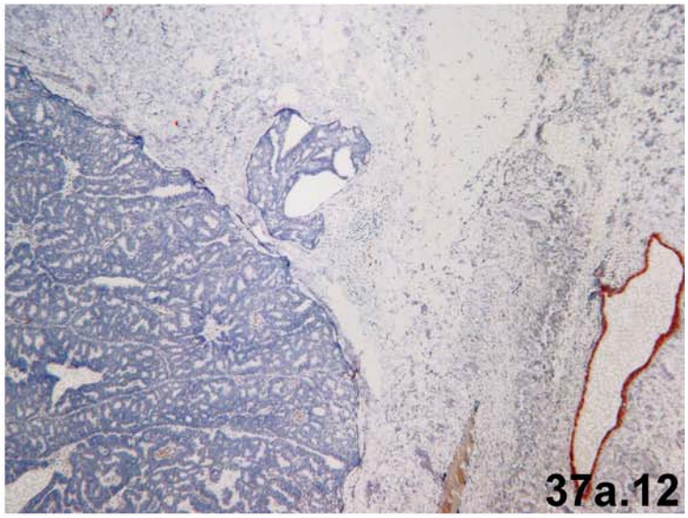
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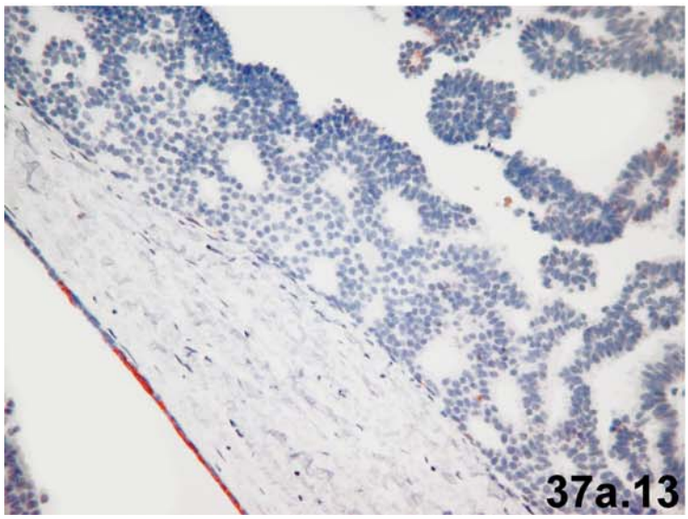
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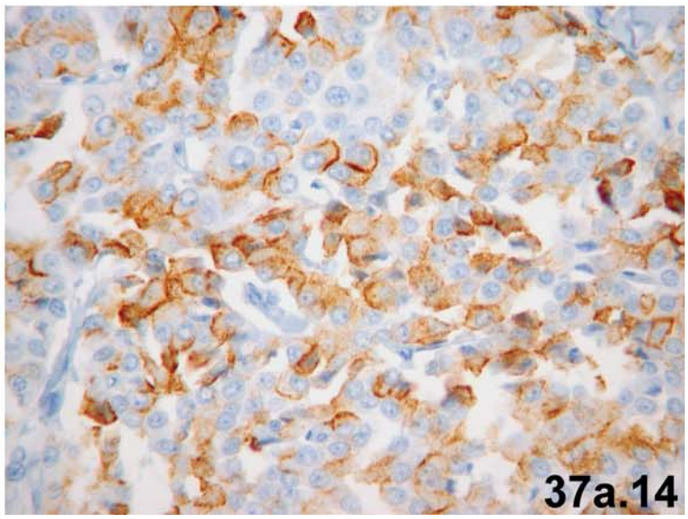
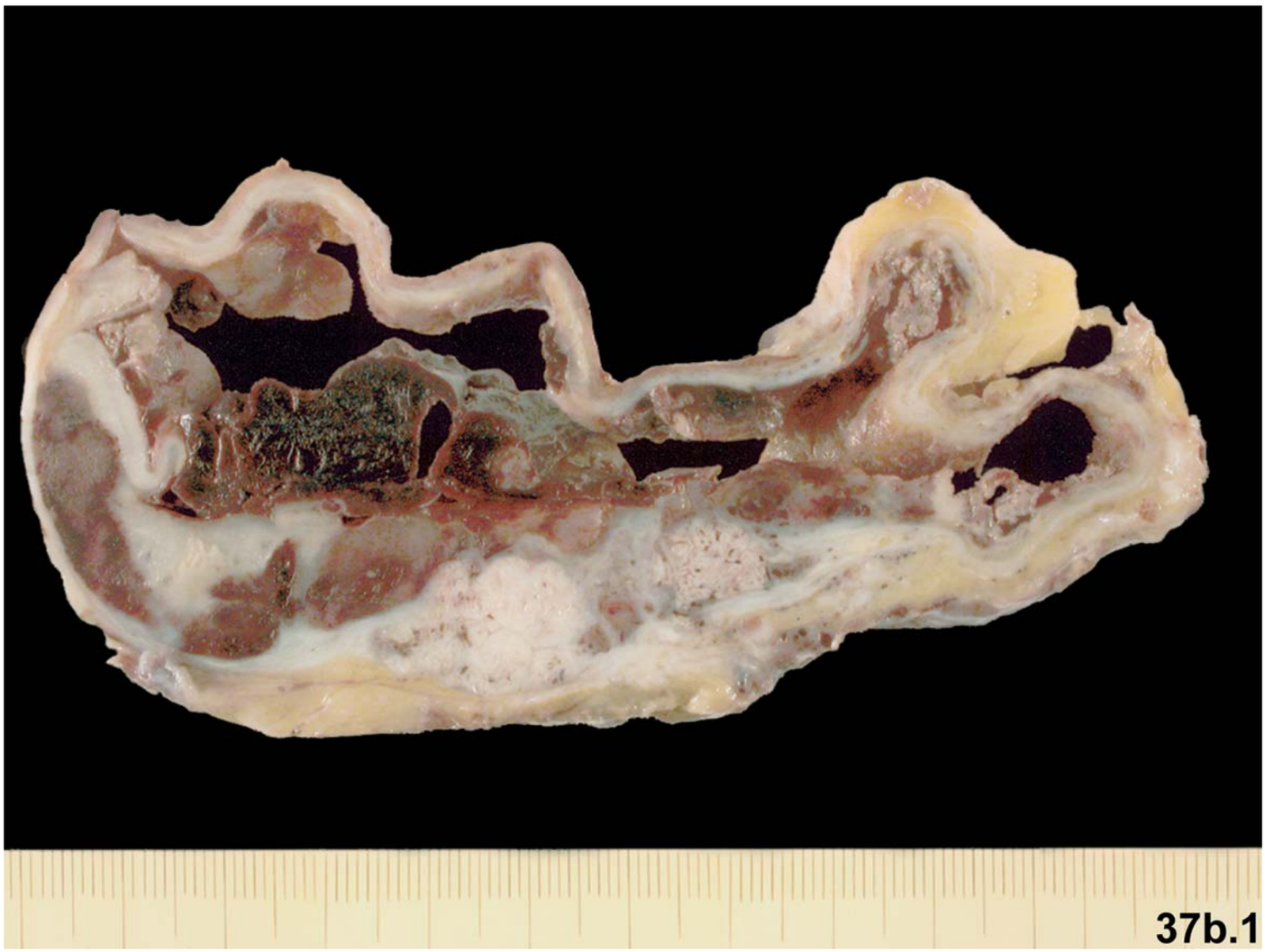

37a.14

Fig. 37b: Intracystic (intraductal) papillary carcinoma (papillary ductal intraepithelial neoplasia).

Case history: A 69-year-old woman presented with a predominantly cystic tumor in her left breast. There was a history of recurrent bloody nipple discharge. Ultrasonography showed a predominantly cystic tumor with somewhat irregular borders. The tumor measured 12 cm at its greatest diameter. Core needle biopsy showed a partly hemorrhagic/necrotic (intraductal) papillary carcinoma. Because of the tumor's large size, a modified radical mastectomy was performed.

Fig. 37b.1: Gross appearance of the tumor, showing a predominantly cystic lesion with large areas of hemorrhage. The cystic tumor measured 12 cm in greatest diameter. Note the solid greyish-white areas of the tumor and areas with necrosis.


37b.1

Figs. 37b.2 and **37b.3:** Low magnification of the tumor shows a cystically dilated duct with papillary configuration. Some areas of the tumor display stromal sclerosis.

Fig. 37b.4: Several areas of the tumor show extensive hemorrhage and necrosis (infarction of a papillary tumor).

Fig. 37b.5: A well-preserved area showing intraductal papillary carcinoma. Within the papillary structures, there are several areas with solid and cribriform growth patterns.

Fig. 37b.6: Intraductal papillary carcinoma associated with significant stromal sclerosis.

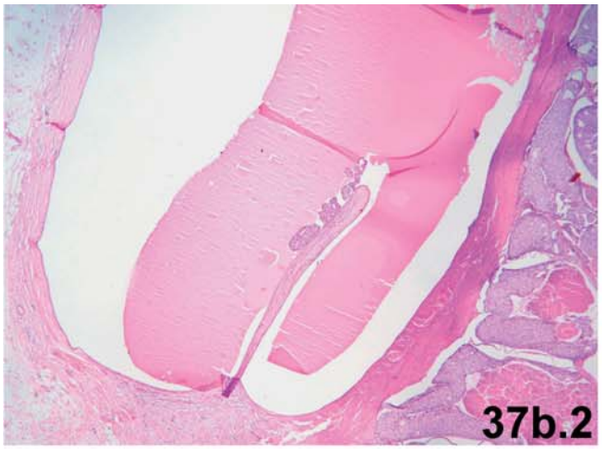
Fig. 37b.7: Several areas of the tumor show a cribriform growth pattern within the papillary structures.

Fig. 37b.8: Cribriform and solid areas of the tumor, consisting of a homogeneous cell population of epithelial cells with low-grade nuclear atypia. Note the lack of myoepithelial cells within the proliferating tumor cells.

Fig. 37b.9: While the tumor cells show low-grade nuclear atypia, some areas reveal luminal necrosis or numerous apoptotic bodies. The luminal necrosis is, however, due to infarction of the large intracystic papillary carcinoma.

Fig. 37: Final remarks

- This is an example of intracystic papillary carcinoma of the breast. The designation of intracystic should be reserved for tumors with grossly cystically dilated ducts.
- Even after extensive sampling of the tumor, no clear-cut invasive carcinoma could be identified.
- The vast majority of intraductal papillary carcinomas are of low grade and lack significant nuclear atypia. While some pathologists regarded this particular tumor as low-grade (grade 1) papillary carcinoma, others wanted to grade it as intermediate or grade 2 intraductal papillary carcinoma because of the presence of central necrosis. In the author's opinion, the presence of luminal necrosis (massive apoptosis) in this case is due to infarction (torsion of the cyst with subsequent hemorrhage and ischemia). In other words, the necrosis is of ischemic type and should not be used as a diagnostic parameter for grading in this case.
- As mentioned before, using the concept of DIN, an alternative and more appropriate terminology for intraductal papillary carcinoma would be papillary ductal intraepithelial neoplasia (papillary DIN).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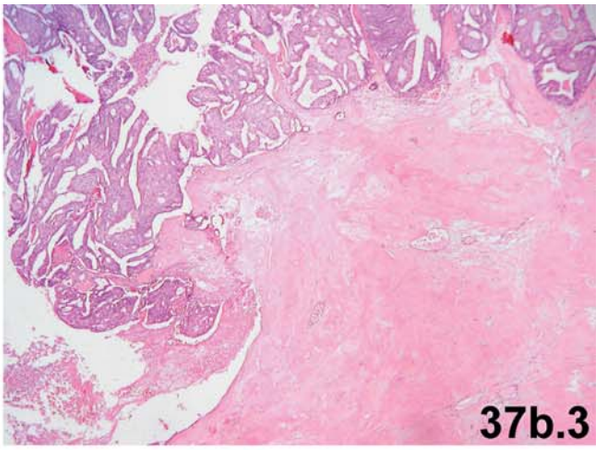
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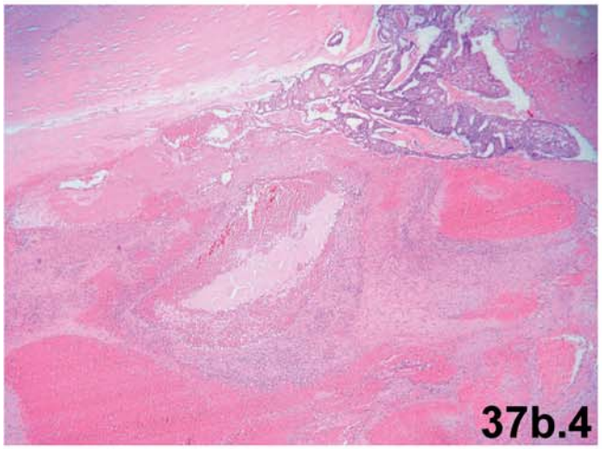
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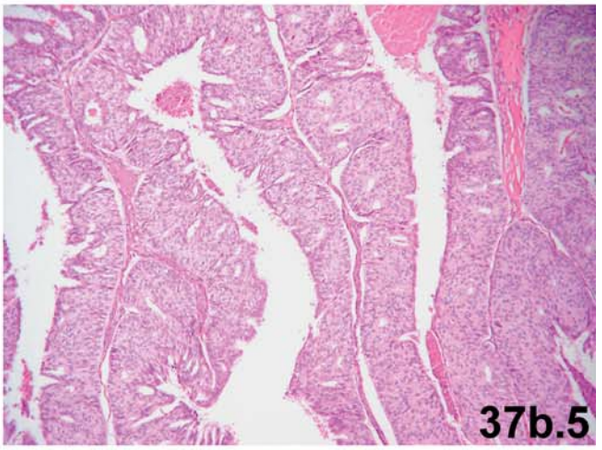
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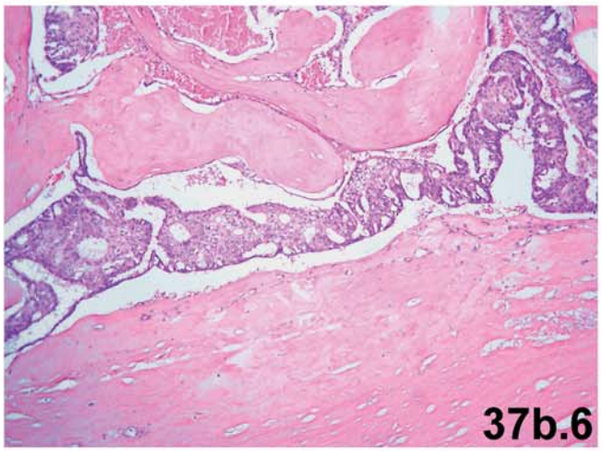
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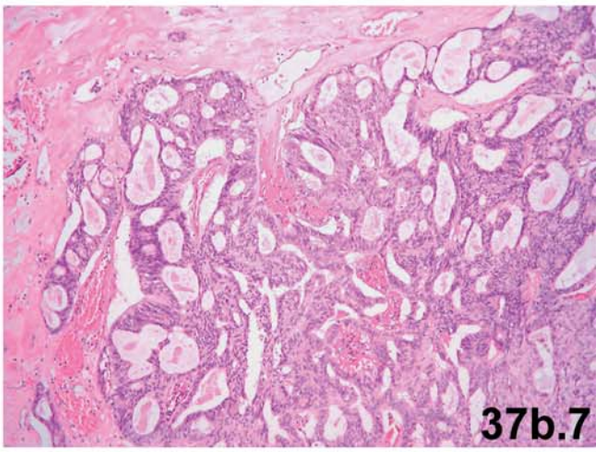
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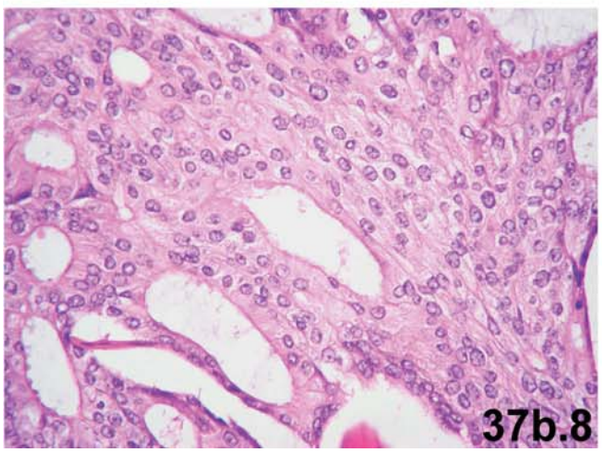
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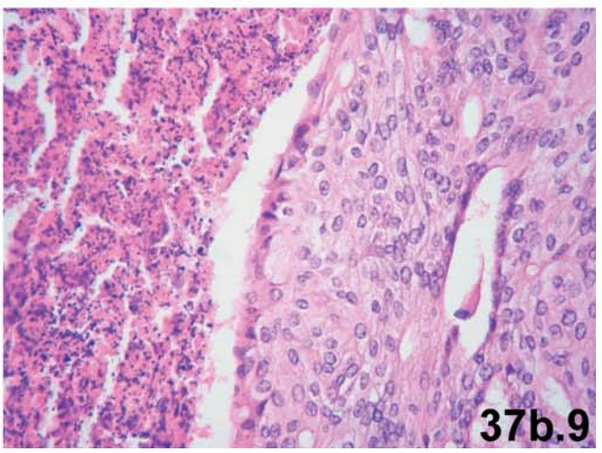
37b.9

Lobular Intraepithelial Neoplasia (LIN)

Contents

CHAPTER 7 Lobular Intraepithelial Neoplasia (LIN)

7.1 Synonyms

Atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), lobular neoplasia.

7.2 Background

- Lobular neoplasia or lobular intraepithelial neoplasia (LIN) encompasses the entire spectrum of so-called atypical lobular hyperplasia and so-called lobular carcinoma in situ. There are no objective and reliable criteria for separating ALH from LCIS. The therapy for ALH and LCIS is the same [7, 27, 30].
- Lobular neoplasia (LIN) is predominantly a pathologic diagnosis. It does not produce a palpable mass, but rather is generally an incidental finding in patients who undergo biopsies for other reasons.
- The lesion is commonly multifocal (separate lesions in the same quadrant) and multicentric (separate lesions in different quadrants), as well as frequently bilateral (40%) [2].
- With prolonged follow-up exceeding 20 years, up to 25–30% of the lesions will progress to an invasive carcinoma of either lobular or ductal histologic type.

Table 7.1. Immunohistochemical distinction between ductal intraepithelial neoplasia (DIN; ductal carcinoma in situ) and lobular intraepithelial neoplasia (LIN)

	DIN	LIN
E-cadherin	+++	Negative
CK34BE12	Negative	++/+++

E-cadherin is almost always positive in DIN but negative in LIN. CK34BE12 (HMW-CK) is negative in about 85–90% of cases with DIN. CK34BE12 is very often (90–95%) positive in LIN (typical punctuated or caplike positivity). It is of note that CK5/6 is negative in both DIN and LIN [8].

7.3 Microscopic Features (Figs. 38–41)

- Atypical (neoplastic) epithelial proliferation within the lobules, characterized by a solid, occlusive proliferation of relatively uniform population of loosely cohesive and often small round cells with scant cytoplasm. Usually indistinct cell margins (so-called type A).
- The cells may deviate from classic appearance: minor variation in size, larger cells with more eosinophilic, granular cytoplasm (apocrine-like features; so-called type B cells with more polymorphism and nucleoli).
- Intracytoplasmic lumens, mucous globules, and a signet-ring cell appearance can occur.
- The native epithelial cells in the terminal duct-lobular units are either completely replaced or simply displaced and lifted by the proliferating cells.
- The neoplastic cells may extend to adjacent terminal ducts in a pagetoid fashion. Sometimes this pagetoid ductal extension may be the only alteration evident in the biopsy specimen.

7.4 Additional Comments

Some cases show combined morphologic features of ductal and lobular intraepithelial neoplasias (hybrid lesion = mammary intraepithelial neoplasia or MIN, not otherwise specified) [8]. In hybrid intraepithelial lesions (MIN), E-cadherin and CK34BE12 can either be both positive (positive hybrid lesions) or negative (negative hybrid lesion) [8].

Rarely, LIN can be associated with luminal (comedo type) necrosis and microcalcifications. This occurs more commonly in a pleomorphic variant or high-grade LIN with highly atypical nuclear morphology.

The presence of LIN at the margin does not require reexcision. Currently, however, due to limited experience, it is unclear how to manage a patient with high-grade LIN when it is present at the resection margin.

In many cases with LIN (with or without invasion), ductal intraepithelial neoplasia (DIN) flat type (low-grade DIN, flat type or flat epithelial atypia) can frequently be identified in the surrounding breast tissue.

Mastectomy is not the therapy of choice in LIN. In most centers, excisional biopsy with close clinical and mammographic examinations (close follow-up) is the recommended therapy. Recently, some breast oncology centers are treating patients with LIN with tamoxifen [14, 27, 29, 41, 43].

To convey the extent and degree of advancement of these lobular changes, Tavassoli [41] subdivides LIN into three grades:

LIN1: Partial or complete replacement of the normal epithelium of the acini that may fill, but does not distend, the acinar lumens (in comparison to adjacent uninvolved acini); no significant distension of the involved acini (subtle changes)

LIN2: More abundant proliferation of small uniform cells that fill and distend some or all acini, but acinar outlines remain dis-

tinct (separation of the involved acini with persistence of intervening lobular stroma)

LIN3:

- Type A: Neoplastic cells similar to those of LIN1 or LIN2 with massive degree of acinar distension to the point that acini appear almost confluent (no remaining intervening lobular stroma)
- Type B: The proliferating cells are completely of the signet-ring cell type with or without significant acinar distension; also includes the large cell variant with highly atypical cells

For practical purposes, LIN can simply be divided into low-grade (the most common type) and high-grade or pleomorphic variants (rare variant).

> *"One cannot leave this subject without discussing which term is most appropriate to designate the condition currently called carcinoma lobular in situ. The writer is in agreement with the increasing number of workers who are dissatisfied with the designation of 'carcinoma' for this condition… The dissatisfaction with the term 'carcinoma' in this context remains and is to a great extent justified… the term 'carcinoma' is too emotive and alarming to patient and to surgeon. It seems that the name 'lobular neoplasia,' adopted by Haagensen (1971), satisfies our need for a different name. It does not dismiss CLIS as a 'marker' while, at the same time, it does not elevate it to the frightening stature of a 'carcinoma.' It is short, accurate, and reasonably distinctive."*
>
> *J.G. Azzopardi*
> Problems in Breast Pathology, 1979, p. 232

7.5 Further Reading

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Fig. 38: Lobular intraepithelial neoplasia focally with central necrosis.

Case history: A 63-year-old woman presented with clinical and mammographic signs of fibrocystic changes. Suspicious microcalcifications were present. The excisional biopsy revealed sclerosing adenosis with microcalcifications. In addition, several sections showed areas with intraepithelial proliferations, as described below.

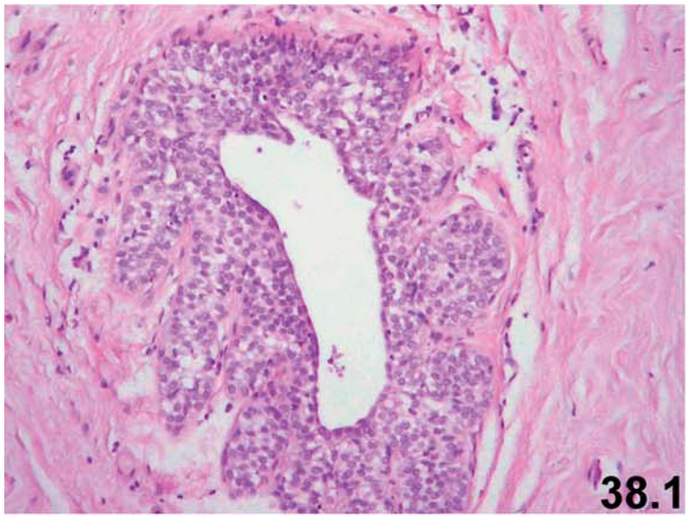
Fig. 38.1: Low magnification of a duct shows a monotonous cell population of small epithelial cells with a cloverleaf pattern.

Fig. 38.2: Acinar (ductular) structures within the lobules show loosely cohesive uniform epithelial cells.

Fig. 38.3: Typical cells of lobular intraepithelial neoplasia showing a pagetoid ductal extension (creeping replacement).

Fig. 38.4: A duct with solid proliferation of mildly atypical cells closely resembling DIN (DCIS). The duct shows, however, loosely cohesive epithelial cells at one peripheral area.

Figs. 38.5 and **38.6:** Some other areas of the lesion show partial involvement of the ducts revealing a monotonous cell population of epithelial cells. Note the presence of central necrosis (apoptosis) in Fig. 38.5.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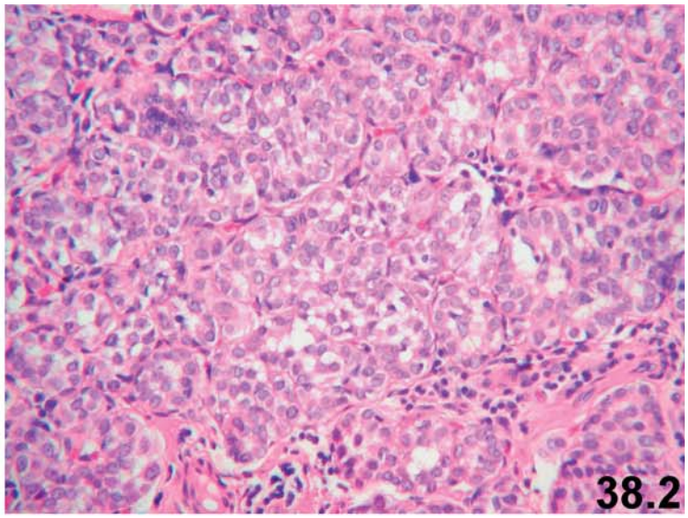
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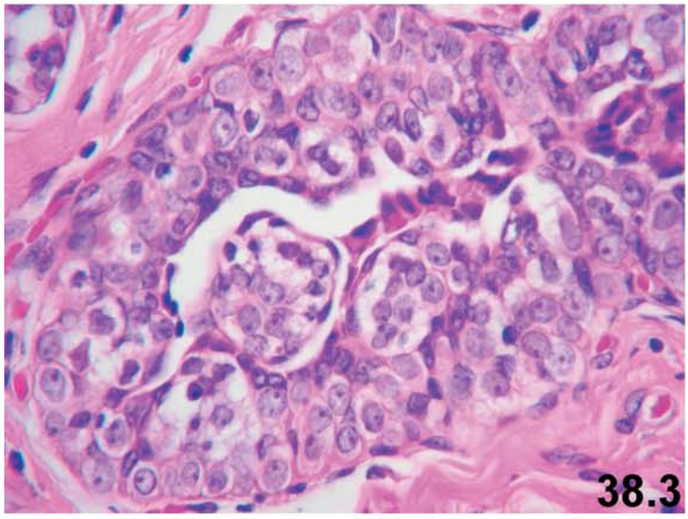
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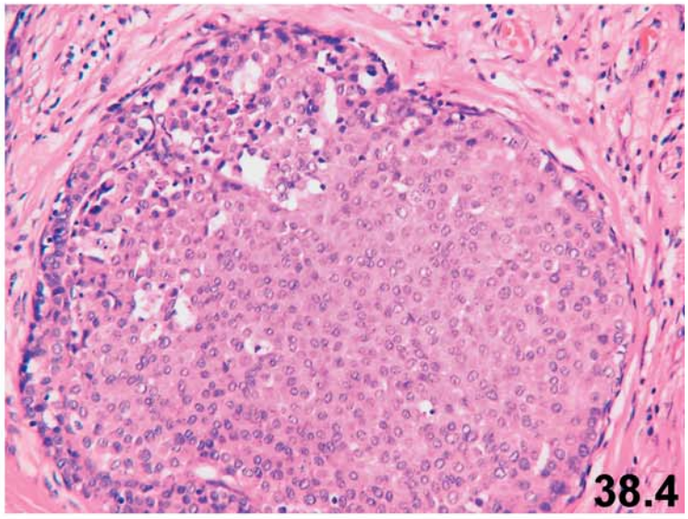
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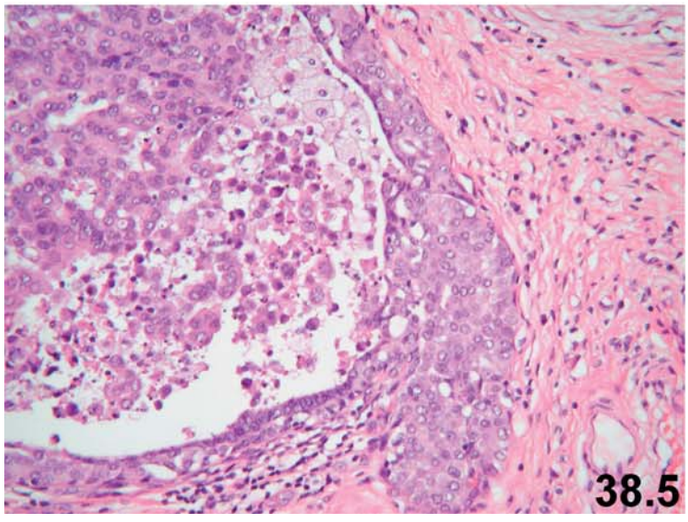
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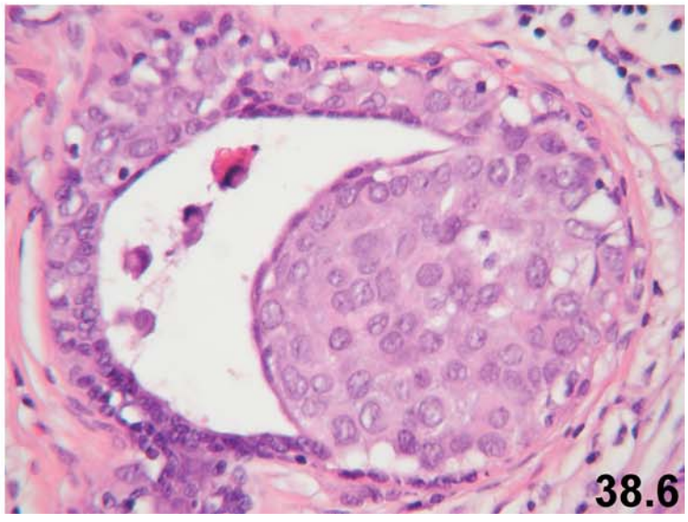
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Fig. 38.7: Negative immunoreaction of neoplastic cells for E-cadherin in a duct with pagetoid extension.

Fig. 38.8: The neoplastic cells in the same duct, however, show a positive immunoreaction for CK34BE12.

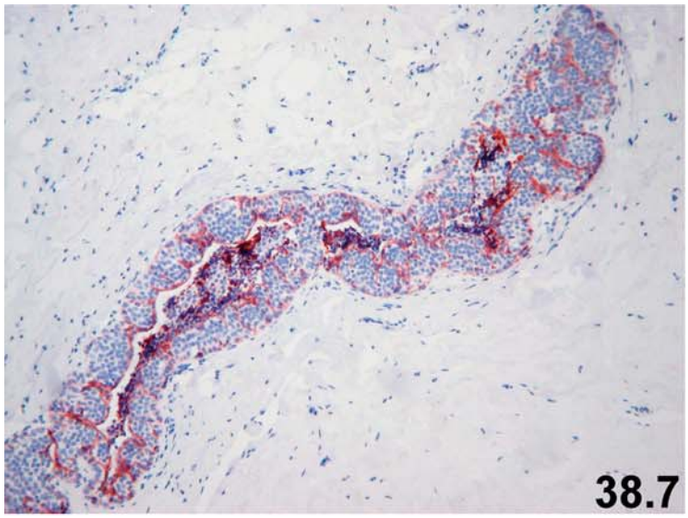
Fig. 38.9: While the luminal epithelial cells are immunoreactive for E-cadherin, the underlying neoplastic cells of lobular intraepithelial neoplasia are completely negative for it.

Fig. 38.10: Lobular intraepithelial neoplasia with a typical perinuclear or dot-like positive immunoreaction for CK34BE12.

Figs. 38.11 and **38.12:** Immunohistochemistry for E-cadherin in solid areas with central necrosis. The neoplastic cells are completely negative for E-cadherin, demonstrating lobular neoplastic nature of the lesion.

Fig. 38: Final remarks

- The solid areas of this case, particularly those associated with central necrosis, may be easily mistaken for DIN (DCIS).
- The tumor cells of lobular intraepithelial neoplasia are characteristically negative for E-cadherin, but positive for CK34BE12. However, like in DIN (DCIS), immunoreaction for CK5/6 is negative in lobular intraepithelial neoplasia. CK5/6 should, therefore, not be used for separation between DIN (DCIS) and lobular intraepithelial neoplasia (LIN).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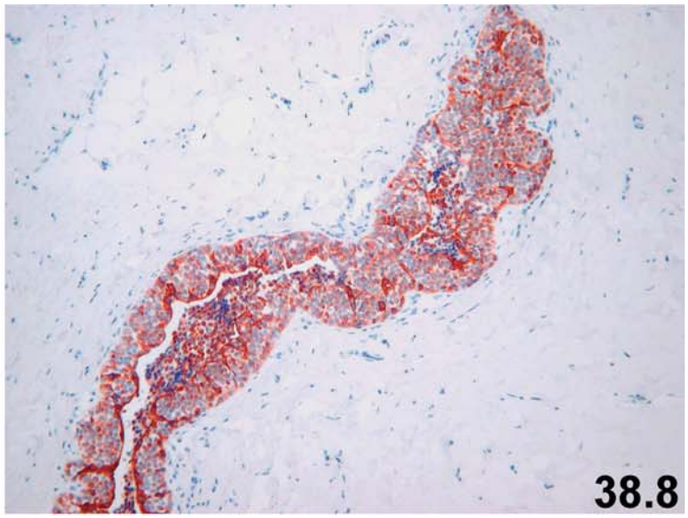
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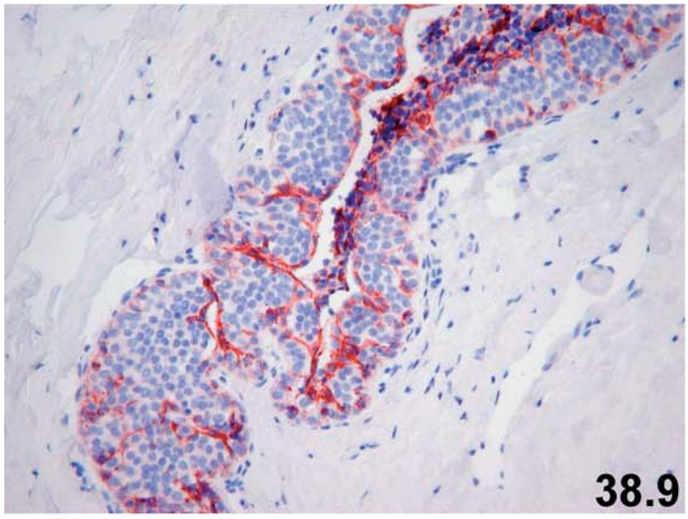
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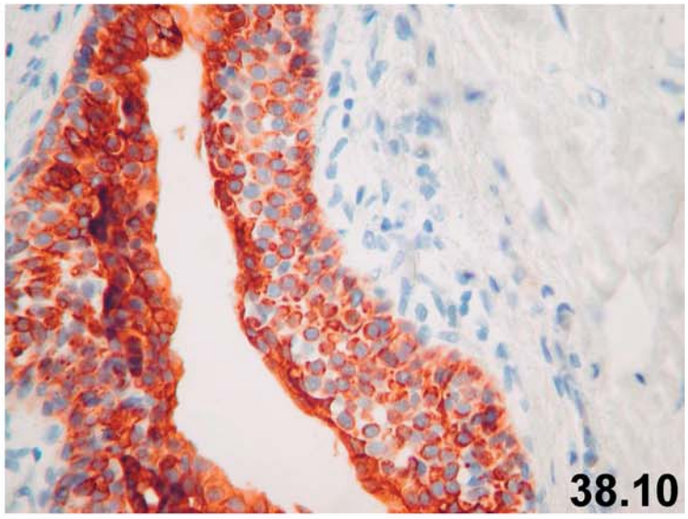
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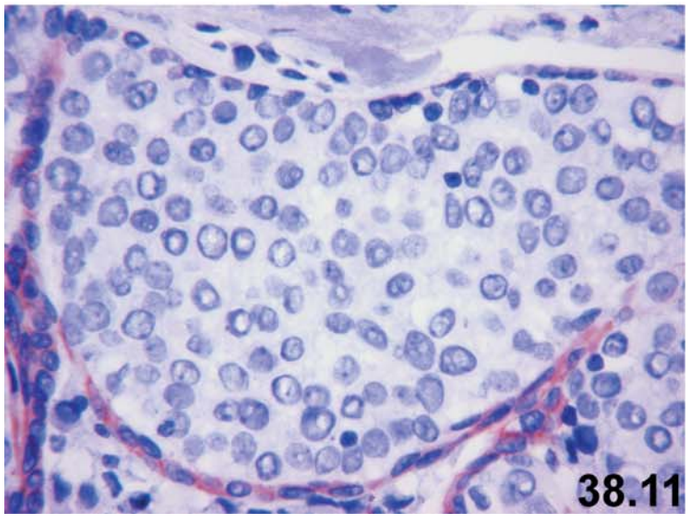
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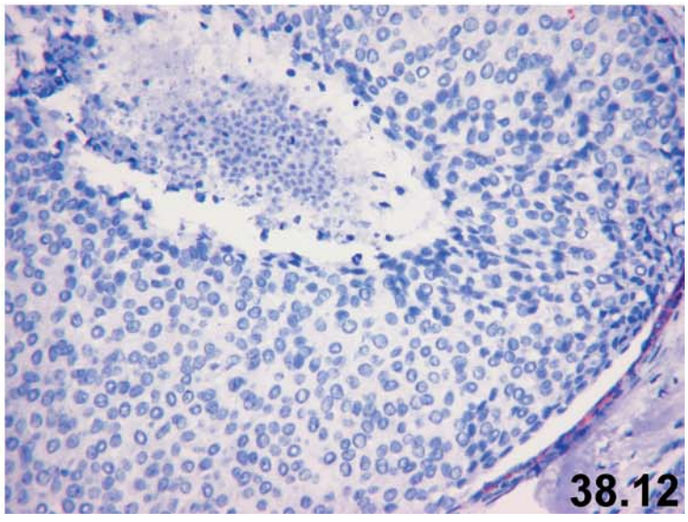
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Fig. 39: Combination of ductal intraepithelial neoplasia (DIN) and lobular intraepithelial neoplasia.

Case history: A 59-year-old woman presented with an abnormal mammogram of her right breast, showing multiple clusters of suspicious microcalcifications. Excisional biopsy was performed.

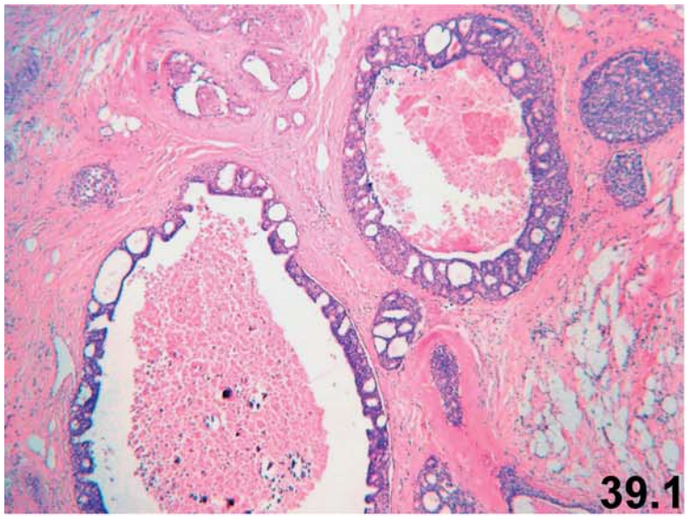
Figs. 39.1 and **39.2:** Several ducts show significant intraepithelial proliferation with a cribriform growth pattern. Some ducts show intraluminal microcalcifications.

Fig. 39.3: In addition to the cribriform growth pattern, some small ducts show a solid intraepithelial proliferation revealing a different cell population.

Fig. 39.4: A solid proliferation showing a monotonous cell population of mildly atypical cells. Note the cytoplasmic pallor of some neoplastic cells.

Fig. 39.5: A duct with solid proliferation of mildly atypical epithelial cells. Note the presence of loosely cohesive cells.

Fig. 39.6: A small duct shows pagetoid extension of uniform and atypical cells.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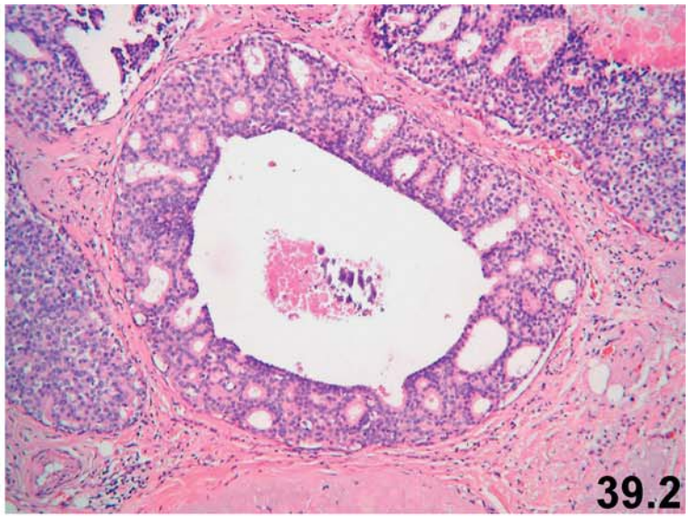
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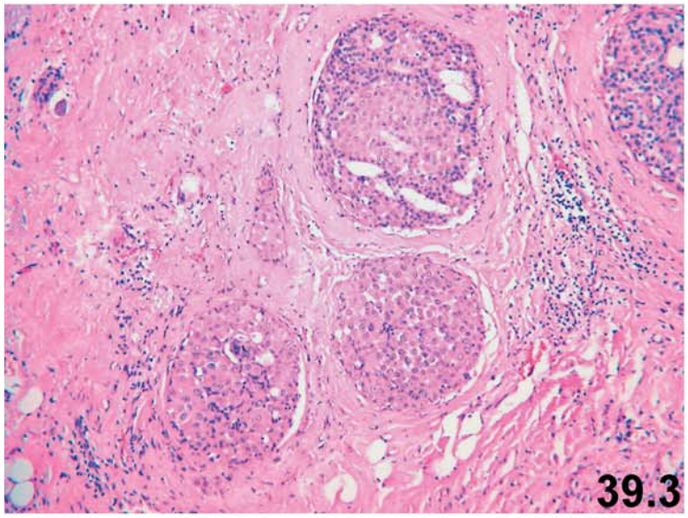
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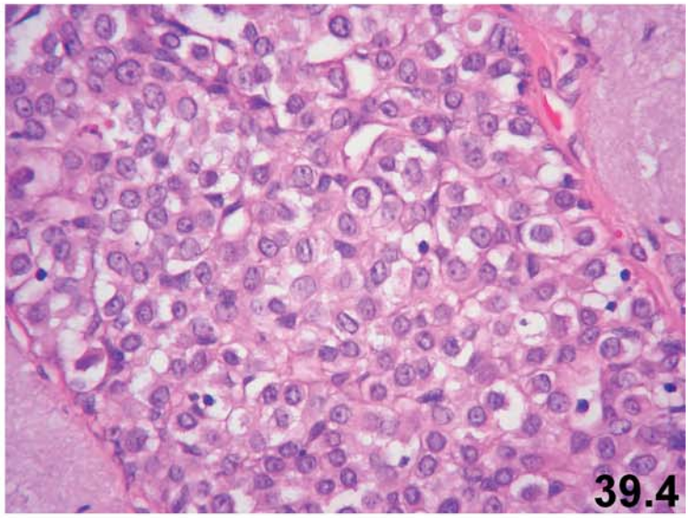
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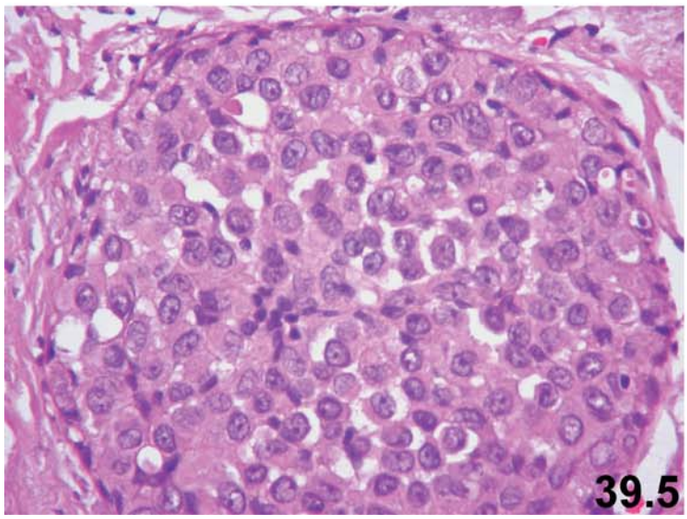
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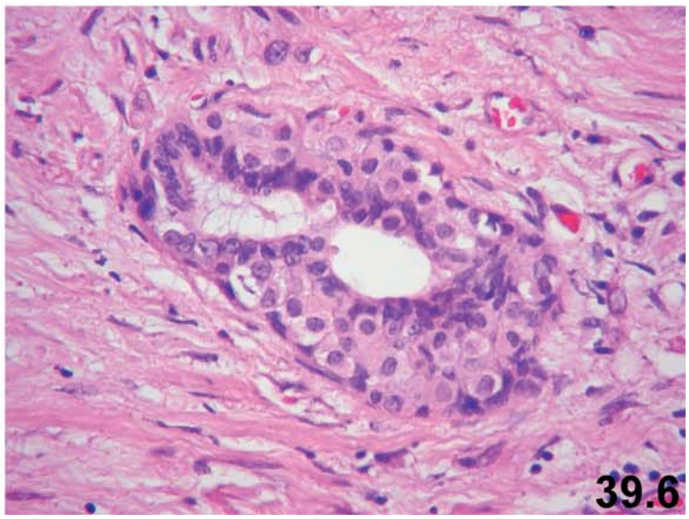
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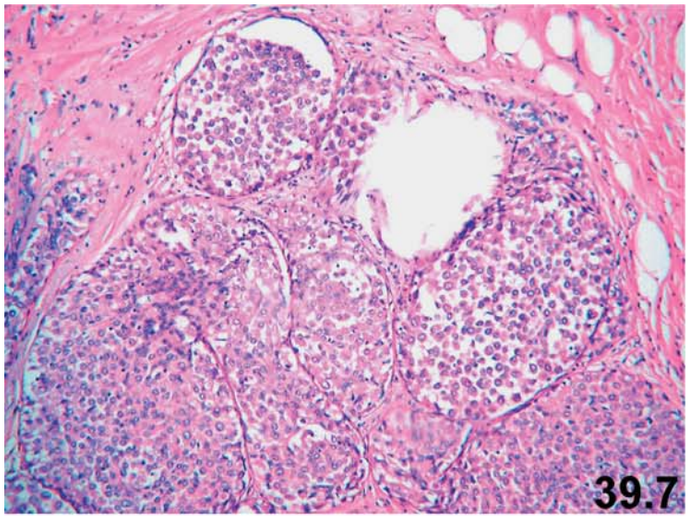
Figs. 39.7 and **39.8:** Several areas in this case show lobules and ducts with loosely cohesive uniform tumor cells. The neoplastic cells display pale or eosinophilic cytoplasm.

Figs. 39.9 and **39.10:** Several areas of the lesion with solid proliferation displaying tumor cells with intracytoplasmic lumens containing centrally located eosinophilic material (targetoid cells).

Fig. 39.11: Other areas of the lesion exhibiting more pleomorphic and larger tumor cells with apocrine-like appearance.

Fig. 39.12: While immunohistochemistry for E-cadherin shows intense positivity in areas with cribriform DIN (DCIS), solid areas of lobular intraepithelial neoplasia are negative for E-cadherin.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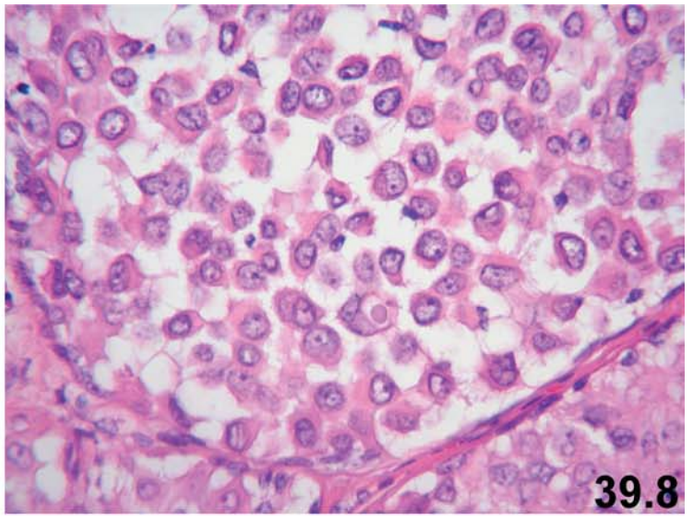
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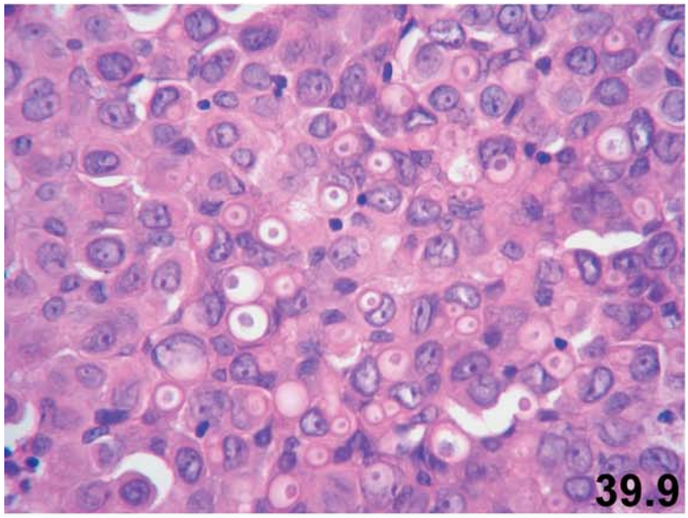
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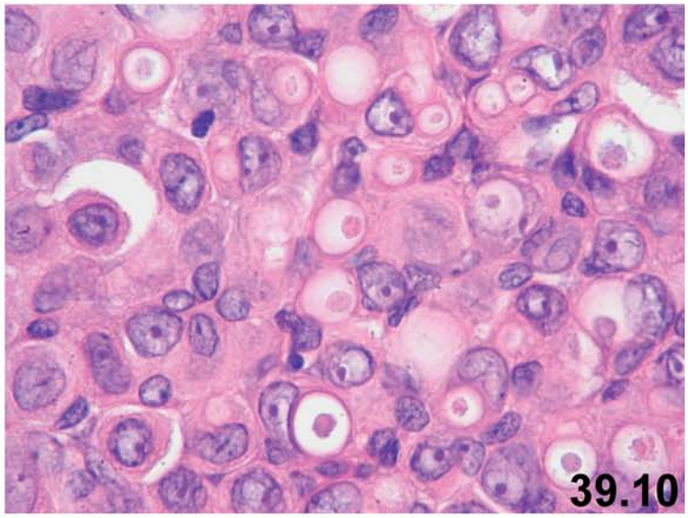
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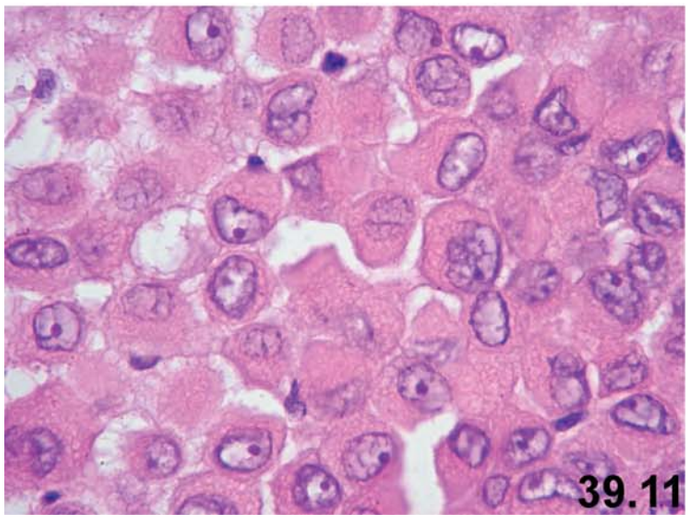
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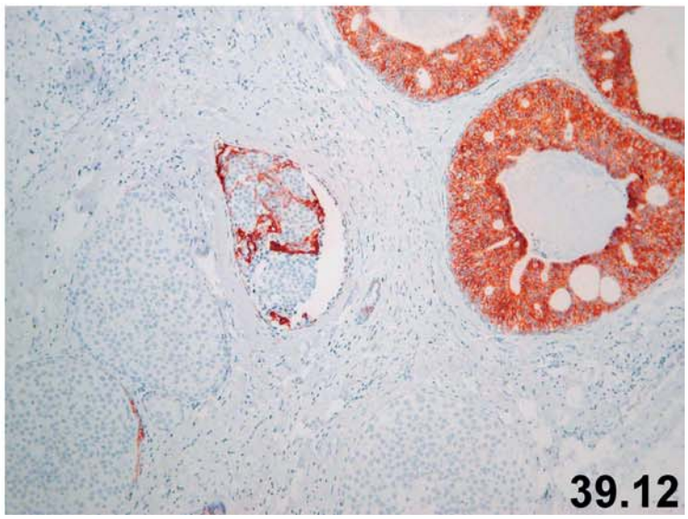
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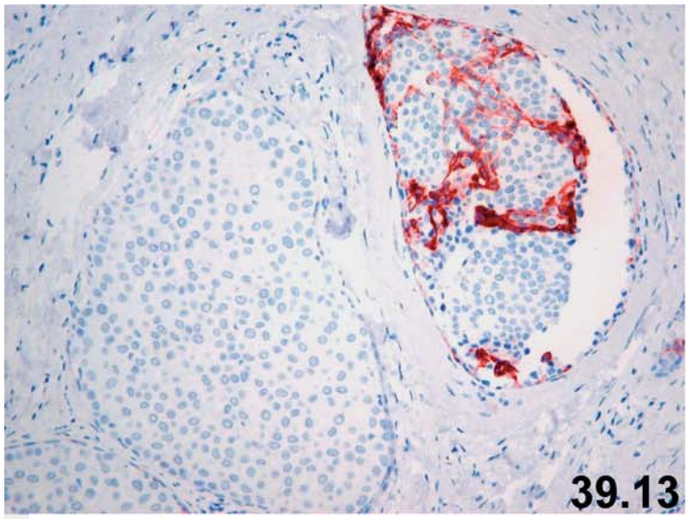
Fig. 39.13: Pagetoid extension of lobular intraepithelial neoplasia lacking E-cadherin immunoexpression.

Fig. 39.14: An area of DIN (DCIS) with typical positive immunoreaction for E-cadherin.

Fig. 39.15: In some areas a combined pattern of DIN (DCIS) and lobular intraepithelial neoplasia is present in the same ducts. Immunohistochemistry for E-cadherin decorates the cribriform growth pattern of DIN (DCIS), while it is negative in the lobular neoplastic cells.

Fig. 39.16: The neoplastic cells of DIN (DCIS) are negative for CK34BE12.

Figs. 39.17 and **39.18:** While immunohistochemistry for CK34BE12 is typically negative (Fig. 39.17) in DIN (DCIS), the tumor cells of lobular intraepithelial neoplasia (Fig. 39.18) reveal a characteristic positive reaction for it.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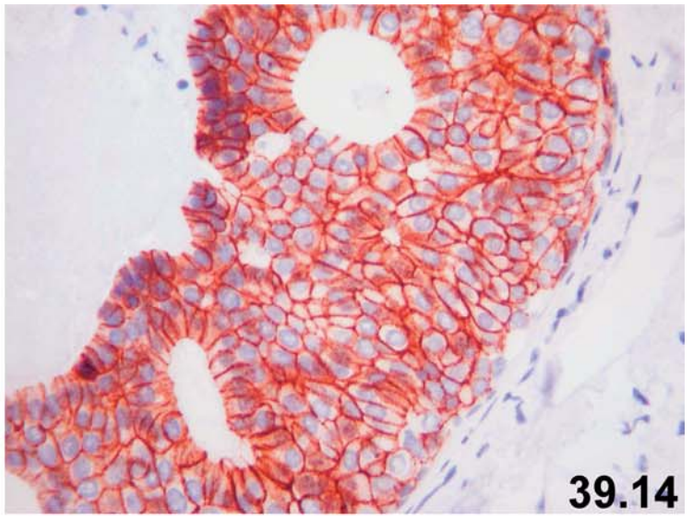
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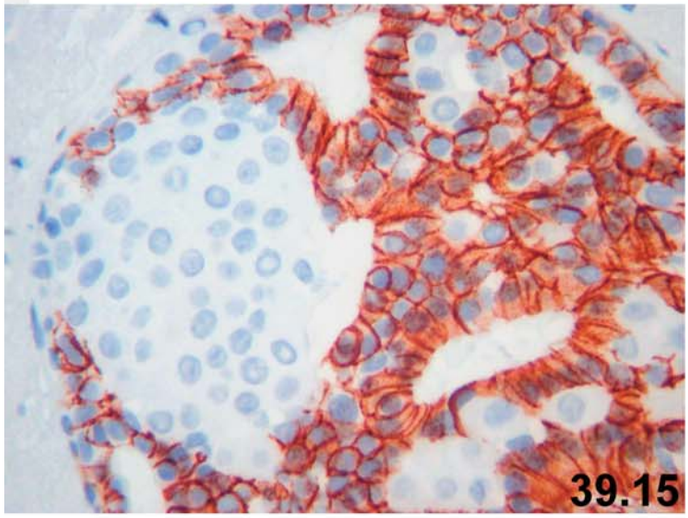
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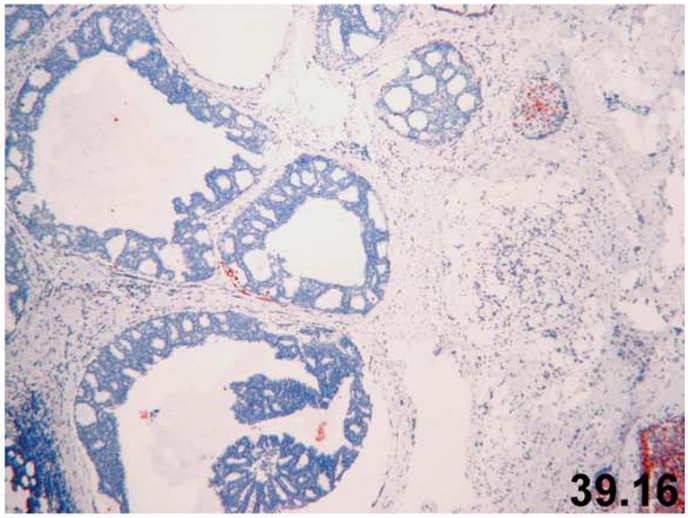
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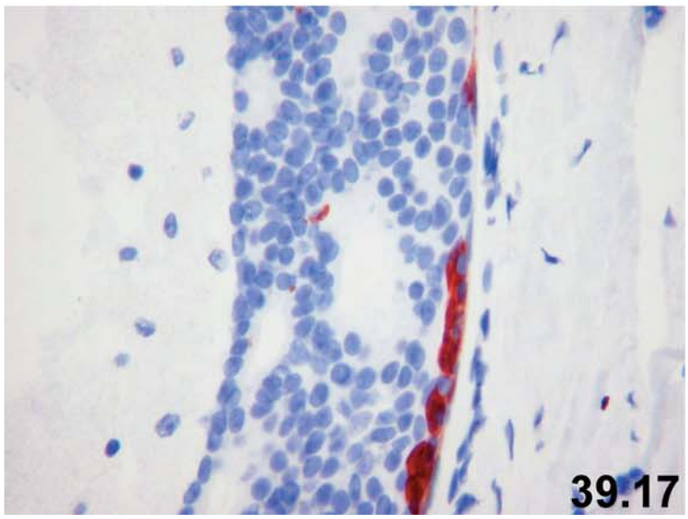
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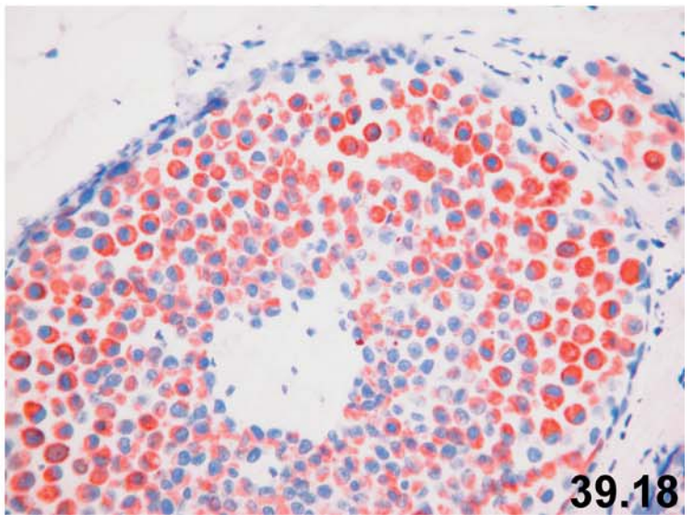
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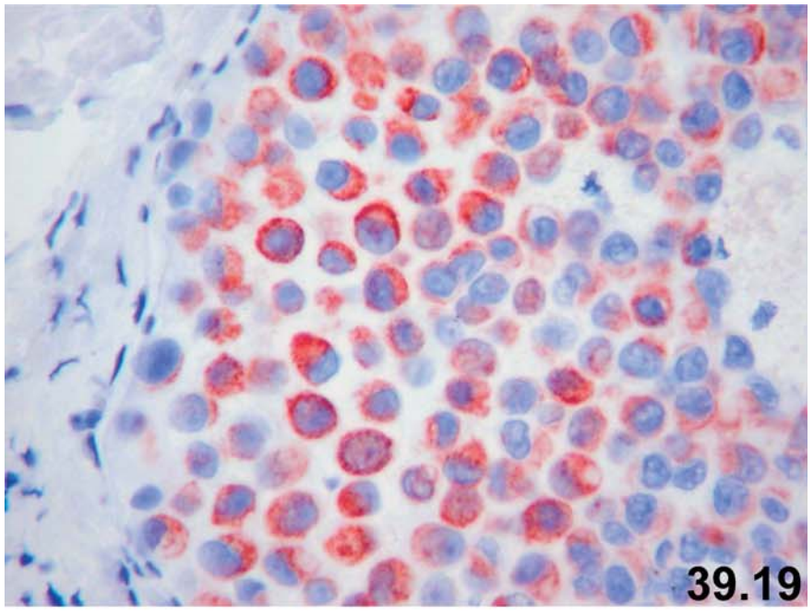
Fig. 39.19: Immunohistochemistry for CK34BE12 reveals a typical asymmetric, perinuclear or dot-like granular cytoplasmic reaction in neoplastic cells of lobular intraepithelial neoplasia.

Fig. 39.20: Comparison of CK34BE12 expression in residual normal ductal epithelial cells and lobular intraepithelial neoplasia. In the normal ductal epithelium, the immunoreaction for CK34BE12 is much more intense and decorates cell membranes. The positivity of lobular intraepithelial neoplasia for CK34BE12 is qualitatively different from that of normal ductal epithelial cells.

Fig. 39.21: This area beautifully demonstrates the simultaneous presence of DIN (DCIS) and lobular intraepithelial neoplasia (LIN) in the same duct. While neoplastic cells of DIN (DCIS) are negative for CK34BE12, a positive granular and cytoplasmic immunoreaction is present in neoplastic cells of LIN that are loosely arranged in the center of the involved duct. Note that the residual normal epithelial cells display an intense positive cell membrane reaction.

Fig. 39: Final remarks

- This case represents an example of combined DIN and lobular intraepithelial neoplasia (LIN). Even some experienced pathologists called the entire lesion DCIS and overlooked or misinterpreted several areas of LIN in this case.
- The targetoid cells of LIN should not be mistaken for signet-ring cells.
- One needs to keep in mind that CK5/6 is negative in both DIN (DCIS) and LIN and therefore cannot be used as a marker for distinguishing between these two entities. While the tumor cells of DIN (DCIS) are typically positive for E-cadherin and negative for CK34BE12, the neoplastic cells of LIN are characteristically negative for E-cadherin and positive for CK34BE12.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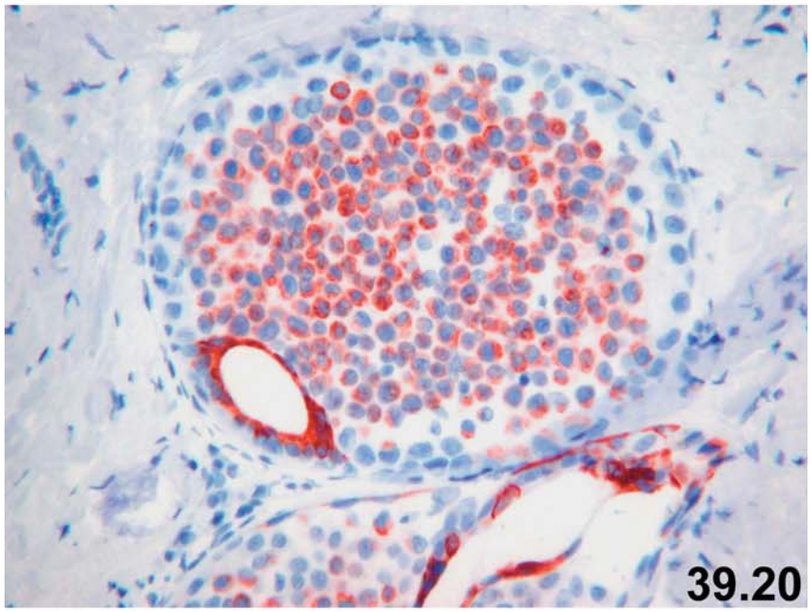
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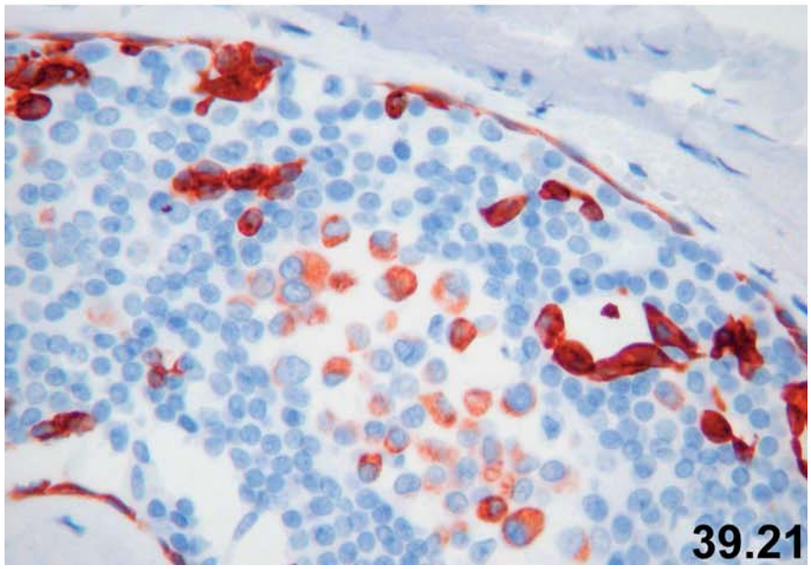
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Fig. 40: Combination of ductal intraepithelial neoplasia (DIN) flat type with lobular intraepithelial neoplasia.

Case history: A 55-year-old woman showed clinical signs of fibrocystic breast changes. Mammography of her left breast showed some irregular densities associated with microcalcifications. There was no palpable tumor. The excisional biopsy revealed fibrocystic changes associated with microcalcifications. One hematoxylin and eosin section, however, showed an incidental finding as described below.

Fig. 40.1: A well-circumscribed area closely resembling adenosis at low magnification.

Fig. 40.2: Examination at higher magnification displays small ducts lined by one cell layer of atypical cells with enlarged and hyperchromatic nuclei.

Fig. 40.3: Higher magnification showing cells with mild atypia associated with luminal microcalcification. Note that the alteration affects only the luminal epithelial cells (no simultaneous alteration of myoepithelial cells).

Fig. 40.4: Moderately atypical luminal cells showing prominent apical snouts. Note that there is no simultaneous alteration of myoepithelial cells.

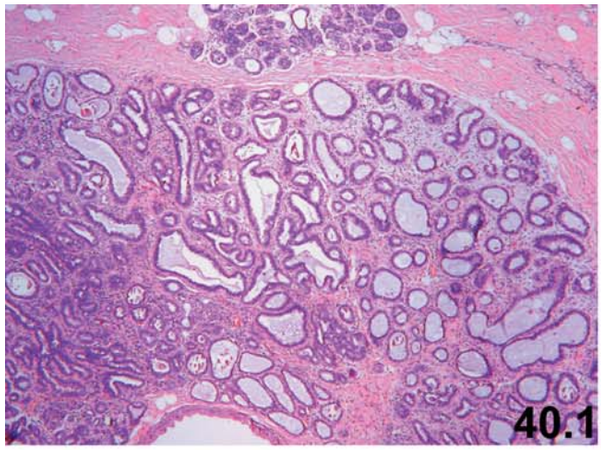
Fig. 40.5: In some other areas within the well-circumscribed and adenosis-like lesion, some ducts display highly atypical epithelial cells. The alteration affects the luminal cells at the expense of myoepithelial cells.

Fig. 40.6: At low magnification, lobular intraepithelial neoplasia with slight enlargement of the lobules and pagetoid ductal extension is present.

Figs. 40.7 and **40.8:** Typical morphology of lobular intraepithelial neoplasia showing pagetoid ductal extension of loosely cohesive cells with low-grade nuclear atypia.

Fig. 40: Final remarks

- This case represents an example of combined DIN flat type and lobular intraepithelial neoplasia. The neoplastic cells in DIN flat type in this case show both low- and high-grade nuclear atypia. Note that the DIN flat type (both low- and high-grade) was overlooked or misinterpreted as adenosis by some experienced pathologists.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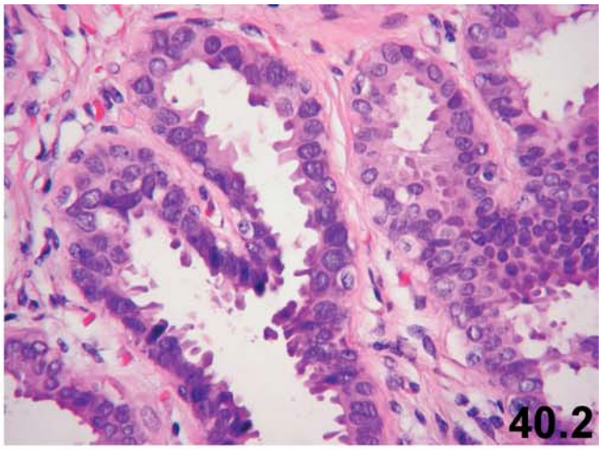
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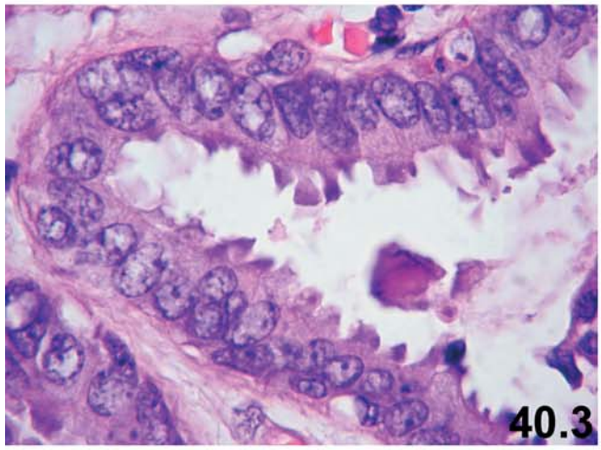
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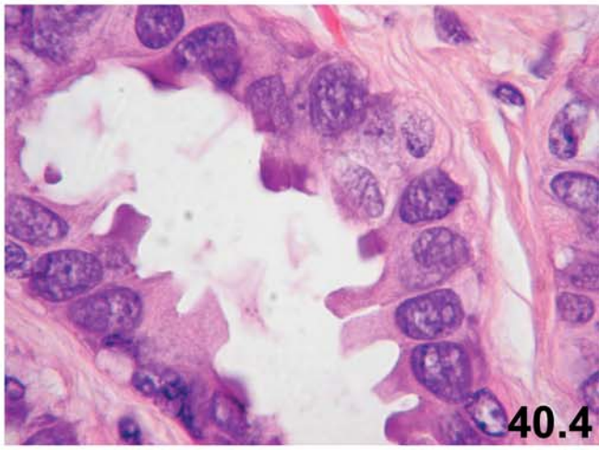
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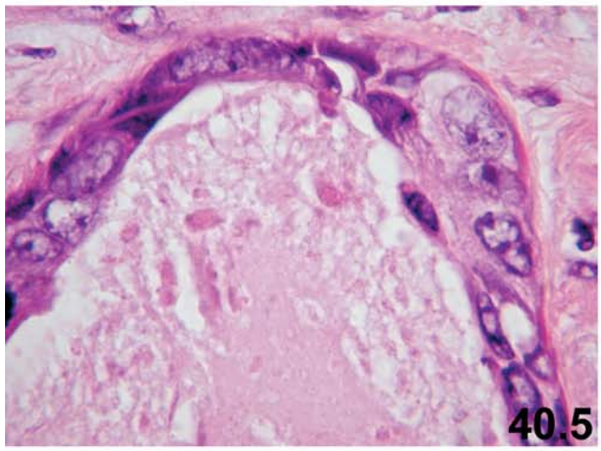
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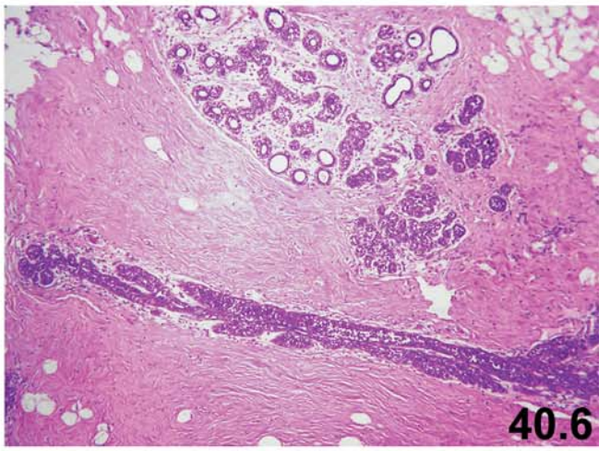
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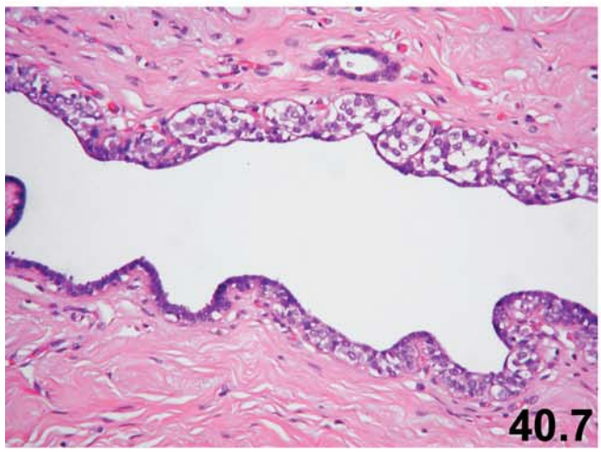
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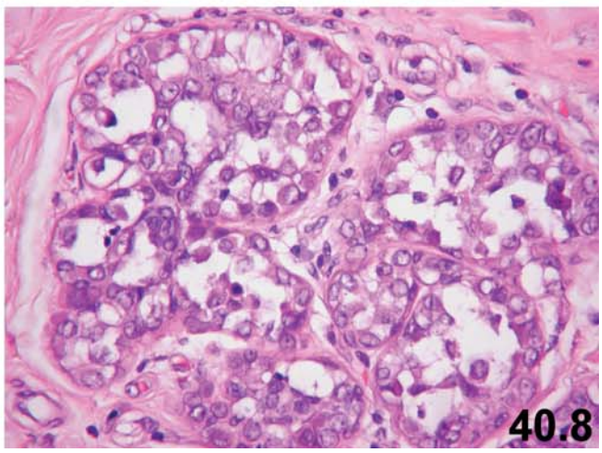
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Fig. 41: Mucinous spherulosis associated with lobular intraepithelial neoplasia.

Case history: A 70-year-old woman with clinical signs of fibrocystic changes of her left breasts. Mammography of her left breast showed some irregular areas. There was no palpable lesion. The irregular areas were removed by vacuum-assisted breast biopsy.

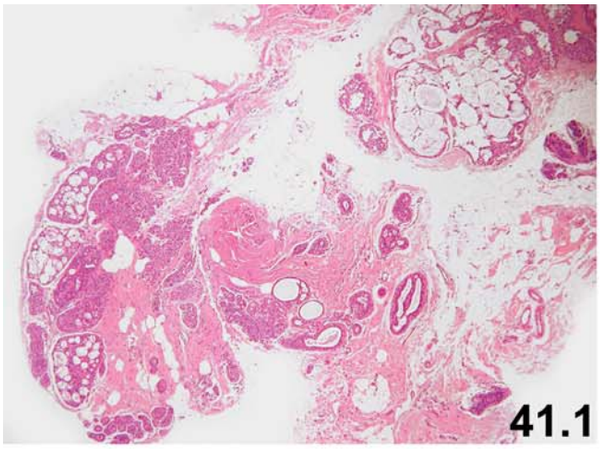
Fig. 41.1: Low magnification of the lesion shows solid proliferation as well as several microcystic areas.

Fig. 41.2: Other areas show intraductal spaces containing pale or basophilic material. The overall appearance of the lesion at low magnification is suspicious for the cribriform growth pattern of DIN (DCIS).

Figs. 41.3 and **41.4:** Lobular intraepithelial neoplasia with mildly atypical cells showing enlargement of the acinar structures within the lobules. Note the monotonous appearance of neoplastic cells.

Figs. 41.5 and **41.6:** Several intraductal secondary spaces that closely resemble a cribriform DIN (DCIS). The spaces contain basophilic mucinous material.

Figs. 41.7 and **41.8:** The secondary spaces are lined by a mixed cell population consisting of epithelial cells with round nuclei and cells with bipolar or spindle-shaped nuclei.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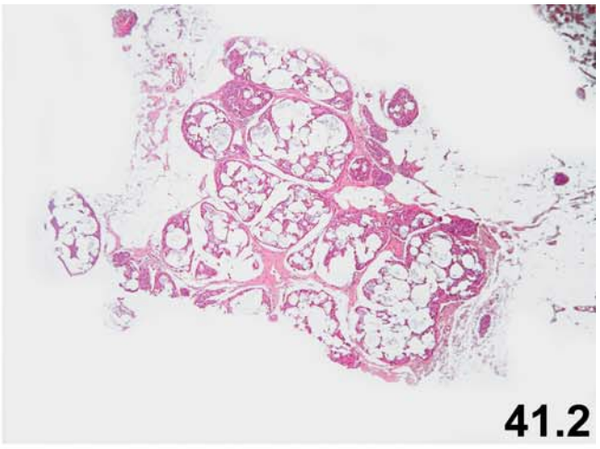
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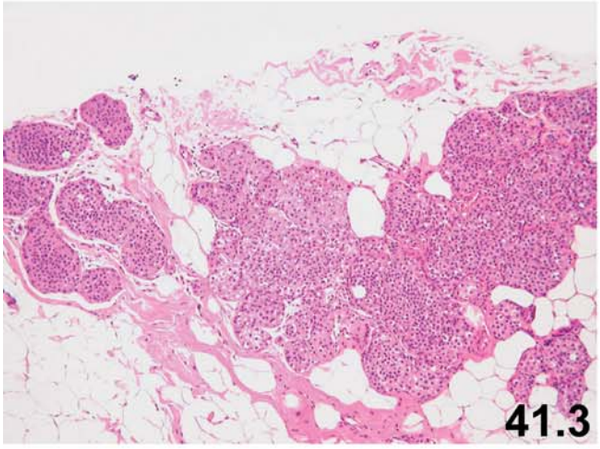
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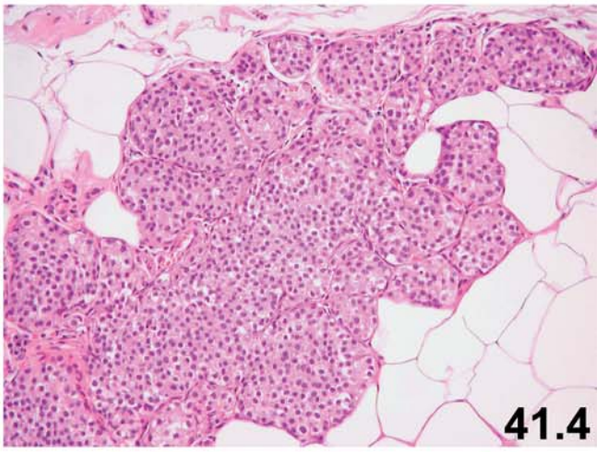
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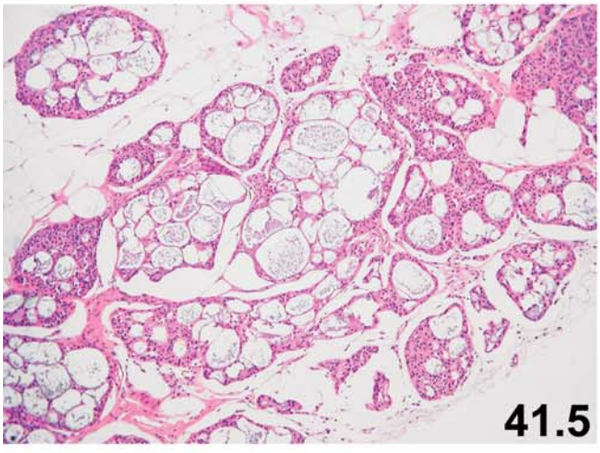
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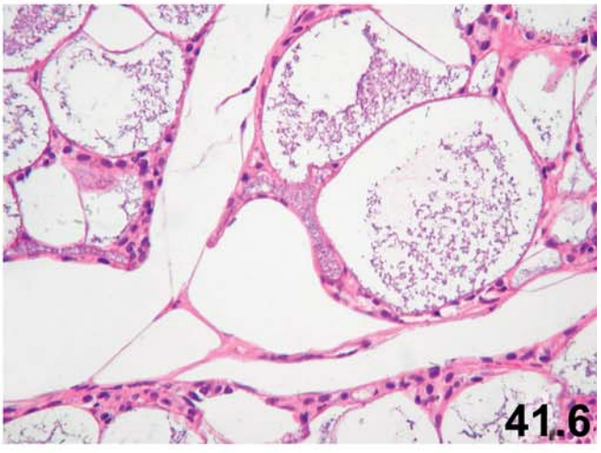
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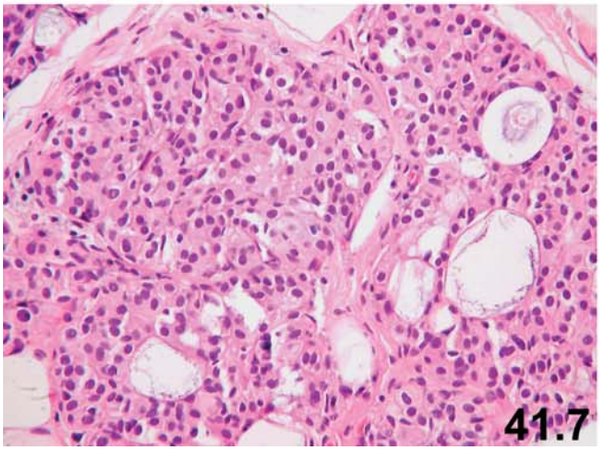
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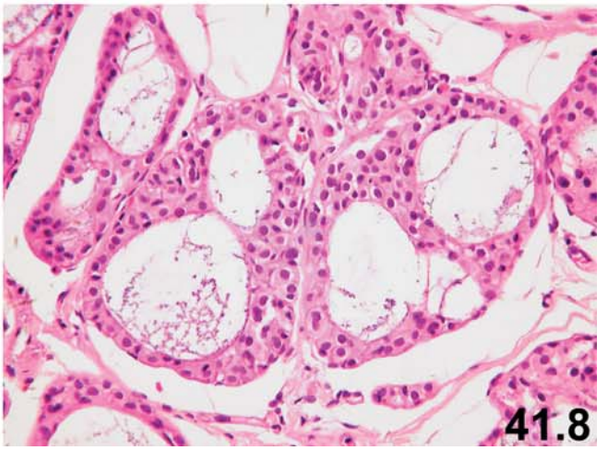
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Figs. 41.9 and **41.10:** Immunohistochemistry for p63 shows myoepithelial cells (cells with bipolar or spindle-shaped nuclei) within the secondary spaces. Note the presence of a second cell population that is negative for p63.

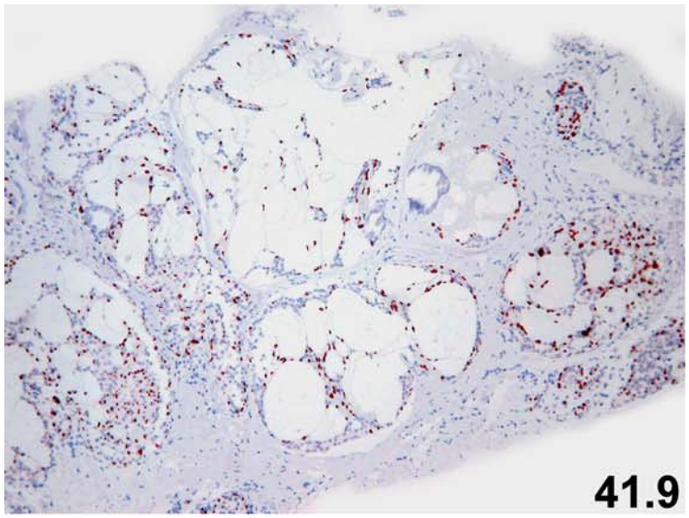
Fig. 41.11: Immunohistochemistry for smooth muscle actin also shows a myoepithelial cell component in secondary spaces. There is a second luminal cell population that is negative for smooth muscle actin.

Fig. 41.12: Immunohistochemistry for E-cadherin shows that both cell components are negative.

Figs. 41.13 and **41.14:** Immunohistochemistry for CK34BE12 displays a positive reaction in solid areas and areas with spherules or secondary spaces.

Fig. 41: Final remarks

- The main differential diagnosis in this case is DIN (DCIS; solid and cribriform variant). The immunohistochemistry for myoepithelial cells and CK34BE12 is helpful in this case in order to recognize the myoepithelial cell component of mucinous spherulosis and the lobular nature of the accompanied neoplastic cells. While the negative immunoreaction for E-cadherin excludes the possibility of DIN (DCIS), the positive reactivity for CK34BE12 is consistent with lobular intraepithelial neoplasia. In this case, the positive immunoreaction for p63 and smooth muscle actin demonstrates that myoepithelial cells are involved in mucinous spherulosis. The luminal mucinous material in the spherules was positive for PAS (after diastase) and alcian blue (not illustrated).
- Mucinous spherulosis represents the earliest stage of collagenous spherulosis.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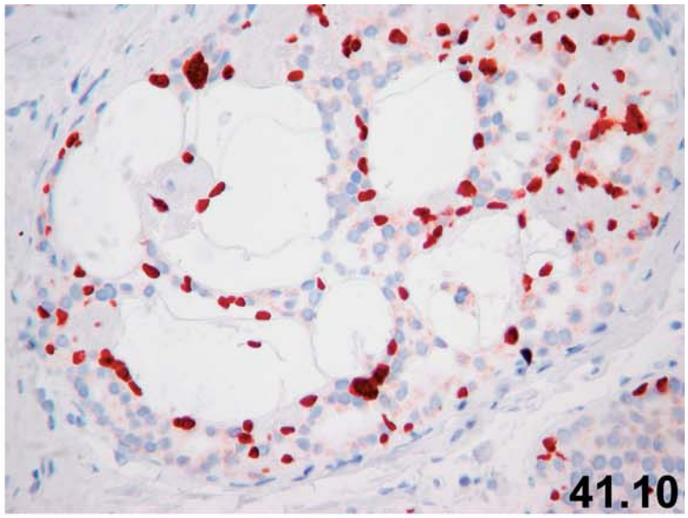
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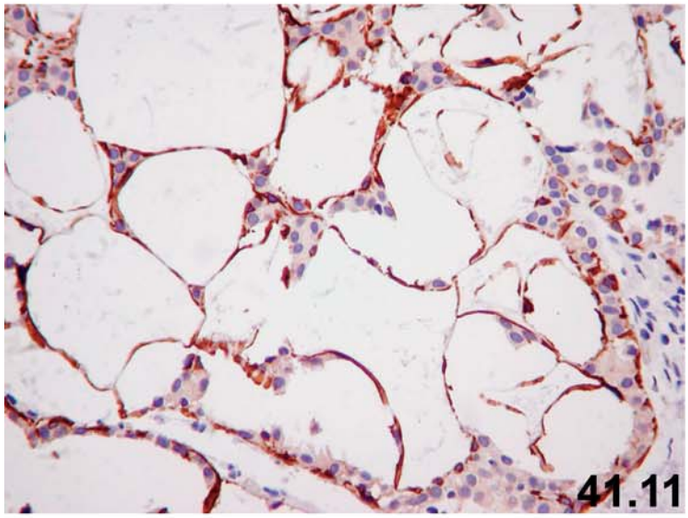
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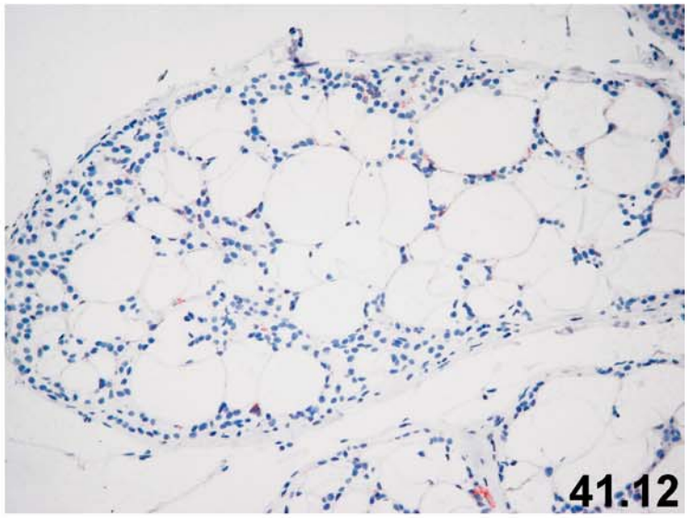
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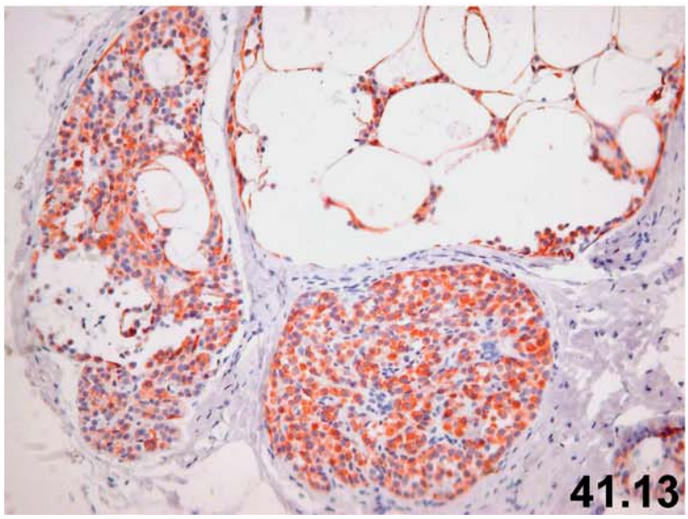
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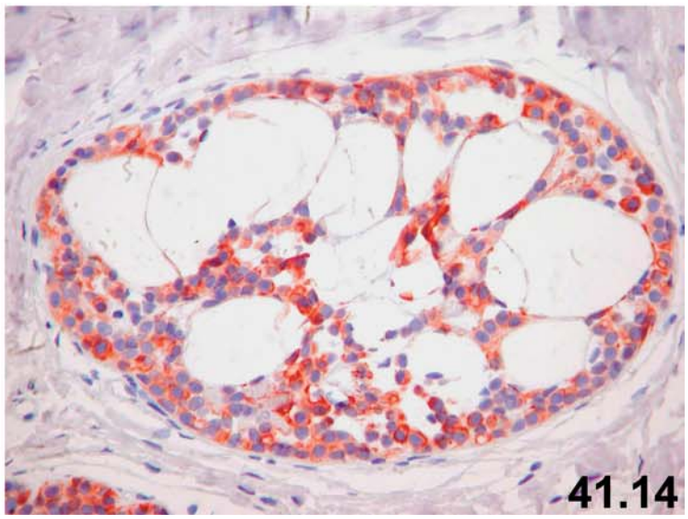
41.14

Infiltrating Ductal Carcinoma (NOS Type)

Contents

CHAPTER 8 Infiltrating Ductal Carcinoma (NOS Type)

8.1 Definition

Infiltrating ductal carcinoma (IDC) is the most common type of invasive breast carcinoma (60–75% of all mammary invasive carcinomas). By definition, the diagnosis of this tumor is made on the basis of exclusion; it is a malignant tumor that cannot be classified as any special type of breast carcinoma (not otherwise specified, or NOS).

8.2 Macroscopy

There is a marked variation in size, from smaller than 1 cm to larger than 10 cm. The tumors can have an irregular, stellate outline or a nodular configuration with pushing margins. There is usually a greyish-white cut surface with hard consistency. Carcinomas frequently feel gritty when cut with a knife. Yellow to white streaks (elastosis) can be present. The fatty tissue close to the tumor often reveals an intense yellow color that differs from the color of fatty tissue away from the carcinoma [1].

8.3 Microscopic Features (Figs. 42 and 43)

- Irregular or rounded, solid epithelial clusters admixed with single cells and cords of tumor cells lacking the morphologic features of any of the special types of invasive carcinoma are present.
- Infiltrating and/or pushing margins are present.
- The tubules and solid cell clusters are not surrounded by myoepithelial cells.
- There is no basal lamina around the glands and solid structures.
- Stromal reaction includes edematous, myxoid, elastotic changes, or, more often, hypercellular and desmoplastic changes with or without lymphocytic infiltration.
- Vascular invasion can be identified.
- (Peri)neural invasion can be present (has no prognostic significance).
- In a majority of well-sampled cases, areas of ductal intraepithelial neoplasia (DIN; ductal carcinoma in situ [DCIS]) are evident.
- In some tumors, both DIN (DCIS) and lobular intraepithelial neoplasia (LIN; lobular carcinoma in situ [LCIS]) may be present.
- In a small proportion of cases, an infiltrating ductal carcinoma may be accompanied by LIN in the absence of DIN (DCIS).

8.4 Grading

There are two methods of grading: nuclear (cytologic) grading and grading according to the modified Bloom and Richardson system (Nottingham, or Elston and Ellis system).

Nuclear grading [5, 15, 16a, 16b, 23, 24, 41] is a cytologic evaluation of the tumor nuclei that compares them with the nuclei of normal mammary epithelial cells. Using high-power magnification, the following parameters should be evaluated: nuclear enlargement, nuclear-cytoplasmic (N/C) ratio, irregularity of nuclear membrane, irregularity of chromatin distribution, prominence of nucleoli, and degree of polymorphism (variation of nuclear size and shape). A low-grade carcinoma is characterized by uniform tumor cells with small regular nuclei showing regular chromatin distribution. A high-grade carcinoma reveals polymorphic tumor cells with significant variation in nuclear size and shape, prominent nucleoli, irregular nuclear membrane, and coarse and irregular chromatin. Because nuclear grading does not assess the tumor's growth pattern and does not rely on mitotic rate, it is applicable to all types of mammary carcinoma.

Histologic grading (modification of Bloom and Richardson system: the Elston and Ellis grading system) [14, 32] is based on the degree of tubular formation, nuclear atypia, and mitotic activity:

Tubule formation is given a score of 1 when an overall evaluation of the tumor shows formation of tubules with visible lumens in a majority (more than 75%) of the lesion. When solid areas of tumor growth are admixed with a moderate degree of the tubular arrangements (10–75%), the tumor is given a score of 2. When little (less than 10%) or no tubule formation is seen, and the cells are growing in sheets or cords, the score is 3 points. In the assessment of nuclear atypia, variation in size and shape of the tumor nuclei is evaluated. Tumors with uniform or regular, small nuclei and those exhibiting minimal variation score 1 point. Tumors with a moderate degree of variation in nuclear size and shape and occasional nucleoli score 2 points. Those with marked variation in nuclear size and shape and those containing bizarre nuclei, often with irregular chromatin distribution and one or more prominent nucleoli, score a 3. If any difficulty is encountered in assessment of nuclear atypia, then the nuclear appearances should be evaluated in the least differentiated area.

For determining mitotic rate, at least 10 high-power fields (hpf) in the most mitotically active areas (mostly at the periphery) of the tumor are evaluated. The number of mitotic figures required for each point varies with the size of the hpf for a given microscope. In the original study by Elston and Ellis, using a microscope field with a diameter of 0.59 mm and an area of 0.274 mm^2 (Leitz Ortholux microscope with wide-angle eyepieces and ×25 objective), tumors with a count of 0–9 mitotic figures per 10 hpf were given 1 point, those with 10–19 mitotic figures per 10 hpf scored 2 points, and those with 20 or more mitotic figures per 10 hpf scored 3 points.

Grade 1 (well differentiated): 3–5 points (Fig. 42)
Grade 2 (moderately differentiated): 6–7 points
Grade 3 (poorly differentiated): 8–9 points (Fig. 43)

Caution

- The separation into three grades of breast carcinoma is arbitrary and artificial. There is in fact a continuous scale of malignancy. However, using the histologic grading system, a good correlation with prognosis is achieved [14, 32].

8.4.1 Problems with Mitotic Counts

To determine the number of mitotic figures for any microscope, it is necessary to have the diameter of the field of view, or field diameter, at high power (×40).

- The number of mitotic figures per 10 hpf in a given carcinoma can vary significantly depending on the microscope used: Olympus, Nikon, Zeiss, Leica, etc.
- Some of the aggressive breast carcinomas (signet-ring cell carcinoma, pleomorphic variant of ILC) do not reveal high mitotic activity.
- There are limited areas for mitotic counts in core needle biopsies.

Caution

- The grading system is still undergoing evolution, and the ultimate system has not been devised yet. Although not identical, both the histologic method and the nuclear grading system have been useful in predicting prognosis of breast carcinomas.

8.4.2 Advantages of Nuclear Grading

Nuclear grading is easy to perform. It uses the same cytologic criteria as those used for DIN (DCIS) grading and can be applied on core needle biopsies. It is applicable to any type of carcinoma (special types) and is independent of the type of microscope used (thus eliminating the problem with mitotic count and hpf variation among different types of microscopes).

8.5 Additional Comments

The following information should be provided in a pathology report: tumor size, tumor type (NOS or special type), presence or absence of vascular (lymphatic) invasion, status of the margins (distance of carcinoma from the next margin), grading (specify nuclear or modified Bloom–Richardson system), and TNM classification. Information concerning accompanying DIN (DCIS) such as grade, size, and type should also be included [5, 26, 30, 33, 36].

Immunohistochemistry for estrogen receptor, progesterone receptor, and HER2/neu needs to be done on invasive carcinoma regardless of the tumor's grade and type [21].

MIB-1 monoclonal antibody is a promising tool for determining cell proliferation on routine histological material. A few recent studies have demonstrated that breast carcinomas with a high MIB-1 index (cut-off value of at least 25%) are sensitive to chemotherapy protocols. It has been suggested that immunohistochemistry for MIB-1 is a valuable adjunct for identifying high-risk breast cancer patients [37, 40].

8.6 Further Reading

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Fig. 42: Well-differentiated infiltrating ductal carcinoma.

Case history: A 75-year-old woman presented with a firm and irregular mass in the upper outer quadrant of her left breast. Mammography showed a tumor with infiltrating borders. Excisional biopsy was performed.

Fig. 42.1: The cut surface of the excisional biopsy shows a greyish-white tumor with infiltrating margins. The adipose tissue adjacent to the tumor shows a very intense yellow color that is different from the color of adipose tissue away from the tumor. The intense yellow color of adipose tissue close to the tumor is a common and characteristic gross feature of breast carcinoma.

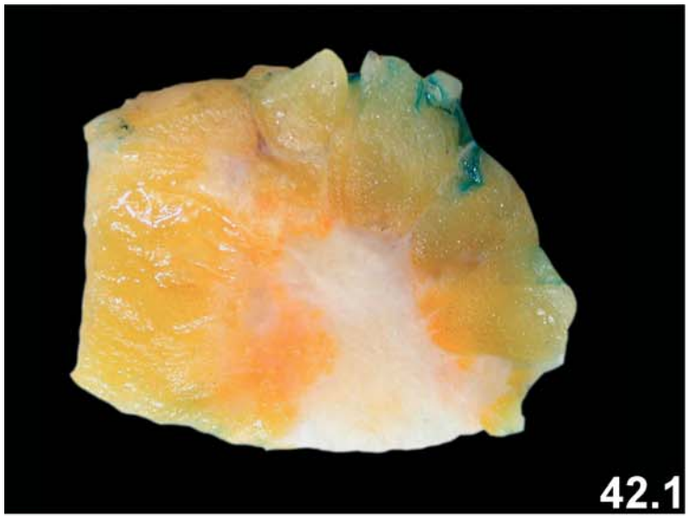
Fig. 42.2: Low magnification of tumor shows haphazardly arranged tubules infiltrating adjacent adipose tissue.

Fig. 42.3: Several small or elongated glands with infiltrating growth pattern are present. Note the reactive or desmoplastic stromal alteration.

Fig. 42.4: Higher magnification reveals tubules and strands of tumor cells with low-grade nuclear atypia. The mitotic activity is very low.

Fig. 42.5: Higher magnification shows a tubule with mildly atypical tumor cells. The lack of a myoepithelial cell layer is evident, which is characteristic of invasive carcinoma.

Fig. 42.6: A few areas of the tumor show microcalcification associated with infiltrating ductal carcinoma. Because of low-grade nuclear atypia (score 1), low mitotic activity (score 1), and predominant tubular formation (score 1), this tumor qualifies as grade 1 or well-differentiated (low-grade) ductal carcinoma.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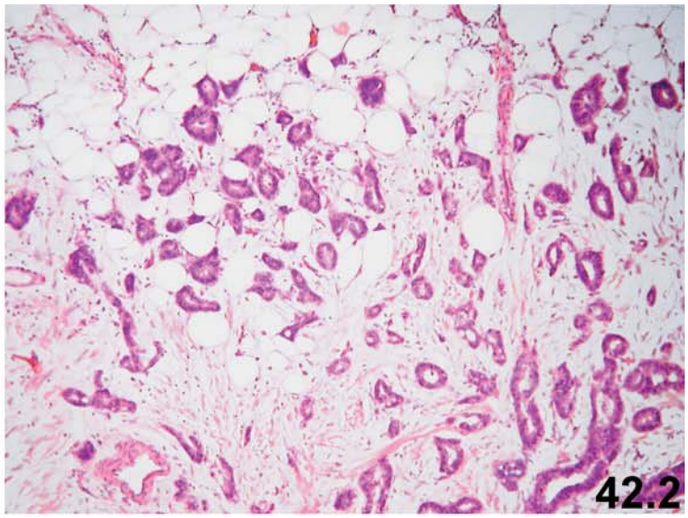
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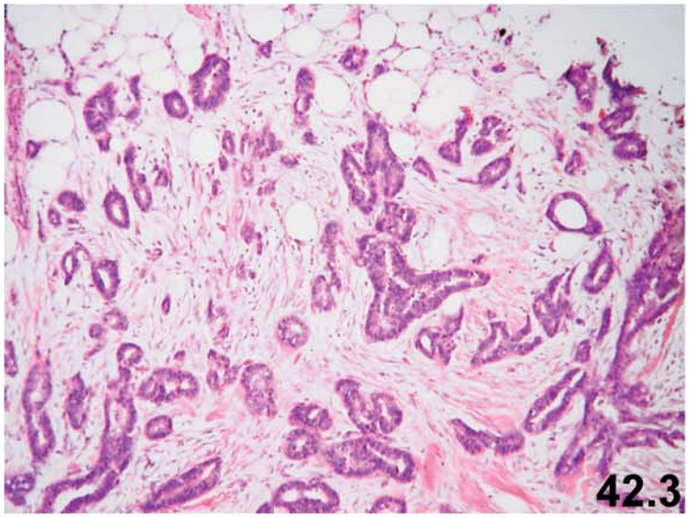
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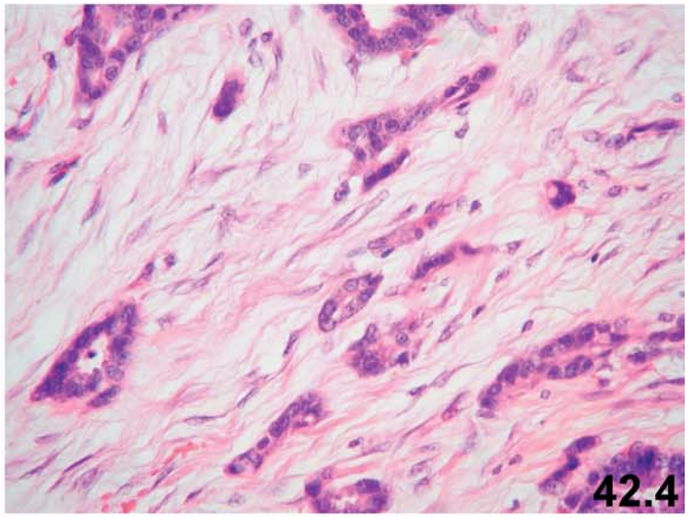
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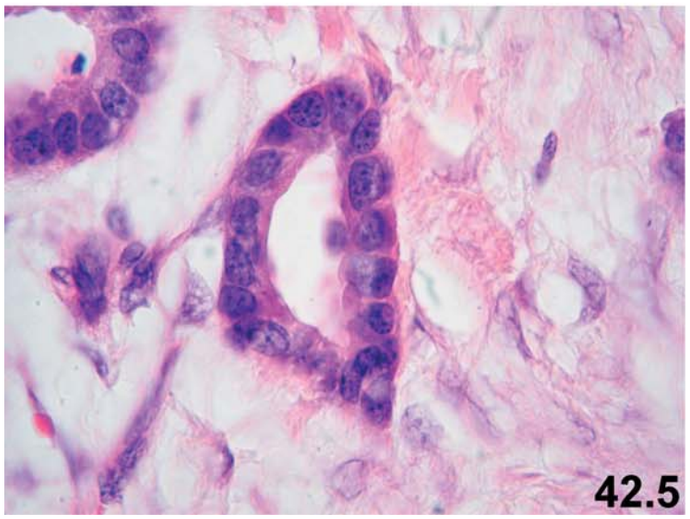
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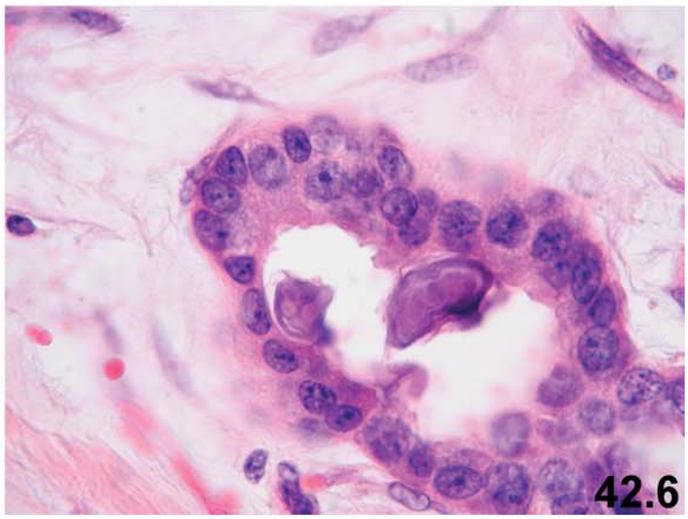

42.6

Fig. 43: Poorly differentiated infiltrating ductal carcinoma.

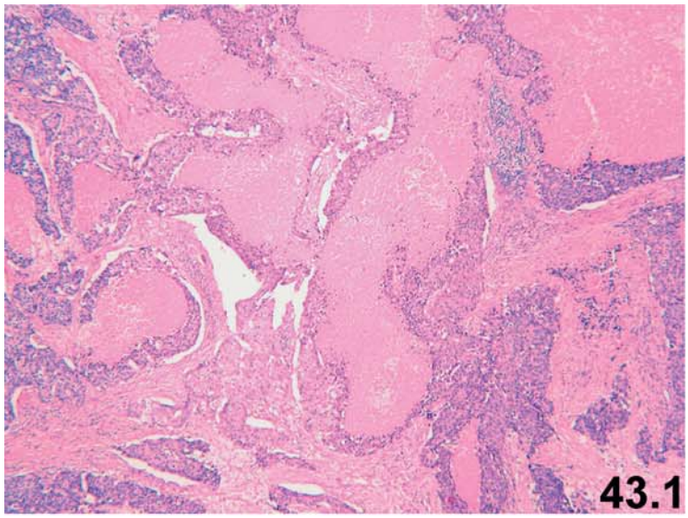
Case history: A 39-year-old woman presented with an ulcerating 12-cm-large tumor in the upper outer quadrant of her right breast. Modified radical mastectomy was performed.

Fig. 43.1: Numerous solid aggregates of the tumor cells show an irregular and infiltrating growth pattern. The tumor shows abundant necrosis.

Figs. 43.2, 43.3: The tumor shows irregular and infiltrating solid epithelial structures.

Fig. 43.4: The tumor cells show high-grade nuclear atypia.

Figs. 43.5 and **43.6:** High magnification of the tumor demonstrates severe nuclear atypia and pleomorphism (pleomorphism of anaplasia). Note the irregularity of chromatin distribution and multiple prominent nucleoli. Several mitotic figures are evident.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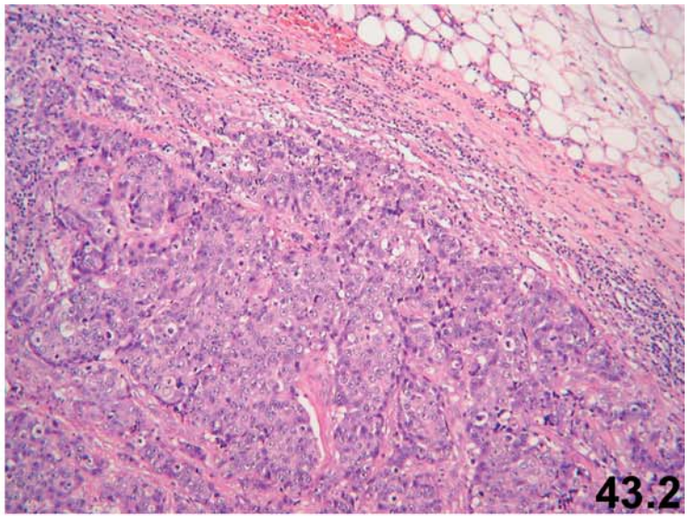
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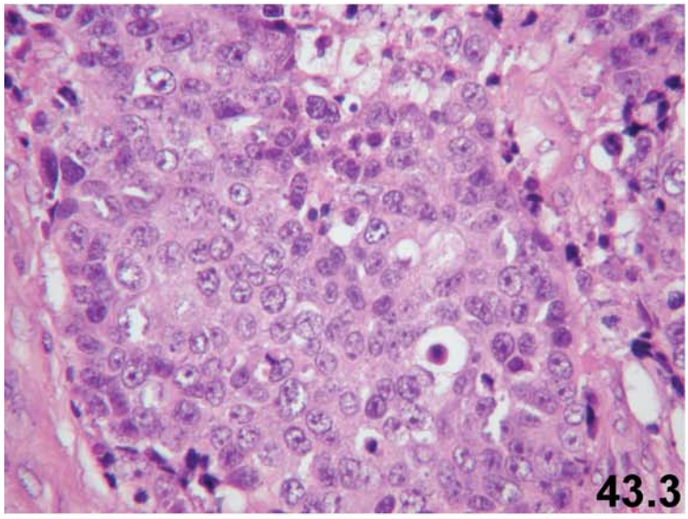
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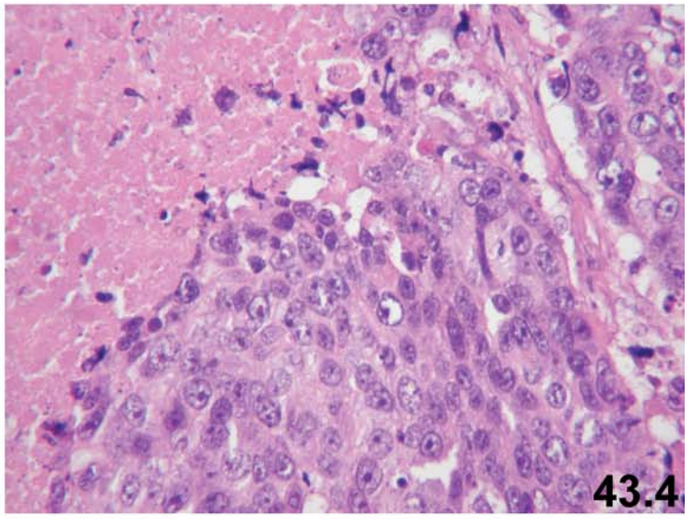
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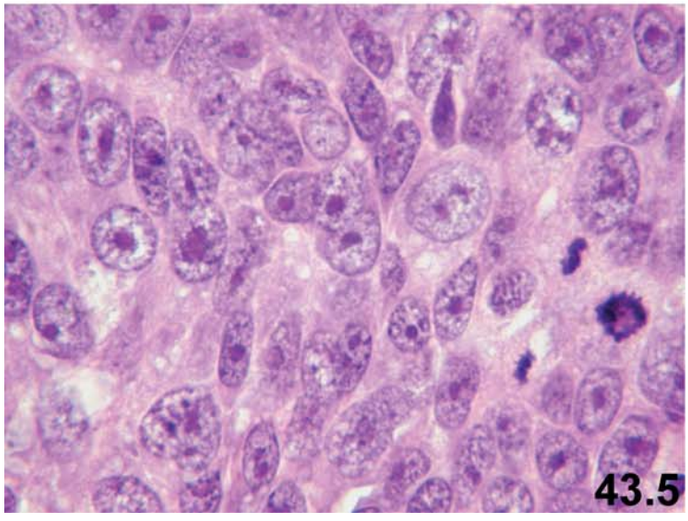
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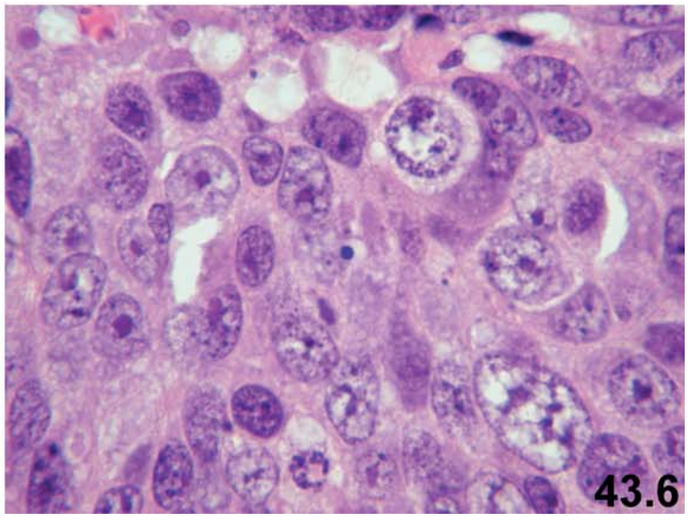
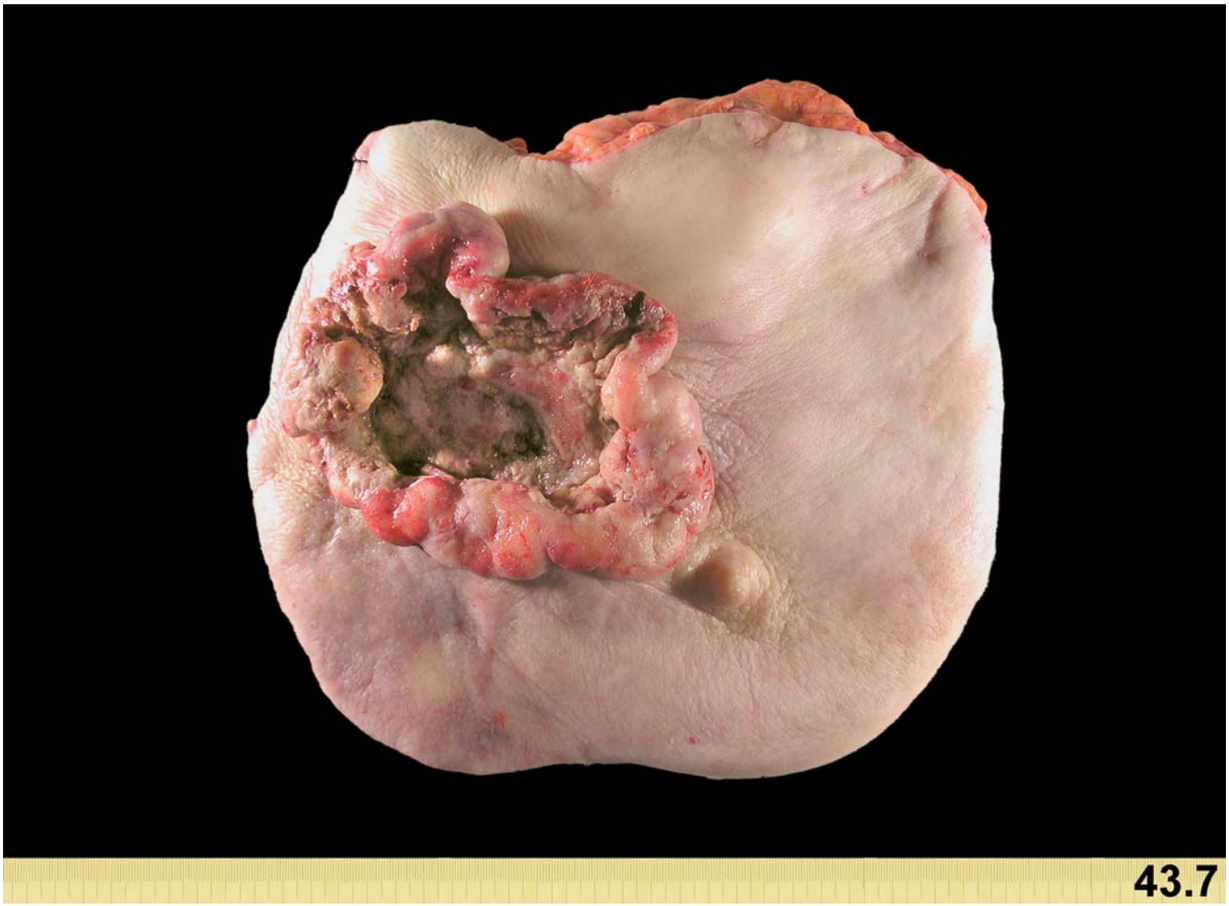

43.6

Fig. 43.7: Mastectomy specimen showing a tumor with extensive skin ulceration and necrosis. The tumor measures 12 cm in greatest diameter.

Figs. 43.8 and **43.9:** Five years after breast surgery, the patient died of multiorgan failure as a consequence of general metastases. Autopsy was performed and showed bone marrow (Fig. 43.8) and liver (Fig. 43.9) metastases. In addition, there were metastases to the lungs, heart, and skin (not shown).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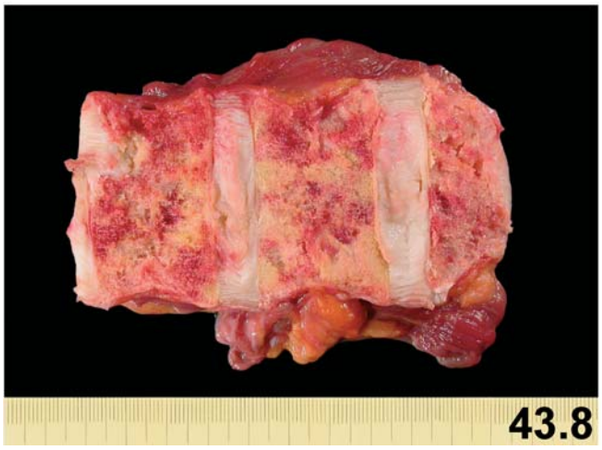
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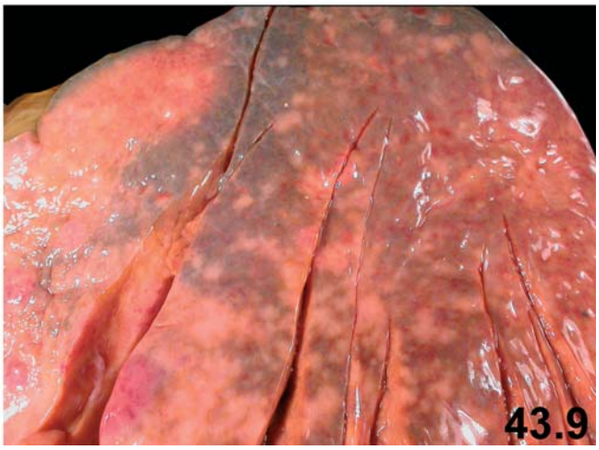
43.9

Invasive Lobular Carcinoma (ILC)

Contents

CHAPTER 9 Invasive Lobular Carcinoma (ILC)

9.1 Macroscopy

Tumor size ranges from occult, grossly unapparent lesions of microscopic dimensions to tumors that diffusely involve the entire breast. Typically, invasive lobular carcinoma forms a firm to hard tumor with irregular borders. In some cases, however, the tumor may not be grossly visible. Another gross manifestation of invasive lobular carcinoma (ILC) is the formation of numerous small hard nodules mimicking sclerosing adenosis, grossly and microscopically [2, 22, 31, 34].

9.2 Microscopic Features (Figs. 44–51)

- Infiltrating pattern of small or medium-sized uniform epithelial cells.
- Linear arrangement of carcinoma cells (single-file pattern) with a tendency to grow in a circumferential fashion around ducts and lobules ("targetoid" growth).
- Isolated uniform cells as well as linear strands of no more than one or two cells across.
- Often, a discontinuous infiltrative pattern with irregular borders [2, 7–9, 11, 22].
- Homogeneous cell population of epithelial cells (no myoepithelial cells).
- Usually mild nuclear atypia, slight hyperchromasia, scant cytoplasm; often eccentric nuclei.
- Some of the tumor cells show irregular nuclear membrane and eosinophilic cytoplasm.
- Tumor cells with intracytoplasmic mucus.
- Sometimes signet-ring cells with hyperchromatic, eccentric nuclei with morphology identical to that of gastrointestinal tract signet-ring cell carcinoma.
- In addition to the classic pattern, a more polymorphic (pleomorphic) cell population can be present, showing severe nuclear atypia, larger cytoplasm, and prominent nucleoli with or without increased mitotic activity (pleomorphic variant of ILC) [2, 7–12, 14–16, 22, 30].

9.3 Additional Comments

The division into lobular and ductal type carcinomas should not be confused with ductal epithelial origin or lobular epithelial origin as if the sites of origin of the two were completely distinct. Lobular and ductal types of carcinoma refer to histologically, cytologically, and immunohistochemically identifiable entities and not necessarily to sites of origin (the most common site of origin is the terminal duct-lobular unit).

A tumor should be classified as ILC independently of the presence or absence and the nature of any in situ (intraepithelial) component. In practice, 80% of ILCs will show foci of lobular intraepithelial neoplasia (LIN; lobular carcinoma in situ [LCIS]) as well, if sampling is adequate.

Variants of ILC include solid, alveolar, histiocytoid, and tubulolobular carcinomas. The solid variant consists of a closely packed proliferation of uniform, small epithelial cells, forming large nests separated by very delicate vascular channels. In the alveolar variant, a similar cell population forms rounded nests and islands of 20 or more cells separated by a minimal amount of stroma. Depending on the results of immunohistochemistry for E-cadherin and CK34BE12, the tubulolobular variant represents either a carcinoma with lobular (ILC) or mixed ductal and lobular differentiation [11, 12, 15, 16].

At least 5% of invasive breast carcinoma cannot be classified as ductal or lobular with certainty, or even as mixed ductal and lobular type. Immunohistochemistry with antibody against E-cadherin (preferably in combination with CK34BE12) can be helpful for classifying some of these primary breast carcinomas.

9.4 Immunohistochemistry of LIN and ILC

E-cadherin is negative in almost all cases of LIN and ILC. CK34BE12 (high molecular weight cytokeratin containing a cocktail of CKs 1, 5, 10, and 14) is characteristically positive in the vast majority of LIN and less common positive in ILC.

9.5 Grading

Although it is possible to grade ILC on the basis of nuclear features, grading on the basis of the modified Bloom and Richardson grading system (Nottingham system) is acceptable (and is encouraged by TNM). ILC will always get a score of 3 for tubule formation, and very often a score of 1 for mitotic activity. It is mainly the cytologic features that account for the variation in grading (most ILCs are G1/G2 tumors) [3, 7, 22].

Caution

- Macroscopically, in addition to presenting as either an irregular, infiltrating, or well-circumscribed, indurated mass, sometimes the tumor is not apparent to the naked eye, or its appearance is not different from that of fibrocystic changes.

- A common but not specific feature of ILC is the presence of intracytoplasmic lumens containing a targetoid eosinophilic secretion (mucus); these should not be mistaken for signet-ring cells, which may be seen as a pattern of differentiation within ILC. Targetoid cells may also occur in infiltrating ductal carcinoma.
- Regardless of the number of mitotic figures, the pleomorphic variant of ILC (with high-grade nuclear atypia) or carcinoma with signet-ring cell component should be regarded as poorly differentiated or G3 (high-grade) carcinoma.
- Due to the lack of desmoplastic stromal alteration and diffuse and irregular growth pattern, the gross assessment of tumor size in ILC may differ in a substantial number of cases from the actual tumor size determined by histopathologic evaluation.
- After formalin fixation, the size (distribution) of ILC may be much larger than that of fresh specimen examined by frozen section. One needs to be aware of the discontinuous and multifocal pattern of ILC.
- Examine the resection margin carefully; it can be involved focally or diffusely.
- ILC with metastasis to the sentinel lymph nodes can be very difficult to detect on hematoxylin and eosin sections. To exclude metastasis of ILC, immunohistochemistry for cytokeratin is recommended.

9.6 Further Reading

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Fig. 44: Well-differentiated infiltrating lobular carcinoma.

Case history: A 70-year-old woman presented with a palpable left breast tumor. Mammography and sonography revealed a tumor (maximum diameter 3 cm) highly suspicious for breast cancer.

Figs. 44.1, 44.2: Infiltrating lobular carcinoma showing small, uniform tumor cells with a typical single-file pattern.

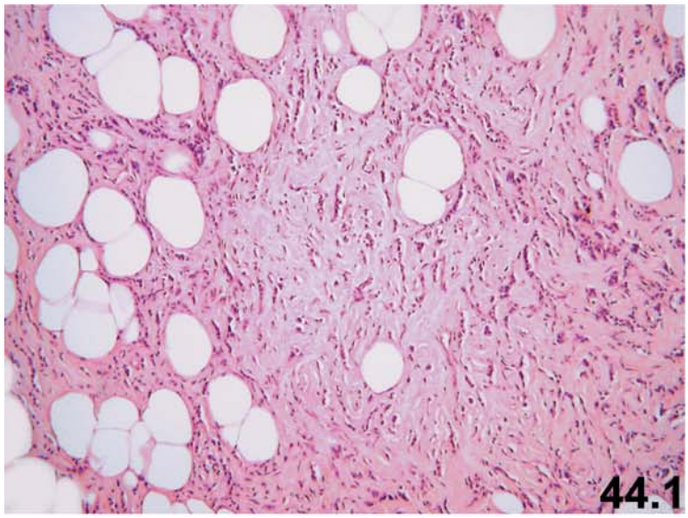
Fig. 44.3: Isolated small and uniform epithelial tumor cells of a well-differentiated infiltrating lobular carcinoma. The bland-looking small tumor cells resemble lymphocytes.

Figs. 44.4 and **44.5:** Positive immunoreaction for estrogen receptors (Fig. 44.4) and progesterone receptors (Fig. 44.5).

Fig. 44.6: The tumor cells of ordinary infiltrating lobular carcinoma frequently display positive immunoreaction for androgen receptors.

Fig. 44: Final remarks

- The vast majority of cases with infiltrating lobular carcinoma (ILC) are grades 1 or 2. This case represents an example of G1 or low-grade ILC. The tumor cells in this case are very uniform with a subtle degree of nuclear atypia. The mitotic activity of carcinoma is very low (Nottingham total score 5, tubular formation score 3, nuclear atypia score 1, and mitotic activity score 1).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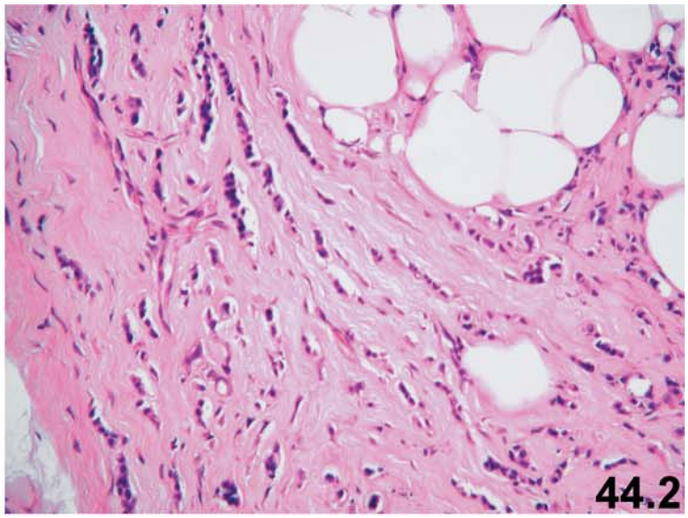
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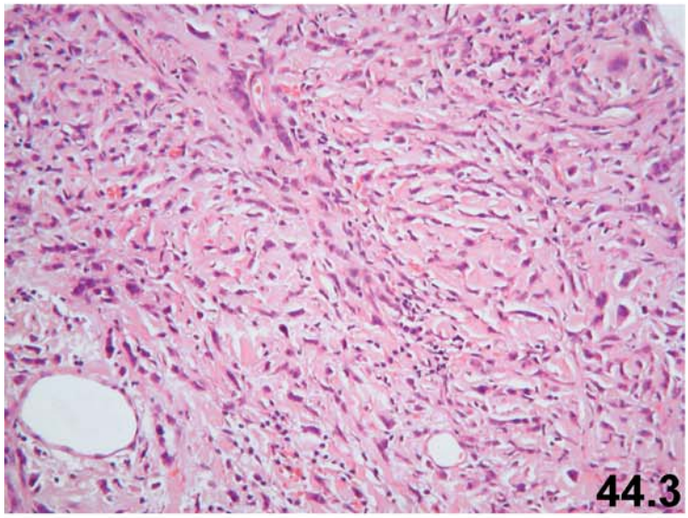
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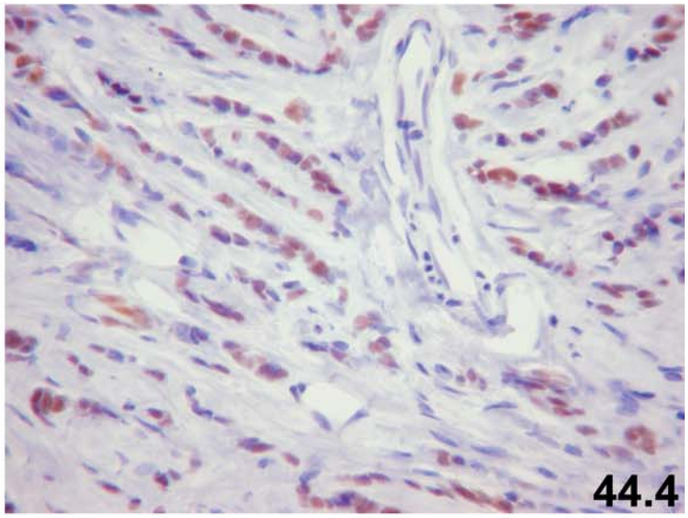
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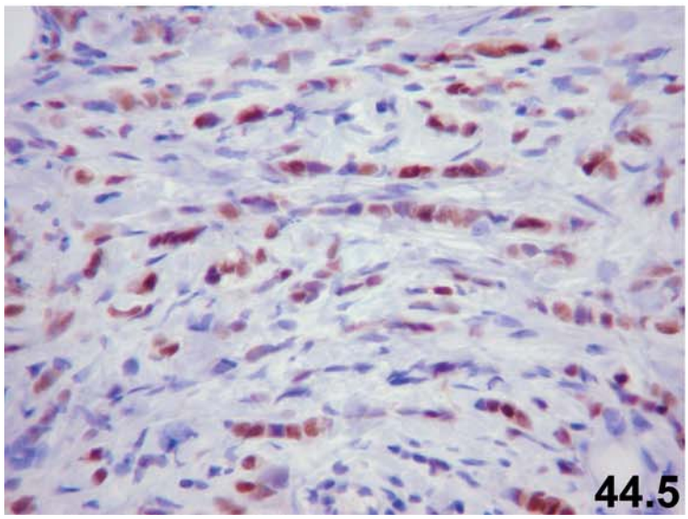
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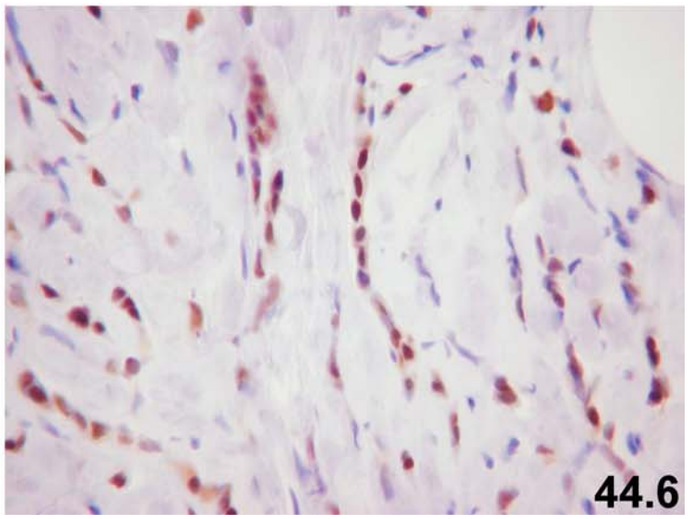

44.6

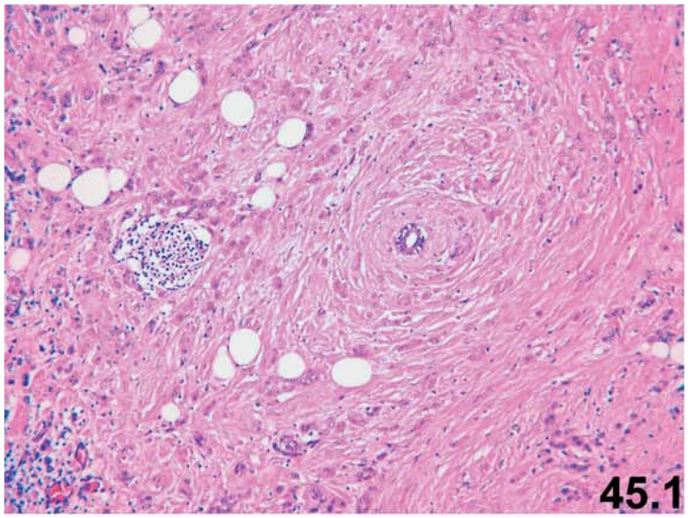
Fig. 45: Well-differentiated infiltrating lobular carcinoma, tubulolobular variant.

Case history: A 48-year-old woman presented with a palpable irregular firm mass of her left breast. The cut surface of the excisional biopsy revealed a greyish-white 2.5×1.5×1-cm tumor with irregular and infiltrating margins.

Figs. 45.1, 45.2, and **45.3:** At low magnification, the tumor shows several tubular structures.

Fig. 45.4: In addition to the tubules, several areas of the tumor display uniform, small epithelial cells and a typical single-file cell pattern, features more characteristic of infiltrating lobular carcinoma.

Figs. 45.5 and **45.6:** Higher magnification shows an infiltrating carcinoma displaying uniform and small tumor cells. The tumor cells lack significant nuclear atypia and form tubules as well as single-file structures. Note the cytological similarity of neoplastic cells in both tubules and single cell files.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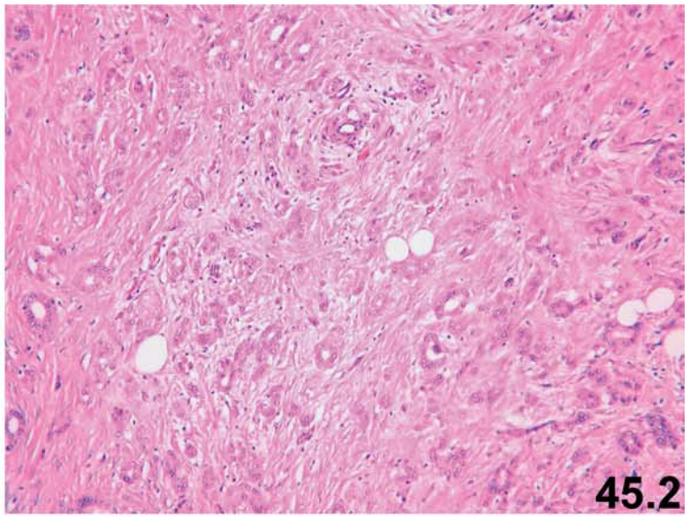
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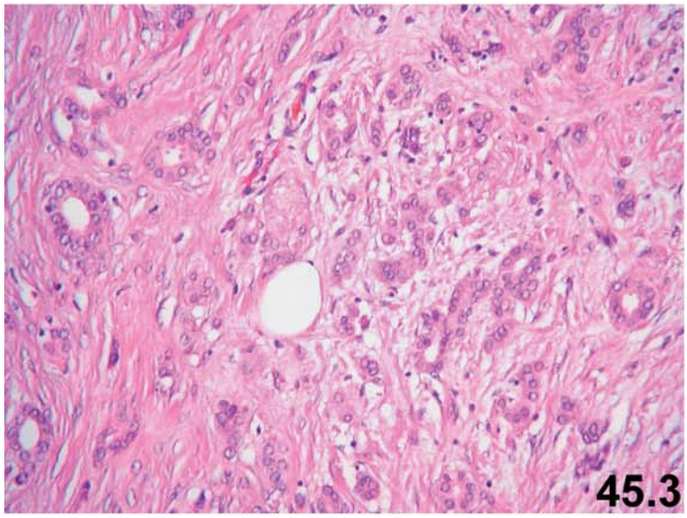
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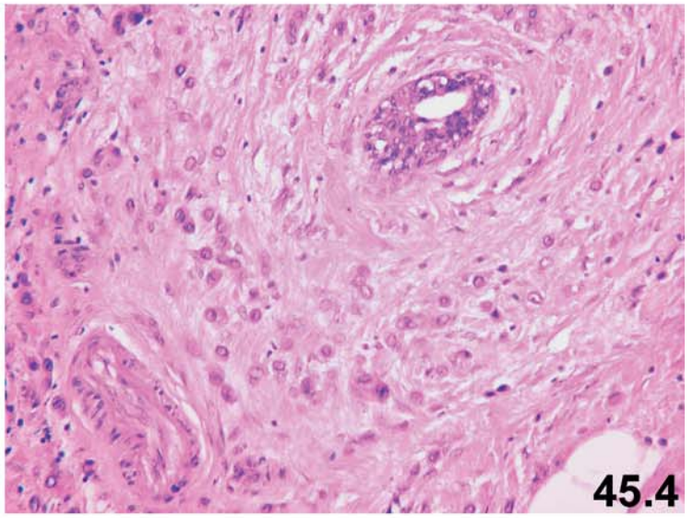
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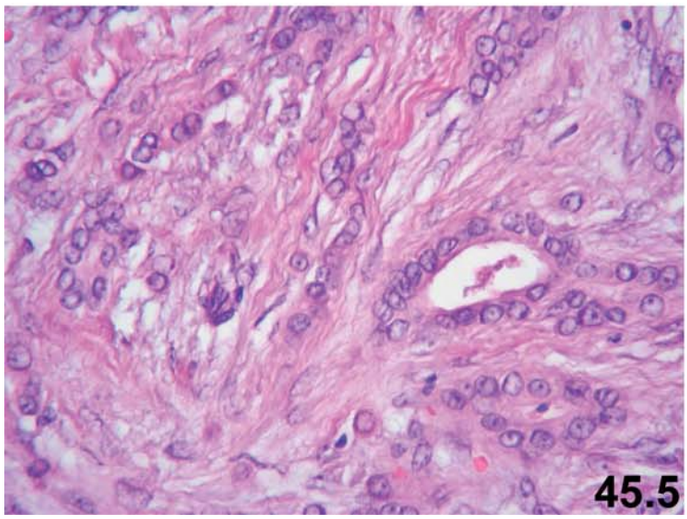
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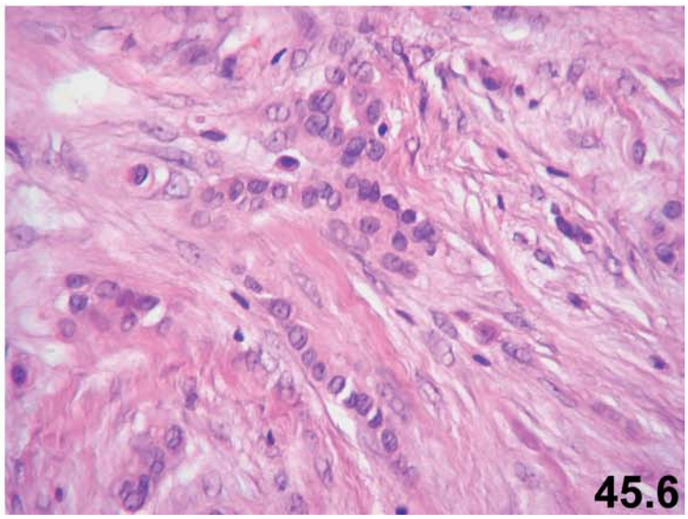
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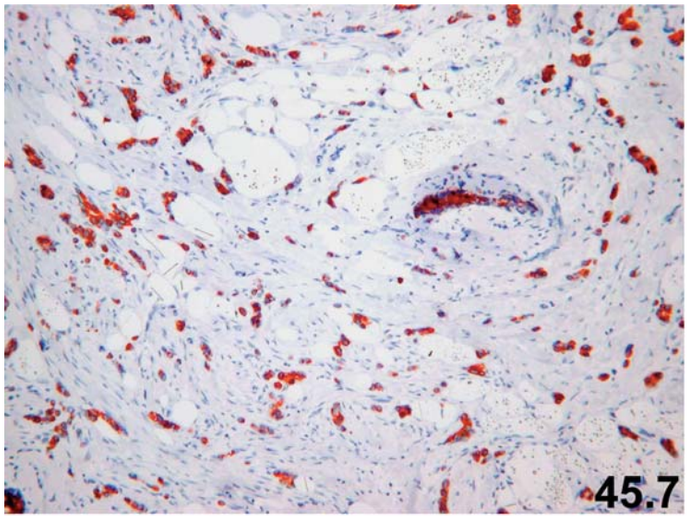
Figs. 45.7 and **45.8:** Immunohistochemistry for CK34BE12 reveals positive reaction in areas with typical lobular morphology.

45.9: Positive immunoreaction for CK34BE12, even in the tubular areas of the tumor.

45.10: The tumor cells are negative for E-cadherin, even in areas with tubular differentiation.

Fig. 45: Final remarks

- Based on the immunohistochemical results (negative reaction for E-cadherin and positivity for CK34BE12), this carcinoma should be classified as an ILC, tubulolobular variant.
- There are cases with mixed tubulolobular pattern in which the tumor cells are positive for E-cadherin but negative for CK34BE12. In such cases, the diagnosis of ductal carcinoma is preferred. In some instances, the tumor cells are positive for both E-cadherin and CK34BE12 (positive hybrid tumors) or negative for both E-cadherin and CK34BE12 (negative hybrid tumors).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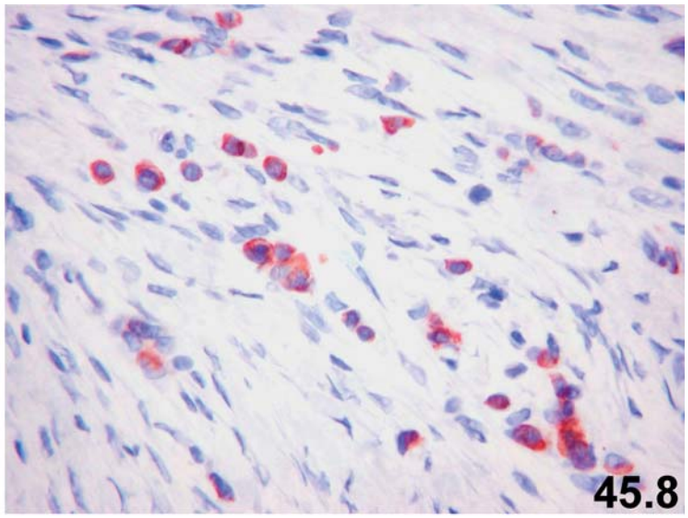
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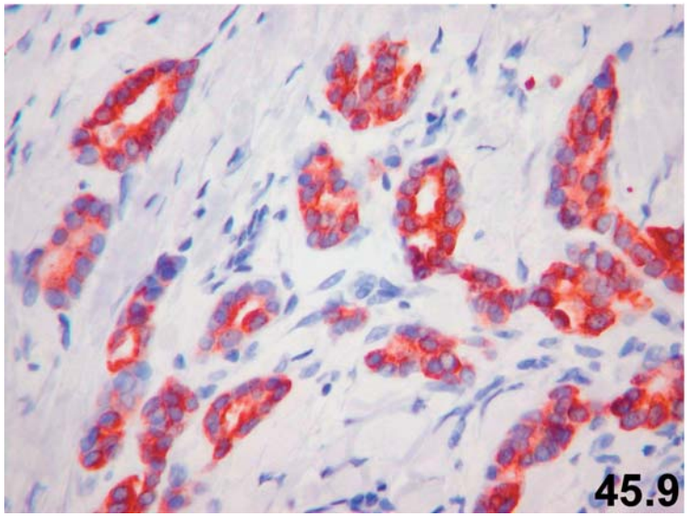
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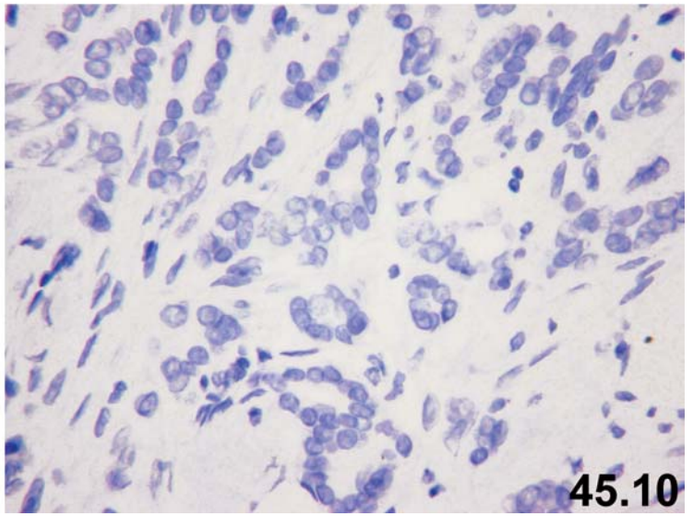

45.10

Fig. 46: Pleomorphic variant of infiltrating lobular carcinoma with neuroendocrine differentiation.

Case history: A 55-year-old woman presented with a mammographically highly suspicious left breast mass (2.5 cm at its maximum diameter). The excisional biopsy showed a tan to pink tumor with infiltrating margins.

Figs. 46.1 and **46.2:** The tumor is composed of loosely cohesive epithelial clusters.

Figs. 46.3 and **46.4:** Tumor cells show large vesicular (pale) nuclei, a high nuclear-cytoplasmic ratio, and eosinophilic cytoplasm.

Fig. 46.5: Higher magnification reveals tumor cells with fine eosinophilic and granular cytoplasm.

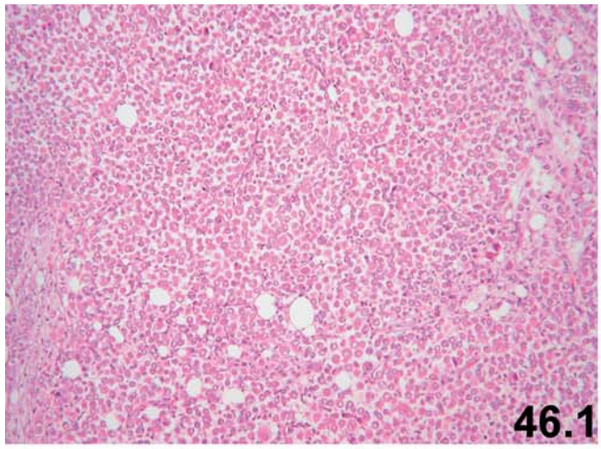
Fig. 46.6: Some areas of the tumor show significant variation in nuclear size and nuclear shape. The tumor cells show large and vesicular nuclei.

Fig. 46.7: Immunohistochemistry for synaptophysin shows a dot-like positive reaction of infiltrating tumor cells.

Fig. 46.8: Tumor cells showing a heterogeneous positive immunoreaction for chromogranin.

Fig. 46: Final remarks

- This case represents an example of pleomorphic variant of ILC (with neuroendocrine differentiation). Pleomorphic variant of ILC occurs rarely and should be considered as a high-grade carcinoma based on the nuclear atypia, regardless of its mitotic activity.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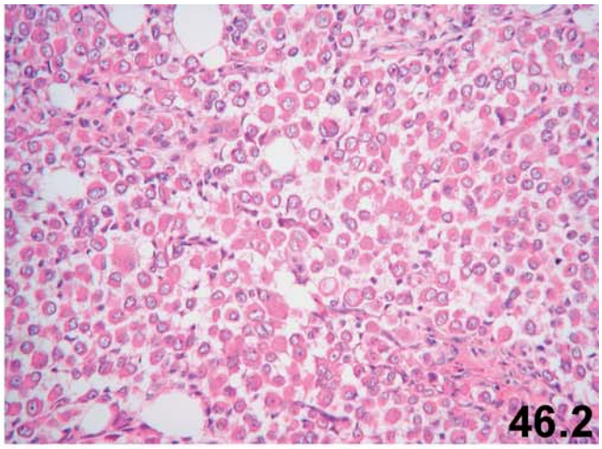
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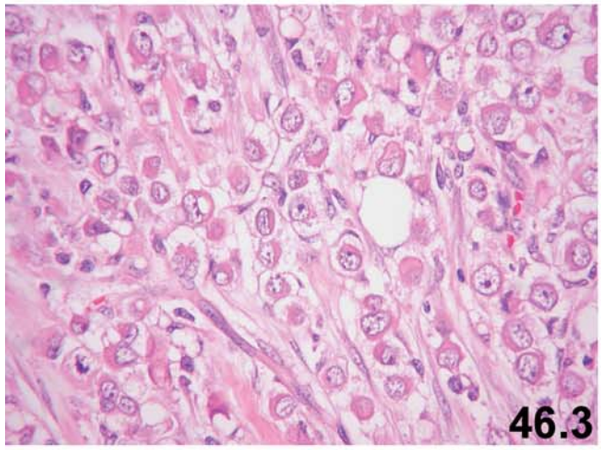
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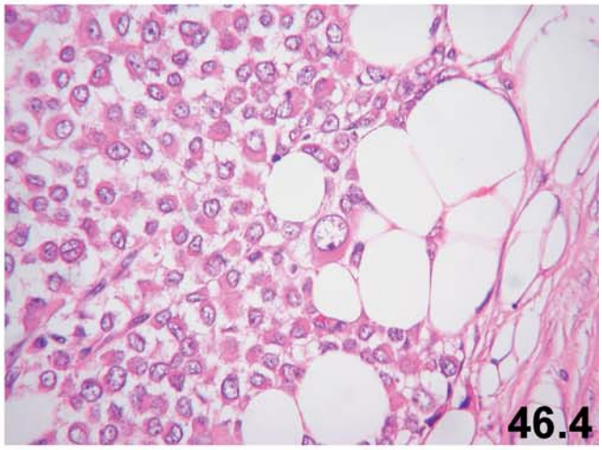
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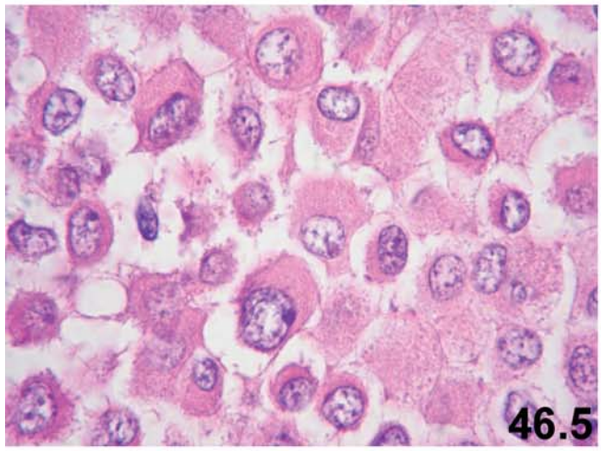
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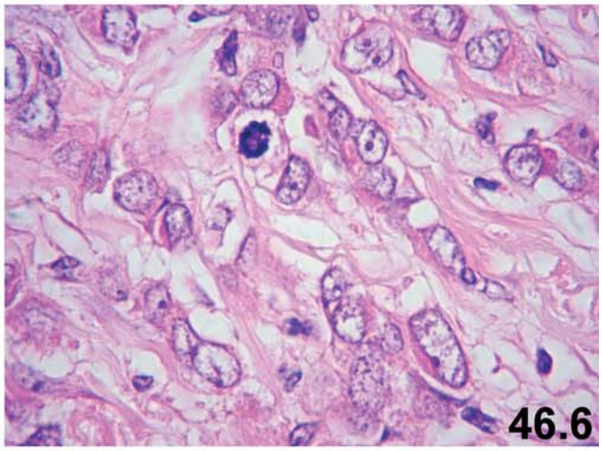
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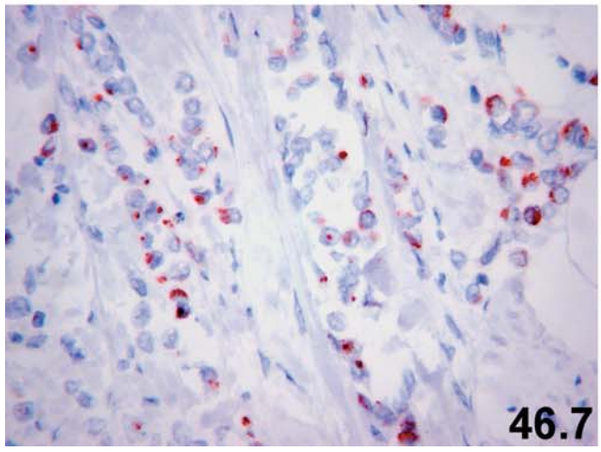
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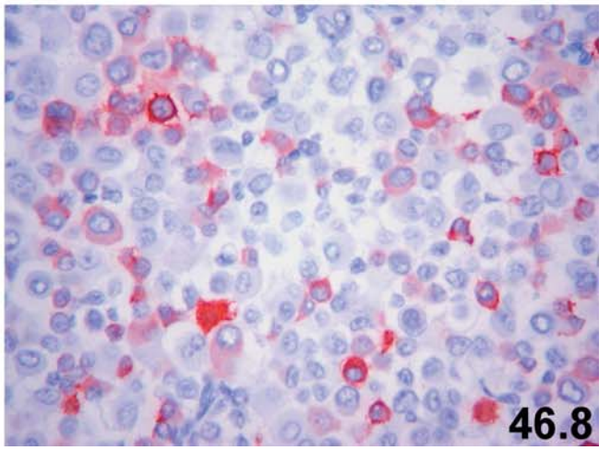

46.8

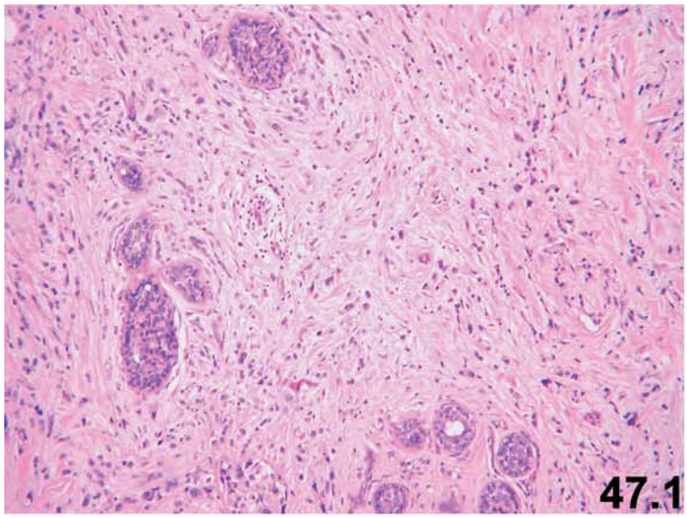
Fig. 47: Pleomorphic variant or poorly differentiated infiltrating lobular carcinoma.

Case history: A 53-year-old woman presented with a rapidly growing right breast tumor (upper outer quadrant). The cut surface of the excised tumor displayed a hard 4.5×3×1.9 cm tumor with infiltrating margins.

Figs. 47.1 and **47.2:** Low magnification of the tumor shows an infiltrating breast carcinoma with lobular growth pattern. In many areas of the tumor, isolated small tumor cells and cells with single cell file pattern are present.

Figs. 47.3 and **47.4:** In addition, several areas of the tumor exhibit extremely atypical cells with hyperchromatic, bizarre-looking nuclei.

Figs. 47.5 and **47.6:** Highly atypical tumor cells with extreme anisonucleosis and nuclear pleomorphism.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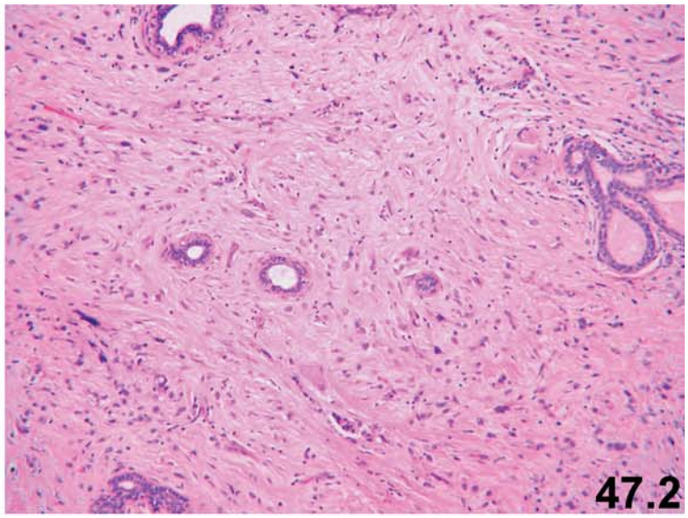
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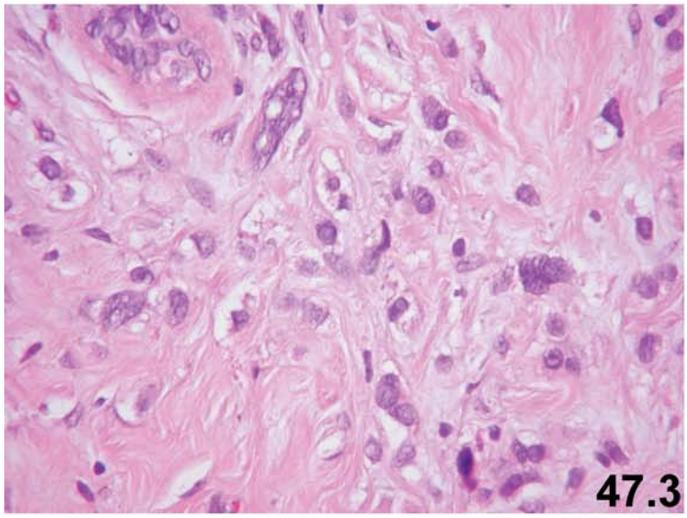
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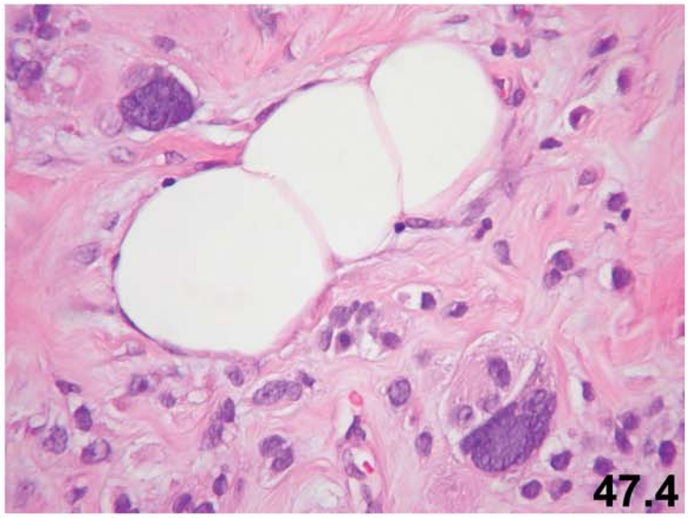
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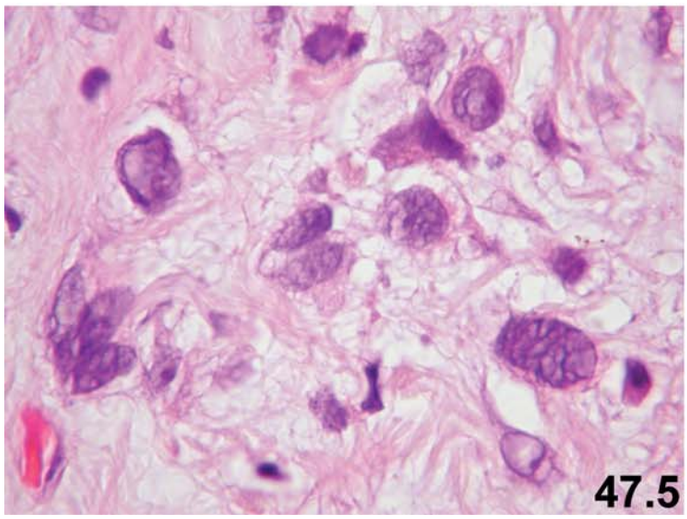
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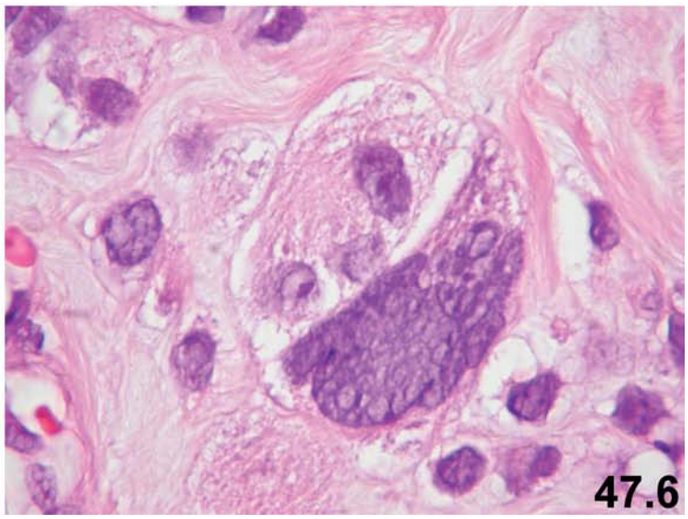

47.6

Fig. 47.7: CK34BE12 immunoreaction in areas of the tumor with more classic Features of ILC. Note the typical asymmetric or caplike pattern of positive reaction.

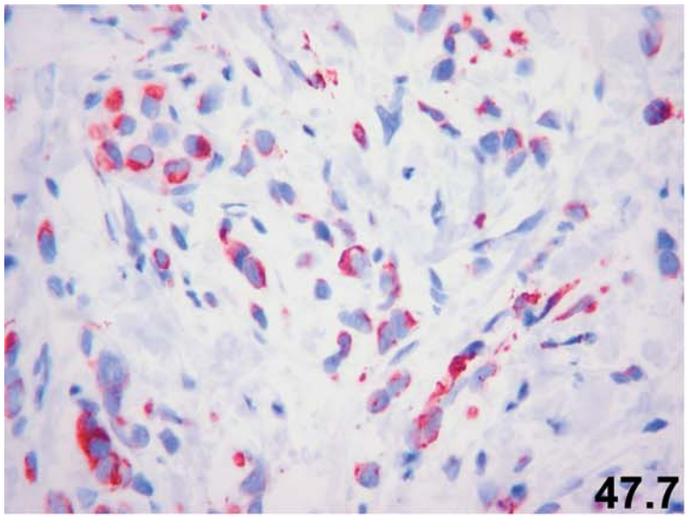
Figs. 47.8 and **47.9:** Positive immunoreactivity for CK34BE12 in areas with significant nuclear atypia. Note the pattern of immunoreaction.

Figs. 47.10 and **47.11:** While normal ducts and lobules are positive for E-cadherin, the highly pleomorphic tumor cells are negative for it. The immunohistochemistry (negativity for E-cadherin and positivity for CK34BE12) in this case confirms the diagnosis of poorly differentiated or pleomorphic variant of ILC.

Fig. 47.12: Immunohistochemistry for HER2/neu shows an intense and circumferential positive reaction (score 3+) of highly atypical tumor cells. The tumor cells were, however, completely negative for EGFR (HER1; not shown).

Fig. 47: Final remarks

- The main differential diagnosis in this case is metaplastic or sarcomatoid carcinoma. The presence of areas with more classical features of ILC and the results of immunohistochemistry (E-cadherin negativity and CK34BE12 positivity) in this case confirms the diagnosis of pleomorphic variant of ILC. The vast majority of metaplastic or sarcomatoid breast carcinomas are negative for HER2/neu but positive for EGFR (HER1). The positive reaction of tumor cells for HER2/neu and the negative immunoreaction for EGFR (HER1) in this case would further exclude a metaplastic carcinoma.
- Using the Nottingham grading system, this carcinoma would be a grade 2 with a total score of 7 (tubular formation score 3, nuclear atypia score 3, and mitosis score 1). Although the mitotic activity is low in this case, the pleomorphic variant of ILC needs to be considered a poorly differentiated carcinoma (G3 or high-grade carcinoma) by using the nuclear grading system for breast carcinoma.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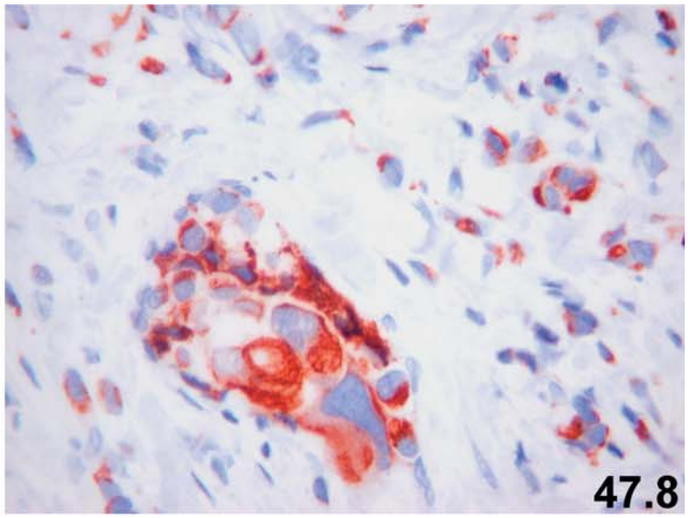
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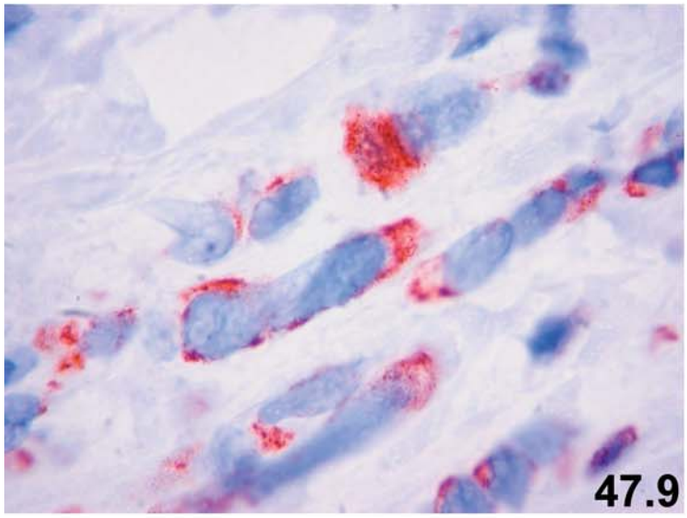
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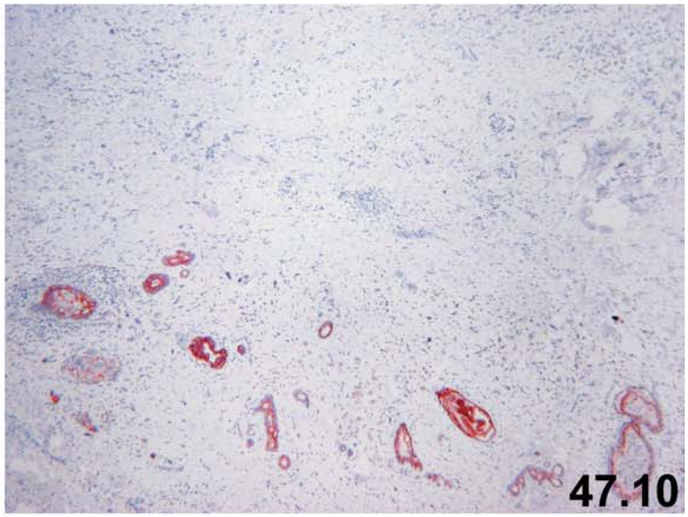
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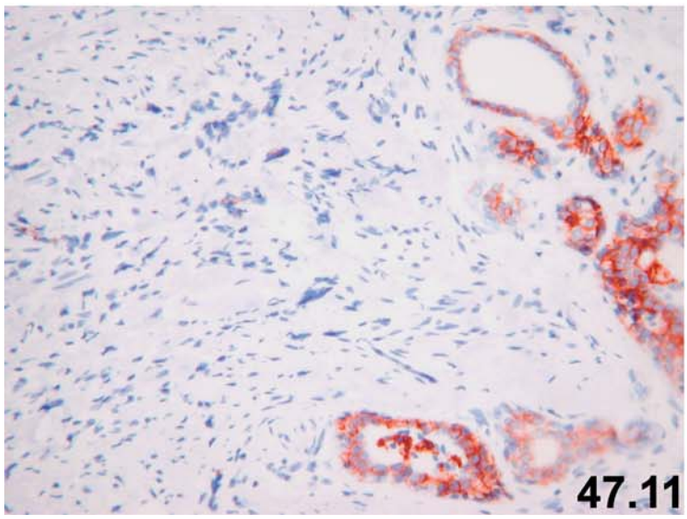
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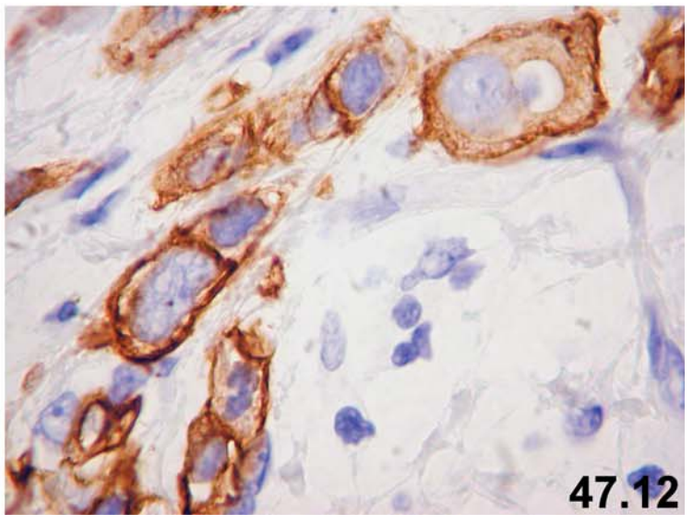
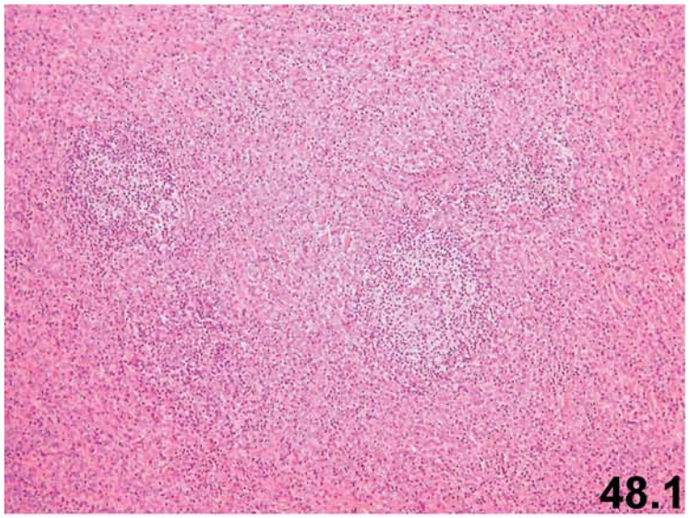

47.12

Fig. 48: Pleomorphic variant of infiltrating lobular carcinoma simulating lymphoma (lymphoma-like carcinoma).

Case history: A 38-year-old woman had a 1.5-cm left breast tumor (upper inner quadrant) identified by a regular mammographic examination. The tumor was relatively well circumscribed and grey to pink on its cut surface.

Figs. 48.1, 48.2, and **48.3:** The tumor predominantly shows severe lymphocytic infiltration of the breast stroma.

Figs. 48.4, 48.5, and **48.6:** At higher magnification, isolated cells and small clusters or nests with a different morphology can be recognized. It is, however, difficult to be sure about the nature of these cells (lymphatic cells versus epithelial cells) without immunohistochemistry.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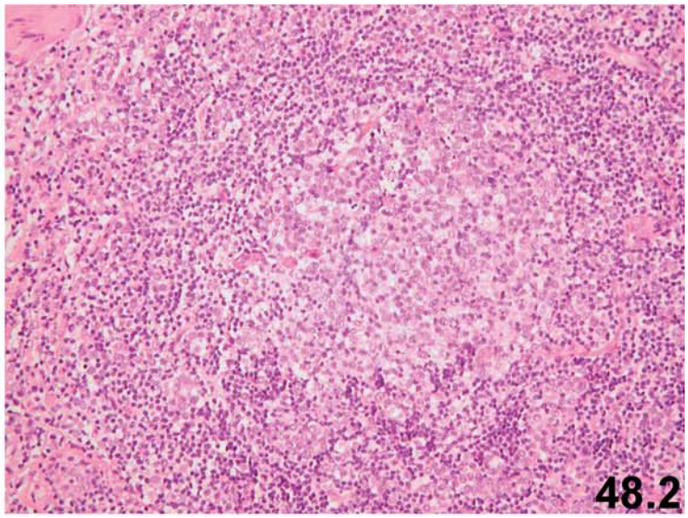
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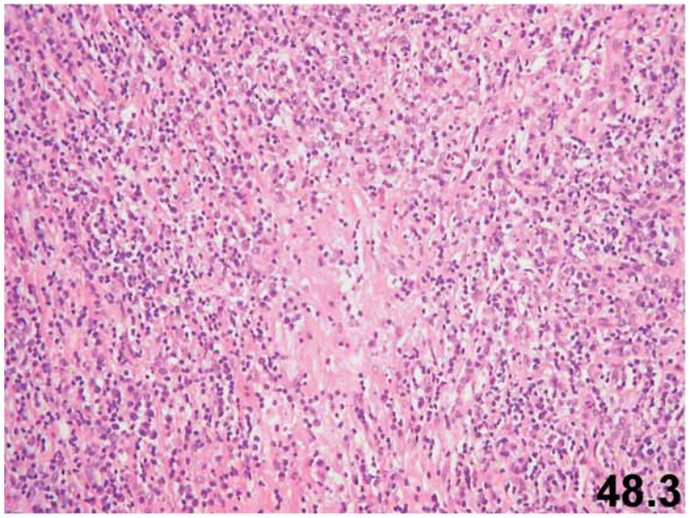
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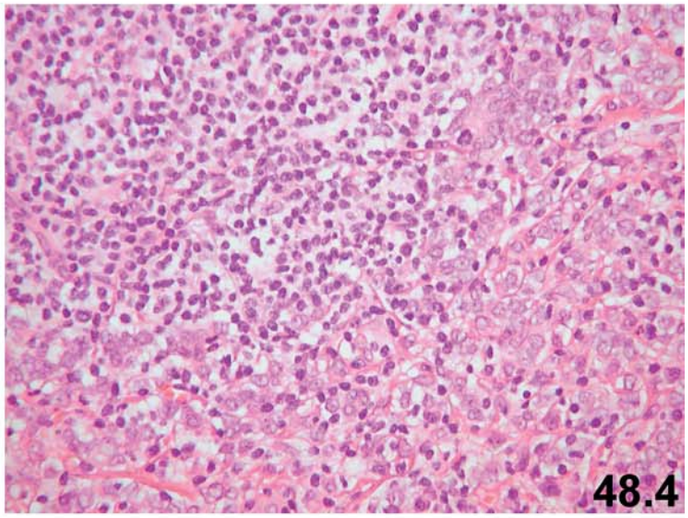
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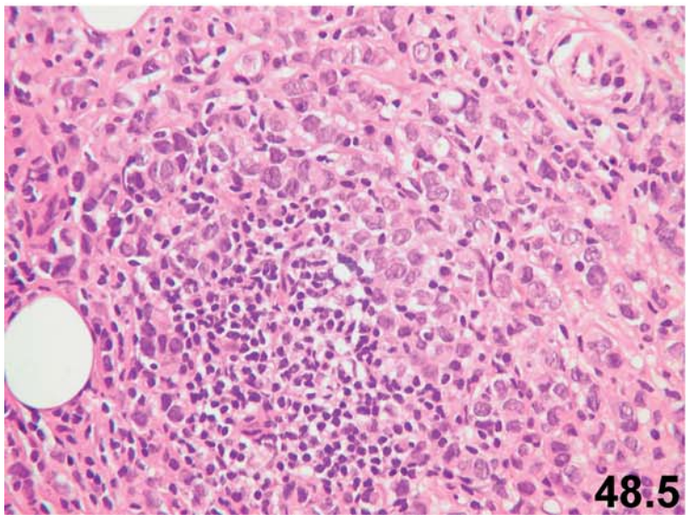
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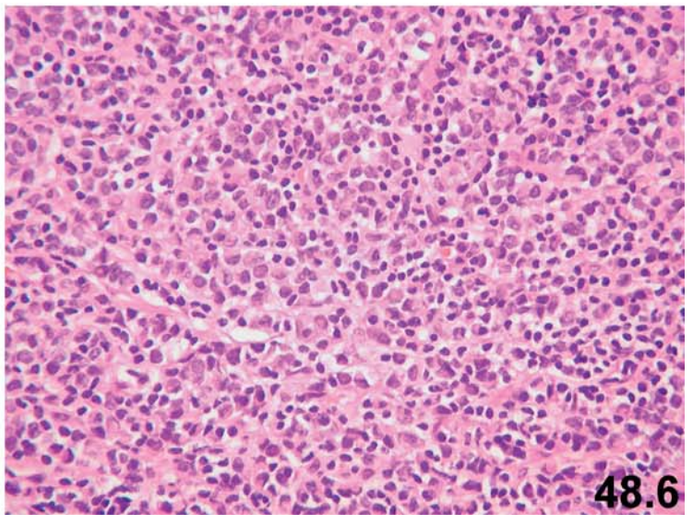
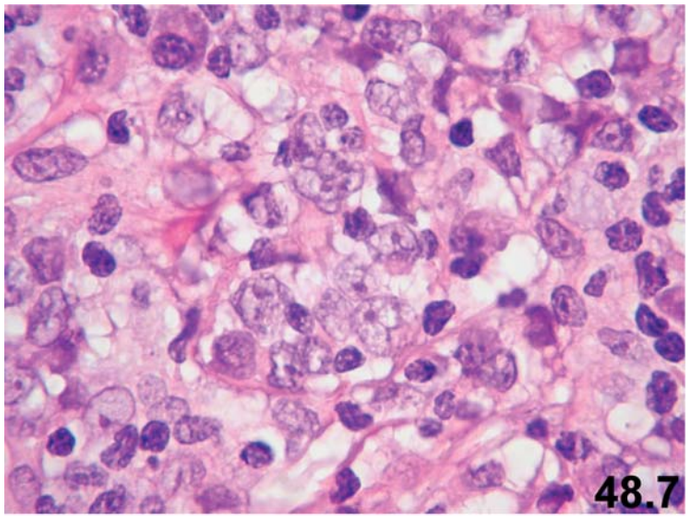

48.6

Figs. 48.7 and **48.8:** A very high magnification (×1,000) of the tumor shows cells with partly vesicular and partly hyperchromatic, large nuclei. It is difficult to determine whether these are epithelial or hematopoietic cells.

Figs. 48.9 and **48.10:** Immunohistochemistry for pancytokeratin reveals an intensely positive reaction in the infiltrating tumor cells demonstrating their epithelial nature. There is a lymphocytic cell population in the background.

Fig. 48: Final remarks

- The hematoxylin and eosin sections of this case have been reviewed by several experienced pathologists. Many were deeply concerned about a malignant lymphoma (NHL, high grade).
- The tumor cells were completely negative for E-cadherin and focally positive for CK34BE12 (data not shown). The immunohistochemistry and morphology of the tumor cells are consistent with the pleomorphic variant of ILC.
- Breast carcinomas with severe lymphatic reaction that closely resemble malignant lymphomas have also been designated as lymphoma-like carcinomas.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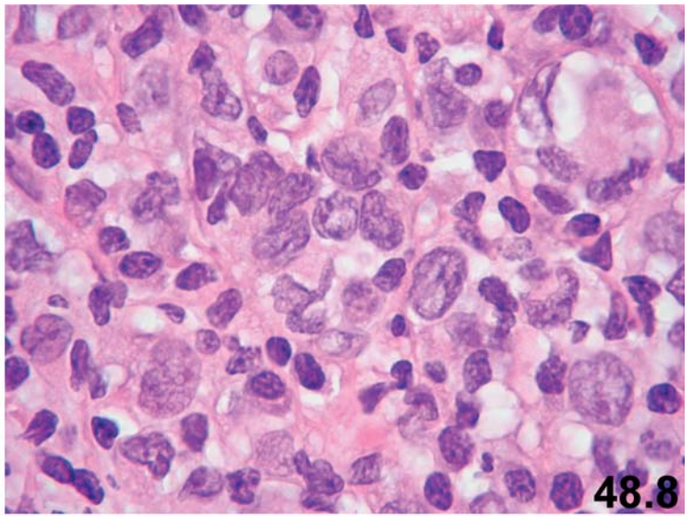
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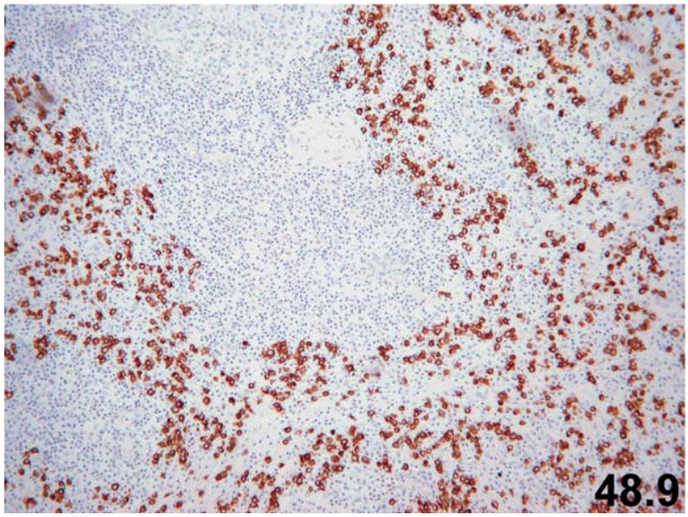
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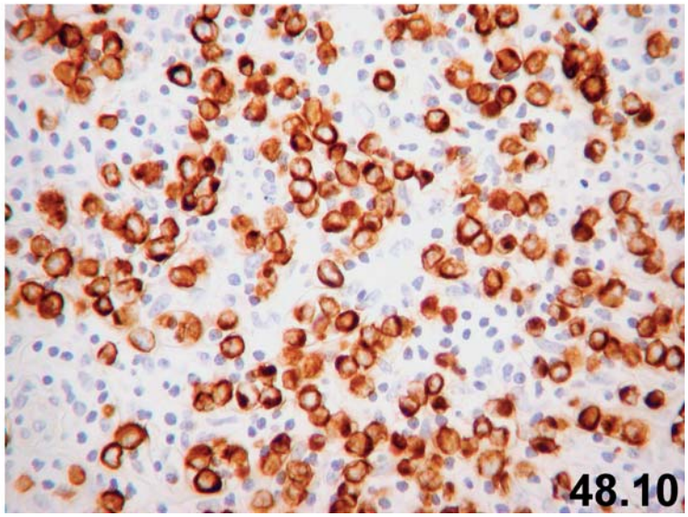

48.10

Fig. 49: Infiltrating lobular carcinoma with signet-ring cell component.

Case history: A 66-year-old woman presented with a clinically and mammographically highly suspicious mass of her right breast. A needle core biopsy of the tumor revealed an invasive lobular carcinoma. The excisional biopsy of the tumor displayed a 3×2×1-cm greyish-white tumor close (<1 mm) to the posterior margin.

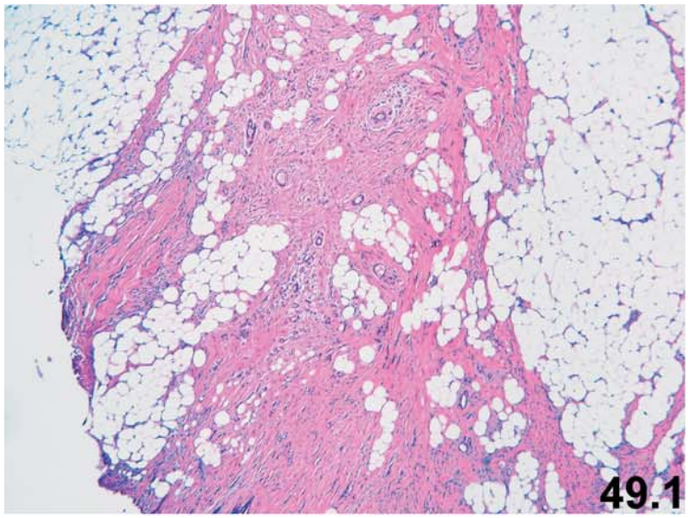
Figs. 49.1 and **49.2:** Infiltrating breast carcinoma with a classic growth pattern of ILC.

Figs. 49.3 and **49.4:** While several areas of the carcinoma show a classic morphology of ILC with uniform and small tumor cells (Fig. 49.3), other areas display numerous signet-ring tumor cells (Fig. 49.4).

Figs. 49.5 and **49.6:** Higher magnification revealing highly atypical tumor cells with hyperchromatic and eccentric nuclei and abundant clear or mucinous (vacuolated) cytoplasm. The mitotic activity of the tumor is very low!

Fig. 49: Final remarks

- It is important to keep in mind that signet-ring cell carcinoma and pleomorphic variant of ILC commonly do not show high mitotic activity. Such tumors should be regarded as poorly differentiated carcinomas based on the nuclear grading system, regardless of their mitotic activity.
- Tumor cells with signet-ring cell differentiation can occur in both ductal and lobular carcinomas.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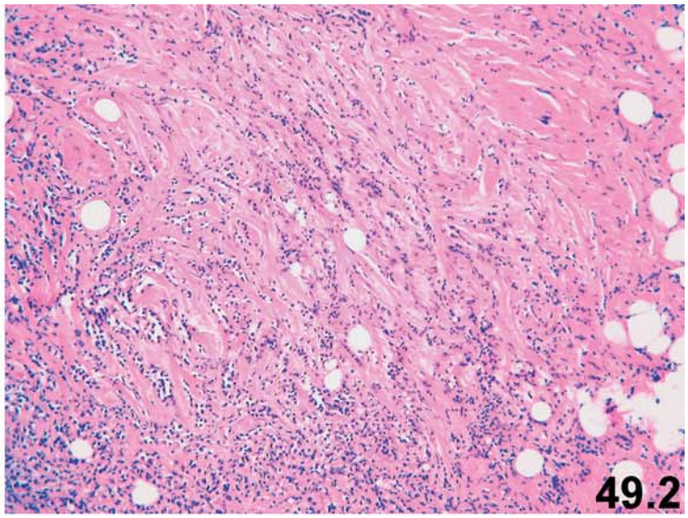
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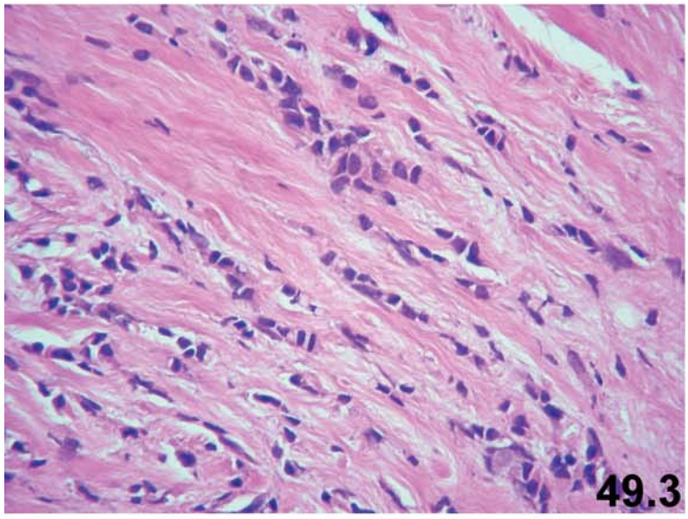
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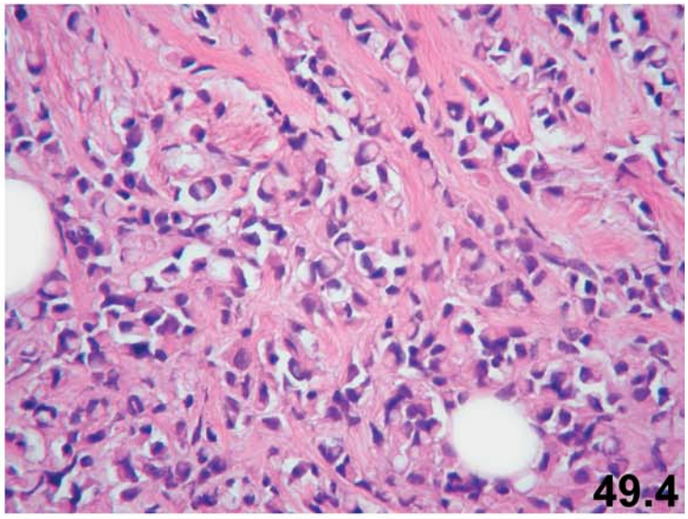
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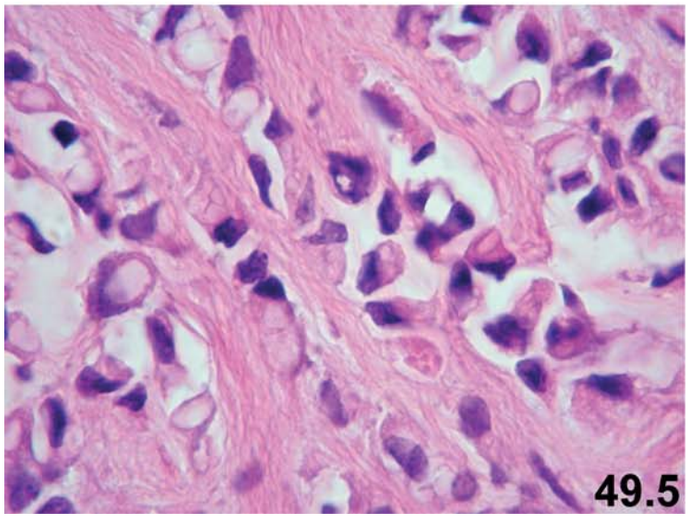
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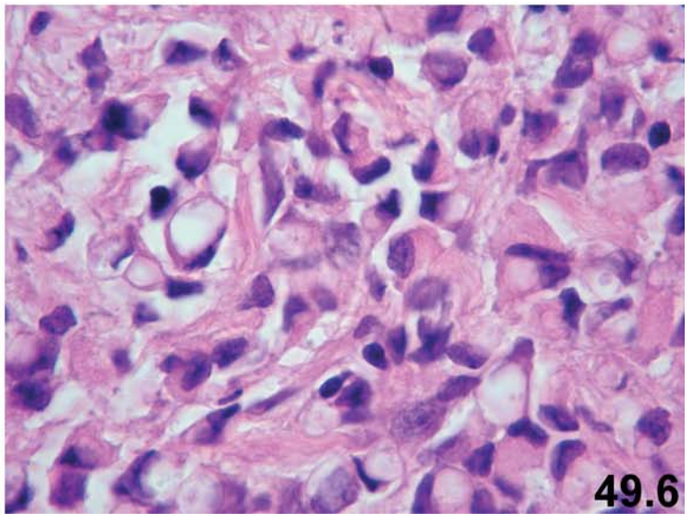

49.6

Fig. 50: Histiocytoid variant of infiltrating lobular carcinoma (histiocytoid carcinoma).

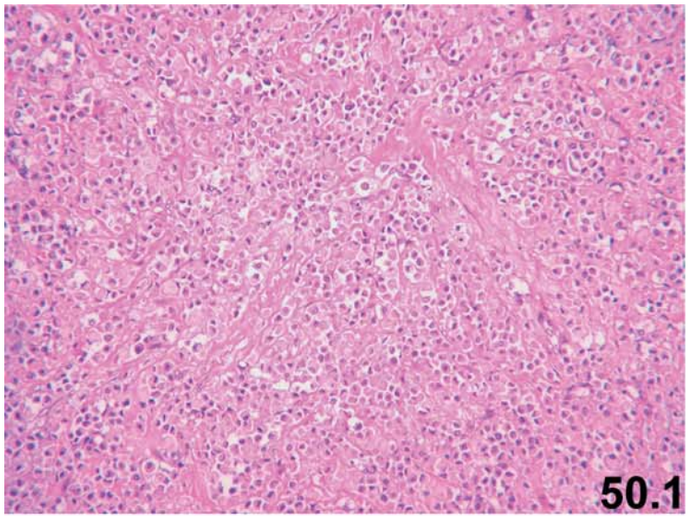
Case history: A 34-year-old woman presented with a hard, ill-defined tumor in her left breast. The clinical examination revealed enlarged axillary lymph nodes (left). Mammography and ultrasonography showed an asymmetric, ill-defined mass (maximum diameter 2.5 cm).

Figs. 50.1 and **50.2:** Invasive carcinoma with numerous isolated tumor cells and loosely cohesive clusters.

Figs. 50.3 and **50.4:** Tumor cells with abundant vacuolated cytoplasm closely resembling histiocytes.

Fig. 50.5: Multiple areas with lymphatic vessel invasion.

Fig. 50.6: The tumor cells show positive immunoreaction for CK34BE12. The immunoreaction for E-cadherin, however, was negative (not shown).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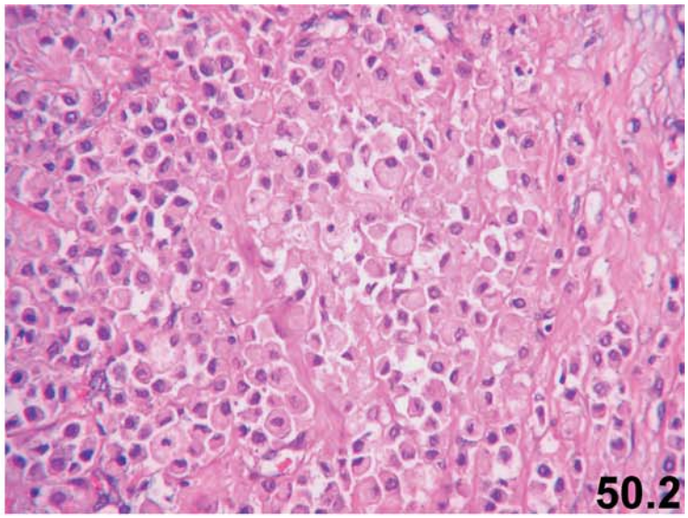
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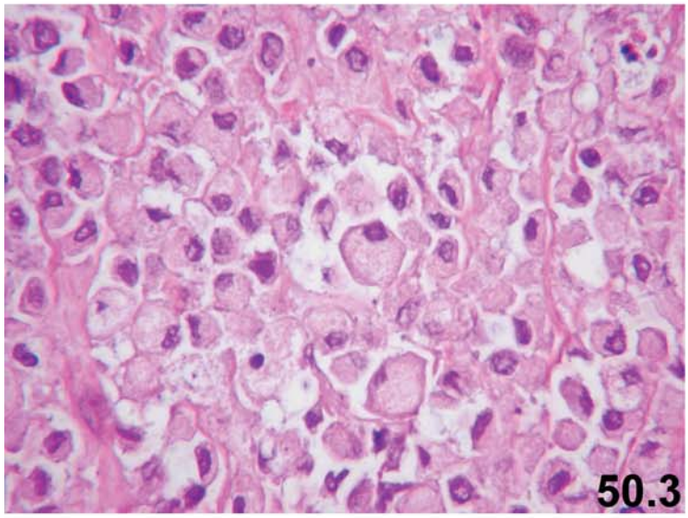
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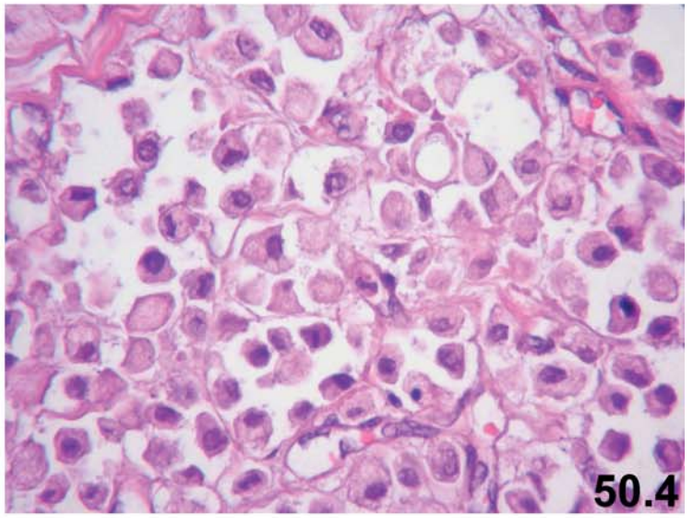
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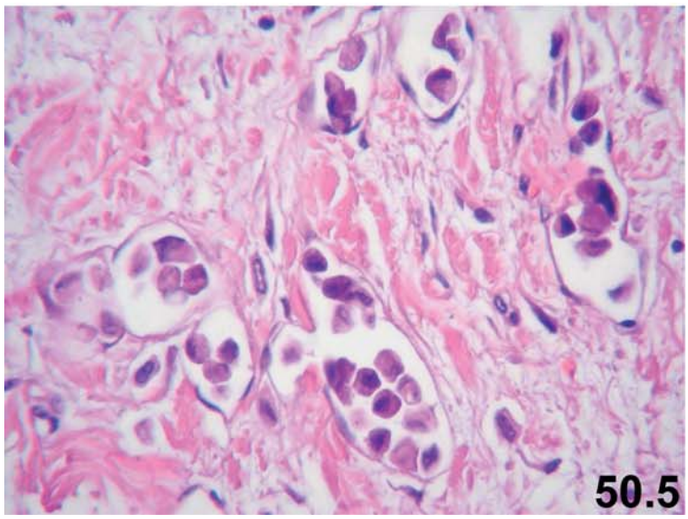
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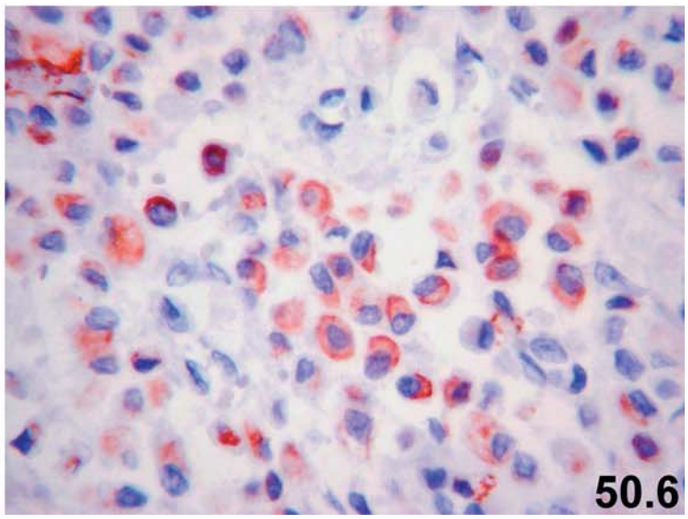
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Fig. 50.7: In addition to the invasive component of the tumor, areas of lobular intraepithelial neoplasia (LIN) are also present. LIN is characterized by loosely cohesive epithelial clusters showing abundant eosinophilic or vacuolated cytoplasm.

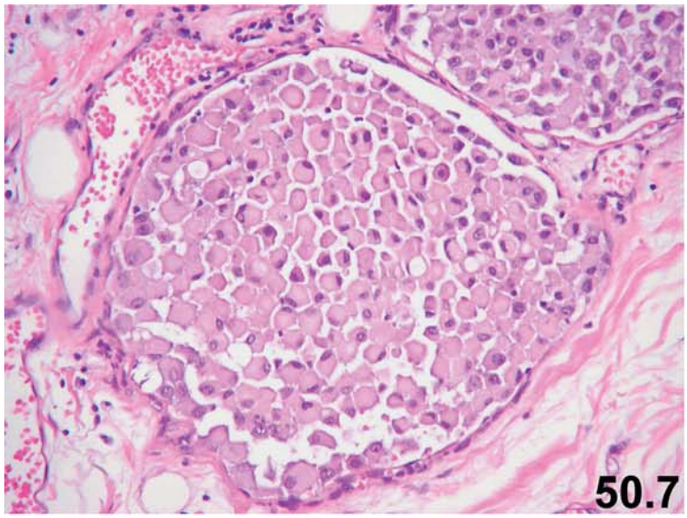
Figs. 50.8 and **50.9:** Very high magnification (×1,000) of lobular intraepithelial neoplasia and invasive carcinoma exhibits numerous tumor cells closely resembling histiocytes.

Fig. 50.10: The tumor cells are immunohistochemically positive for estrogen receptors.

Figs. 50.11 and **50.12:** Metastatic involvement of an axillary lymph node with several areas closely resembling histiocytes.

Fig. 50: Final remarks

- Histiocytoid carcinoma of the breast is mainly found among infiltrating lobular carcinomas. It can be easily mistaken for benign conditions or other breast tumors that are also composed of tumor cells with foamy to pink granular cytoplasms and eccentric nuclei.
- The tumor cells in histiocytoid carcinoma commonly show granular immunoreactivities for gross cystic disease fluid protein-15 (GCDFP-15). Based on the morphology and immunohistochemistry, several studies suggested that histiocytoid carcinoma represents a variant of carcinoma with apocrine differentiation (apocrine carcinoma).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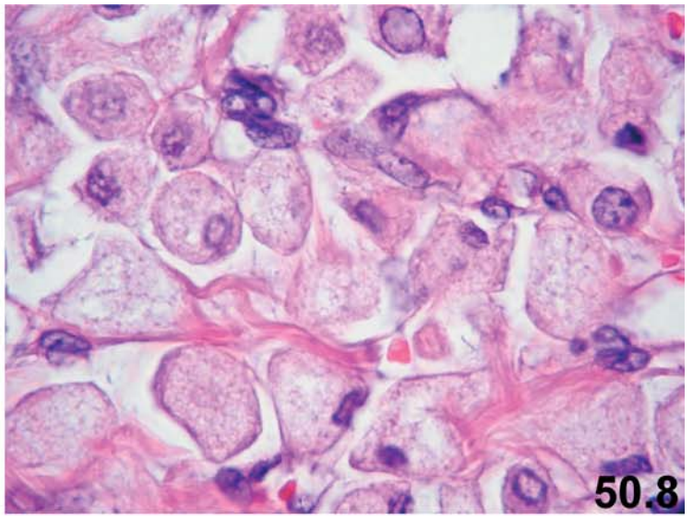
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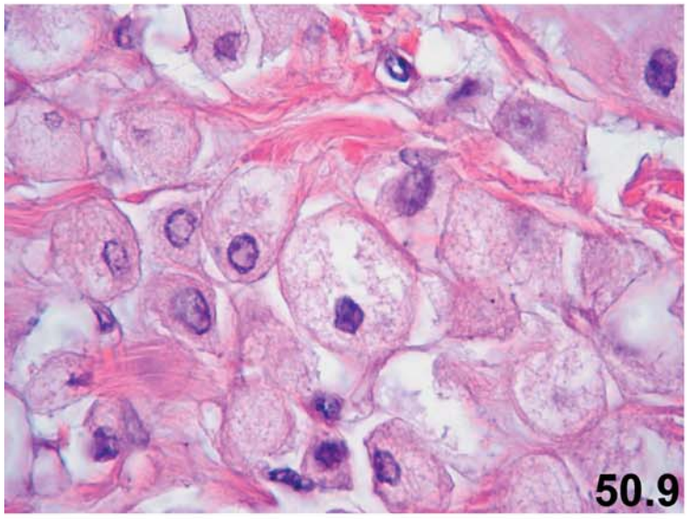
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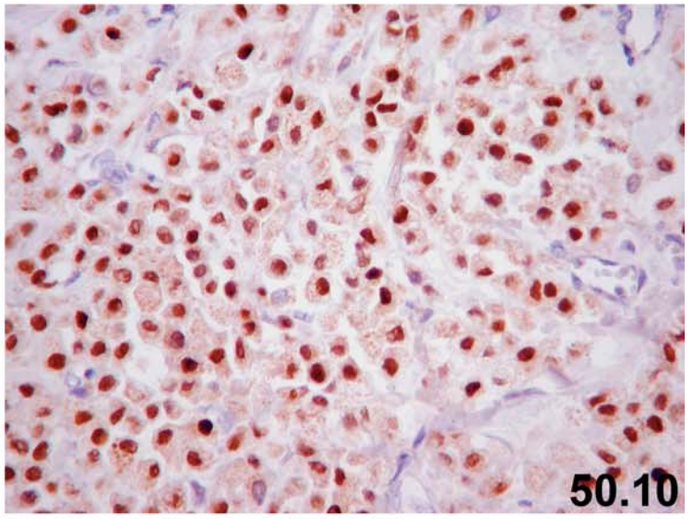
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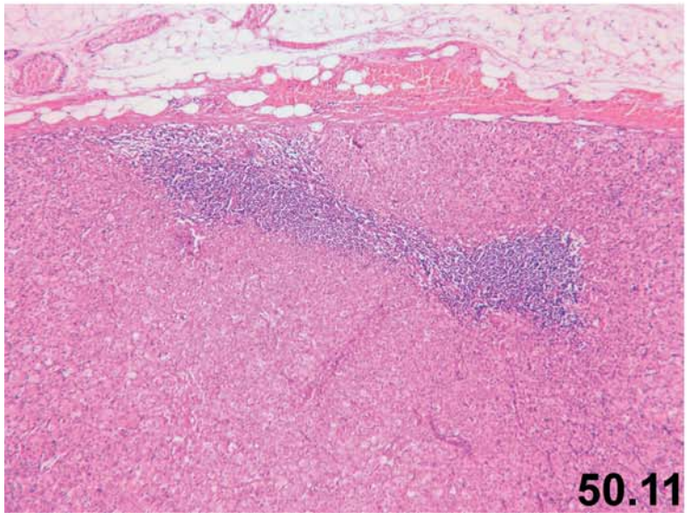
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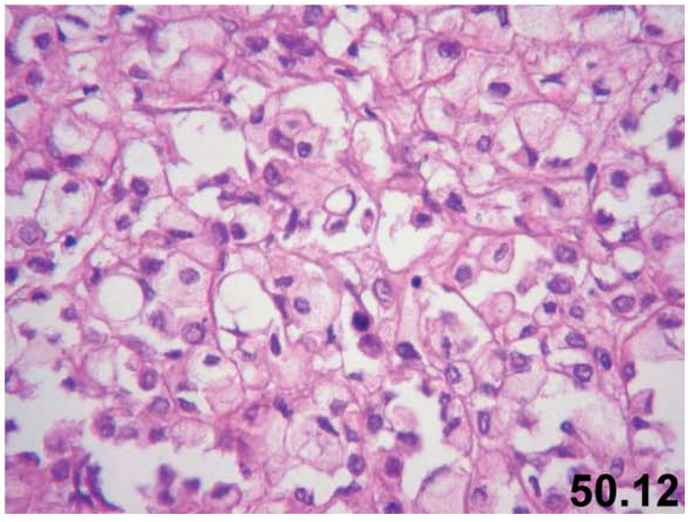
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Fig. 51: Histiocytoid variant of infiltrating lobular carcinoma associated with histiocytoid/ apocrine type of lobular intraepithelial neoplasia.

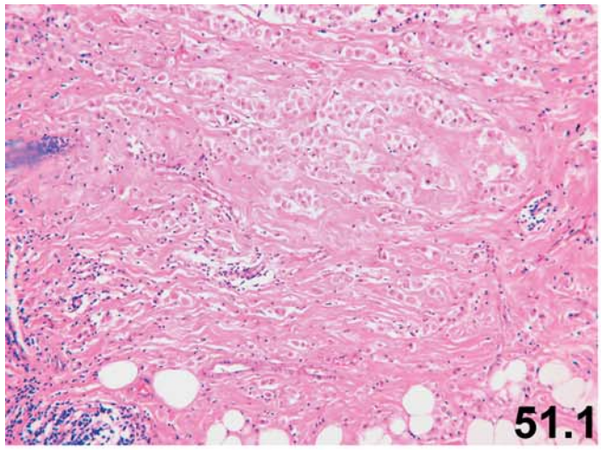
Case history: A 30-year-old woman presented with a 4-cm irregular left breast mass and a positive family history of breast cancer (sister). The cut surface of the tumor showed a firm greyish-white tumor with irregular margins.

Figs. 51.1 and **51.2:** At low magnification, a monotonous cell population of tumor cells with infiltrative single file pattern is present. The tumor cells show fine eosinophilic granular or foamy cytoplasm.

Fig. 51.3: A small normal duct (ductule) is surrounded by tumor cells with bland nuclei.

Figs. 51.4, 51.5 and **51.6:** Uniform tumor cells show infiltration of the lobules (acinar structures). The tumor cells show abundant vacuolated cytoplasms and round nuclei, features that can easily be misinterpreted as aggregates of histiocytes.

Figs. 51.7 and **51.8:** Several areas of solid intraepithelial neoplasias within and at the periphery of invasion. The tumor cells are large with abundant cytoplasm and could easily be misinterpreted as DIN (DCIS).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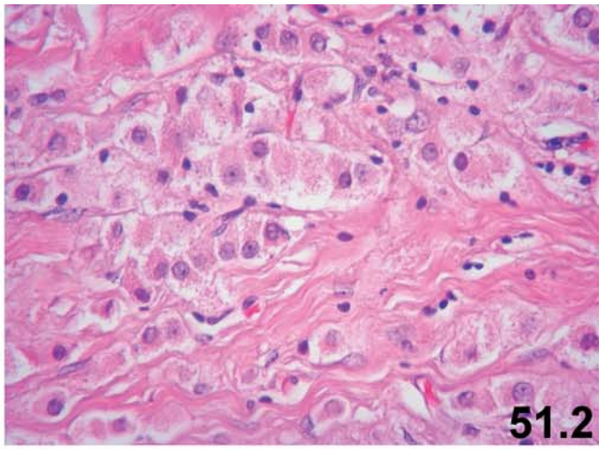
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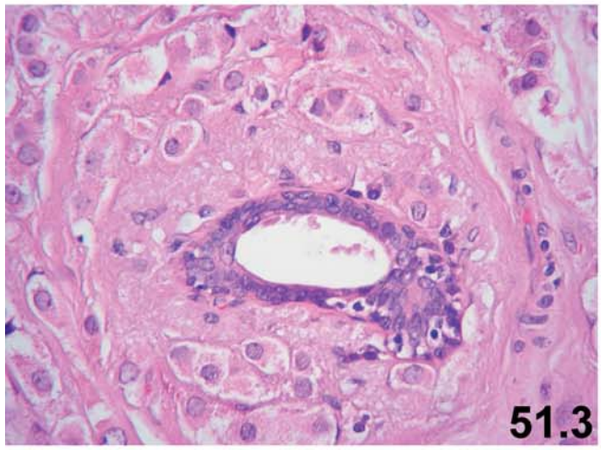
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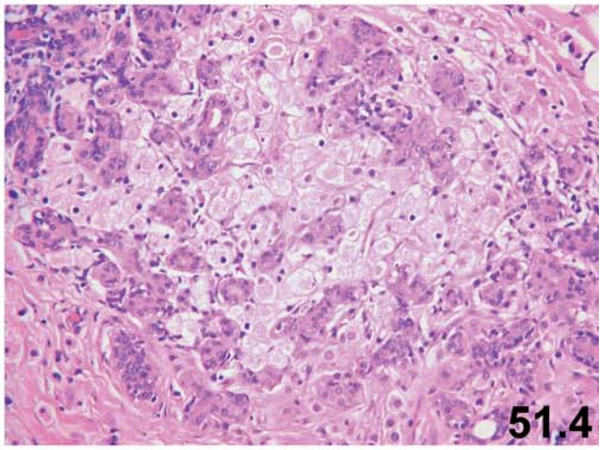
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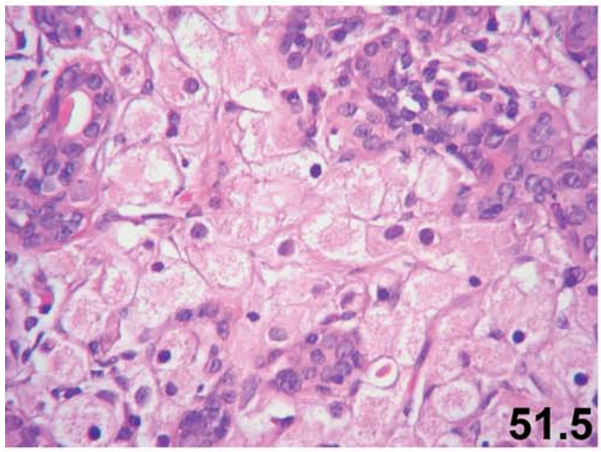
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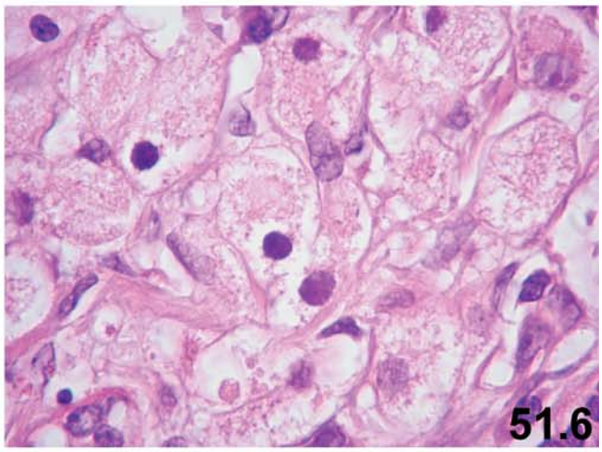
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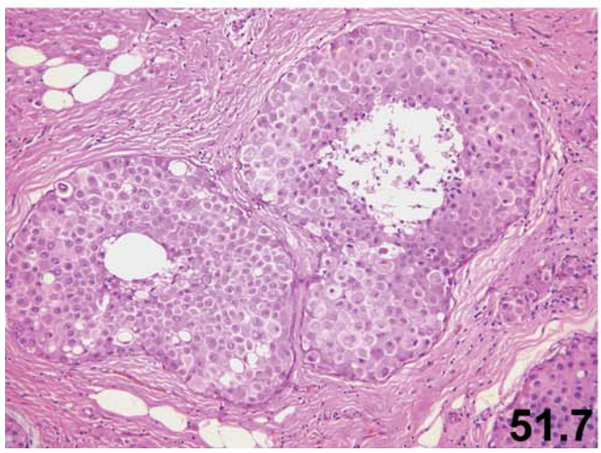
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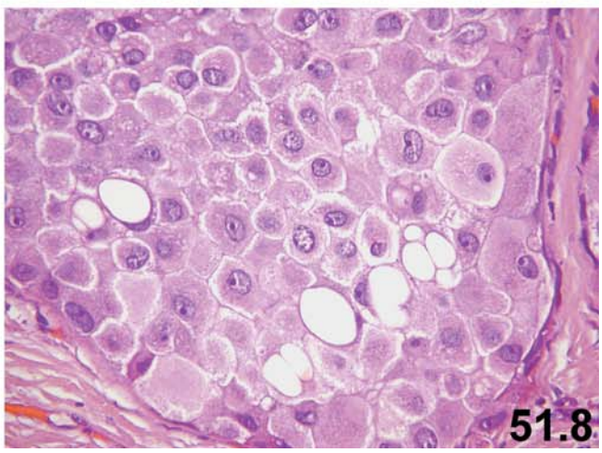
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Figs. 51.9 and **51.10:** Intraepithelial neoplasia with large tumor cells showing either vacuolated cytoplasm with histiocytic-like differentiation (Fig. 51.9) or intense eosinophilic cytoplasm with apocrine-like differentiation (Fig. 51.10).

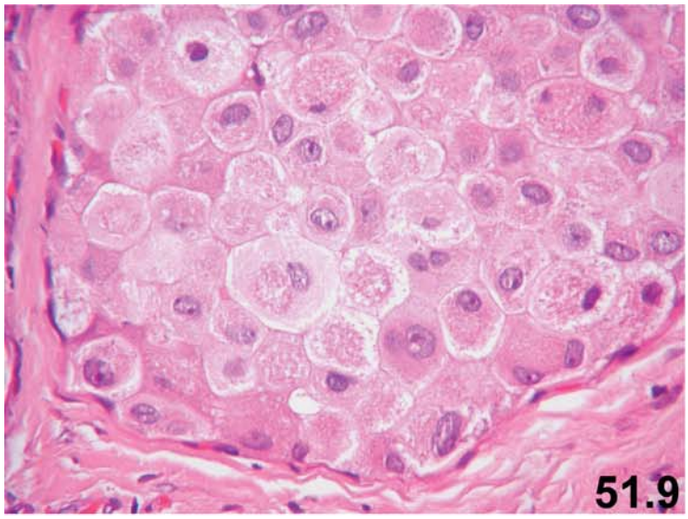
Fig. 51.11: Negative immunoreaction for E-cadherin in lobular intraepithelial neoplasia. The invasive component of the tumor was completely negative for E-cadherin (not shown).

Fig. 51.12: Immunohistochemistry for CK34BE12 reveals a positive reaction in both the lobular intraepithelial neoplasia and the invasive carcinoma.

Figs. 51.13 and **51.14:** Typical positive immunoreaction for CK34BE12 in lobular intraepithelial neoplasia (51.13) and ILC (51.14).

Fig. 51: Final remarks

- This case demonstrates that histiocytoid breast carcinoma is closely related to apocrine carcinoma. The infiltrating tumor cells with foamy or pink cytoplasm could easily be mistaken for granular cell tumor. However, the tumor cells in this case are immunohistochemically positive for pancytokeratin and CK34BE12. The negative immunoreaction for E-cadherin and positivity for CK34BE12 is a common finding in lobular breast carcinoma.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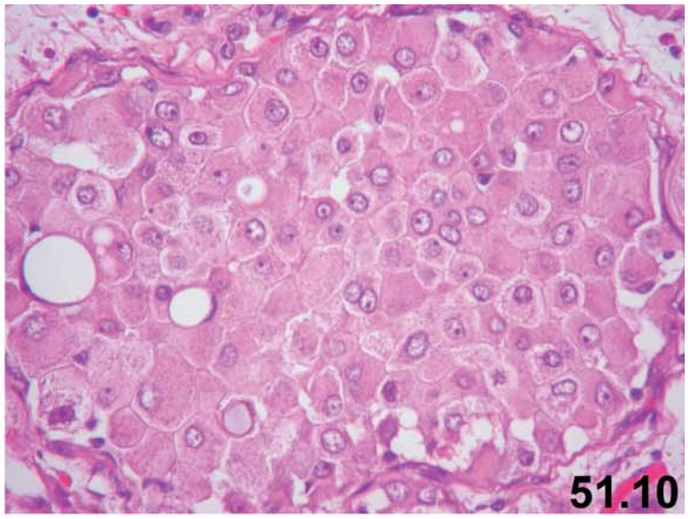
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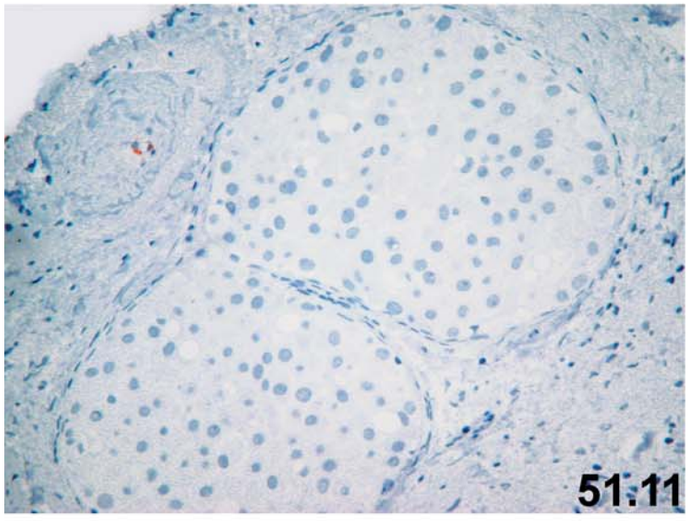
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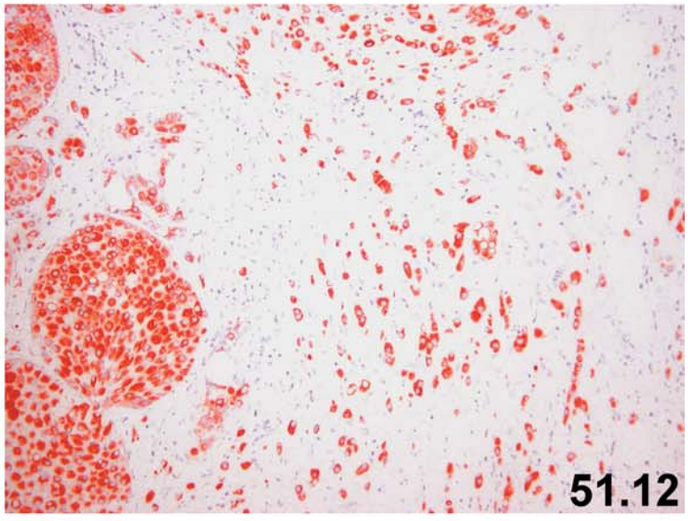
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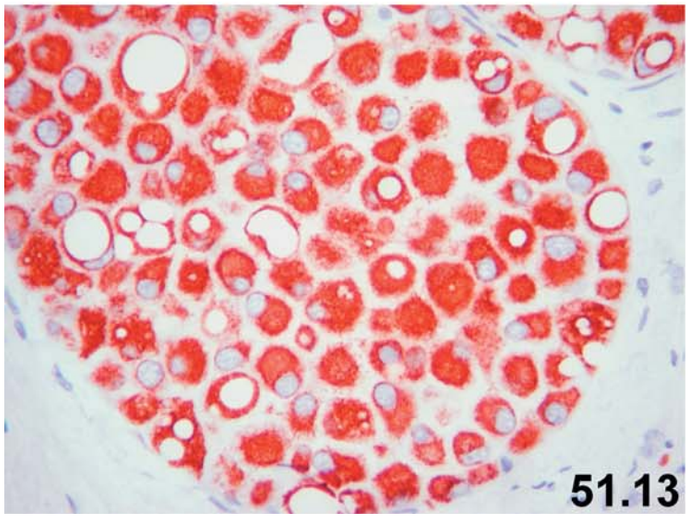
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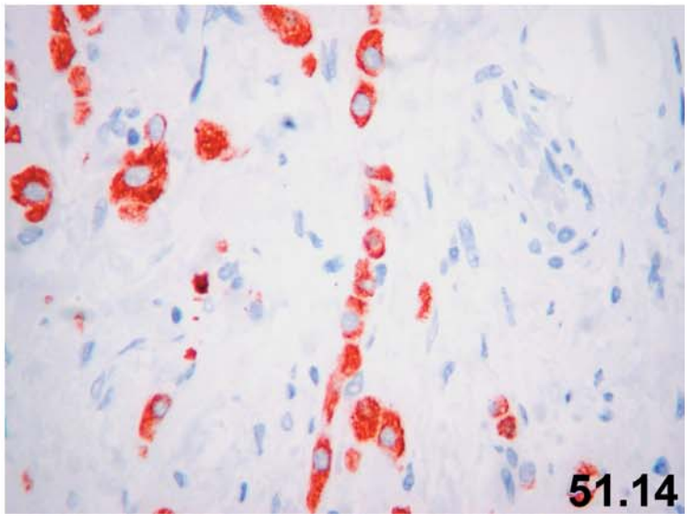
51.14

Special Types of Breast Carcinomas

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CHAPTER 10 Special Types of Breast Carcinomas

10.1 Tubular Carcinoma

10.1.1 Definition

A very-well differentiated infiltrating carcinoma with an excellent prognosis.

10.1.2 Macroscopy

Ill-defined firm to hard greyish-white tumor usually 2 cm or less in diameter. The tumor is often stellate, and the cut surface is likely to retract (becoming depressed in relation to the surrounding breast tissue). The gross appearance is often similar to that of a radial scar (complex sclerosing lesion).

10.1.3 Microscopic Features (Fig. 52)

- It is characterized by proliferation of angulated, oval, or elongated tubules with haphazard arrangement.
- The overall configuration tends to be stellate and has ill-defined margins.
- There is a homogeneous cell population (only epithelial cells, no myoepithelial component).
- Tumor cells do not show significant nuclear atypia (at higher magnification, slight nuclear enlargement can be identified).
- Stromal alterations include reactive-appearing (granulation tissue-like or desmoplastic) changes and/or stromal elastosis.
- The glands infiltrate into the surrounding breast tissue.
- Apical snouts (cytoplasmic protrusions) of the tubules are present in about 30% of cases.
- Conventional types of ductal intraepithelial neoplasia (DIN; ductal carcinoma in situ [DCIS]) are present in almost 60% of the cases. Most of these are low-grade cribriform or micropapillary DIN (DCIS, G1). The close examination of cases with tubular carcinoma reveals that in the vast majority of cases, several ducts (or ductules) with DIN flat type (flat epithelial atypia) are present adjacent to and at the periphery of carcinoma. These ducts or ductules are lined with a very few cell layers of mildly atypical cells. These areas represent a low-grade DIN flat type.
- Lobular intraepithelial neoplasia can also be present within the tumor.
- A pure tubular carcinoma is 100% tubular; a mixed tubular carcinoma is 75% or more tubular.
- Tubulolobular carcinoma has been designated as a variant of lobular carcinoma; not infrequently, however, it represents a mixed ductal and lobular carcinoma.
- Calcifications are found in at least 50% of tubular carcinomas.
- About 10–20% of patients are found to have multifocal (multicentric) tubular carcinomas growing as separate foci in one or more quadrants. Multifocality is encountered in 30% of patients with tubulolobular carcinoma [1, 2, 6, 9, 11, 12, 14, 18].

10.1.4 Differential Diagnosis

Sclerosing adenosis, radial scar (benign complex sclerosing lesion), microglandular adenosis, and tubular adenosis need to be considered. With the exception of microglandular adenosis, the glands in all types of mammary adenosis have a myoepithelial component. Tubular carcinoma, as other types of breast carcinomas, does not have myoepithelial cells within the infiltrating glands [6, 7, 10, 13, 16].

10.1.5 Immunoprofile

Markers for myoepithelial cells (smooth muscle [SM] actin, SM myosin, calponin, p63, CD10, etc.) do not show a myoepithelial cell layer around the tubules. CK5/6 is negative in the vast majority of cases. E-cadherin is positive.

10.1.6 Additional Comments

Tubulolobular carcinoma has been regarded as a variant of tubular carcinoma by some authors and as a form of invasive lobular carcinoma by others. This variant of carcinoma has a good prognosis comparable to well-differentiated ductal or lobular carcinoma. If immunohistochemistry is negative for E-cadherin but shows positivity for CK34BE12, the tumor can be considered a variant of invasive lobular carcinoma (ILC; tubulolobular variant of ILC). Many of these tumors, however, show a positive immunoreaction for both E-cadherin and CK34BE12 (positive hybrid neoplasia with mixed ductal and lobular differentiations) [18].

10.1.7 Further Reading

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10.2 Mucin-Producing Carcinomas of the Breast

There are three subtypes of mucin-producing carcinomas of the breast: (1) mucinous (colloid) carcinoma, including hypercellular variant, (2) signet-ring cell carcinoma, and (3) mucinous cystadenocarcinoma.

10.2.1 Mucinous (Colloid) Carcinoma

10.2.1.1 Macroscopy

Well-circumscribed tumor with pushing margin and typical gelatinous, soft cut surface.

10.2.1.2 Microscopic Features (Figs. 53 and 54)

- Small clusters of uniform epithelial cells with mild nuclear atypia float in abundant "lakes" of mucus.
- Delicate bands of fibrovascular connective tissue are often present within the mucus lakes.
- The cell clusters floating in the mucus may be solid or micropapillary, or form secondary lumens.
- The neoplastic cells consist only of epithelial cells (no myoepithelial component).
- Mainly extracellular mucin. Rarely, a few cells with intracytoplasmic mucin or signet-ring like cells can be found.
- DIN (DCIS) with solid, cribriform, micropapillary, or spindle cell pattern is often present.
- The neoplastic cells may show "salt-and-pepper" chromatin and fine granular eosinophilic cytoplasm. These features indicate some (neuro)endocrine differentiation. Indeed, (neuro)endocrine markers such as NSE, chromogranin, and synaptophysin can be positive in some of the tumor cells [1, 2, 4, 6, 8, 14, 20, 23, 26].

10.2.1.3 Differential Diagnosis

Colloid (mucinous) carcinoma should be distinguished from the rare mucocele and myxoid fibroadenoma. Mucous lakes are occasionally seen in association with fibrocystic changes and reflect a ruptured cyst (rarely exceeding 2–3 mm in diameter). Mucocele-like lesions are generally hypocellular (or acellular). Larger mucous lakes may contain strips of epithelium within them; invariably, however, the myoepithelial cell layer is clearly present in some of these nests.

Caution

- Occasionally, mucocele-like lesions are associated with ruptured DIN (DCIS). This should not be interpreted as a mucinous carcinoma.
- In rare cases, tumor cells may display moderate to severe nuclear atypia. This unusual variant should be separated from the classic mucinous carcinoma, which has an excellent prognosis.
- The myxoid fibroadenomas with significant myxoid stromal change can be mistaken for a mucinous carcinoma, both grossly and histopathologically. The presence of attenuated layers of epithelial and myoepithelial cells lining compressed spaces helps differentiate the two.

10.2.1.4 Further Reading

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10.2.2 Signet-Ring Cell Carcinoma (Fig. 55)

This rare variant of mucin-producing carcinoma should be clearly separated from mucinous (colloid) breast carcinoma. Whereas mucinous carcinoma has an excellent prognosis, signet-ring carcinomas of the breast are very aggressive. Signet-ring carcinoma can be a subtype of invasive lobular or ductal carcinoma. Signet-ring cells should de distinguished from cells with intracytoplasmic lumens ("targetoid" tumor cells).

Caution

- The presence of signet-ring cells (ductal or lobular in origin) within the carcinoma indicates a more aggressive behavior of the tumor, regardless of the number of such cells.

Because of distinctive morphology and clinically more aggressive behavior, signet-ring cell carcinoma should be designated as a specific variant of breast carcinoma when present in its pure form. The presence of even a 10% signet-ring cell population in infiltrating lobular carcinoma has been reported with a higher frequency of recurrences and metastases in patients with stage I disease. It is important to note that primary signet-ring cell carcinomas of the breast and carcinomas (infiltrating ductal carcinoma or invasive lobular carcinoma) with a signet-ring cell component are capable of metastasizing to unusual sites such as the bladder, stomach and other gastrointestinal sites, and serosal surfaces (ovary, uterus), where they may mimic a primary carcinoma of the involved organ [1, 3–6].

10.2.2.1 Immunoprofile

Mammary signet-ring cell carcinomas are generally immunohistochemically positive for gross cystic disease fluid protein (GCDFP-15 or BRST2), whereas gastrointestinal tract signet-ring cell carcinomas are negative. Estrogen receptor and MUC1 are very often positive in primary signet-ring cell carcinoma of the breast but are commonly negative in gastric and colonic signet-ring cells. While primary signet-ring cell carcinoma of the breast is typically positive for CK7 and negative for CK20, the gastrointestinal signet-ring cell carcinomas are commonly positive for CK20 but usually negative for CK7. These differences can be helpful in distinguishing the primary site of some difficult cases when metastatic mammary carcinoma to the gastrointestinal tract closely simulates a primary tumor [2, 8].

10.2.2.2 Further Reading

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10.2.3 Mucinous Cystadenocarcinoma

A very rare variant of mucin-producing breast carcinoma closely mimicking an ovarian mucinous cystadenocarcinoma.

10.2.3.1 Microscopic Features

- Several solid and multiloculated cysts are evident.
- Many of the cysts are lined by columnar mucinous cells without significant atypia; other spaces, however, display significant proliferation, forming multiple layers, tufts, and papillae.
- Some of the neoplastic cells show nuclear atypia and loss of intracytoplasmic mucin.
- Disruption of the cystic walls and infiltration of the stroma with reactive stromal alterations may occur.
- Areas of squamous differentiation (metaplasia) may also be present.
- Areas of DIN (DCIS) with mucinous differentiation or more conventional types of DIN (DCIS) can also be present.

Caution

- The possibility of a metastatic mucinous carcinoma (ovary, gastrointestinal tract) into the breast needs to be excluded.

10.2.3.2 Further Reading

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10.3 Carcinoma with Neuroendocrine Differentiation

10.3.1 Definition

The term "carcinoma with neuroendocrine differentiation" should be reserved for mammary carcinomas that show any of the growth patterns of a "carcinoid" tumor (including insular pattern with or without rosettes or rosette-like structures, trabecular and spindle cells, and oat cells), or for those in which some of the tumor cells are positive for at least two neuroendocrine markers (chromogranin, synaptophysin, NSE).

10.3.2 Macroscopy

No specific gross pathologic features. The tumors are mostly grossly well circumscribed.

10.3.3 Microscopic Features (Figs. 56–58)

- There is an infiltrative growth pattern with solid aggregates (nesting or alveolar pattern), trabecular, rosette, or rosette-like structures.
- Not infrequently, extracellular mucin is evident.
- Cytologically, the neoplastic cells frequently show different cell morphology (mixed cell population of epithelial cells displaying round cells, spindle cells, etc). The tumor cells often show a "salt-and-pepper" chromatin pattern and fine granular, eosinophilic cytoplasm. Intracytoplasmic mucin can also be present.
- Rare examples of primary small cell carcinoma of the breast have been reported. These tumors show poorly differentiated small cells with high mitotic activity and necrosis. A dimorphic histologic appearance can be present in this rare carcinoma, showing small cell carcinoma merging with invasive lobular or ductal carcinoma [1, 4, 10, 12, 20].

10.3.4 Immunoprofile

Immunohistochemistry reveals a specific but quite heterogeneous positive reaction with antibodies against chromogranin or synaptophysin. Neural cell adhesion molecule (NCAM) is not infrequently positive. NSE alone is not specific [5, 6, 8, 12, 13, 15, 21]! Other hormones such as adrenocorticotropic hormone, human chorionic gonadotropin, prolactin, neurotensin, and norepinephrine can also be positive in the tumor cells.

10.3.5 Additional Comments

Whether or not these tumors behave differently from a morphologically comparable carcinoma lacking neuroendocrine granules has not been well established. One study showed no significant difference in either overall or disease-free survival between patients with or without neuroendocrine differentiation [14]. It seems that the stage at diagnosis is the major determinant of prognosis in breast cancer with neuroendocrine differentiation.

Neuroendocrine tumors (carcinoma) can metastasize to the breast and should be distinguished from primary breast carcinoma with neuroendocrine differentiation. The presence of DIN (DCIS), preferably with similar morphology, supports the diagnosis of primary breast carcinoma. In the absence of an intraepithelial neoplastic component, careful attention to the patient's history and clinical findings is needed to prevent misinterpretation of a metastatic neuroendocrine carcinoma.

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10.4 Invasive Papillary Carcinoma

10.4.1 Definition

Infiltrating carcinoma with clear-cut papillary configuration. Infiltrating papillary carcinomas with truly infiltrating papillary configurations are extremely rare.

10.4.2 Macroscopy

Usually a well-circumscribed tumor. It cannot be separated from invasive breast carcinomas of no special type.

10.4.3 Microscopic Features

- Clear-cut invasive carcinoma showing exclusively or predominantly a papillary configuration.
- Neoplastic cells with mild to moderate nuclear atypia.
- Papillary DCIS (DIN) present in more than 70% of cases.

Caution

- Most of the published cases concerning papillary carcinomas include both noninvasive (intraductal) papillary and invasive tumors, as they do not generally specify features of an invasive process. In the vast majority of cases, when papillary intraductal carcinomas invade, they usually show the infiltrating pattern of ductal carcinoma (NOS type) and lack a papillary architecture. It should be emphasized that invasive papillary breast carcinomas are very rare.

10.4.4 Further Reading

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10.5 Invasive Micropapillary Carcinoma

10.5.1 Definition

A rare but distinctive variant of infiltrating carcinoma composed of small clusters of tumor cells closely resembling the micropapillary pattern of DIN (DCIS). It can occur as pure or mixed type.

10.5.2 Macroscopy

Lobulated outline due to expansive growth pattern.

10.5.3 Microscopic Features (Fig. 59)

- Aggregates of small epithelial clusters are seen, which on cross-section show the appearance of tubules.
- Micropapillary structures (pseudopapillary structures lacking a fibrovascular core) are present that closely resemble the micropapillary pattern of DIN (DCIS).
- Tumor cell clusters lie within artifactual clear empty stromal spaces (shrinkage artifact) simulating vascular spaces.
- Several areas of lymphatic invasion are clearly present.
- Tumor cells may show moderate or high-grade nuclear atypia.
- Mitotic activity may be low or high.

Caution

- Invasive micropapillary carcinoma represents a rare but aggressive variant of carcinoma in various anatomic sites, including the breast, urinary bladder, lung, and major salivary glands. This malignant tumor has a high propensity for lymphovascular invasion and lymph node metastases.
- Several reports demonstrate a poor clinical outcome compared with that of patients with conventional carcinoms arising in the same organ site.
- One should not rely on a negative result from a sentinel lymph node biopsy because this variant is often associated with axillary lymph node metastasis.
- Using the Nottingham grading system, many of the micropapillary breast carcinomas may fall into the category of moderate differentiated (G2) carcinomas. The mitotic activity can be low, and the majority of cases are also positive for estrogen receptor (ER). These findings, however, should not mislead pathologists and oncologists to consider this variant of breast carcinoma as a "low-risk" cancer.
- The vast majority of tumor cells in this variant overexpress HER2/neu. The tumor cells are also often positive for p53.

10.5.4 Further Reading

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10.6 Apocrine Carcinoma

10.6.1 Definition

A rare variant of infiltrating carcinoma with prominent apocrine differentiation. The apocrine morphology (differentiation) needs to be seen in more than 90% of the cancer cells.

10.6.2 Macroscopy

Often not distinguishable from infiltrating ductal carcinoma, NOS type. It may show a brownish-tan cut surface.

10.6.3 Microscopic Features (Fig. 60)

- Hypercellular tumor composed of tubules, cords, and solid aggregate of tumor cells.
- Large epithelial tumor cells with hyperchromatic round nuclei, prominent nucleoli, and abundant eosinophilic granular cytoplasm are present.
- Tumor cells with bizarre, multilobulated nuclei may be present.
- Some tumor cells may show lipid droplets simulating sebaceous cells. The tumor cells may have a foamy cytoplasmic appearance resembling histiocytes.
- Often, a noninvasive apocrine component (DIN, DCIS) with high nuclear grade is present.

Caution

- Prominent apocrine metaplasia with or without atypia can be associated with sclerosing adenosis or radial scar (complex sclerosing lesion). The irregular and pseudoinfiltrative glandular pattern accompanied by cytologic atypia in the apocrine cells may easily be overinterpreted as apocrine carcinoma. Identification of basally located myoepithelial cells helps avoid such misinterpretation.

10.6.4 Differential Diagnosis

Oncocytic carcinoma [5, 7]: Very rare and newly described variant of invasive carcinoma with tumor cells that look identical to apocrine cells at the hematoxylin-eosin level. Oncocytic tumor cells seem to differ from apocrine cells based on the electron microscopic studies performed on a few cases. Currently, however, immunohistochemistry cannot be used reliably to separate these two types of carcinoma.

Histiocytoid carcinoma [6, 21]: The nuclei are small compared with those of apocrine carcinoma. While the nuclei of histiocytic carcinoma often show dense chromatin and inconspicuous nucleoli, apocrine carcinoma typically show prominent nucleoli. Some investigators believe that histiocytoid carcinoma is a variant of invasive lobular carcinoma that is characterized by a proliferation of cells with abundant vacuolated or eosinophilic cytoplasm.

Lipid-rich (lipid-secreting) carcinoma [6]: Abundant intracytoplasmic neutral fat demonstrated by oil red O-stain in tumor cells with foamy or vacuolated cytoplasm.

Granular cell tumor [6]: Small to pyknotic nuclei, often no cytology atypia, no prominent nucleoli.

10.6.5 Additional Comments

The vast majority of apocrine cells in the breast (apocrine metaplasia, apocrine hyperplasia, and apocrine carcinoma) are negative for ER and PR. But they are typically (but not always) positive for androgen receptor (AR) [2, 9, 11, 17, 19]. Although the clinical significance of AR expression is uncertain, this finding may have an impact on the choice of adjuvant hormonal treatment of apocrine carcinoma or carcinoma with apocrine features in the future.

Apocrine cells are usually (but not always) positive for GCDFP-15 (BRST-2). Nonapocrine epithelial cells can also be positive for GCDFP-15 [9, 10, 14]. It has been shown that benign and malignant apocrine cells are characteristically positive with monoclonal antibody against B72 [3].

Apocrine carcinomas are often of high grade. However, survival of patients with apocrine carcinoma does not differ from those with other high-grade, non-apocrine breast carcinomas [3, 13, 18].

Any type and grade of breast carcinoma can show areas with apocrine differentiation, including NOS-type invasive ductal carcinoma, medullary, micropapillary, and neuroendocrine types as well as invasive lobular carcinoma. The designation of apocrine carcinoma is used when more than 90% of the tumor cells are of apocrine differentiation.

10.6.6 Further Reading

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10.7 Secretory Carcinoma

10.7.1 Definition

A rare carcinoma showing abundant intracellular and extracellular secretion with a tendency to occur relatively more frequently during the first three decades of life.

10.7.2 Synonym

Juvenile or juvenile-type carcinoma.

10.7.3 Macroscopy

Usually well-circumscribed, lobulated, firm greyish-white or grey-yellow tumor often simulating fibroadenoma. Irregular and infiltrating margins also occur. The tumors tend to be 3 cm or smaller in diameter.

10.7.4 Microscopic Features (Fig. 61)

- Predominantly pushing margin of the tumor, but areas of irregular invasion of the adipose tissue can often be found.
- Abundant intracellular and extracellular eosinophilic secretory material is present.
- Usually three patterns in varying combinations are present: (1) a microcystic or honeycombed pattern composed of small cysts that often merge into larger spaces, closely simulating thyroid follicle, (2) a tubular pattern containing luminal secretions, (3) a solid pattern.
- Intracytoplasmic lumina are numerous.
- The tumor consists of cells with pale to clear, pink, or amphophilic cytoplasm and small round nuclei with minimal atypia. The tumor cells occasionally show more granular or deeply eosinophilic cytoplasm and round nuclei with prominent nuclei.
- There is no significant mitotic activity or tumor necrosis.
- The secretory material is usually positive for alcian blue and PAS after diastase digestion.
- DIN (DCIS) of cribriform, papillary, solid, and, infrequently, comedo type may be found.

10.7.5 Additional Comments

The prognosis is excellent in children and adolescents but seems slightly less favorable in older patients [5, 11–14, 18].

Immunohistochemically, secretory carcinoma is positive for alpha-lactalbumin, beta-casein, and HMFG-2 (all regarded as milk proteins). The tumor cells are positive for S100 protein and CEA. ER is usually negative. It has been shown that the tumor cells are positive for salivary-type amylase, lysozyme, and alpha 1-antitrypsin, raising the possibility that secretory breast carcinoma and acinic cell carcinoma are closely related entities [3, 4, 6].

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10.8 Adenoid Cystic Carcinoma

10.8.1 Definition

Adenoid cystic carcinoma is a carcinoma with low malignant behavior, histologically similar to the salivary gland counterpart.

10.8.2 Macroscopy

Mostly nodular, well-circumscribed tumor with grey, pale yellow, to pink cut surface. Small cystic areas are not unusual. Most tumors are between 1 and 3 cm.

10.8.3 Microscopic Features (Fig. 62)

- Despite its grossly well-circumscribed appearance, the tumor shows an irregular, infiltrating growth pattern revealing solid, cribriform, tubular, and trabecular arrangements.
- The tumor is composed of proliferating glands (adenoid component) and stromal or basement membrane elements (cylindromatous component).
- Two type of cells exist within the island: a basaloid cell population and a smaller population of cells with bright eosinophilic cytoplasm.
- Often, eosinophilic basement-membrane-like material (hyaline bodies), mucoid secretory material, or a bright thick eosinophilic band deposited on the lining cells can be observed.
- The stroma may be edematous, hyalinized, or chondroid in appearance.
- In addition to two cell types (epithelial and myoepithelial cells/basaloid cells), a third type, sebaceous cells within the nests and tubules of the tumor, may be present. Squamous metaplasia can also be present.
- Perineural invasion is found in a minority of tumors. Although shrinkage artifacts are relatively common in adenoid cystic carcinoma, lymphatic vessel invasion is extremely rare.

Caution

- Adenoid cystic carcinoma needs to be separated from collagenous spherulosis, cribriform DIN (DCIS), and infiltrating cribriform carcinoma.
- Shrinkage artifacts are commonly seen in adenoid cystic carcinoma. These should not be mistaken for lymphatic invasion.

10.8.4 Differential Diagnosis

Collagenous spherulosis may simulate adenoid cystic carcinoma. Collagenous spherulosis, however, is often an incidental microscopic finding (no gross tumor) and does not show an infiltrating pattern [8, 12–14, 17].

Cribriform variant of DIN (DCIS) is composed of one cell type (homogeneous cell population of epithelial cells) and does not show the typical basement membrane material of adenoid cystic carcinoma.

Infiltrating cribriform carcinoma is composed of a monotonous cell population showing only epithelial cells (no myoepithelial/basaloid component). No hyaline bodies and no irregular and thick basement membrane material can be identified in infiltrating cribriform carcinoma.

10.8.5 Immunoprofile

The tumor cells are characteristically positive for both LMW-CK (such as CK8/18) and HMW-CK or basal-type cytokeratins (such as CK34BE12, CK5/6, CK14). The immunoreaction for HMW-CK is quite heterogeneous. SM actin, SM myosin (heavy-chain), calponin, and p63 are positive in some (or many) areas of the tumor. CD117 (C-kit) is commonly positive. ER, PR, and HER2/neu are very often negative in adenoid cystic carcinoma [2, 3, 11, 15].

10.8.6 Additional Comments

Adenoid cystic carcinoma is one of the least aggressive mammary carcinomas. It hardly ever metastasizes to the axillary nodes, but it does recur. Distant metastases (lung) can occur many years after diagnosis [1, 6, 7, 9, 12, 13].

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10.9 Acinic Cell Carcinoma

10.9.1 Definition

A very rare primary adenocarcinoma of the breast with morphology similar to that of salivary gland carcinoma showing acinic cell (serous) differentiation.

10.9.2 Macroscopy

Mostly well-circumscribed palpable tumor. Some tumors are irregular shaped, ill-defined, or multinodular. The cut surface is lobular with a tan to reddish color. It varies in consistency from firm to soft and solid to cystic.

10.9.3 Microscopic Features

- Many areas of the tumor show infiltrating irregular borders.
- A combination of microglandular, microcystic, and solid areas is common.
- Areas of the tumor may show comedo-type necrosis simulating high-grade DIN (DCIS) with central comedo-type necrosis.
- The tumor cells usually have abundant granular eosinophilic cytoplasm and round to ovoid, usually bland nuclei.
- Intracytoplasmic granules may be coarse and bright red, similar to those in Paneth cells.
- Microglandular areas of the tumor commonly display intraluminal eosinophilic colloid-like secretory material closely resembling microglandular adenosis (see section on differential diagnosis).
- Some areas of the tumor may show highly atypical tumor cells associated with high mitotic activity.
- Some areas of the tumor may show cells with abundant clear or vacuolated cytoplasm.
- A papillary-cystic growth pattern may be present. Hemorrhage in a papillary-cystic tumor can produce a focally dense deposition of hemosiderin pigment (iron stain) in the collagenous stroma.

10.9.4 Differential Diagnosis

Acinic cell carcinoma can be mistaken for microglandular adenosis (MGA), atypical MGA, or carcinoma arising in the background of MGA. All of these tumors lack a myoepithelial cell layer, show areas with colloid-like secretory luminal material, and typically express S100 protein. The tumor cells in acinic cell carcinoma (but not in MGA) stain heterogeneously with antibodies against alpha-1-antitrypsin, alpha-1-antichymotrypsin, lysozyme, and amylase. EMA is negative in MGA but positive in acinic cell carcinoma [2, 4, 6–8].

10.9.5 Additional Comments

Due to the rarity of this type of carcinoma, experience regarding prognosis and appropriate treatment is limited. Most of the few reported cases were negative for ER and PR.

10.9.6 Further Reading

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10.10 Sebaceous Carcinoma

10.10.1 Definition
A very rare primary breast carcinoma with sebaceous differentiation without evidence of association with cutaneous adnexal sebaceous glands.

10.10.2 Macroscopy
Usually a well-circumscribed tumor with a solid white to yellow cut surface.

10.10.3 Microscopic Features (Fig. 63)
- Lobules or nests of large tumor cells with abundant clear to foamy cytoplasm and distinct cell borders. Some of the tumor cells may show eosinophilic cytoplasm without vacuolization.
- The nuclei are round and show a minimal degree of atypia. Focally, significant nuclear atypia may be present. A few tumor cells with spindled configuration may be identified.
- Mitotic activity is usually low. Focally, however, mitotic figures can be numerous.
- Areas of small squamous morules or keratinizing squamous epithelium lacking any atypia may be found.
- Delicate fibrovascular areas separate many of the lobules.
- Both the skin and the adjacent skin adnexal glands appear normal; there is no continuity between the carcinoma and any of these structures.

10.10.4 Immunoprofile
Positive immunoreaction for pancytokeratin (AE1/AE3). While PR is usually positive, ER can be negative. Vimentin, S100 protein, and CEA are reported to be negative [1, 5, 6].

10.10.5 Differential Diagnosis
Lipid-rich carcinoma is the main differential diagnosis. While sebaceous carcinoma shows a lobulated, well-defined solid growth pattern, lipid-rich carcinoma infiltrates like a regular invasive ductal carcinoma with infiltrating, irregular tumor borders. In contrast to sebaceous carcinoma, the vacuolization in lipid-rich carcinoma is much more subtle and is easily overlooked on low magnification [5].

10.10.6 Additional Comments
By definition, primary sebaceous carcinoma of the breast shows no connection with skin adnexal glands. Indeed, this rare type of breast carcinoma can be regarded as another type of metaplastic carcinoma with prominent sebaceous differentiation [5].

10.10.7 Further Reading
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10.11 Infiltrating Cribriform Carcinoma

10.11.1 Definition
A special and rare type of breast carcinoma in which infiltrating cribriform structures are formed. This type of carcinoma is associated with an excellent prognosis.

10.11.2 Macroscopy
A firm greyish-white tumor with relatively smooth or occasionally stellate borders.

10.11.3 Microscopic Features (Fig. 64)
- Islands of uniform tumor cells with low-grade atypia are present that resemble those seen in cribriform DIN (DCIS).
- There is a clear-cut infiltrating pattern with a homogenous cell population without a myoepithelial cell layer.
- Minor areas of tubular differentiation are intermixed in 25% of cases, and both patterns can have apical cytoplasmic protrusions (snouts).
- In the vast majority of cases, adjacent DIN (DCIS) with cribriform and micropapillary growth pattern is present.

10.11.4 Differential Diagnoses
DIN (DCIS), cribriform growth pattern: At higher magnification, a myoepithelial cell layer is almost always present. If in doubt, immunohistochemistry for myoepithelial cells is helpful (refer to information on DIN).

Tubular carcinoma (TC): Classic or pure TC does not have a significant cribriform growth pattern. Mixed-type tubular carcinoma, however, often shows a cribriform component. Such well-differentiated tumors have been designated as either mixed type tubular or mixed type cribriform carcinomas (see section on TC).

Adenoid cystic carcinoma: The presence of two or three cell populations (epithelial, myoepithelial/basaloid, squamous or sebaceous cells) and hyaline bodies as well as thick basement-membrane-like material is characteristic for adenoid cystic carcinoma (refer to section on adenoid cystic carcinoma). These features are absent in cribriform carcinoma.

10.11.5 Additional Comments
Like tubular carcinoma, infiltrating cribriform carcinoma has an excellent prognosis [3]. In cases with combined growth patterns of cribriform and tubular carcinoma, the designation of well-differentiated mixed cribriform-tubular carcinoma is appropriate.

10.11.6 Further Reading

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10.12 Medullary Carcinoma

10.12.1 Definition

A rare malignant tumor with well-circumscribed margins and a firm (medulla-like) consistency. Most authors regard this malignant tumor to be associated with less aggressive behavior despite its anaplastic morphology, although this is controversial.

10.12.2 Macroscopy

A well-circumscribed, occasionally encapsulated fleshy tumor (soft consistency). The color of the cut surface varies from tan to greyish-white with yellow zones of necrosis and red or brown hemorrhagic foci. Central necrosis may lead to cyst formation. The gross appearance can easily be mistaken for a fibroadenoma.

10.12.3 Microscopic Features of Typical Medullary Carcinoma (Fig. 65)

- A well-delineated tumor with pushing, expansile margins (smooth, rounded contour).
- Syncytial growth pattern of tumor cells (solid clusters of tumor cells without recognizable cell borders), forming anastomosing cords and sheets.
- Diffuse lymphoplasmacytic infiltration of stroma (the lymphocytic infiltration must involve at least 75% of the periphery and be present diffusely in the central portions of the tumor).
- Tumor cells with severe nuclear atypia and easily recognizable mitotic figures.
- No significant desmoplastic stromal change.
- No glandular (tubular) formation.
- Absence of glandular or fatty tissue within the invasive portion of the tumor (no areas of the tumor similar to IDC, NOS type).
- Presence or absence of DCIS (DIN): controversial in the literature!

10.12.4 Histopathology of So-Called Atypical Medullary Carcinoma

Atypical medullary carcinoma resembles medullary carcinoma but lacks all of the necessary microscopic features mentioned above. Atypical features include focal invasive growth at the periphery of the tumor, diminished lymphoplasmacytic reaction, well-differentiated nuclear cytology, dense collagenous stroma, desmoplastic stroma, few mitoses, and conspicuous glandular or papillary growth [5, 11, 15, 18–22].

Caution

- To prevent underdiagnosis of a poorly differentiated carcinoma, formation of glandular (tubular) structures by the tumor cells should not be present. The presence of these formations or any other pattern of infiltrating ductal carcinoma of NOS type (atypical features as mentioned above) disqualifies the lesion as a classic medullary carcinoma.
- It has been shown that the behavior of "atypical medullary carcinoma" is not significantly different from that of poorly differentiated infiltrating ductal carcinoma. *A case that does not fulfill all diagnostic criteria for medullary carcinoma should, therefore, be classified as poorly differentiated infiltrating ductal carcinoma.*
- Typical or classic medullary carcinomas of the breast are extremely rare if one adheres to strictly defined morphologic criteria. There is substantial interobserver and intraobserver variability in the diagnosis of medullary carcinoma.
- Medullary carcinoma has been reported to have a better prognosis than the common ductal carcinoma, but this has been questioned by others. The outcome of medullary carcinoma associated with more than three metastatic axillary lymph nodes has been reported to be poor or no different from that of usual ductal tumors [1, 5, 13].

10.12.5 Immunoprofile

ER and PR are almost always negative. HER2/neu is usually negative. The tumor cells can focally be positive for HMW-CK and CK19. Some of the basal/myoepithelial markers such as CK5/6, CK14, p63, and CD10 can focally be positive [4, 9, 11].

10.12.6 Additional Comments

The histology of medullary carcinoma or so-called atypical medullary carcinoma sometimes resembles a poorly differentiated epidermoid carcinoma. Some tumors also display well-formed foci of squamous metaplasia.

Medullary carcinomas share a number of features with BRCA1-associated breast cancers, including a relatively young age at diagnosis, high-grade nuclear atypicality, numerous mitotic figures, prominent lymphocytic stromal infiltration, absence of steroid hormone receptors, and frequent p53 alterations. A recent study, however, has suggested that medullary breast cancers are not an indication for BRCA1 mutation screening in the absence of significant family risk factors [8].

10.12.7 Further Reading

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10.13 Metaplastic Carcinomas

10.13.1 Definition

A heterogeneous group of rare malignant neoplasms characterized by an admixture of (adeno)carcinoma with areas of spindle, squamous, osseous, or chondroid differentiation [13, 36].

10.13.2 Background

- Mammary metaplastic carcinomas account for less than 1% of all breast cancers. The rubric designation of metaplastic carcinoma is traditionally used to encompass a broad group of tumors with different histologic appearances (Fig. 66). The heterogeneity of these unusual breast cancers is reflected by somewhat confusing terminology such as spindle cell carcinoma, sarcomatoid carcinoma, matrix-producing carcinoma, low-grade fibromatosis-like carcinoma, carcinosarcoma, and carcinoma with pseudosarcomatous metaplasia.
- With regard to diverse cell differentiation, these tumors can be classified as monophasic spindle cell or sarcomatoid carcinoma; biphasic carcinosarcoma; and adenocarcinoma with divergent stromal differentiation, including chondroid, osseous, and rarely rhabdoid "metaplasia" as well as adenosquamous and pure squamous cell carcinomas.
- Several studies have shown that metaplastic carcinomas are mostly negative for ER, PR, and HER2/neu [3, 23, 24]. While some recent studies have shown that metaplastic carcinomas (particularly spindle cell/sarcomatoid carcinomas and carcinosarcomas) are highly aggressive neoplasms with a high rate of extranodal metastases [8, 11, 23, 38], others have found comparable outcomes (recurrence, survival) with matched typical breast cancer cases (matched for age, TNM stage, ER/PR/HER2, and grade) [4, 10].
- Recent studies have shown that most cases of metaplastic carcinomas (particularly spindle cell/sarcomatoid carcinomas and carcinosarcomas) show immunohistochemical evidence for myoepithelial differentiation [24]. Basal-type cytokeratins or HMW-CKs such as CK5/6, CK14, and CK34BE12 are, at least focally, positive in metaplastic carcinomas [24]. The concept that metaplastic carcinomas of the breast are of myoepithelial differentiation or even origin is tempting, as it could explain their morphological diversity.
- While approximately 70–80% of mammary metaplastic carcinomas overexpress the human epidermal growth factor receptor (EGFR), gene amplification of EGFR can be found in about one-third of these tumors. It is hopeful that some patients with metaplastic breast carcinomas might benefit from therapies targeting EGFR [25, 30, 31].

10.13.3 Current (2003) WHO classification [13]

Purely epithelial
Squamous
- Large cell keratinizing
- Spindle cell
- Acantholytic

Adenocarcinoma with spindle cell differentiation
Adenosquamous, including mucoepidermoid

Mixed epithelial and mesenchymal
Carcinoma with chondroid metaplasia
Carcinoma with osseous metaplasia
Carcinosarcoma

10.13.4 Squamous (Cell) Carcinoma

If a carcinoma is composed purely of squamous cells, then it should be called squamous carcinoma. To qualify as primary squamous carcinoma of the breast, the tumor should not be connected with the overlying cutaneous squamous epithelium [5, 13, 36, 39].

10.13.4.1 Macroscopy

Well-circumscribed or highly irregular tumor with small or large cysts with or without necrosis.

10.13.4.2 Microscopic Features (Figs. 67a, 67b, 68)

- Large-cell keratinizing, spindled, acantholytic, or a combination of these cell types, often proliferate around a cyst.
- Intercellular bridges, keratin pearls, keratohyaline granules, and areas of necrosis are common.
- The cyst portions of the tumor are often lined by squamous epithelium without significant nuclear atypia.
- Branches of the tumor emanate from the cyst and infiltrate the surrounding stroma.
- Sometimes the tumor consists predominantly of spindle cells with rare nests of clearly identifiable squamous epithelium.
- The acantholytic variant is characterized by an admixture of spindle cells and edematous-appearing spongiotic foci forming channels; the channels are either empty or filled with mucoid material.
- "Anastomosing" channels simulate a vascular tumor (pseudoangiomatous pattern); the lining cells are CK-positive but negative for endothelial markers.

Caution

- When the spindle cells dominate, it is important to confirm the tumor's epithelial nature by immunohistochemistry (cytokeratin).
- The acantholytic variant of squamous cell carcinoma can easily be mistaken for a vascular neoplasm, particularly angiosarcoma.

10.13.4.3 Additional Comments

Opinions vary regarding the prognosis of squamous carcinoma. The acantholytic variant [14] possibly reflects a poorly differentiated tumor capable of a more aggressive behavior. Some squamous carcinomas, on the other hand, are very well differentiated (low-grade carcinoma).

The origin of squamous metaplasia is uncertain: Epithelial cells? Myoepithelial cells? Poststem cells?

10.13.5 Adenocarcinoma with Squamous Differentiation (Fig. 67a)

- The adenocarcinoma is generally an infiltrating ducal carcinoma. The squamous component may be spindled, but it is generally a well-differentiated, large cell type with keratinization and intercellular bridges.
- In many cases, the central portion of the tumor shows the most highly differentiated and bland-looking keratinizing squamous element and becomes less differentiated and nonkeratinizing away from the center. The most peripheral areas have the most poorly differentiated adenocarcinoma component [13, 36].
- Areas of transition from adenocarcinoma to squamous carcinoma are readily evident within ducts and duct-like structures.

10.13.6 Sarcomatoid (Spindle Cell) Carcinoma (Figs. 69–71, 73)

- Three subtypes can be recognized: (1) pure spindle cell proliferation, (2) solid spindle cell proliferation with large areas of heterologous, benign-looking chondroid or osseous elements (matrix-producing carcinoma), and (3) carcinosarcoma with high-grade invasive ductal carcinoma set in a sarcomatoid spindle cell or highly polymorphic background [8, 24].
- Pure spindle cell proliferation mostly exhibits interlacing spindle cell fascicules or trabeculae arranged in a whorled pattern, often concentrated around preexisting ducts and lobules.
- While most tumors show infiltrative margins, rare cases display pushing borders.
- The tumor cells often show moderate to high-grade nuclear atypia with numerous mitotic figures. In rare cases, there is no significant cytologic atypia or increased mitotic activity (low-grade sarcomatoid carcinoma).
- Storiform growth pattern may occur.
- Stromal hyalinization or focal areas of myxoid change can be present.
- Rare cases contain scattered multinucleate osteoclast-like giant cells.
- Occasionally, the spindle cells form microcystic and/or pseudovascular spaces.

10.13.7 Carcinoma with Chondroid Differentiation (Fig. 72)

- The carcinoma in this group is most frequently a regular infiltrating ductal carcinoma, but any type of carcinoma may be present.
- The chondroid cells (mature or immature) are positive for S100 protein. A majority of the tumor cells coexpress S100 protein and cytokeratin [13, 36].

10.13.8 Carcinoma with Osseous Differentiation

The carcinoma is most frequently an infiltrating ductal carcinoma, but other types of carcinoma, including mucinous carcinoma, can be present [13, 36].

- A zone of reactive stromal cells may separate the carcinoma from the bone.
- Osteoblasts may abound around the bone, but osteoclastic cells are less commonly seen in large numbers.

Caution

- Primary sarcomas of the breast are exceedingly rare! If a malignant mesenchymal-looking tumor is present, the possibility of a metaplastic (sarcomatoid) carcinoma needs to be considered. Immunohistochemical examinations for cytokeratin (pancytokeratin, CK5/6, CK34BE12, etc.) should be performed [24, 26].
- Recent studies have convincingly shown that sarcomatoid (metaplastic) carcinomas of the breast represent tumors with a myoepithelial differentiation. Immunohistochemistry of sarcomatoid carcinomas often shows positive reaction for basal cell type CKs (CK5/6, CK14, CK34BE12) and a variety of myoepithelial markers such CD10, p63, SMA, S100, and 14-3-3 sigma [24].
- It is of note that "myoepithelial carcinoma" ("malignant myoepithelioma") represents the same entity as sarcomatoid (metaplastic) carcinoma with myoepithelial differentiation [24].
- So-called basal-like carcinomas of the breast very often express one or several myoepithelial markers if one uses a panel of conventional (SM actin, SM myosin, p63, calponin, CD10, S100 protein, etc.) and novel (14-3-3 sigma, CD29, NGFR/p75) myoepithelial markers. While some of the myoepithelial markers are completely negative in "basal-like" carcinomas, others are, at least focally, positive in the tumor cells that also express basal-type cytokeratins. Indeed, many cases of so-called basal-like carcinomas in the breast represent sarcomatoid (metaplastic) carcinoma [8, 24, 33].
- It is noteworthy that metaplastic carcinomas and carcinomas with basal-like phenotype do not have an invariably aggressive behavior. It is important to emphasize that metaplastic and basal-like carcinomas do not reflect a single, biologically uniform group of breast carcinomas. For example, squamous carcinomas or carcinomas with heterologous chondro/osseous differentiation are not necessarily aggressive high-grade tumors. Adenoid cystic carcinomas – one of the least aggressive breast carcinomas – belong to carcinomas that typically show basal-like phenotype and immunotype and reveal myoepithelial differentiation [28, 33]. In other words, there is a range of myoepithelial or basal-derived carcinomas with variation in their phenotypes, immunoprofiles, and clinical behavior, just as a wide range of subtypes and behaviors is seen among epithelial/luminal-derived breast cancers.
- In rare cases, sarcomatoid carcinoma does not show significant cytologic atypia or increased mitotic activity, and the pattern may resemble fibromatosis or nodular fascitis. Pathologists should be alert to the presence of the bland monophasic sarcomatoid carcinoma, which has a pure mesenchymal appearance on light microscopy, but epithelial components are identifiable by CK immunohistochemistry [6, 8, 36].
- Carcinosarcoma represents a biphasic variant of metaplastic carcinoma that often shows high-grade epithelial and mesenchymal components. It is a very aggressive tumor. While some mammary carcinosarcomas metastasize as mixed epithelial and mesenchymal tumors, others exhibit only the epithelial or the sarcomatous component in metastasis. Note that separation between carcinosarcoma and carcinoma with chondroid or osseous differentiation is arbitrary.
- Metaplastic breast carcinomas are commonly negative for HER2/neu but frequently express EGFR (HER1) immunohistochemically. About one-third of metaplastic carcinomas, however, show EGFR gene amplification [25, 30, 31]. Metaplastic carcinomas are mostly negative for ER, PR, and AR.

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10.14 Clear Cell (Glycogen-Rich) Carcinoma

10.14.1 Definition

A carcinoma in which more than 90% of the tumor cells have abundant clear cytoplasm containing glycogen.

10.14.2 Macroscopy

Does not differ from that of carcinoma of usual type (NOS type).

10.14.3 Microscopic Features (Fig. 74a)

- Solid, tubulocystic, or papillary growth pattern.
- Columnar and polygonal cells display abundant clear cytoplasm. The tumor cells tend to have sharply defined cytoplasmic borders.
- The tumor cells form clusters of various sizes and may be either circumscribed and well delineated or have a typical infiltrating pattern.
- The neoplastic cells are characterized by an optically clear cytoplasm that contains glycogen but no mucin or lipid. The vast majority of the tumor cells are PAS-positive; PAS-diastase, however, is negative.
- Some areas of the tumor may show cells with deep eosinophilic cytoplasm; these cells represent an oxyphilic variant of clear cells (with a morphology similar to that of clear cell carcinoma in the ovary or endometrium).
- The clear cell morphology should be the predominant pattern (more than 90%).
- The intraepithelial component (DIN, DCIS) often has a compact solid, comedo, or papillary growth pattern.

10.14.4 Additional Comments

Several reports suggest that glycogen-rich carcinoma is probably more aggressive than typical infiltrating carcinoma, with frequent lymph node metastasis and high mortality [4, 5, 7, 10, 11, 13]. The differential diagnosis includes lipid-rich carcinoma and clear cell myoepithelial carcinoma.

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10.15 Lipid-Rich Carcinoma (Lipid-Secreting Carcinoma)

10.15.1 Definition

A very rare variant of infiltrating breast carcinoma breast in which the vast majority (90%) of tumor cells contain abundant cytoplasmic neutral lipids.

10.15.2 Macroscopy

Ill-defined tumor with greyish-white to yellow cut surface.

10.15.3 Microscopic Features

- Infiltrating carcinoma with ductal or lobular growth pattern showing tumor cells with foamy or vacuolated cytoplasm.
- Presence of abundant intracytoplasmic neutral fat (within at least 80% of the neoplastic cells) demonstrated by oil red O-stain.
- Some of the tumor cells show cytoplasmic vacuolization in addition to abundant intracytoplasmic lipid.
- The tumor cells usually show uniform round to oval nuclei. Prominent nucleoli may be present.

10.15.4 Immunoprofile

Lipid-rich carcinoma usually shows a diffuse and intense immunoreactivity for lactoferrin and alpha-lactalbumin. Most of the reported cases were negative for ER and PR.

10.15.5 Additional Comments

Some authors subdivide lipid-secreting carcinomas into histiocytoid, sebaceous, and apocrine types. The possibility that lipid-rich (lipid-secreting) carcinoma may be more aggressive that regular invasive duct carcinomas has not been established.

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10.16 Metastatic Carcinoma

10.16.1 Macroscopy

Solitary or multiple well-circumscribed firm to hard nodules. The symptoms of metastatic carcinoma are similar to those of primary breast carcinoma.

10.16.2 Microscopic Features

- Sharply demarcated tumor.
- Lack of intraepithelial neoplasia (DIN, DCIS).
- Often unusual morphology for a primary breast tumor.

Caution

- The most common metastatic carcinoma of the female breast is metastatic carcinoma from the contralateral breast. Aside from hematopoietic and lymphatic malignancies, the three most common cancers metastasizing to the breast are malignant melanoma, lung, and prostatic carcinomas. Cancers of the gastrointestinal tract, ovary, and uterine cervix can also metastasize to the breast.
- Signet-ring cell carcinoma of the stomach can mimic a primary signet-ring cell carcinoma of the breast. On the other hand, metastatic lobular carcinoma with signet-ring cell differentiation to the stomach can simulate a primary gastric cancer (linitis plastica!). While invasive lobular carcinoma with signet-ring cell differentiation is often ER- and CK7-positive, gastrointestinal signet-ring cell carcinomas are negative for

ER and CK7 but show positivity for CK20. Primary gastrointestinal signet-ring cell carcinomas are negative for MUC1. In contrast, signet-ring cell carcinomas of the breast are positive for MUC1.

- Ovarian carcinoma may rarely be associated with axillary lymphadenopathy or with simultaneous breast and axillary node metastases.
- Malignant melanoma is one of the most common metastatic cancers in the breast. It should, however, be kept in mind that primary melanocytic lesions (primary malignant melanoma of the skin of the breast, blue nevus, etc.) do occur in the breast. Very rarely, metaplastic breast carcinoma with melanocytic differentiation (melanocytic breast carcinoma) also occurs.
- Occasionally, the mammary lesion reflects the first manifestation of a clinically occult malignancy.
- The presence of intraepithelial neoplasia (in situ carcinoma) is the only absolute proof of the primary nature of breast carcinoma.
- As a rule, whenever a well-circumscribed tumor is identified in the breast without showing an intraepithelial (in situ) component, and the histomorphology looks unusual for a primary breast carcinoma, the possibility of metastatic cancer should be considered and excluded.

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10.17 Inflammatory Carcinoma (Fig. 74b)

10.17.1 Definition

- *Clinical definition* (accepted by TNM, UICC): The criteria for clinical diagnosis of inflammatory carcinoma include diffuse erythema, edema extending to greater than two-thirds of the breast, peau d'orange, tenderness, induration, warmth, and diffusiveness of tumor by palpation. Not all of these features are necessarily prominent in each case [1, 4, 12, 13, 21].
- *Pathologic definition*: The presence of malignant tumor cells in the dermal lymphatics (lymphangiosis carcinomatosa cutis) [5, 10, 18a, 19].

In most cases, the clinical features and the pathologic finding of dermal lymphatic involvement coincide. Occasionally, though, clinical signs of inflammation are present, but no dermal lymphatic involvement can be identified after histopathologic examination. On the other hand, in some cases histopathology reveals lymphatic involvement of the skin but there are no clinical signs of inflammatory carcinoma. Such tumors have been classified as "occult" inflammatory breast carcinomas.

Caution

- It remains controversial whether exclusively pathologic findings without clinical symptoms are sufficient for diagnosing inflammatory carcinoma. While some studies have shown that "occult inflammatory carcinoma" has a poor prognosis similar to that of clinical inflammatory carcinoma, a recent retrospective analysis [1] of a large number of clinically diagnosed and "occult" inflammatory carcinomas revealed that clinically diagnosed cases are much more aggressive with a poorer prognosis (shorter 5-year disease-free survival and shorter overall survival).
- The current TNM (UICC) classification [18b] recognizes only the clinical definition of inflammatory breast carcinoma. Thus, a breast carcinoma with dermal infiltration and dermal lymphatic invasion with no clinical sign of inflammatory carcinoma should not be reported as pT4d.
- The presence of dermal lymphatic invasion should, however, be documented in the surgical pathology report.

10.17.2 Further Reading

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Fig. 52: Tubular carcinoma associated with low-grade ductal intraepithelial neoplasia (DIN) flat type.

Case history: During the course of a routine physical examination, a 60-year-old woman was found to have a palpable mass in the outer lower quadrant of her right breast. A needle core biopsy was performed and showed an infiltrating ductal carcinoma. The excisional biopsy revealed a hard 2-cm tumor with gritty cut surface and irregular borders.

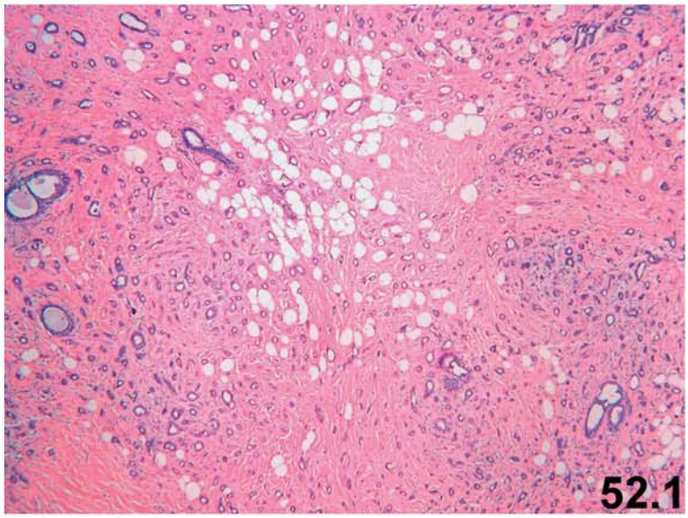
Fig. 52.1: Numerous tubules with irregular distribution are present at low magnification.

Fig. 52.2: Small open glands with infiltration of adjacent adipose tissue.

Fig. 52.3: Infiltrating tubular structures with a minor degree of glandular confluence.

Fig. 52.4: The infiltrating tubules are composed of uniform epithelial cells without significant cytologic atypia. Note the absence of a myoepithelial cell layer within the infiltrating tubules.

Figs. 52.5 and **52.6:** Several areas adjacent to the tubular carcinoma show dilated ducts closely simulating benign cystic changes.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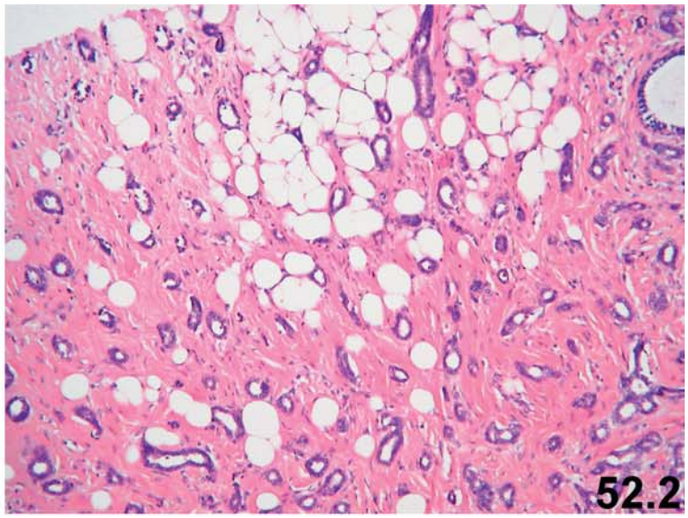
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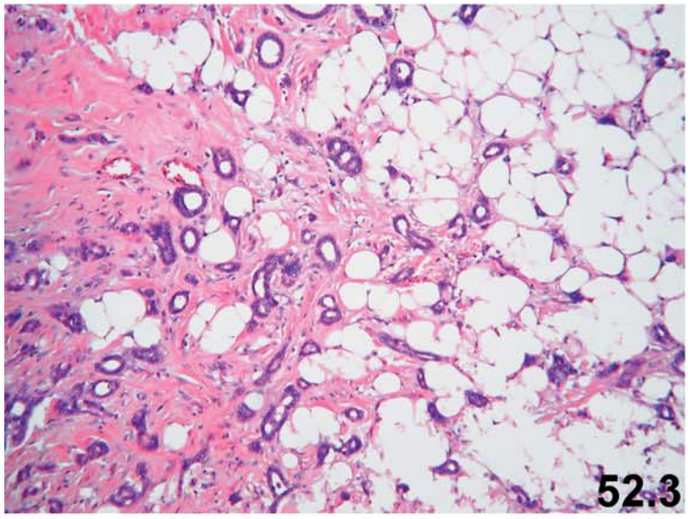
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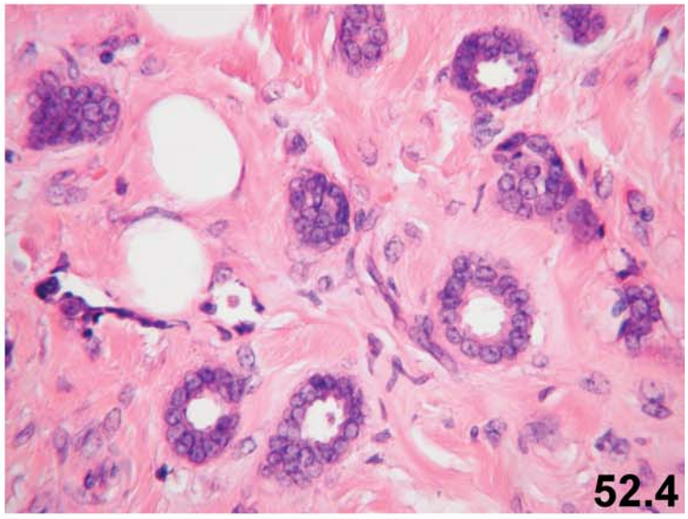
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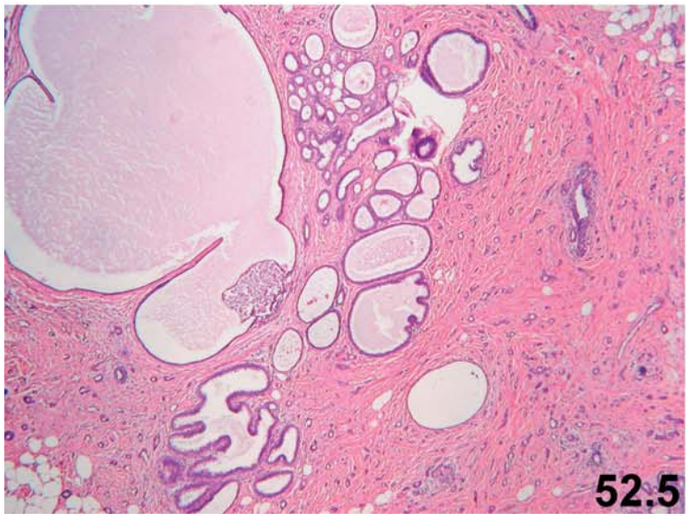
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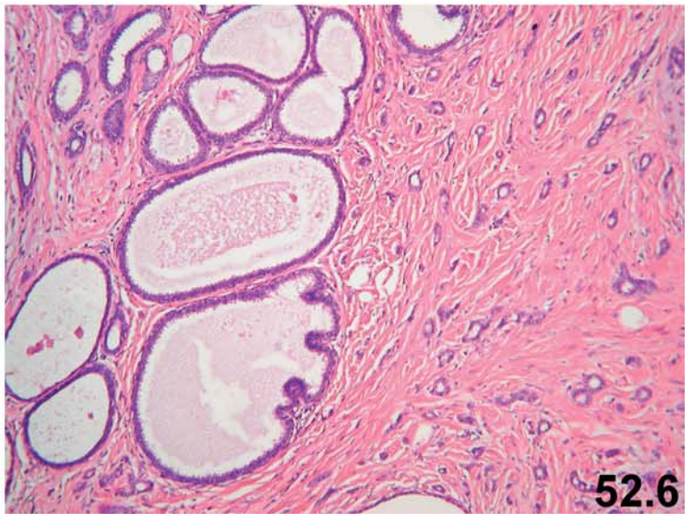
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Fig. 52.7: Another area of the tumor showing tubular carcinoma and a small cyst. The cyst is lined by one or very few cell layer(s) of epithelial cells with occasional tufts.

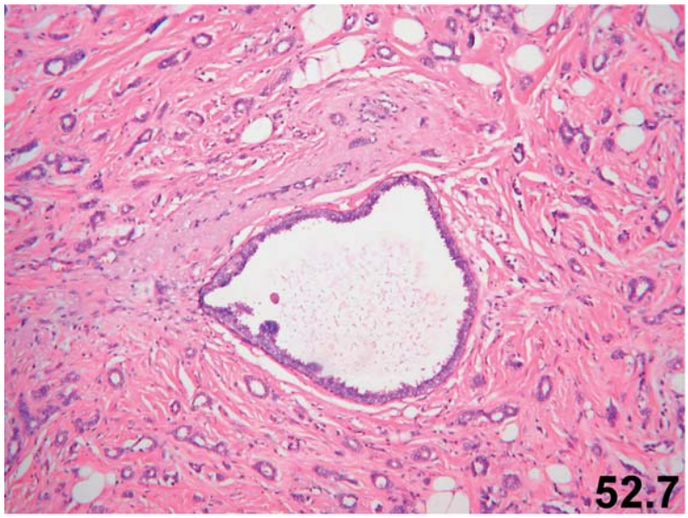
Fig. 52.8: The lining epithelial cells of the cyst show exactly the same cytomorphologic features as those of the adjacent tubular carcinoma. Note the apical snouts of the lining epithelial cells.

Fig. 52.9: Small ducts with rigid dilation of their lumens lined by only one layer of epithelial cells showing very subtle cytologic atypia. This is an example of low-grade DIN flat type (flat epithelial atypia). Note that in contrast to adenosis, the alterations affect luminal epithelial cells at the expense of underlying myoepithelial cells. In other words, there is no simultaneous alteration of epithelial and myoepithelial cells.

Fig. 52.10: Comparison of low-grade DIN flat type (flat epithelial atypia) and very-well-differentiated tubular carcinoma. The morphology of neoplastic cells in DIN flat type and tubular carcinoma is almost identical.

Fig. 52: Final remarks

- This case demonstrates that neoplastic cells in low-grade DIN flat type (flat epithelial atypia) and tubular carcinoma are very similar. Low-grade DIN flat type (flat epithelial atypia) can frequently be found within or at the periphery of tubular carcinoma.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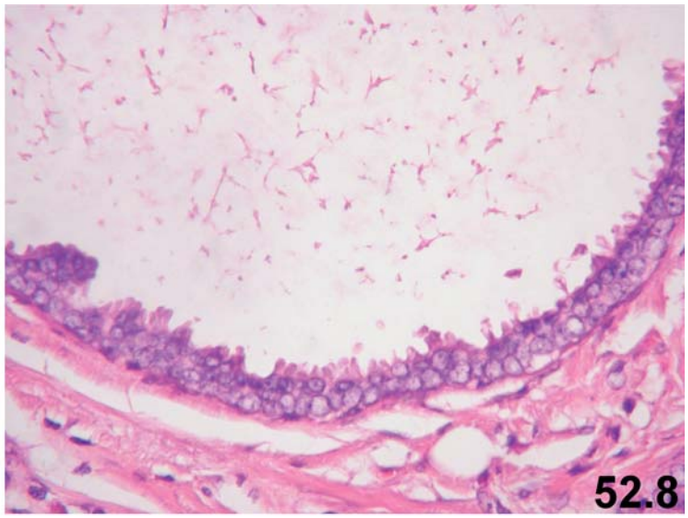
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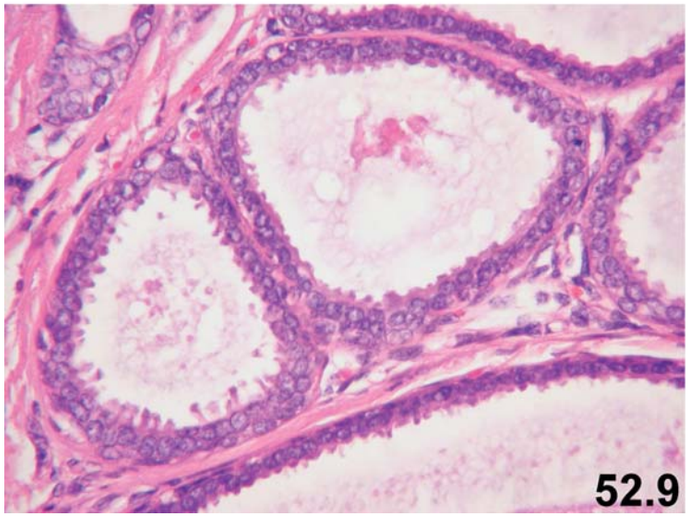
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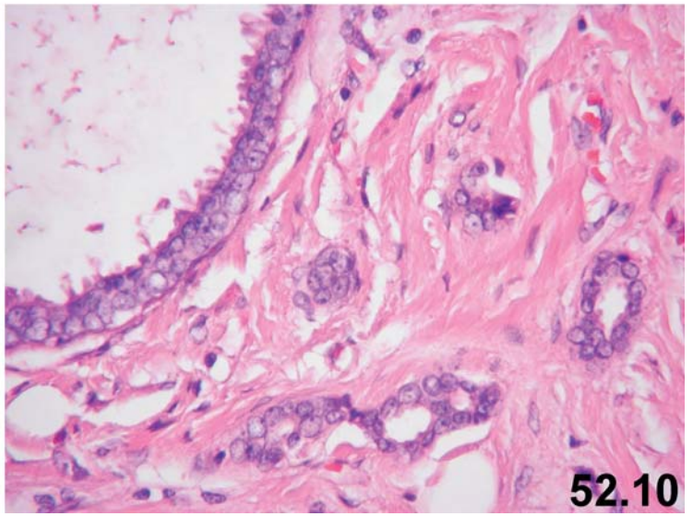
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Fig. 53: Mucinous carcinoma.

Case history: A 55-year-old woman had noticed a gradually enlarging left breast mass but failed to report it to her physician until it had reached a very large size (12 cm at its greatest diameter). A needle core biopsy was performed and revealed an infiltrating carcinoma with abundant extracellular mucin (consistent with a mucinous carcinoma). Because of the tumor's large size, a modified radical mastectomy was performed.

Figs. 53.1 and **53.2:** The cut surface (mastectomy specimen) shows a relatively well-circumscribed yellow-pink to greyish-white tumor with mucinous appearance.

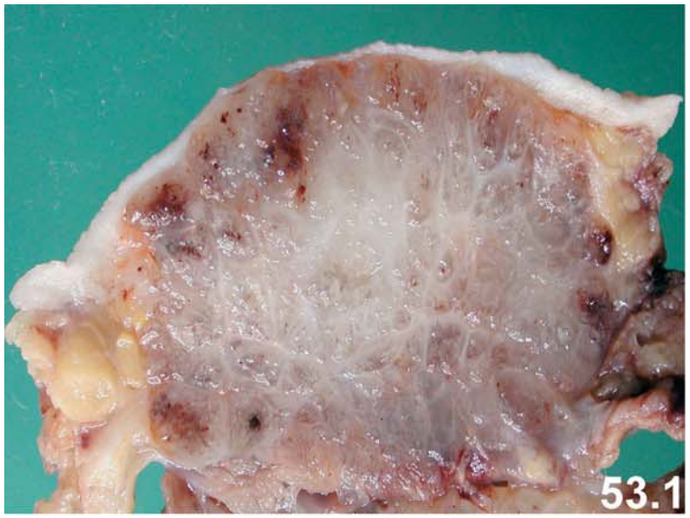
Figs. 53.3 and **53.4:** Histology of the tumor shows uniform epithelial clusters in large pools of extracellular mucin. The cohesive tumor cells form solid tubular or trabecular structures.

Fig. 53.5: The tumor cells are typically positive for estrogen receptors.

Fig. 53.6: Immunohistochemistry for progesterone receptors is also positive.

Fig. 53: Final remarks

- A typical mucinous (colloid) carcinoma of the breast is always of low grade (G1 carcinoma). The tumor cells of mucinous carcinoma should not show significant nuclear atypia or increased mitotic activity.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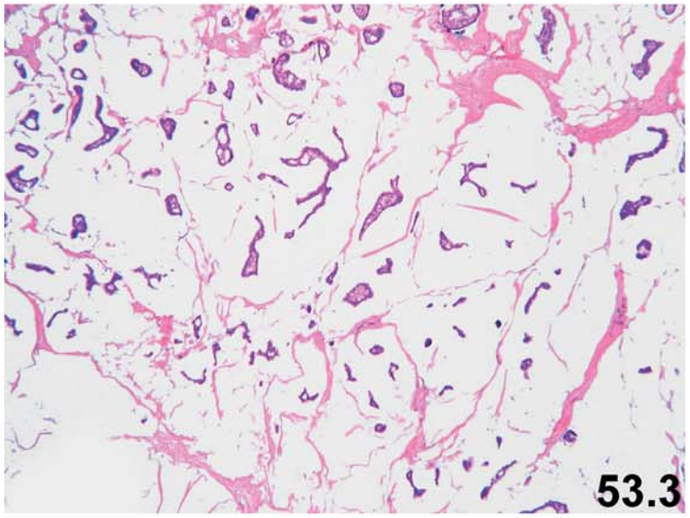
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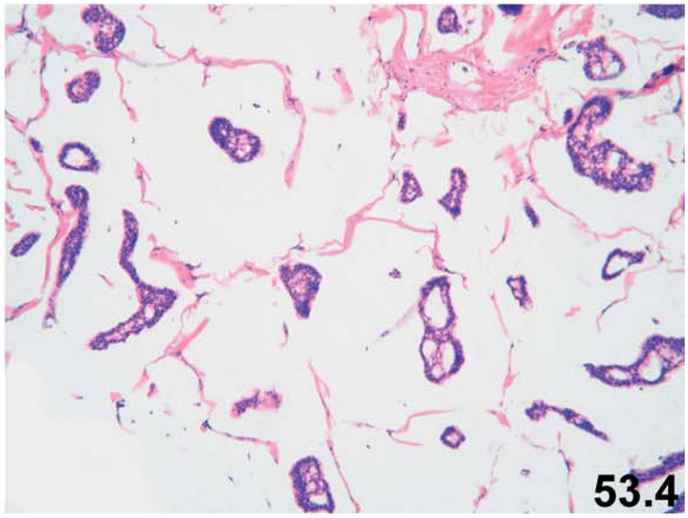
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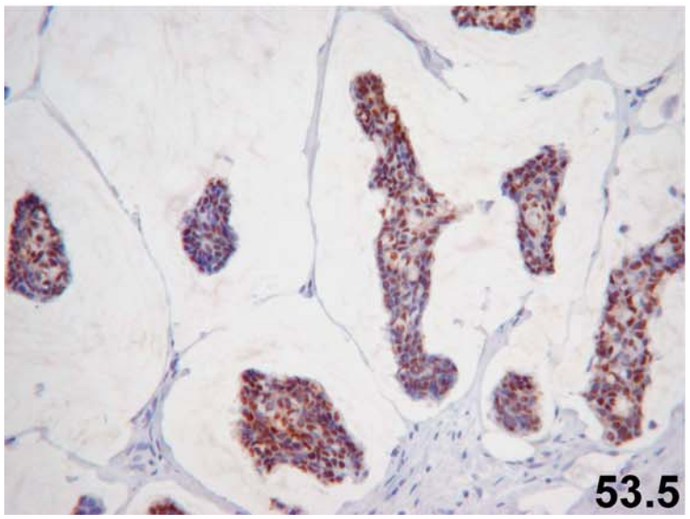
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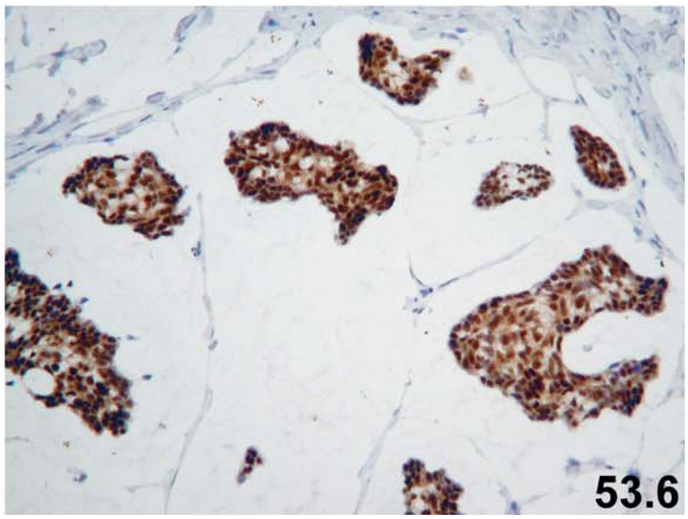
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Fig. 54: Mucinous carcinoma, hypercellular variant.

Case history: A 66-year-old woman presented with a 14-cm large tumor of her left breast. A needle core biopsy was performed and showed an invasive breast carcinoma focally associated with extracellular mucinous component. A modified radical mastectomy was done.

Fig. 54.1: Gross appearance of the cut surface shows a well-demarcated greyish-white to yellow tumor. When drawing a scalpel across the tumoral cut surface, the pathologist noticed strings of mucin adherent to the blade.

Fig. 54.2: The tumor is very cellular and shows solid and trabecular epithelial structures with a focal component displaying extracellular mucin.

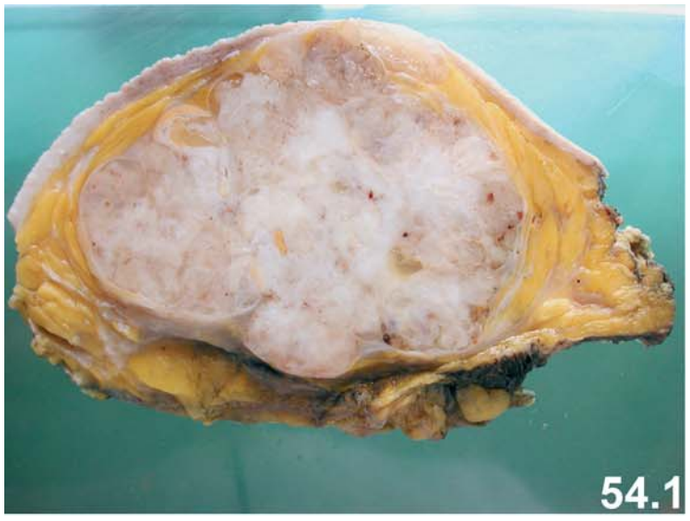
Fig. 54.3: Another area of the tumor exhibits centrally located extracellular mucin surrounded by solid aggregates of malignant tumor cells.

Figs. 54.4 and **54.5:** Solid aggregates of epithelial tumor cells showing intracellular as well as extracellular mucin.

Figs. 54.6: Solid aggregates and trabecular arrangement of the tumor cells revealing a mild degree of nuclear atypia. Note the extracellular mucinous component in the background.

Fig. 54: Final remarks

- This case represents a hypercellular variant of mucinous carcinoma. Compared with the usual type of mucinous carcinoma that is much less cellular and very rich in extracellular mucin, this tumor does not show abundant extracellular mucinous pools.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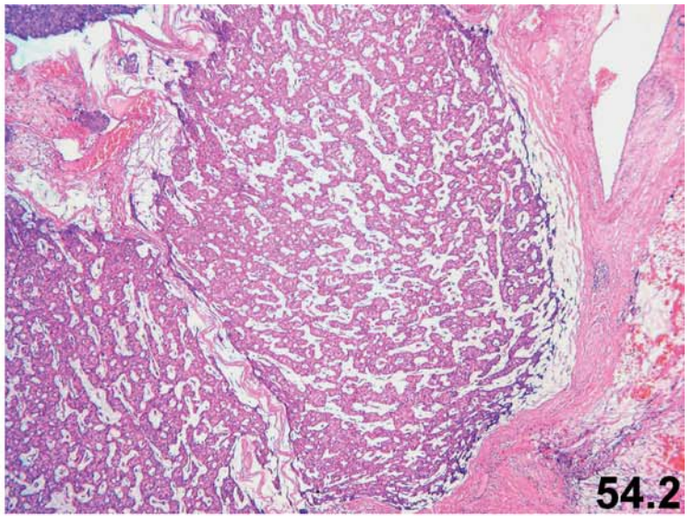
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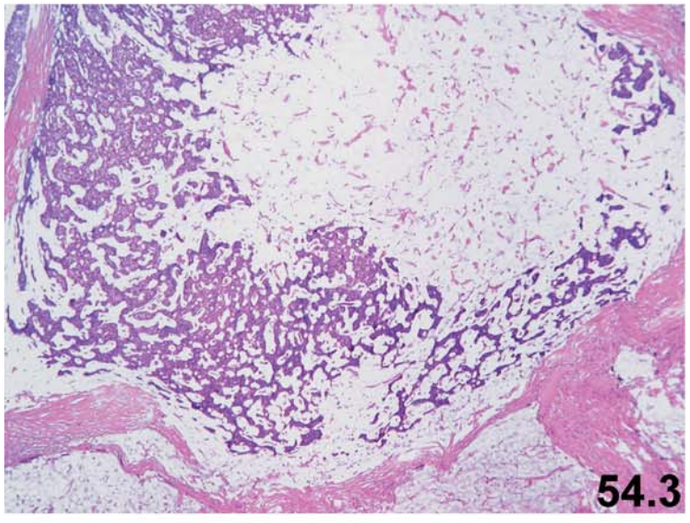
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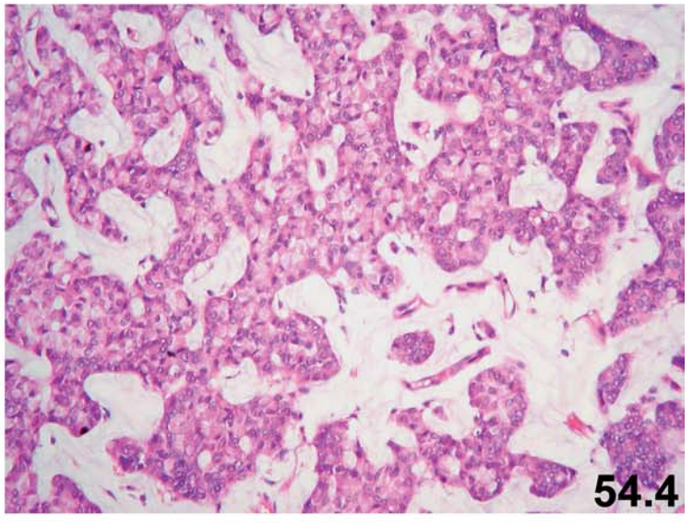
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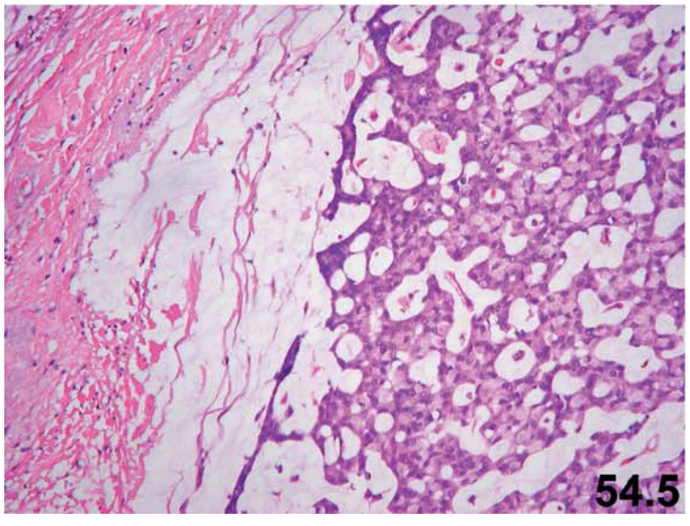
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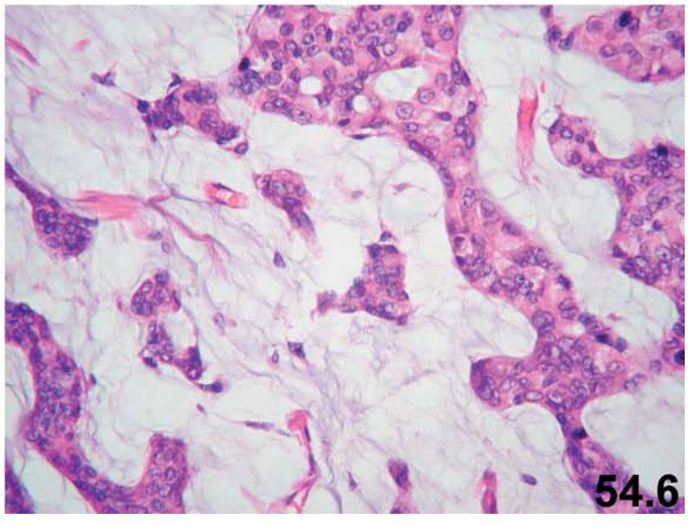
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Fig. 55: Signet ring cell carcinoma.

Case history: A 57-year-old woman presented with a 3-cm hard mass in her left breast. A needle core biopsy of the tumor was performed.

Fig. 55.1: The core shows numerous isolated tumor cells and loosely cohesive epithelial clusters.

Fig. 55.2: Infiltrating carcinoma displaying tumor cells with pale cytoplasm.

Figs. 55.3 and **55.4:** Higher magnification reveals signet-ring tumor cells with eccentric nuclei and abundant intracytoplasmic mucin.

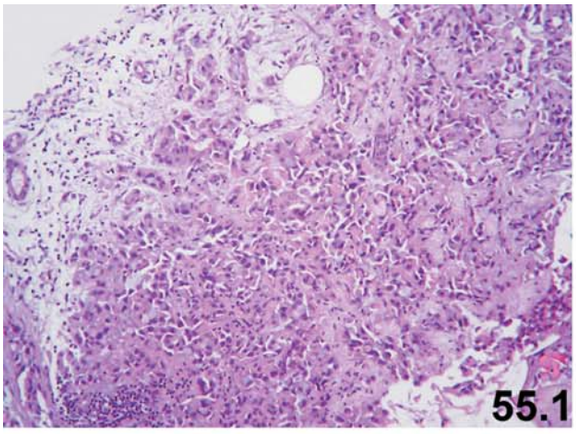
Fig. 55.5: Signet ring tumor cells showing intracytoplasmic mucin demonstrated by PAS stain (after diastase).

Fig. 55.6: Imprint cytology performed on the fresh core needle biopsy reveals numerous isolated tumor cells and epithelial clusters showing abundant pale and vacuolated cytoplasm (Diff-Quik stain).

Figs. 55.7 and **55.8:** Comparison of imprint cytology (Fig. 55.7) and histology of core needle biopsy (Fig. 55.8) showing aggregates of signet-ring carcinoma cells.

Fig. 55: Final remarks

- Signet-ring carcinoma is a variant of mucin producing breast carcinoma that must be separated from ordinary mucinous carcinoma. In contrast to mucinous carcinoma, which shows abundant extracellular mucin pools and low-grade nuclear morphology, signet-ring cell carcinoma shows tumor cells with intracytoplasmic mucin and lacks an extracellular mucinous component.
- Signet-ring cell carcinoma represents a poorly differentiated breast carcinoma (high-grade carcinoma) even in the absence of high mitotic activity.
- Because of distinctive morphology and clinically more aggressive behavior, this type of carcinoma should be regarded as a specific variant of breast cancer when present in its pure form. When signet-ring cells are present as a component of a typical infiltrating lobular or ductal carcinoma, the diagnosis should reflect the presence of signet cells by stating infiltrating carcinoma with [%] signet-ring cell differentiation.
- Signet ring cells should be distinguished from cells with intracytoplasmic lumens which contain centrally located, deeply eosinophilic material (targetoid cells).
- Signet ring cell carcinoma of the breast is capable of metastasizing to unusual sites such as the bladder, gastrointestinal sites, and serosal surfaces, mimicking a primary carcinoma of the involved organ.
- Primary signet-ring cell carcinoma of the breast is typically positive for CK7 but negative for CK20. In contrast, primary gastrointestinal signet-ring cell carcinomas are negative for CK7 but positive for CK20.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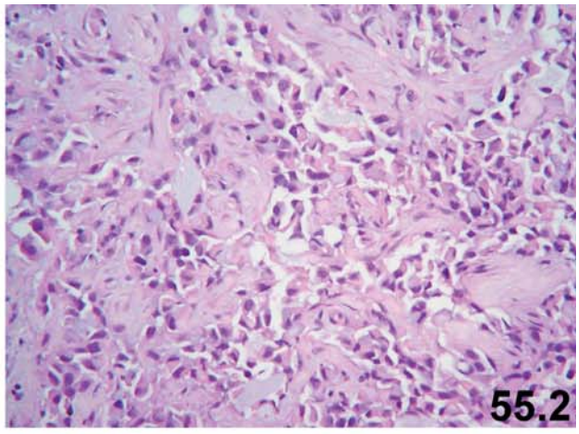
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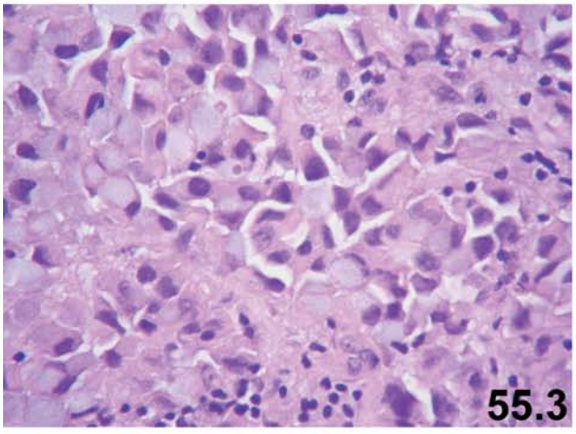
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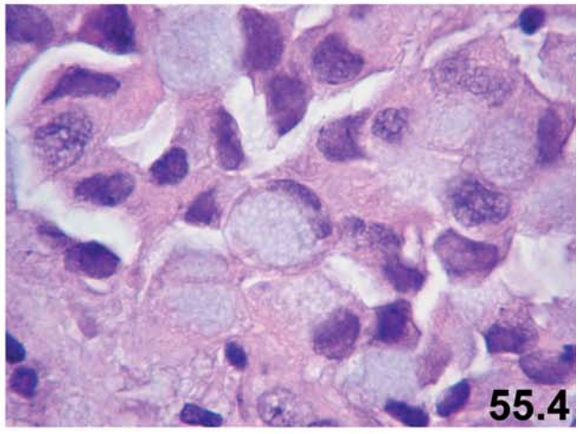
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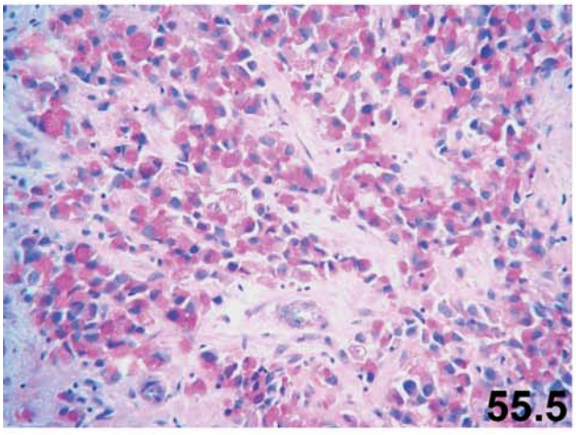
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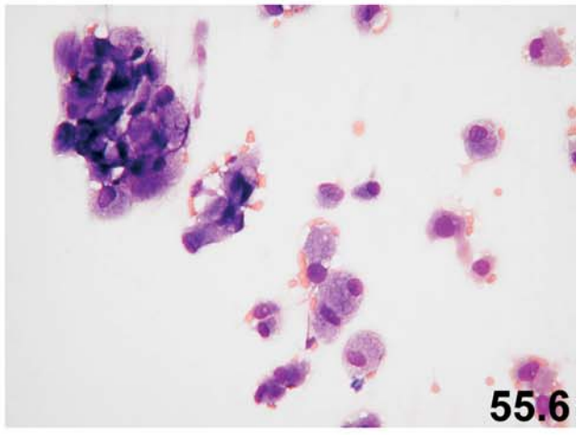
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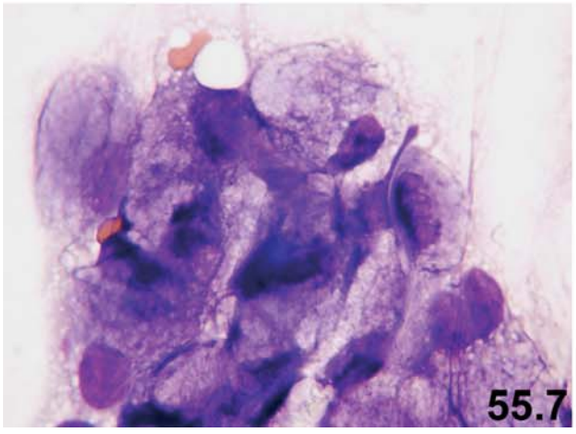
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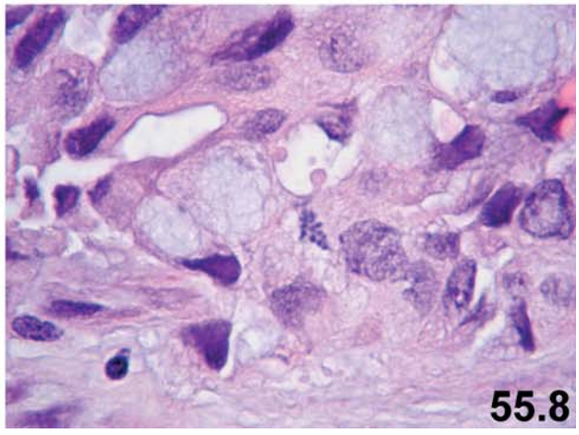
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Fig. 56: Infiltrating carcinoma with neuroendocrine differentiation (case 1).

Case history: A 62-year-old woman had an abnormal mammogram of her left breast, showing an ill-defined lesion. There was no palpable breast tumor. The excisional biopsy revealed a 0.8-cm greyish-white tumor with infiltrating margins.

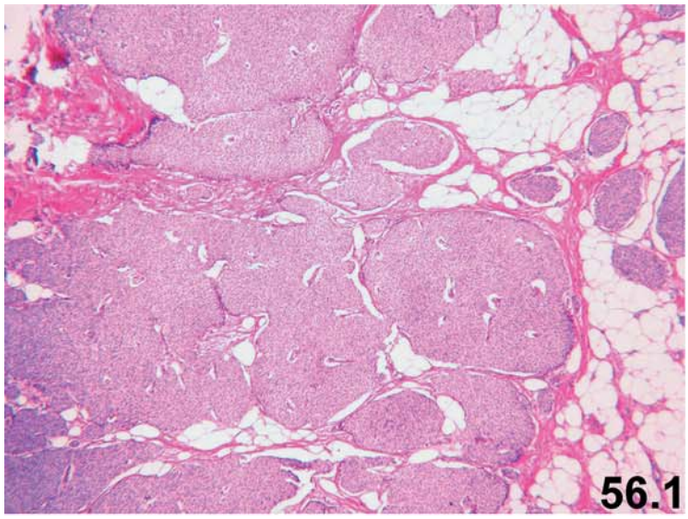
Fig. 56.1: At low magnification, solid aggregates of tumor cells with infiltration of adipose tissue are present.

Fig. 56.2: Solid and large nests of tumor cells showing infiltration of adipose tissue.

Figs. 56.3 and **56.4:** The tumor cells are quite uniform with mild nuclear atypia. Note the presence of fine eosinophilic cytoplasmic granules.

Fig. 56.5: Immunohistochemistry for synaptophysin reveals positive reactivity.

Fig. 56.6: The tumor cells display positive immunoreaction for chromogranin (A).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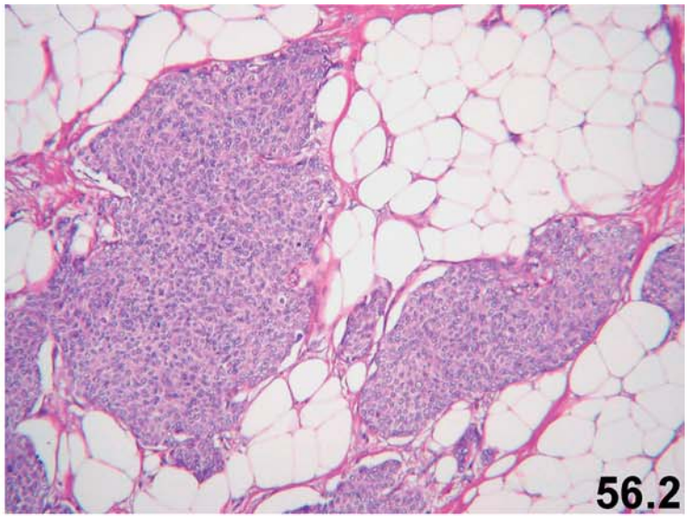
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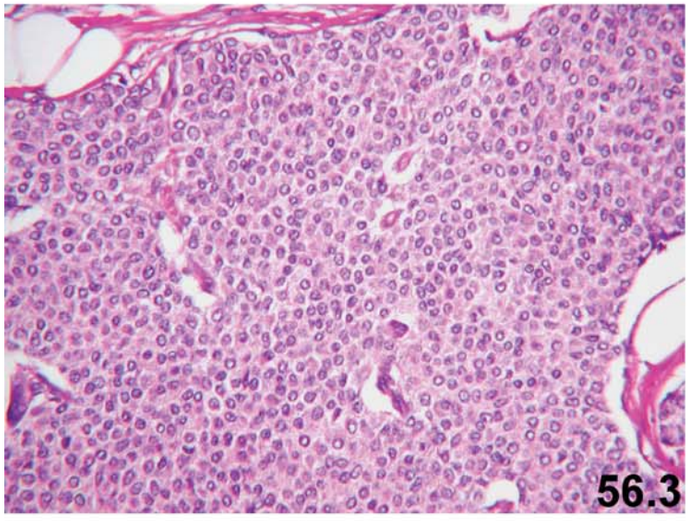
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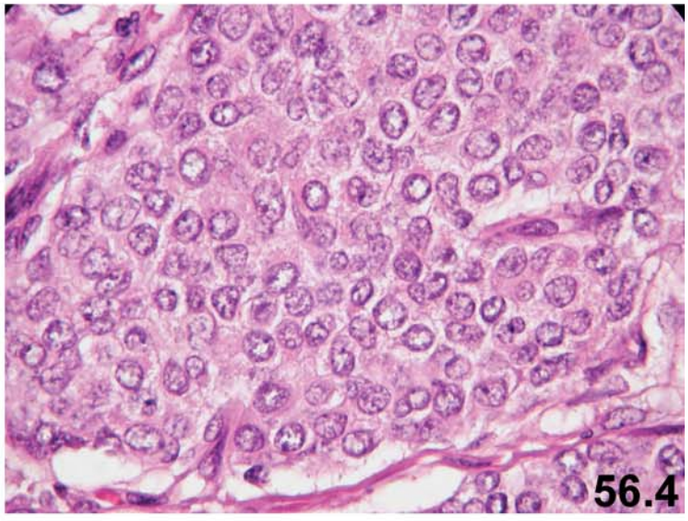
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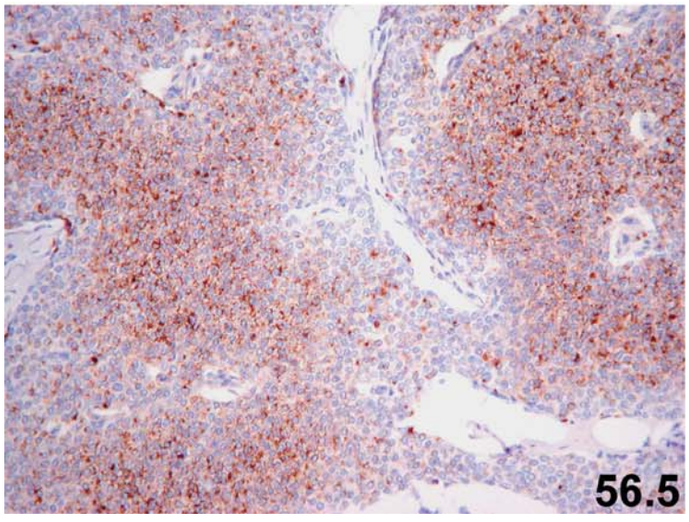
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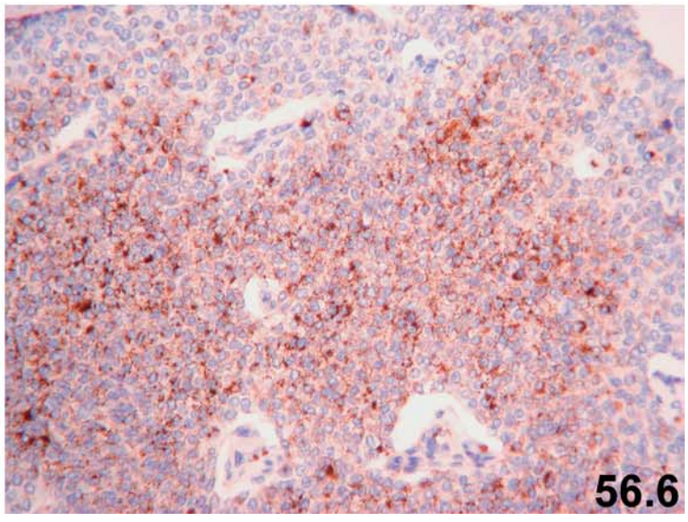
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Fig. 57: Infiltrating carcinoma with neuroendocrine differentiation (case 2).

Case history: Physical examination of a 39-year-old woman revealed a firm tumor in her left breast. Her mammogram showed a relatively well-circumscribed nodule (2 cm, lower inner quadrant). Excisional biopsy of the lesion was performed.

Fig. 57.1: The tumor shows large solid epithelial clusters.

Fig. 57.2: Several areas of the tumor display uniform tumor cells with elongated or spindle-shaped nuclei.

Figs. 57.3 and **57.4:** The tumor cells show fine eosinophilic granular cytoplasm.

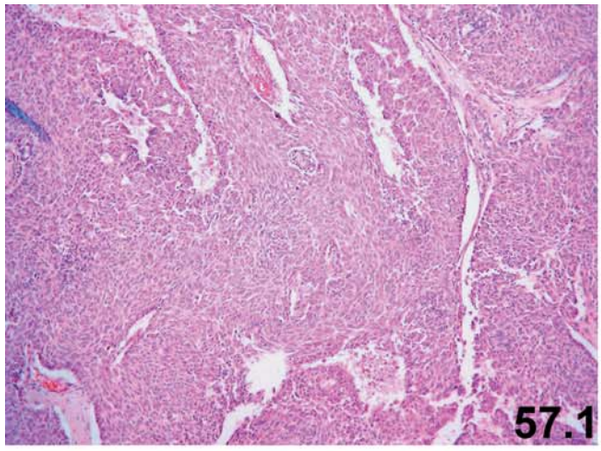
Fig. 57.5: A solid aggregate of uniform epithelial cells without significant nuclear atypia. Note the focal rosette-like arrangement of the uniform tumor cells.

Figs. 57.6 and **57.7:** Carcinoma cells with positive immunoreaction for chromogranin (A)

Fig. 57.8: The tumor cells are positive for synaptophysin.

Fig. 57: Final remarks

- The presence of tumor cells with fine eosinophilic granular cytoplasm and a rosette-like arrangement of tumor cells should raise the possibility of neuroendocrine differentiation in this carcinoma. The immunoreaction for synaptophysin, chromogranin, and other neuroendocrine markers in breast carcinomas with neuroendocrine differentiation may be focal and heterogeneous.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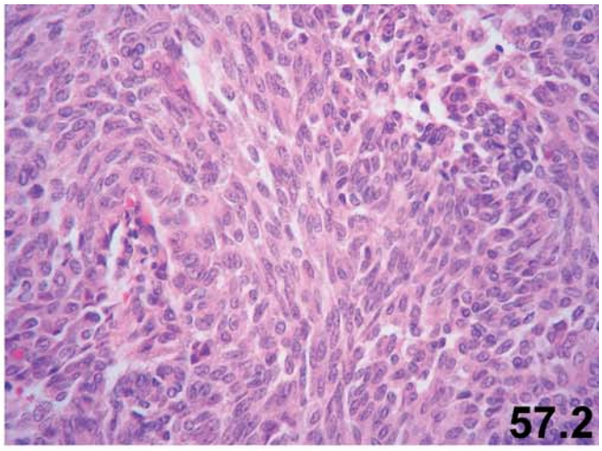
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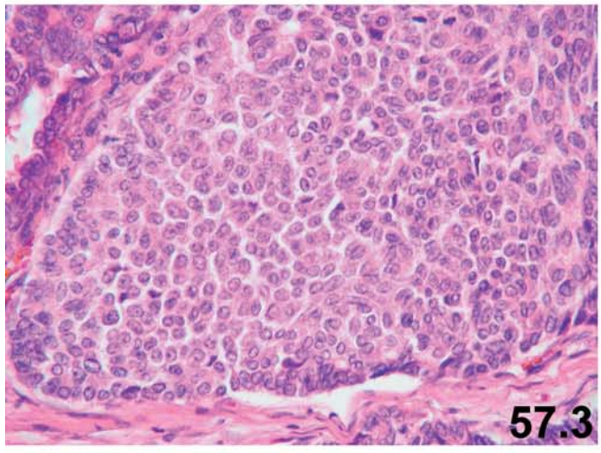
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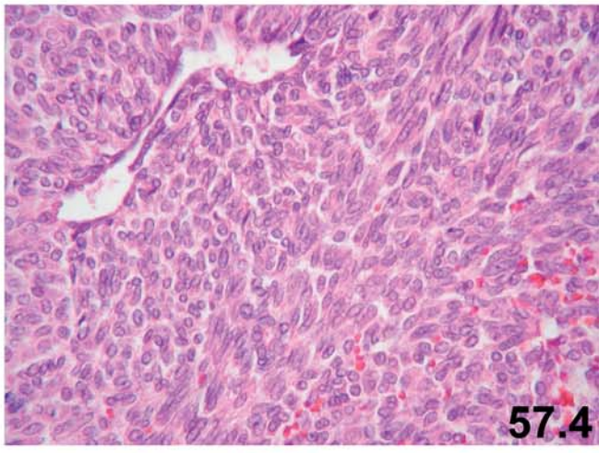
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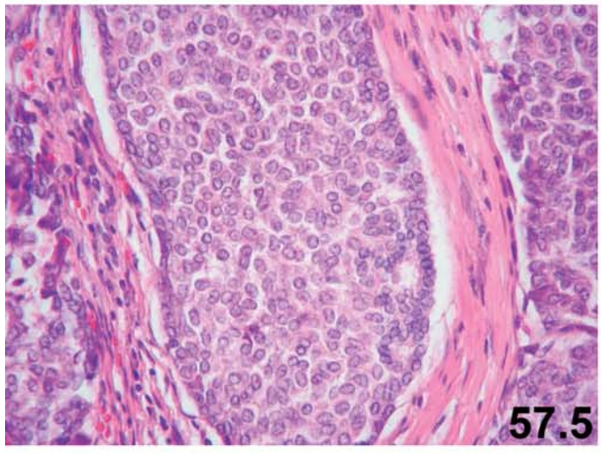
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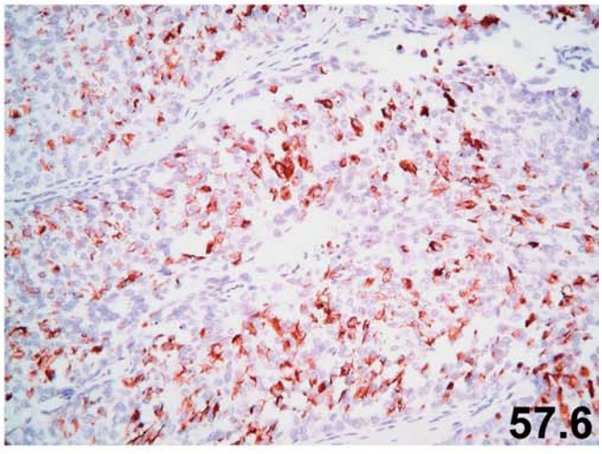
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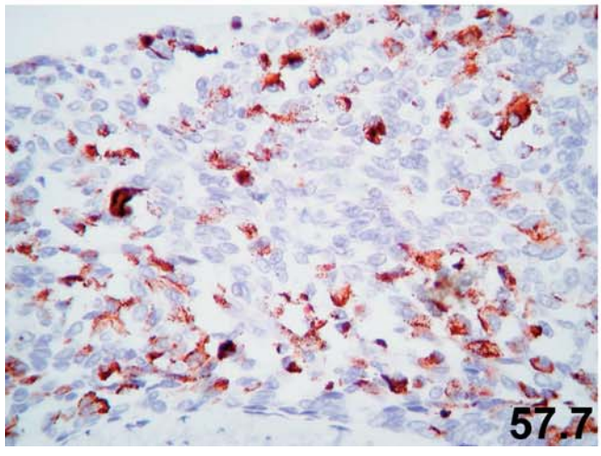
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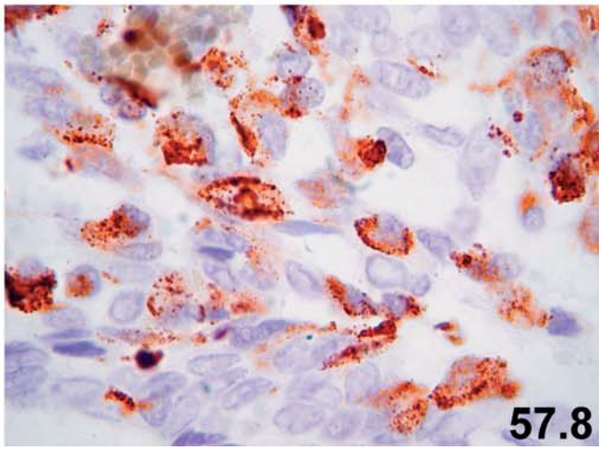
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Fig. 58: Infiltrating carcinoma with neuroendocrine differentiation (case 3).

Case history: A 58-year-old woman presented with an ill-defined right breast mass. Mammographic examination revealed a tumor highly suspicious for cancer. Excisional biopsy was performed and showed a 4×2.5×1.5-cm greyish-white tumor with infiltrating borders.

Fig. 58.1: The tumor shows closely packed solid and trabecular structures.

Figs. 58.2, 58.3, and **58.4:** Several areas of the tumor display a trabecular or unusual sex-cord-like growth pattern closely mimicking an ovarian sex-cord tumor.

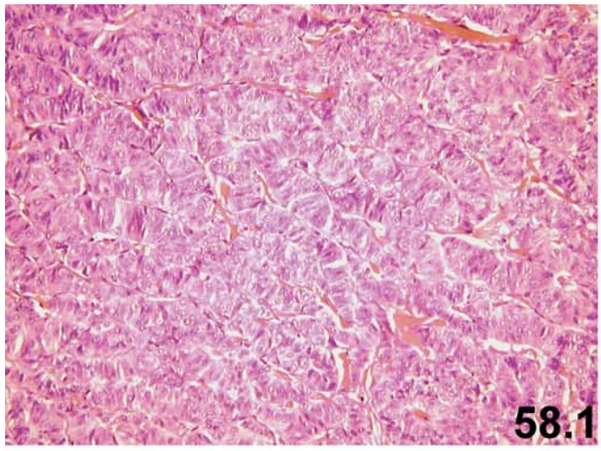
Figs. 58.5 and **58.6:** Tumor cells at higher magnification exhibiting mild nuclear atypia with stratified enlarged nuclei and relatively scant cytoplasm.

Fig. 58.7: Immunohistochemistry for NSE shows a positive, but heterogeneous, reaction.

Fig. 58.8: Focally, the tumor cells show a positive immunoreaction for synaptophysin.

Fig. 58: Final remarks

- The unusual trabecular or sex-cord-like pattern of this invasive carcinoma created diagnostic problems for several practicing pathologists. It should be kept in mind that any unusual growth pattern of breast carcinoma, carcinoma with different cell populations, or carcinoma with spindle and mucinous cells could be due to neuroendocrine differentiation. In such situations, immunohistochemical examination for neuroendocrine markers is advised.
- NSE is a highly sensitive, but nonspecific, marker for neuroendocrine differentiation. In carcinoma with neuroendocrine differentiation, a positive immunoreaction for NSE therefore needs to be accompanied by another positive reaction for either synaptophysin or chromogranin.
- In the absence of an intraepithelial neoplastic component, careful attention to the patient's history and clinical findings is required to prevent misinterpreting as a metastatic neuroendocrine carcinoma.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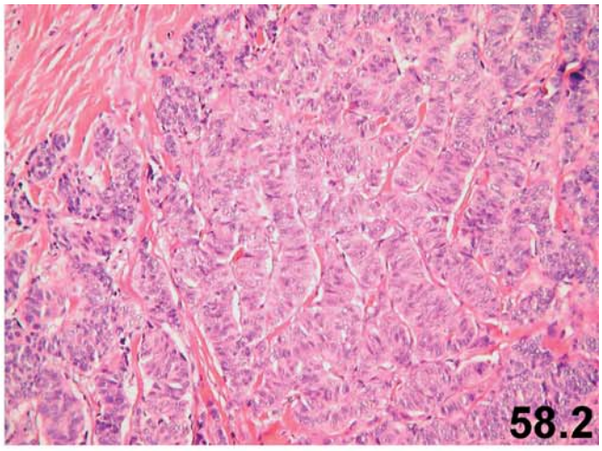
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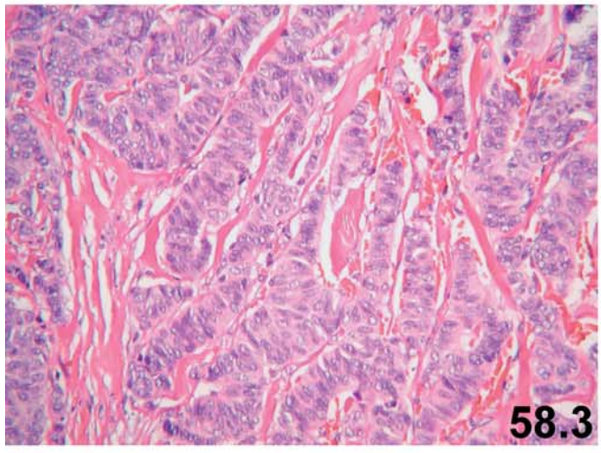
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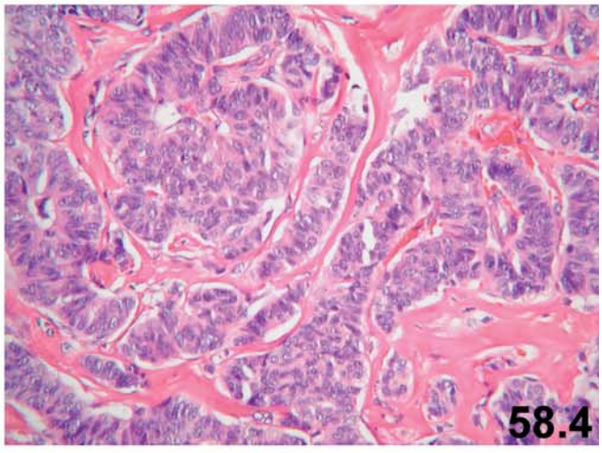
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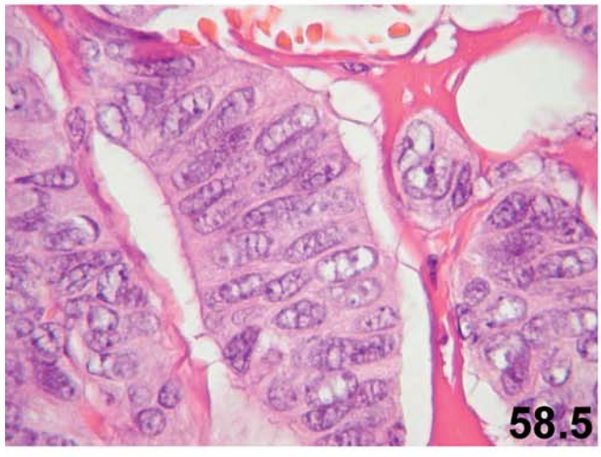
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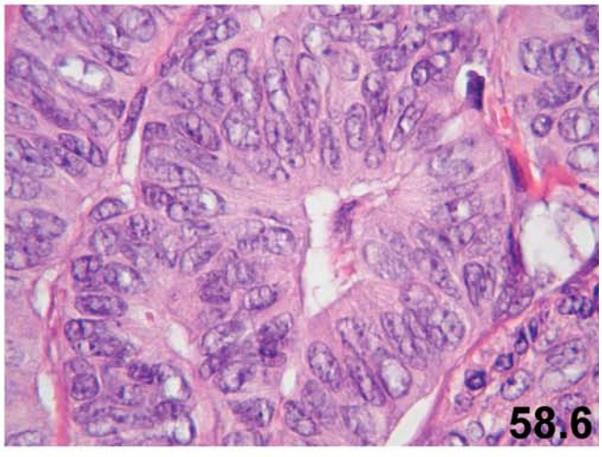
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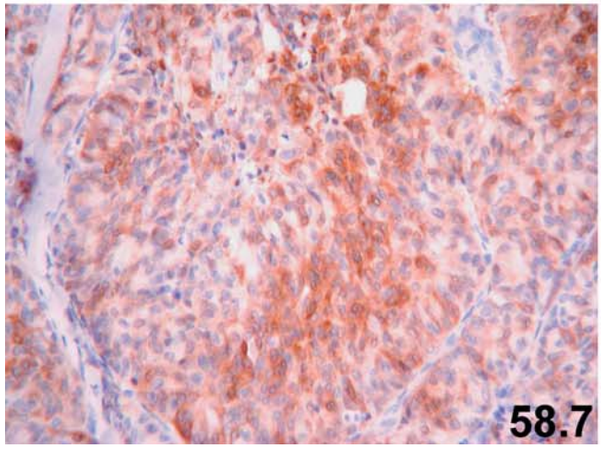
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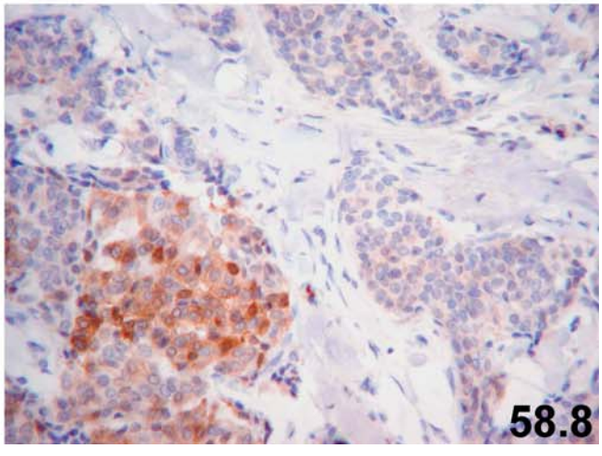
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Fig. 59: Invasive micropapillary carcinoma.

Case history: A 63-year-old woman presented with a firm nodule in the upper outer quadrant of her left breast. The left axillary lymph nodes were enlarged but painless.

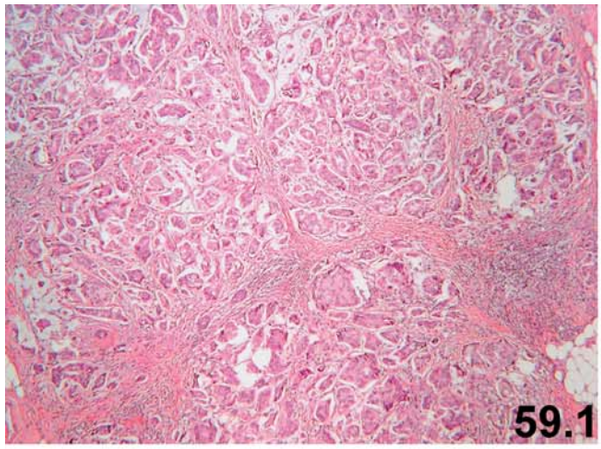
Figs. 59.1 and **59.2:** Infiltrating carcinoma showing numerous aggregates of small epithelial clusters. On cross-section the clusters reveal the appearance of tubules.

Fig. 59.3: A minor component of the tumor shows extracellular mucin.

Fig. 59.4: Numerous micropapillary structures (pseudopapillary epithelial aggregates lacking fibrovascular cores) are present. The infiltrating glands resemble a micropapillary growth pattern of DIN (DCIS).

Figs. 59.5, 59.6, and **59.7:** Tumor cell clusters lie within artifactual clear empty stromal spaces (shrinkage artifact) simulating vascular spaces.

Fig. 59.8: In addition, the tumor shows several areas of true lymphovascular invasion (lymphangiosis carcinomatosa).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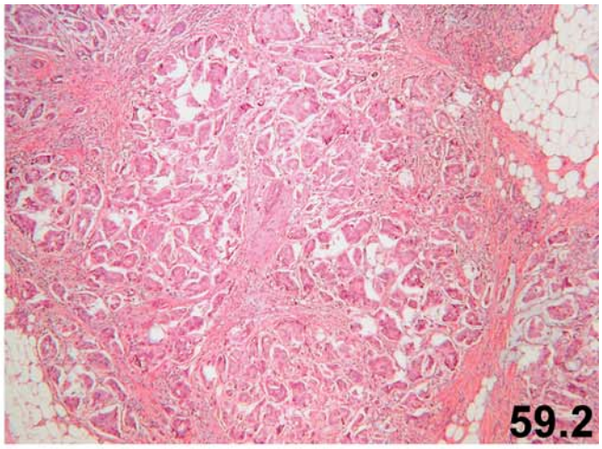
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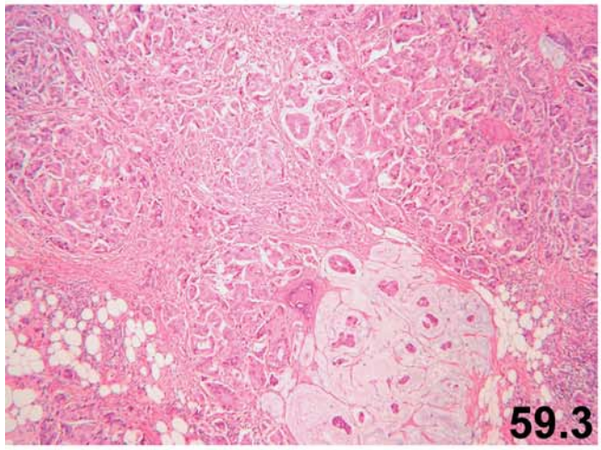
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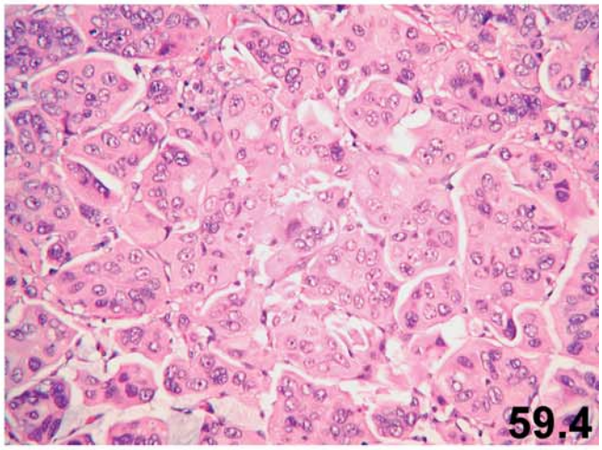
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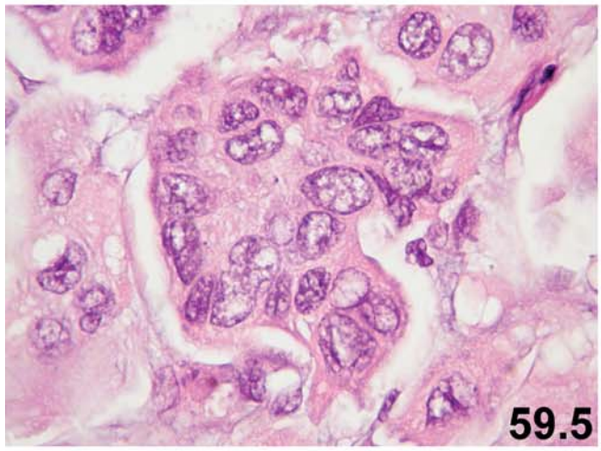
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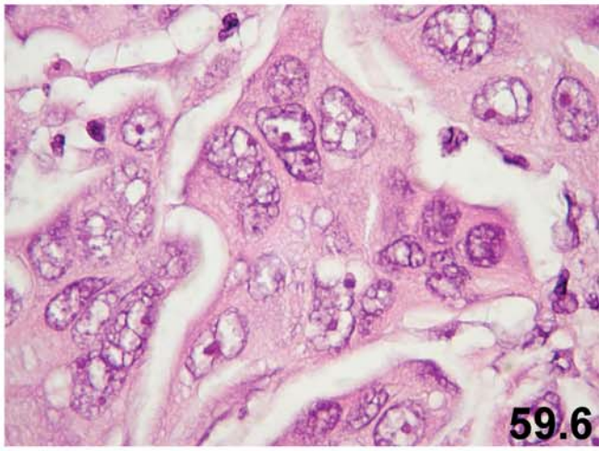
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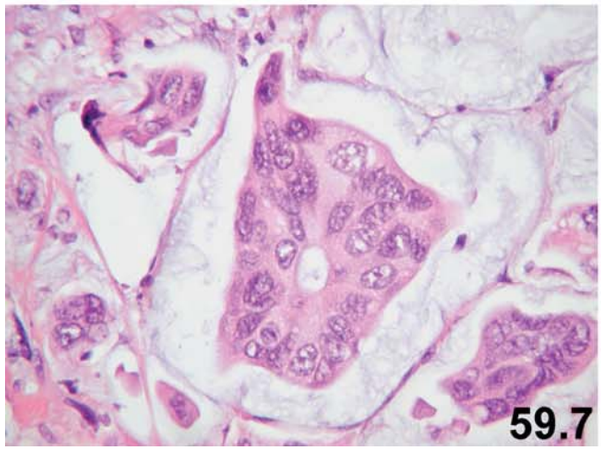
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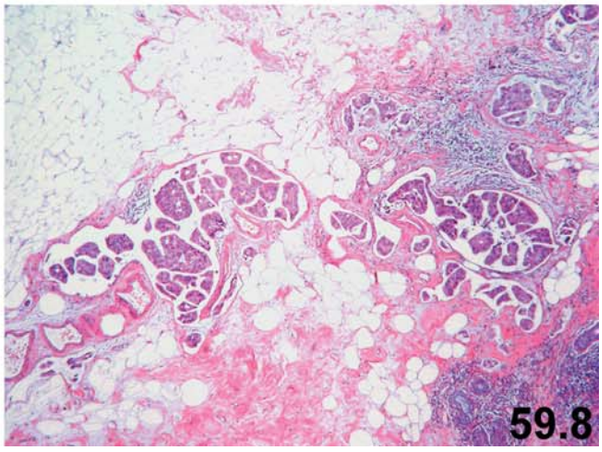
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Fig. 59.9: Dilated lymphovascular spaces containing tumor cells with micropapillary pattern.

Fig. 59.10: An axillary lymph node showing metastasis.

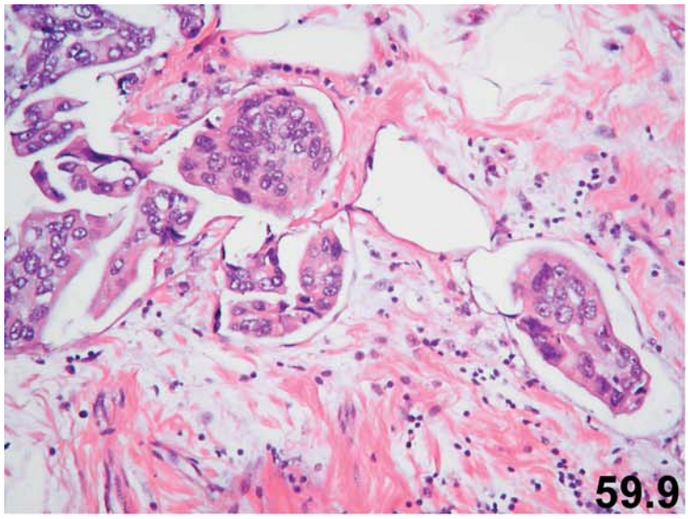
Fig. 59.11: Axillary lymph node metastasis showing a micropapillary growth pattern.

Figs. 59.12 and **59.13:** Invasive micropapillary carcinoma displaying an intense and diffuse (3+) immunoreaction for HER2/neu.

Fig. 59.14: The cancerous cells are also positive for estrogen receptors.

Fig. 59: Final remarks

- This case represents a rare but aggressive variant of breast carcinoma. Invasive micropapillary carcinoma of the breast has a high propensity for lymphovascular invasion.
- One should not rely on a negative result of sentinel lymph node biopsy because this variant of carcinoma is very often associated with axillary lymph node metastasis.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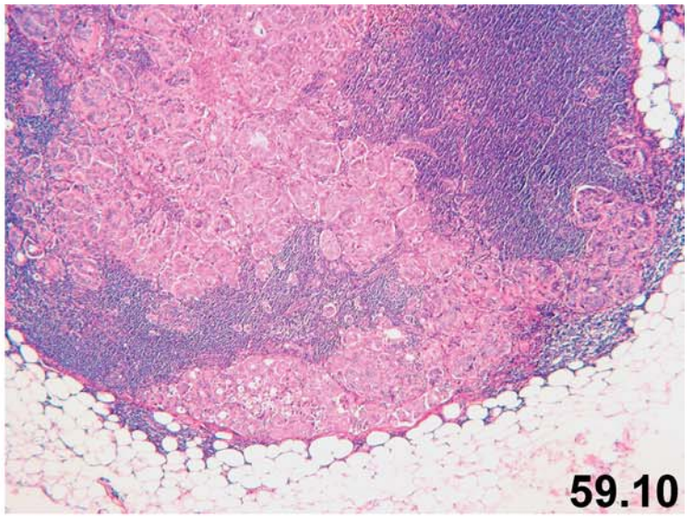
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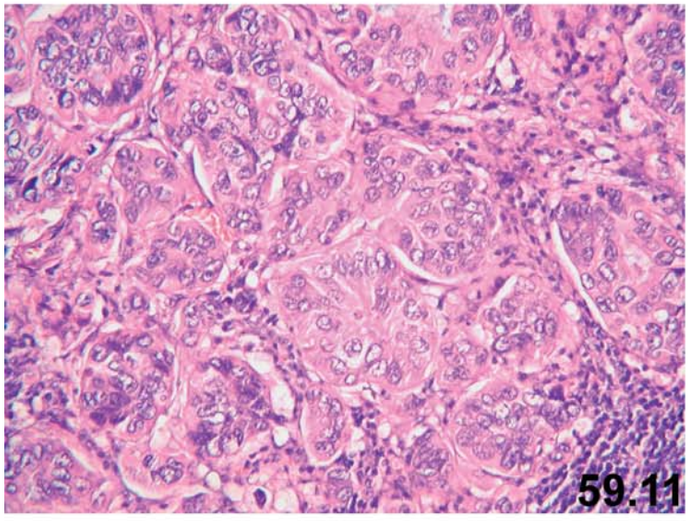
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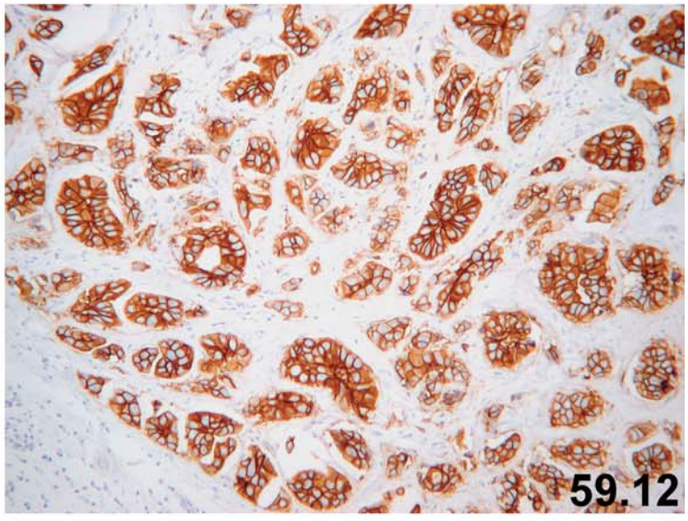
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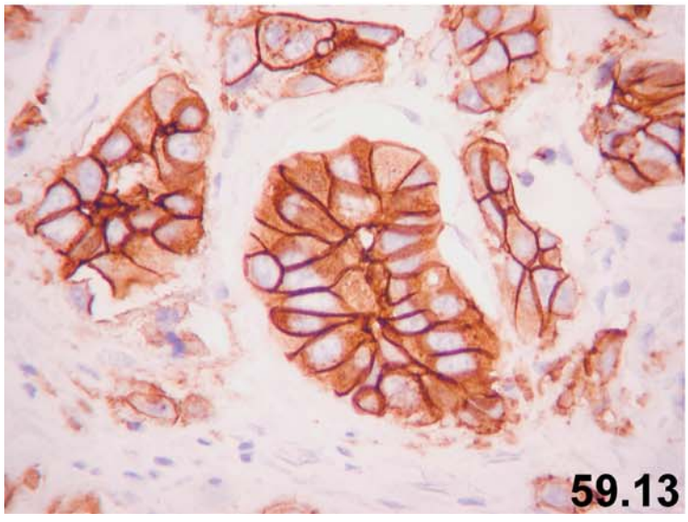
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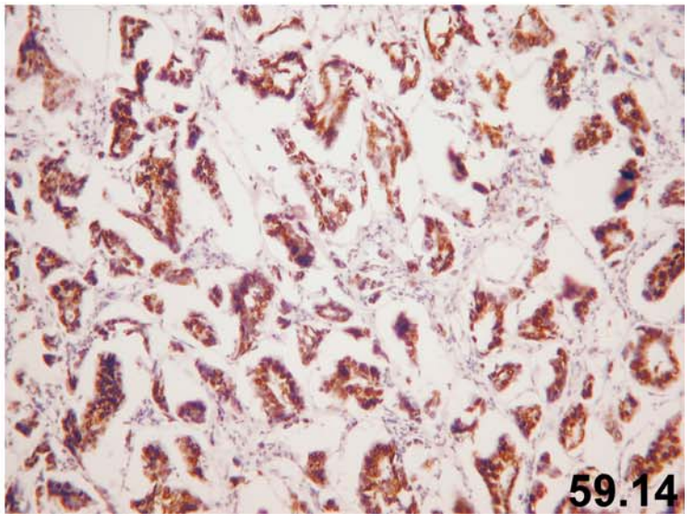
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Fig. 60: Apocrine carcinoma.

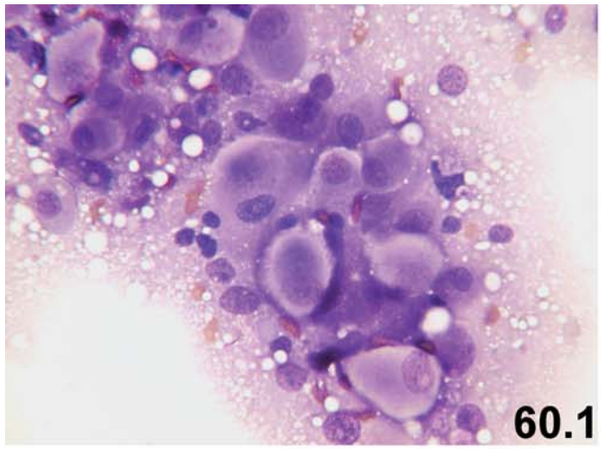
Case history: A 29-year-old woman presented with a nonmobile hard tumor in the upper outer quadrant of her left breast. Her mammogram revealed a 3.5-cm tumor with ill-defined margins. There was no positive family history of breast or ovarian cancer. Excisional biopsy of the tumor was done. In addition, imprint cytology of the fresh lumpectomy specimen was performed.

Figs. 60.1 and **60.2:** Imprint cytology of the cut surface of the tumor (excisional biopsy) shows numerous clusters of large epithelial cells with abundant cytoplasm. The nuclei are round and show prominent nucleoli (Diff-Quik stain).

Figs. 60.3 and **60.4:** Imprint cytology (Papanicolaou stain) displays numerous isolated tumor cells with large hyperchromatic nuclei and abundant amphophilic cytoplasm.

Figs. 60.5 and **60.6:** Higher magnification of imprint cytology showing multinucleated tumor cells with severe nuclear atypia. Some of the giant tumor cells show intracytoplasmic vacuoles. Note the large and amphophilic cytoplasm, which is typical of tumor cells with apocrine differentiation.

Figs. 60.7 and **60.8:** Hematoxylin and eosin sections of the tumor show an infiltrating carcinoma with highly atypical tumor cells and irregular tumor borders.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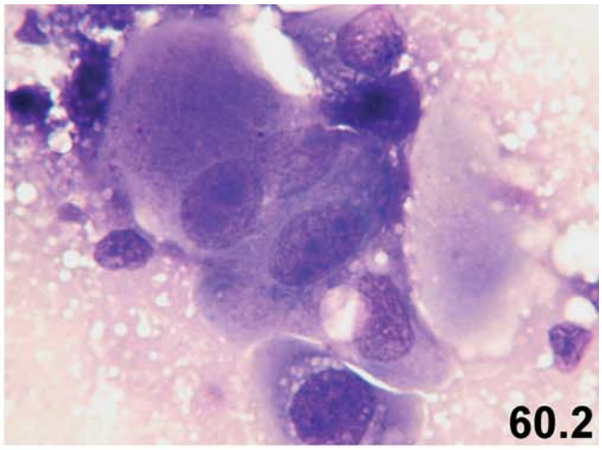
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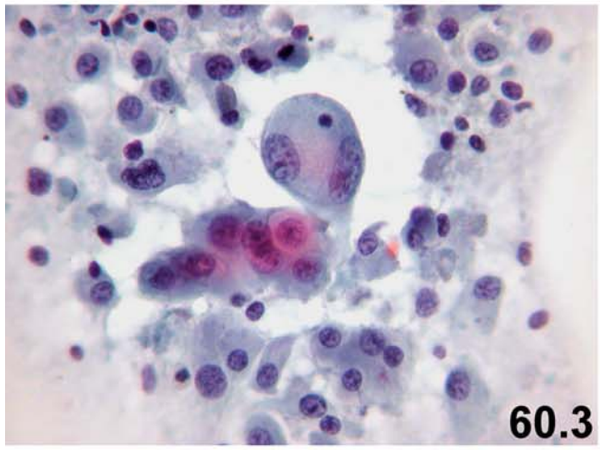
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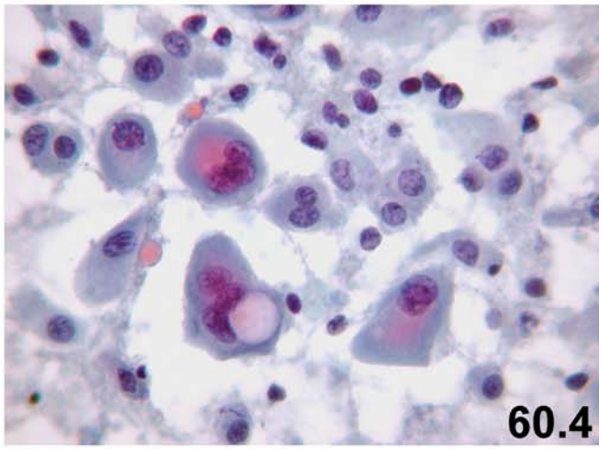
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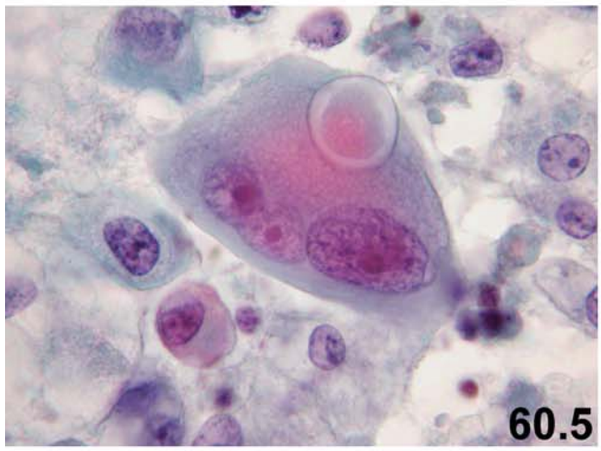
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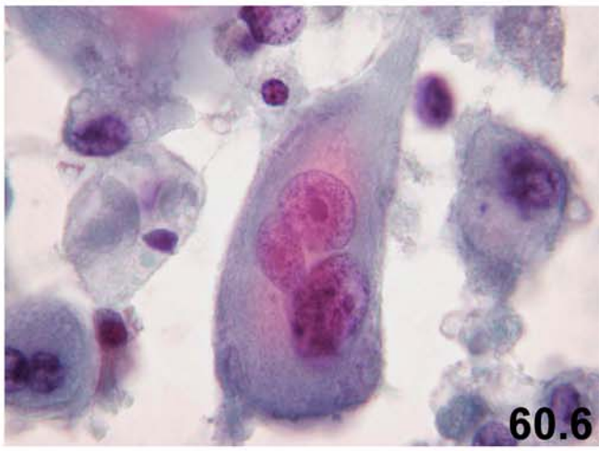
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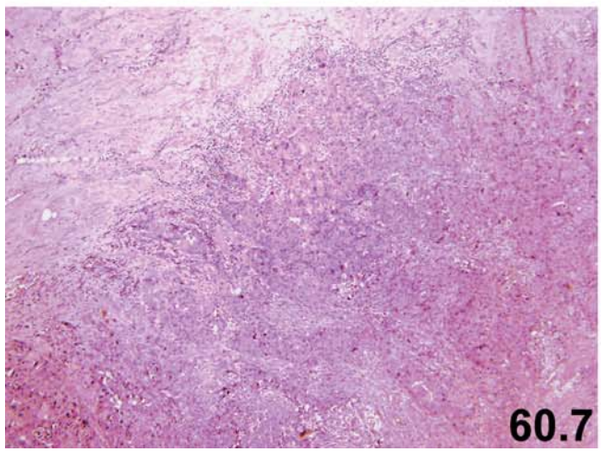
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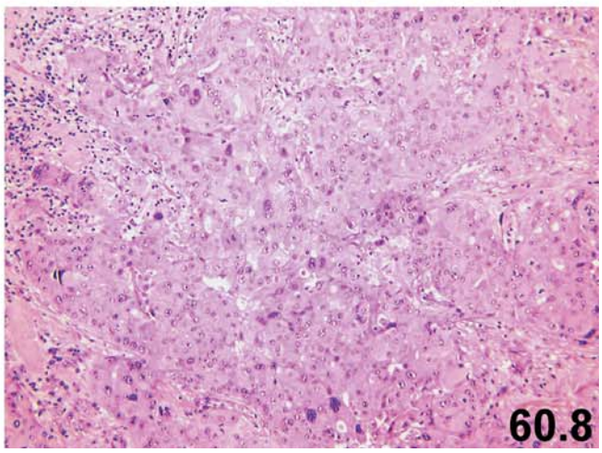
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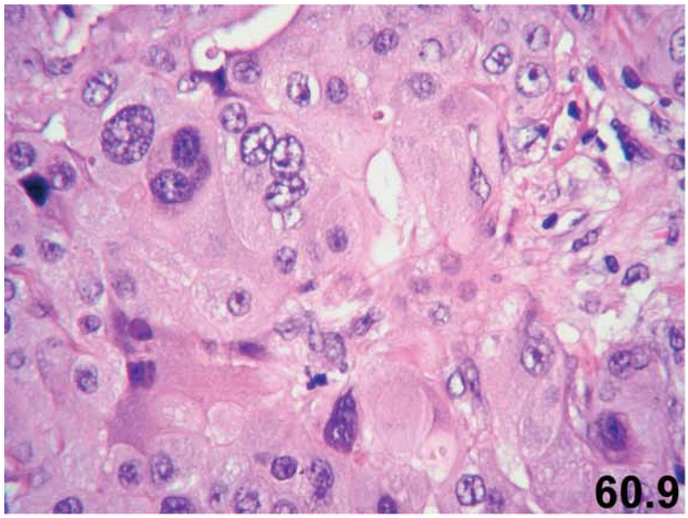
Figs. 60.9 and **60.10:** Higher magnification of the tumor displaying highly atypical epithelial cells with abundant eosinophilic cytoplasm and hyperchromatic large nuclei. The tumor cells show single or multiple prominent nucleoli.

Figs. 60.11 and **60.12:** Immunohistochemistry for HER2/neu in the tumor cells with apocrine differentiation reveals a diffuse and 3+ reaction.

Figs. 60.13 and **60.14:** The apocrine tumor cells show a heterogeneous, positive immunoreaction for androgen receptors (positive nuclear reaction for androgen receptor). The immunoreactions for estrogen receptors and progesterone receptors, however, were completely negative (not shown).

Fig. 60: Final remarks

- This case represents a rare variant of infiltrating carcinoma with prominent (more than 90% of the cancer cells) apocrine differentiation. The presence of androgen receptors and the lack of estrogen receptors and progesterone receptors is a typical finding for apocrine carcinoma of the breast.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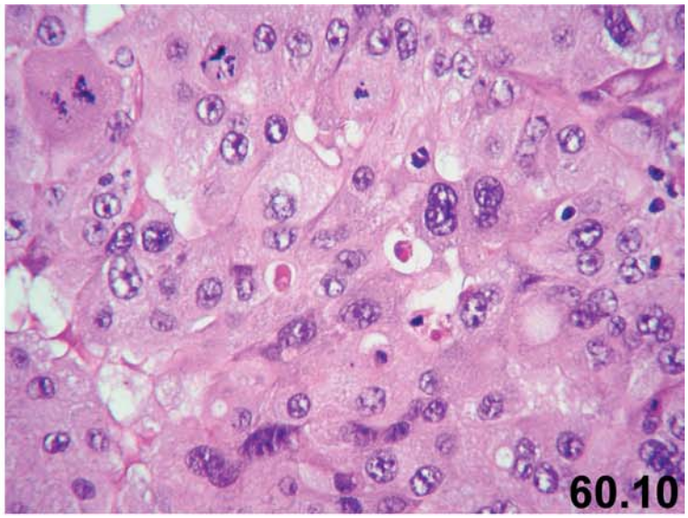
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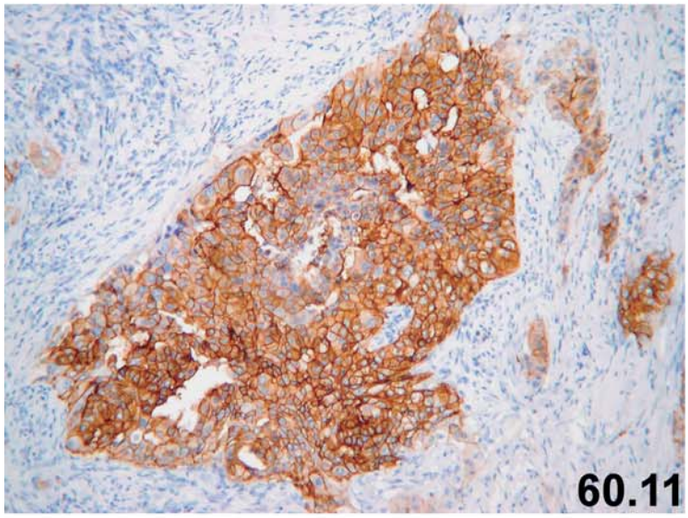
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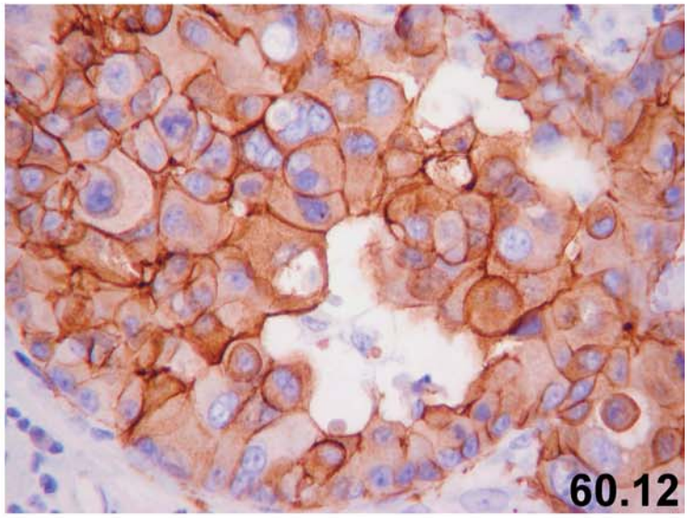
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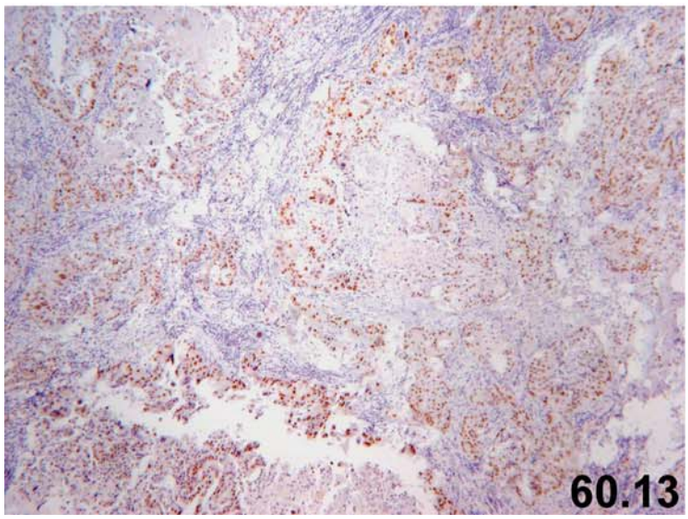
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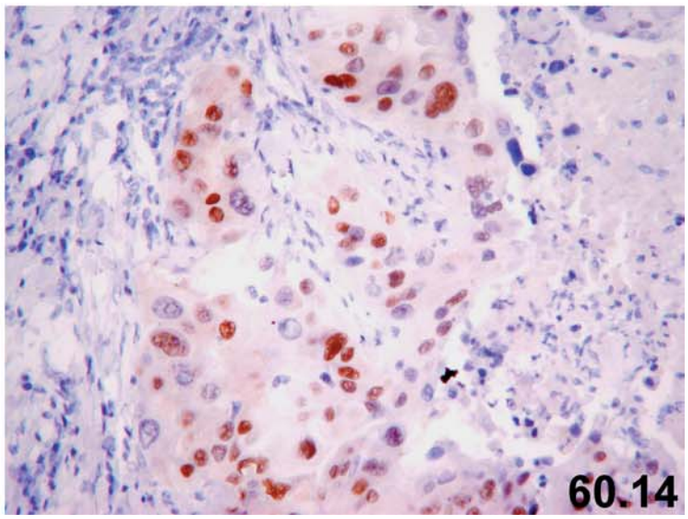
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Fig. 61: Secretory (juvenile) carcinoma.

Case history: A 20-year-old woman presented with a well-circumscribed tumor in her right breast. The tumor was clinically interpreted as fibroadenoma. Fine needle aspiration of the lesion was performed and revealed numerous cell clusters with some degree of nuclear atypia. Excisional biopsy of the lesion was finally performed and showed a lobulated firm, greyish-white tumor (1.5 cm in greatest diameter) with focal irregular margins.

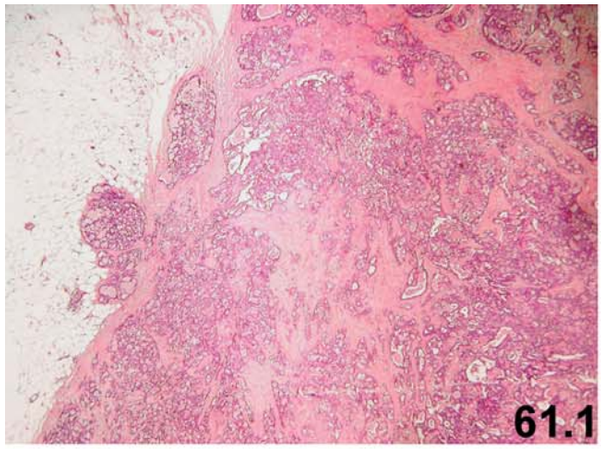
Fig. 61.1: The tumor shows a predominantly pushing margin.

Figs. 61.2 and **61.3:** Several areas of the tumor show a microcystic growth pattern. The small cystic structures contain abundant luminal secretions. Note infiltration of the normal lobules by the tumor.

Figs. 61.4 and **61.5:** Several areas show a honeycombed growth pattern composed of small cysts that often merge into larger spaces. The growth pattern simulates that of thyroid follicles.

Fig. 61.6: Microcystic glands with luminal colloid-like material closely mimicking thyroid tissue.

Figs. 61.7 and **61.8:** Tubules and microcysts with abundant intracellular and extracellular secretory material. Note the mixed cell population of cancerous cells showing epithelial cells with round, vesicular nuclei and cells with elongated or bipolar dark nuclei.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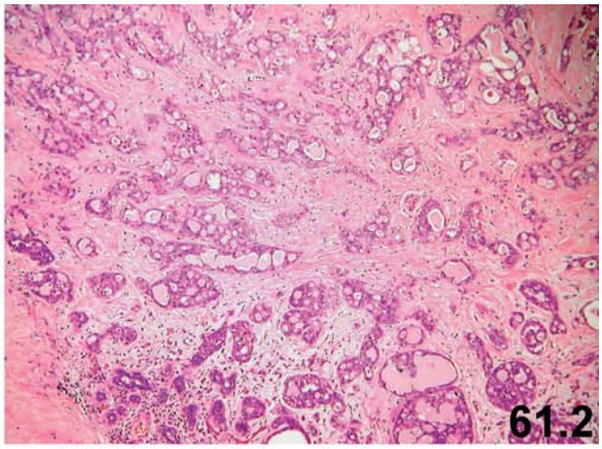
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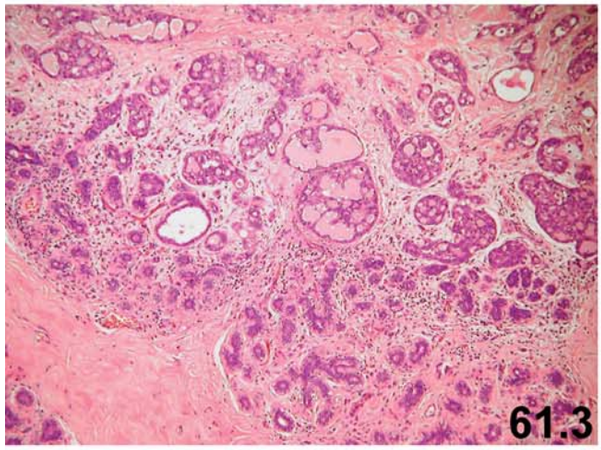
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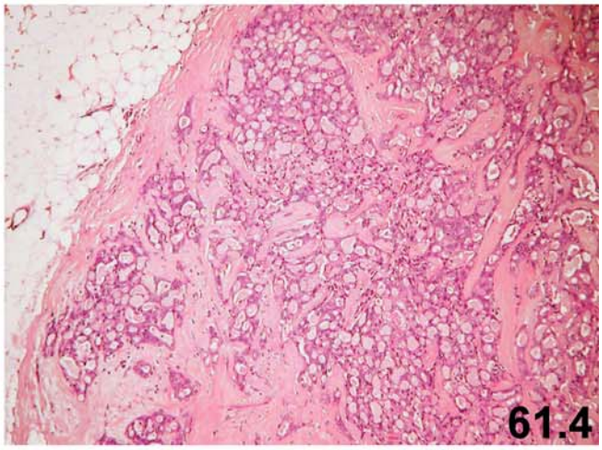
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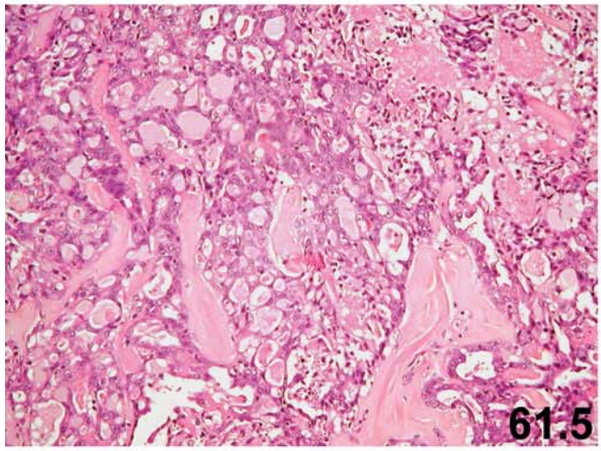
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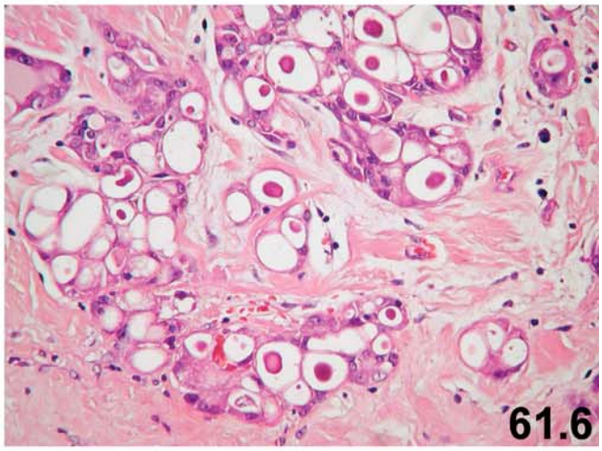
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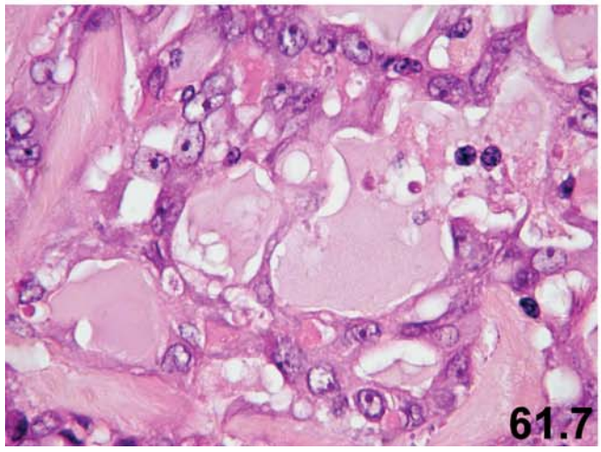
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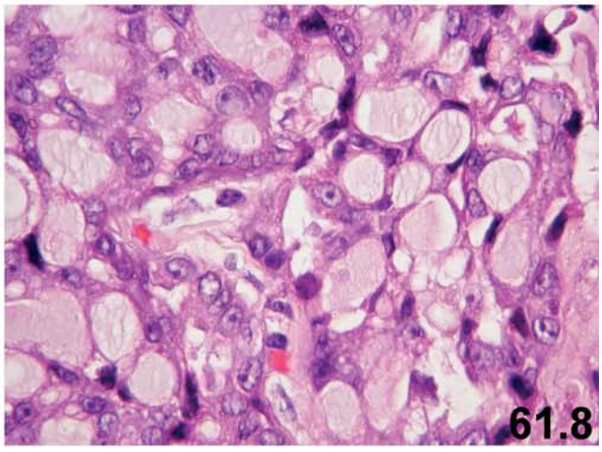
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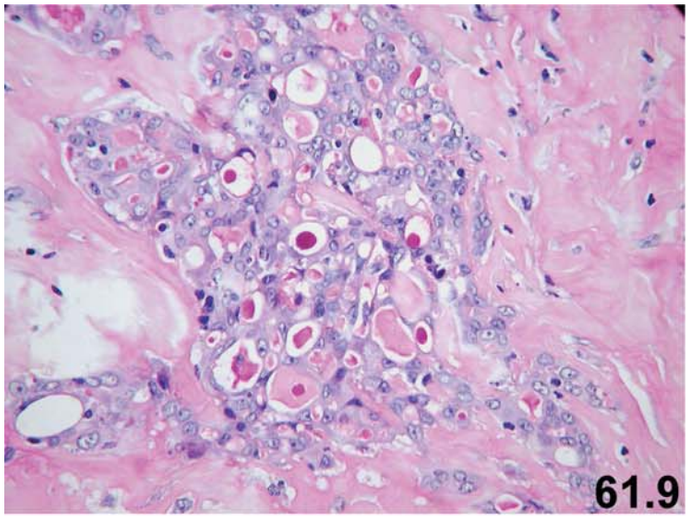
Figs. 61.9 and **61.10:** PAS (after diastase) reveals abundant luminal mucin in microcystic or honeycombed areas.

Figs. 61.11 and **61.12:** Immunohistochemistry for CK5/6 reveals many positive tumor cells. Note the heterogeneity of immunoreaction reflecting the heterogeneous cell population of tumor cells.

Figs. 61.13 and **61.14:** The tumor cells show an intense positive immunoreaction for S100 protein.

Fig. 61: Final remarks

- Immunoreaction for CK5/6 is positive in this case. The immunoreactions for estrogen receptors, progesterone receptors, and HER2/neu were negative (not illustrated).Therefore, some investigators may consider this carcinoma an example of so-called basal-like carcinoma. Note that secretory (juvenile) carcinoma of the breast has an excellent prognosis. As in adenoid cystic carcinoma, the cell population of tumor cells in secretory carcinoma is often heterogeneous, consisting of epithelial and modified myoepithelial cells.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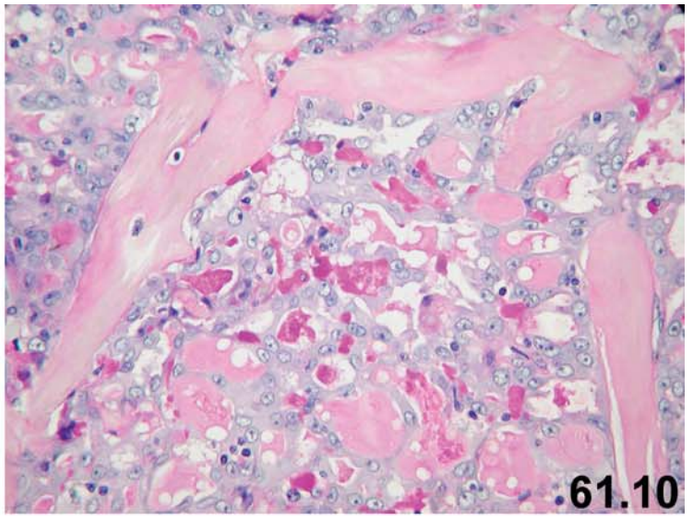
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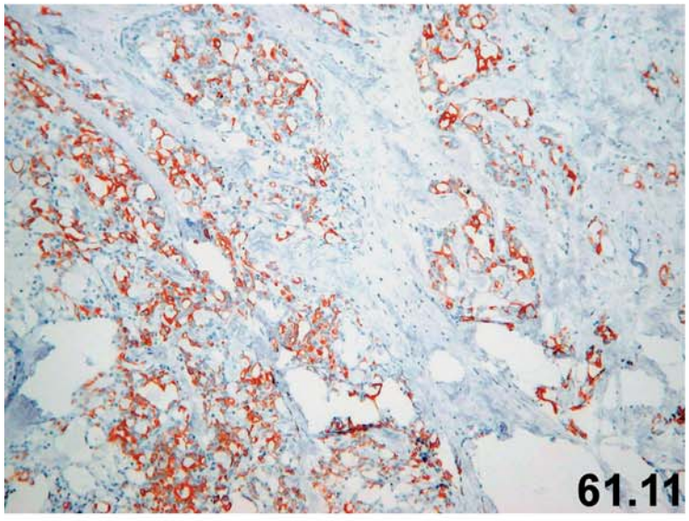
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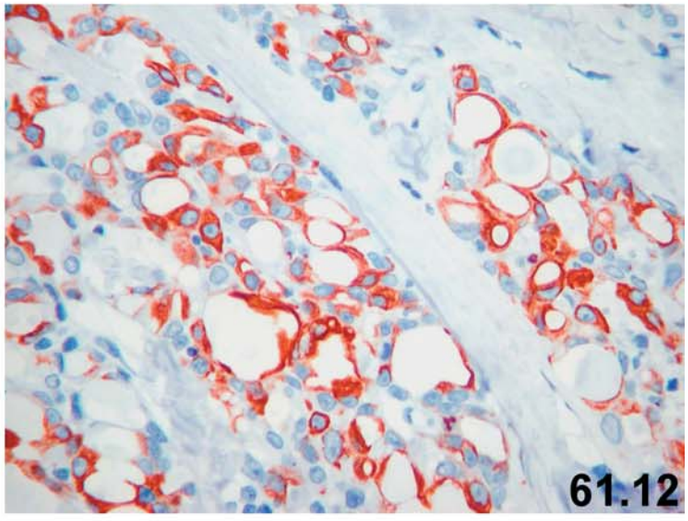
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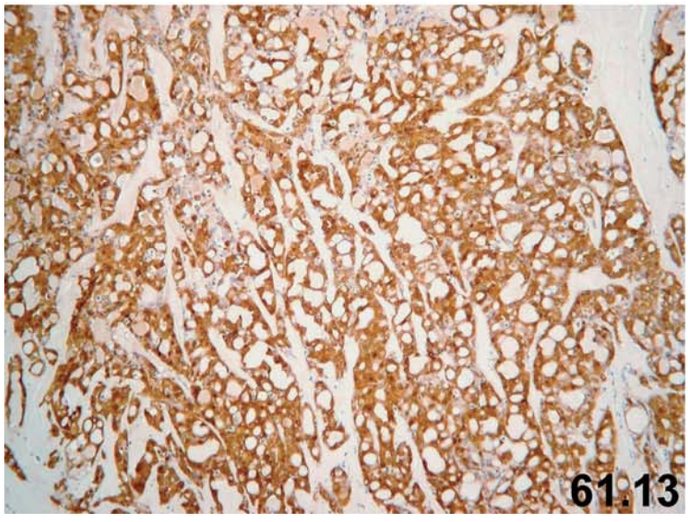
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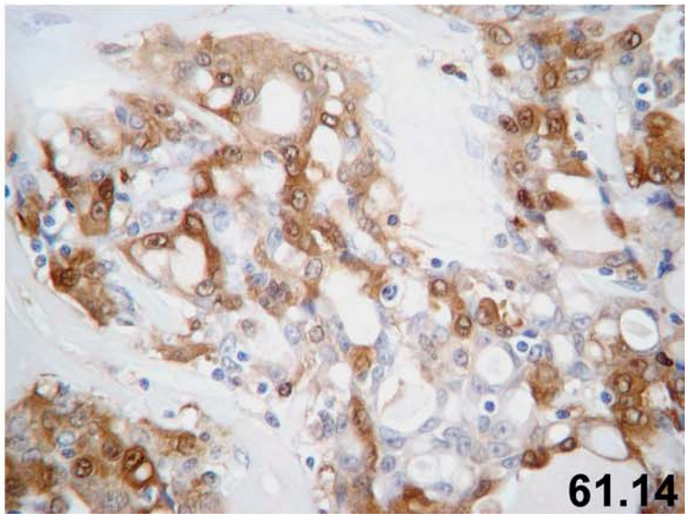

61.14

Fig. 62: Adenoid cystic carcinoma.

Case history: A 51-year-old woman complained to her physician about a sensation of heaviness in the right breast. Clinical and mammographic examinations revealed a 3.5-cm mass in the outer upper quadrant. Core needle biopsy of the tumor was performed and reported as infiltrating ductal carcinoma. The excisional biopsy showed a 3.5×2×1.4-cm tumor with partly well-circumscribed and partly infiltrating borders. Imprint cytology from the cut surface of lumpectomy specimen was performed.

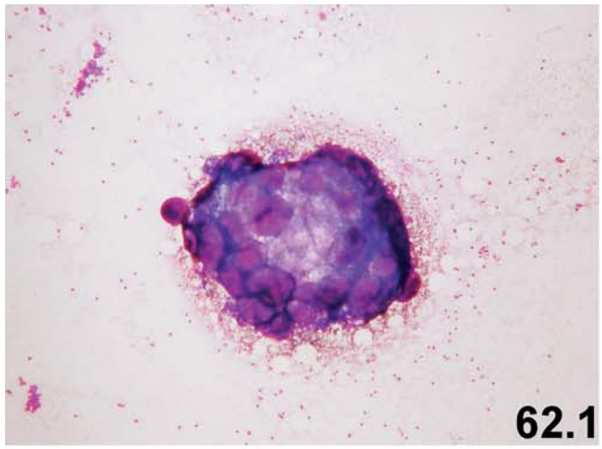
Figs. 62.1 and **62.2:** Imprint cytology of the tumor is highly cellular and reveals numerous cohesive round structures or spherules (Diff-Quik stain).

Fig. 62.3: Several spherules showing a central acellular or hypocellular component (Diff-Quik stain.

Fig. 62.4: One spherule showing a hypocellular central component and peripheral cells with elongated nuclei (Diff-Quik stain).

Figs. 62.5 and **62.6:** Cytology shows numerous hyaline bodies with homogeneous, basement membrane-like material. Note the presence of numerous isolated cells in the background of 62.5 (Diff-Quik stain).

Figs. 62.7 and **62.8:** In addition to rounded hyaline structures, several areas show irregular or bizarre shaped basement membrane-like material (Diff-Quik stain).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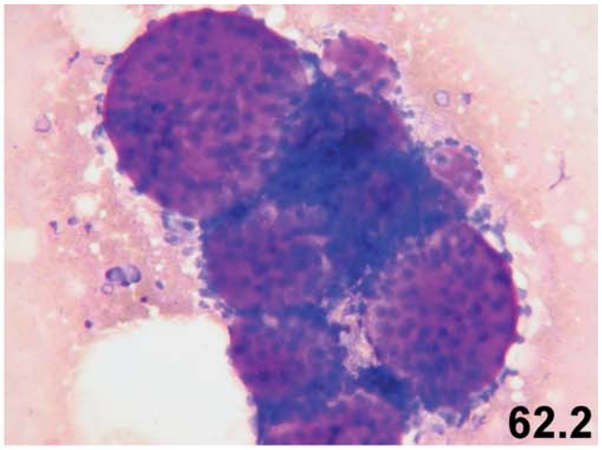
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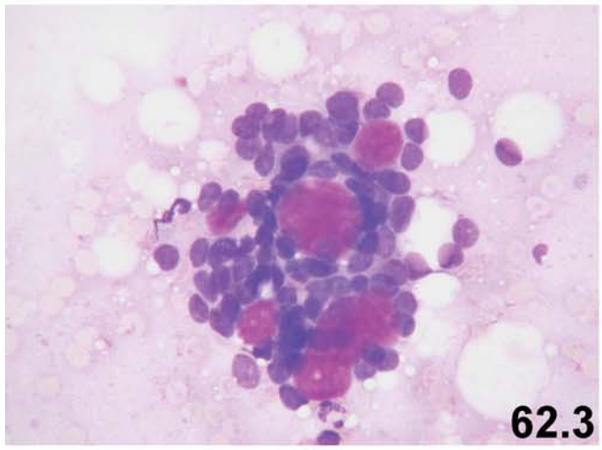
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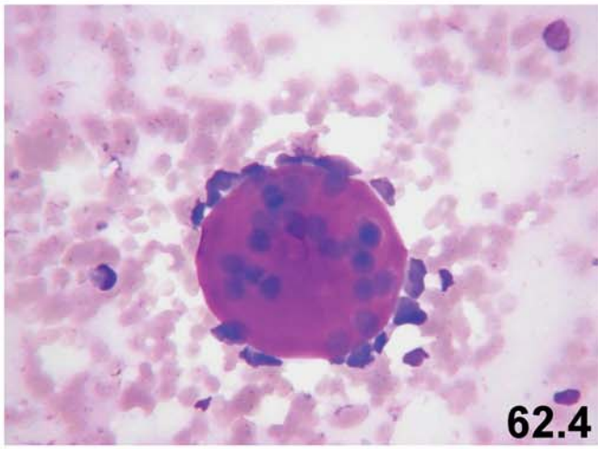
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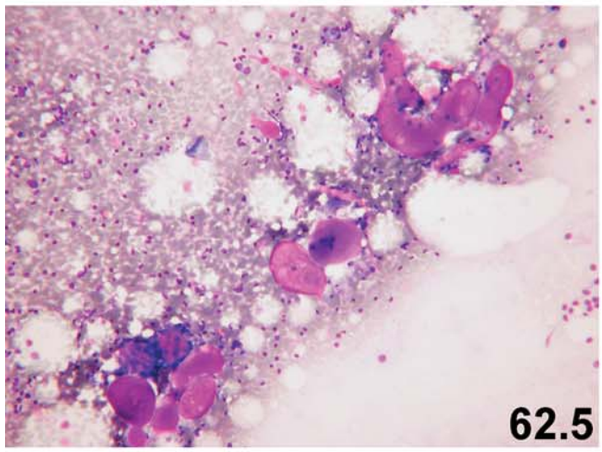
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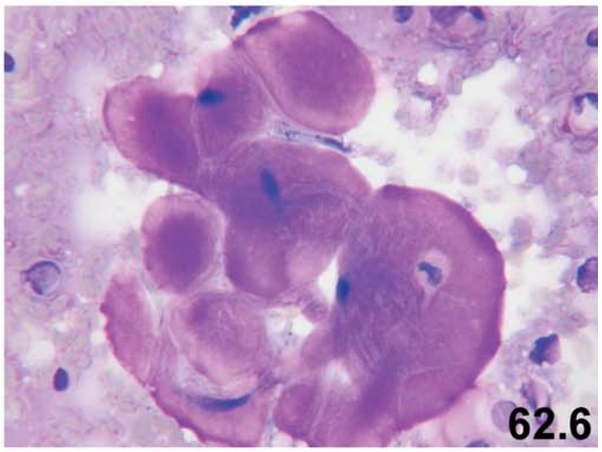
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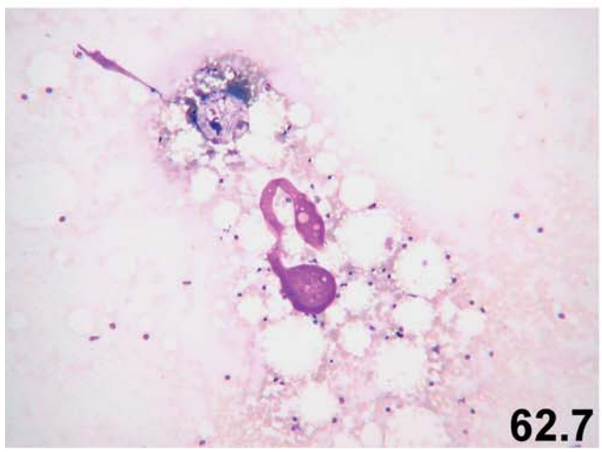
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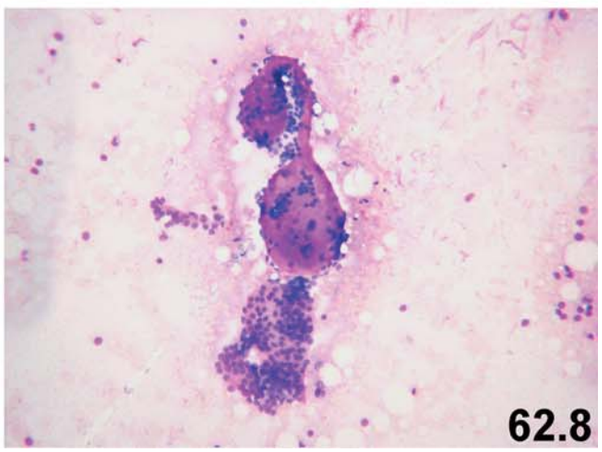
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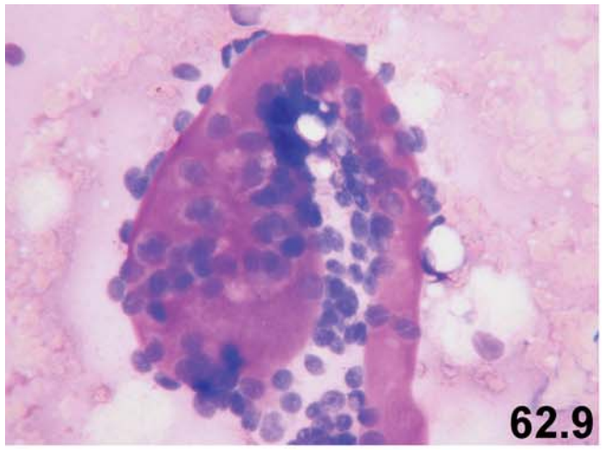
Fig. 62.9: Diff-Quik stain showing basement membrane-like hyaline material associated with cells with round and elongated (bipolar) nuclei.

Fig. 62.10: Another bizarre-shaped hyaline structure representing abnormal configuration of basement membrane in this tumor.

Figs. 62.11 and **62.12:** Papanicolaou stain of the imprint cytology shows numerous hyaline spherules. While some spherules are quite hypocellular, others are covered by numerous epithelial cells.

Figs. 62.13 and **62.14:** Comparison of Papanicolaou stain (Fig. 62.13) and Diff-Quik stain (Fig. 62.14) focusing on hypocellular hyaline spherules.

Figs. 62.15 and **62.16:** Comparison of Papanicolaou stain (Fig. 62.15) and Diff-Quik stain (Fig. 62.16) focusing on hypercellular hyaline spherules. Note that the spherules or hyaline bodies contain several cells with elongated or bipolar nuclei (myoepithelial cells).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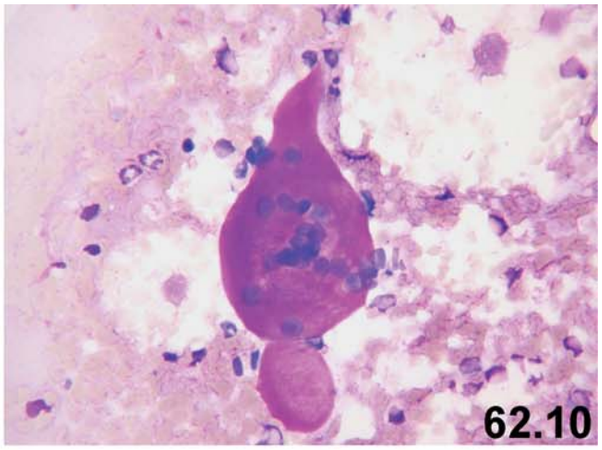
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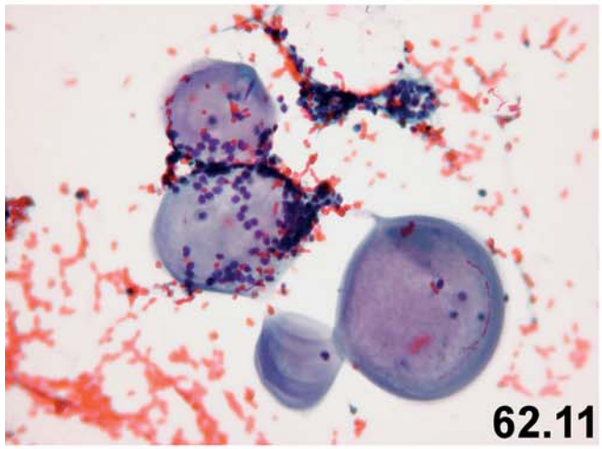
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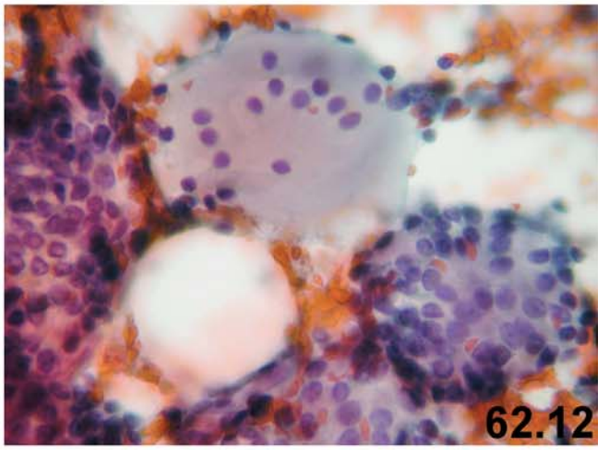
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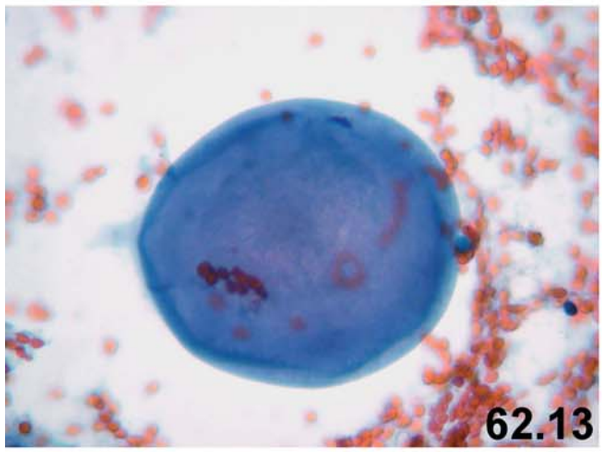
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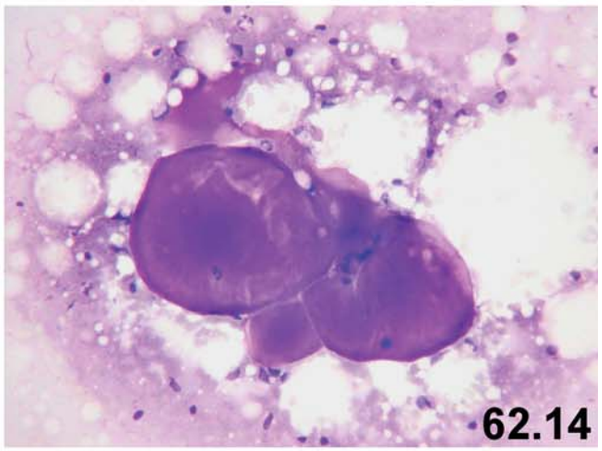
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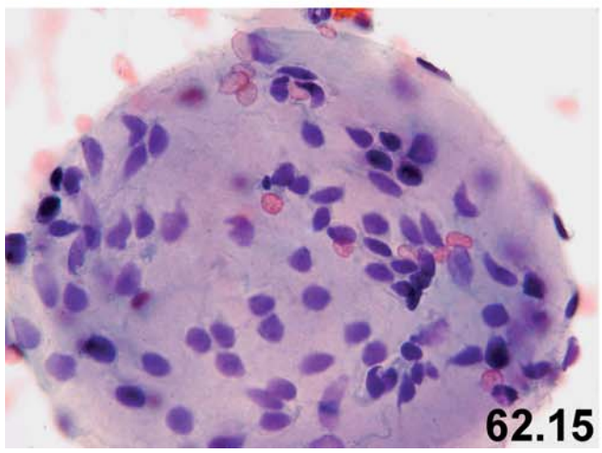
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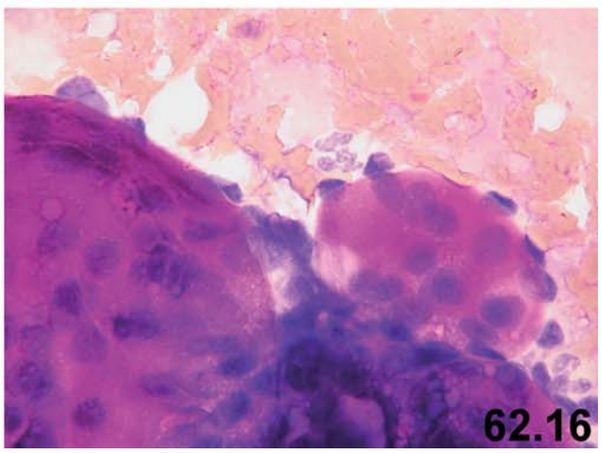

62.16

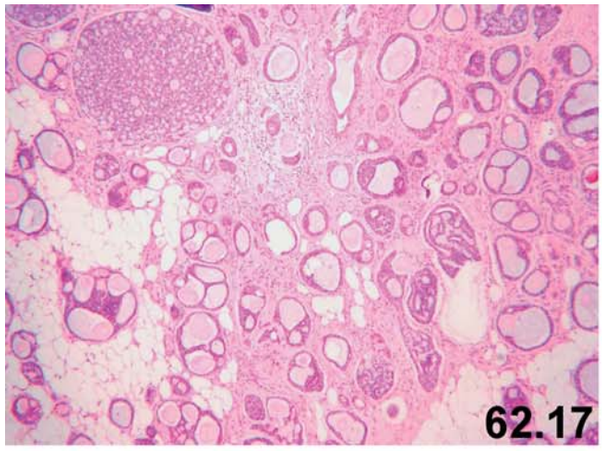
Figs. 62.17, 62.18, and **62.19:** Histological examination of the tumor shows an infiltrating tumor forming cribriform, tubular, and trabecular structures. Several tubules or cribriform structures are filled with eosinophilic basement-membrane-like or mucoid secretory material.

Fig. 62.20: Cribriform areas are punctuated by spaces filled with basement-membrane-like material (hyaline bodies).

Fig. 62.21: Tumor cells with glandular confluence or cribriform growth pattern containing mucoid secretory material.

Fig. 62.22: Other areas show nests or islands of tumor cells with infiltrating pattern. Two types of cells can be recognized within the islands and tubules: a basaloid cell population, which predominates, and a smaller population of cells with more eosinophilic cytoplasm.

Figs. 62.23 and **62.24:** In contrast to cribriform DIN (DCIS) or cribriform invasive carcinoma, the spaces in adenoid cystic carcinoma (ACC) are filed with hyaline bodies or spherules representing basement membrane-like material. Also note the heterogeneity of cell population of the proliferating cells, which is a characteristic feature of ACC.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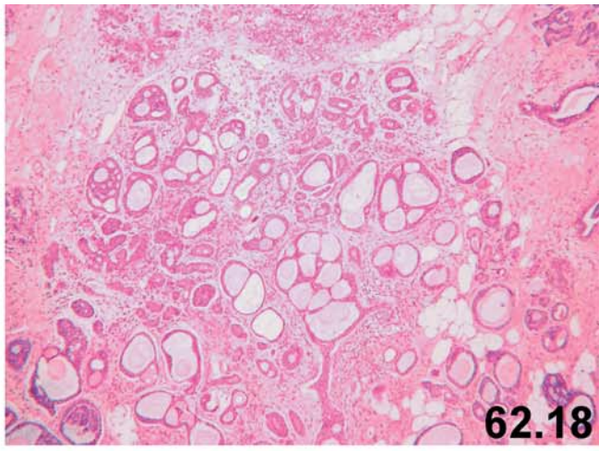
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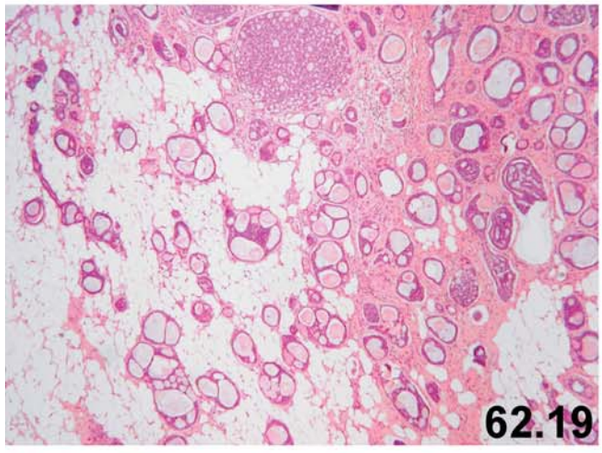
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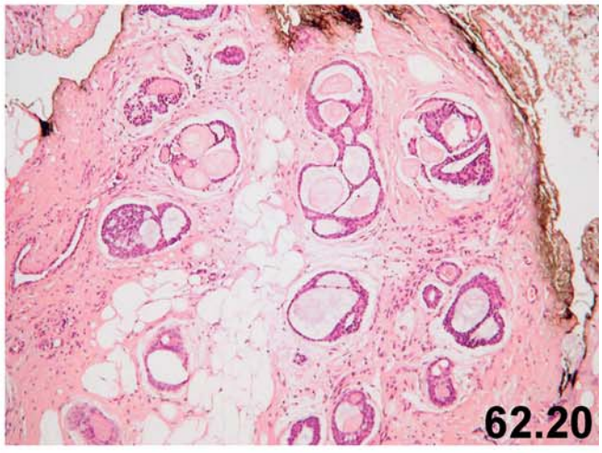
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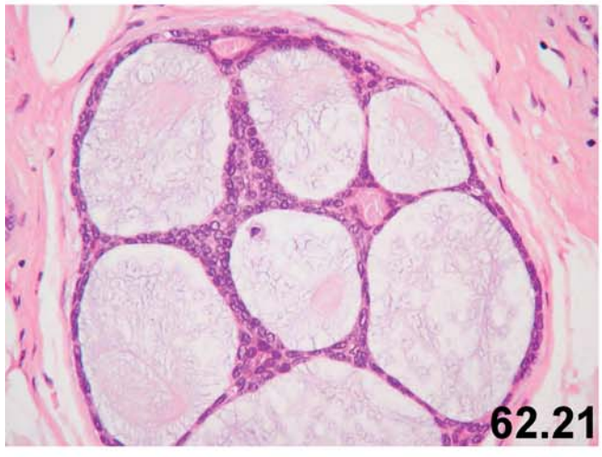
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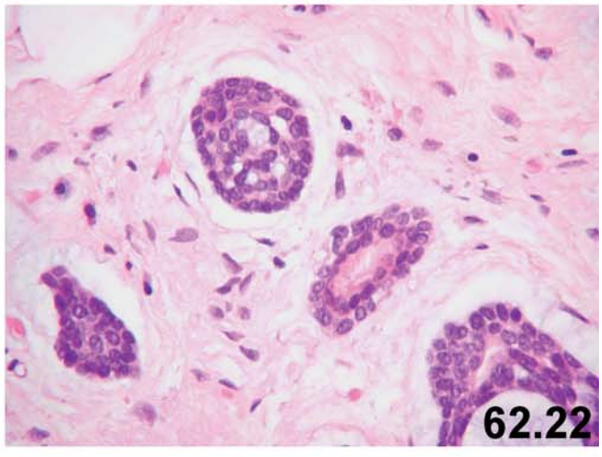
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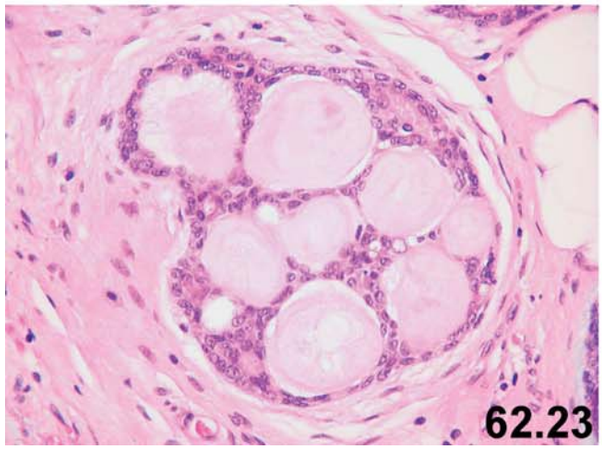
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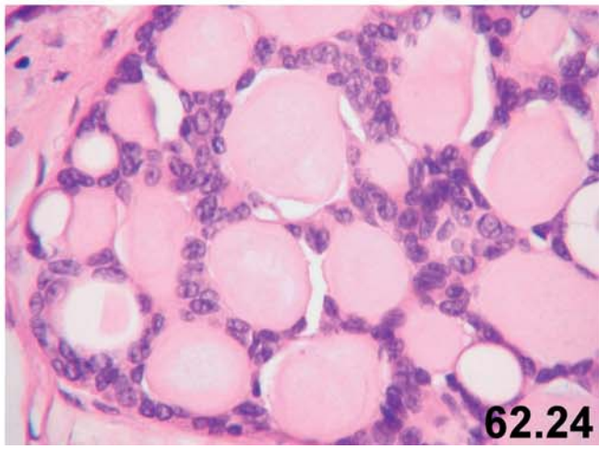
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Figs. 62.25 and **62.26:** Higher magnification of several hyaline bodies in adenoid cystic carcinoma showing that the tumor cells proliferate around and eventually engulf these hyaline bodies, gradually incorporating them into the nests of tumor cells. One should also pay attention to the different cell populations within the proliferating cells (epithelial and basaloid/myoepithelial cells).

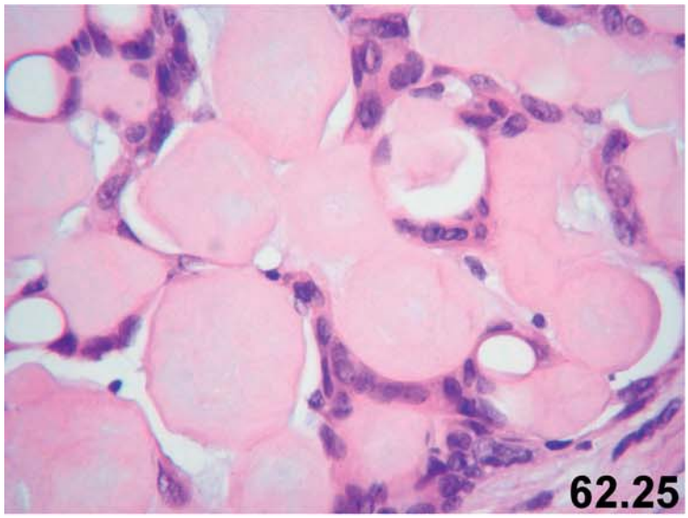
Fig. 62.27: Immunohistochemistry for smooth muscle actin demonstrates an intense positivity in many cribriform areas of the tumor. Note also the negative actin immunoreaction in one cribriform area.

Fig. 62.28: While many tumor cells are negative for CK5/6, others show a positive immunoreaction for it (heterogeneous positive reaction).

Figs. 62.29 and **62.30:** Immunohistochemistry for p63 shows a strong positive reaction in numerous tumor cells. Note the heterogeneity of immunoreaction, which correlates with the heterogeneity of neoplastic cells in adenoid cystic carcinoma.

Fig. 62: Final remarks

- ACC represents a rare breast carcinoma with heterogeneous epithelial and myoepithelial/basaloid cell differentiation. Many cases of ACC reveal positive immunoreaction for a variety of myoepithelial and/or basal cell markers. ACC usually shows a heterogeneous positive reaction for CK34BE12, CK5/6 or CK14.
- The positive immunoreaction for basal type cytokeratins (CK34BE12, CK5/6, CK14) (basal-like differentiation) in this breast carcinoma should not be misinterpreted as a sign for poor prognosis. In deed, mammary ACC has an excellent prognosis.
- Due to the presence of epithelial and myoepithelial cells and numerous bipolar naked nuclei in the background of cytologic specimens (fine needle aspiration, touch imprint), ACC can easily be underdiagnosed. The presence of hyaline bodies and irregular basement-membrane-like material in conjunction with several clusters of epithelial and myoepithelial cells is, however, diagnostic for ACC.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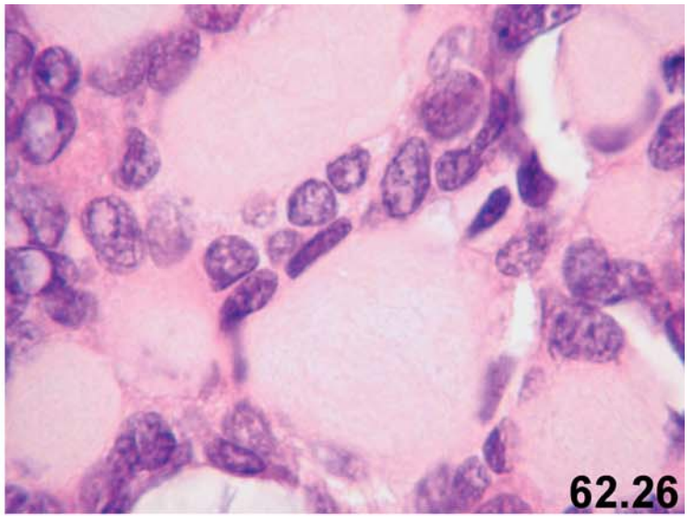
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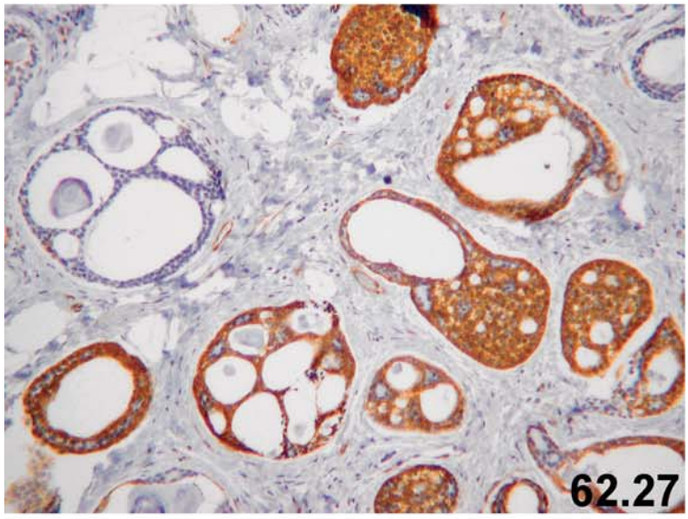
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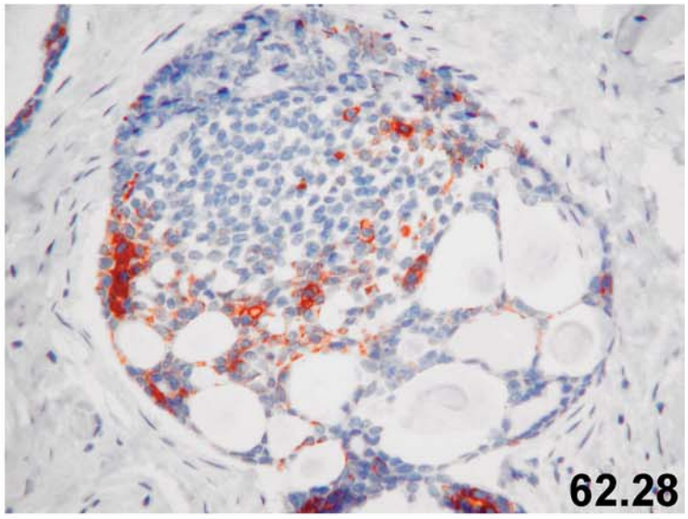
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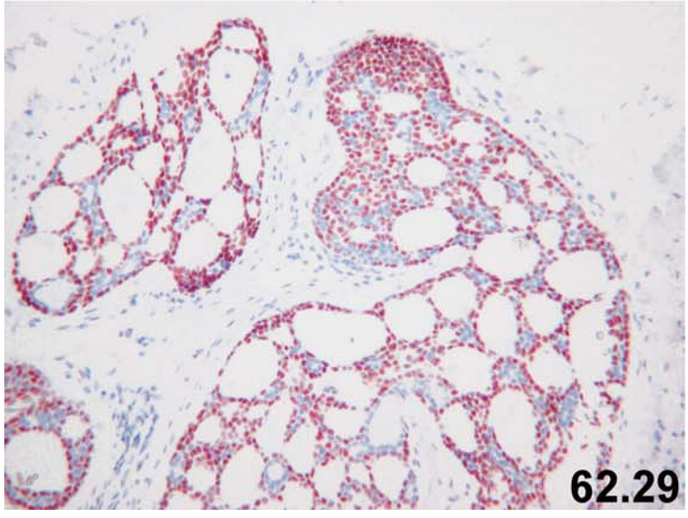
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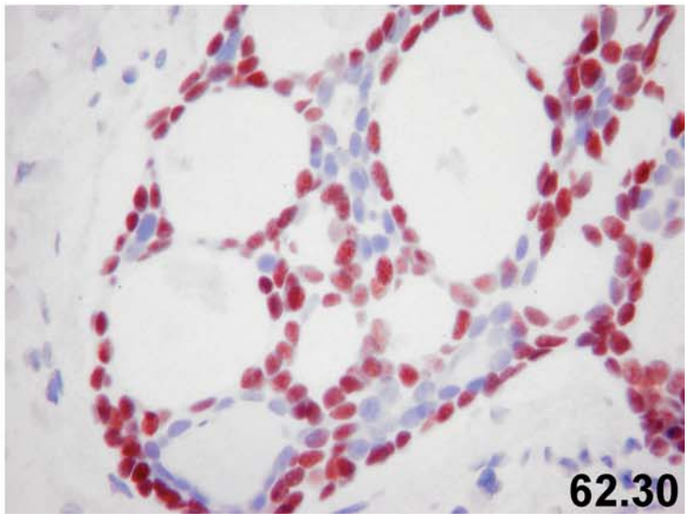
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Fig. 63: Sebaceous carcinoma of the breast.

Case history: Physical examination of a 75-year-old woman revealed a well-circumscribed firm tumor in the upper outer quadrant of her right breast. The skin of the breast appeared normal.

Fig. 63.1: Low magnification of the excised tumor shows large solid areas and nests of tumor cells.

Figs. 63.2 and **63.3:** Tumor cells displaying abundant clear cytoplasm. Note the irregular and infiltrating tumor borders.

Figs. 63.4 and **63.5:** Large tumor cells with sebaceous differentiation displaying round nuclei with minimal degree of atypia. The tumor cells show abundant clear to foamy cytoplasm and distinct cytoplasmic borders.

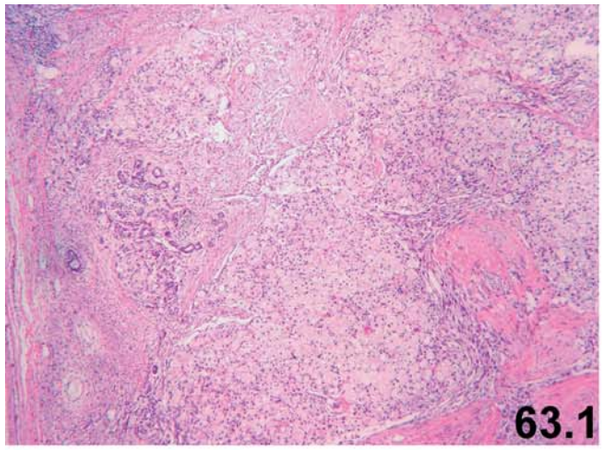
Fig. 63.6: In addition to the clear or foamy cells, a second cell population of tumor cells with squamous cell differentiation is present.

Fig. 63.7: Another area of the tumor showing a squamous cell component with keratinization.

Fig. 63.8: Higher magnification of tumor cells showing very distinct cell borders and abundant foamy cytoplasm.

Fig. 63: Final remarks

- The main differential diagnosis in this case is lipid-rich carcinoma. While sebaceous carcinoma shows a lobulated and well-defined solid growth pattern, lipid-rich carcinoma infiltrates like a regular invasive ductal carcinoma with irregular, infiltrating tumor margins. In contrast to sebaceous carcinoma, the vacuolization in lipid-rich carcinoma is very subtle and easily overlooked at low magnification. The presence of tumor cells with squamous cell differentiation is more common in sebaceous carcinoma.
- Primary sebaceous carcinoma of the breast should not show any connection with skin adnexal glands. Indeed, mammary sebaceous carcinoma represents a rare variant of metaplastic breast carcinoma that shows prominent sebaceous differentiation.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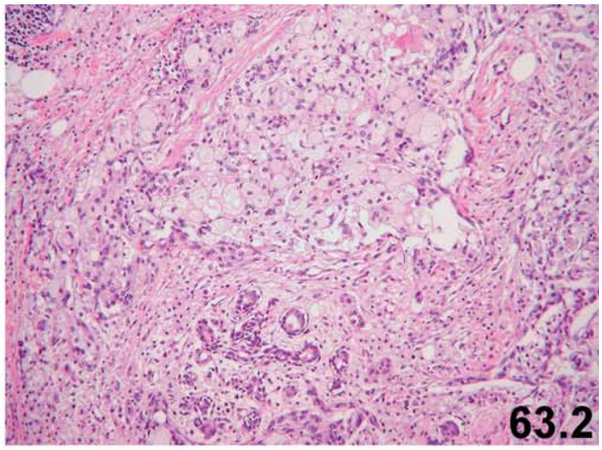
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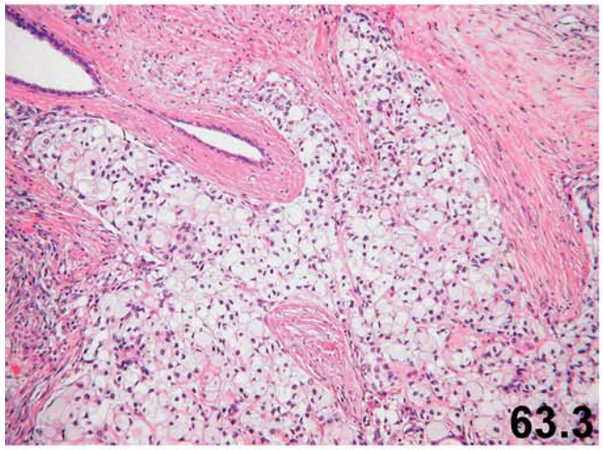
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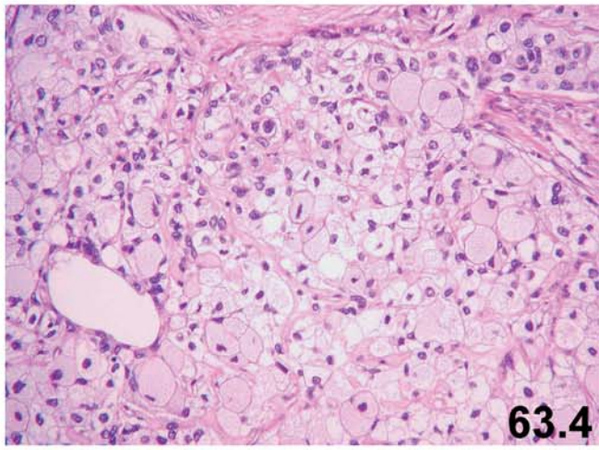
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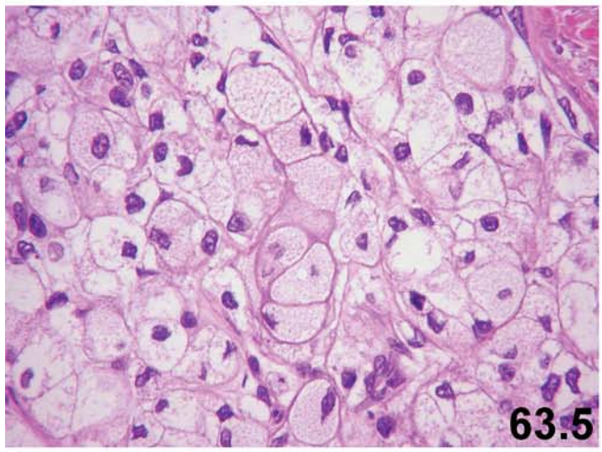
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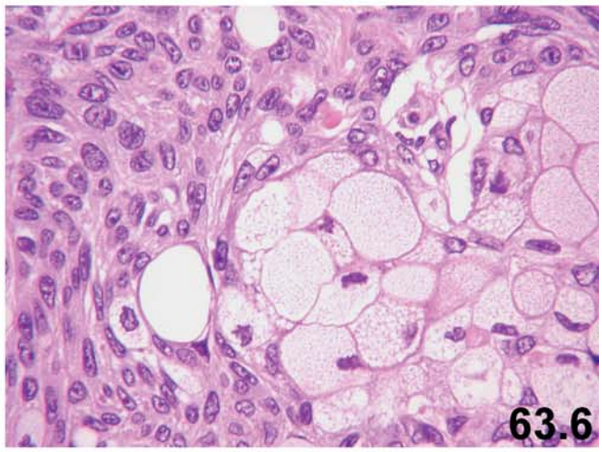
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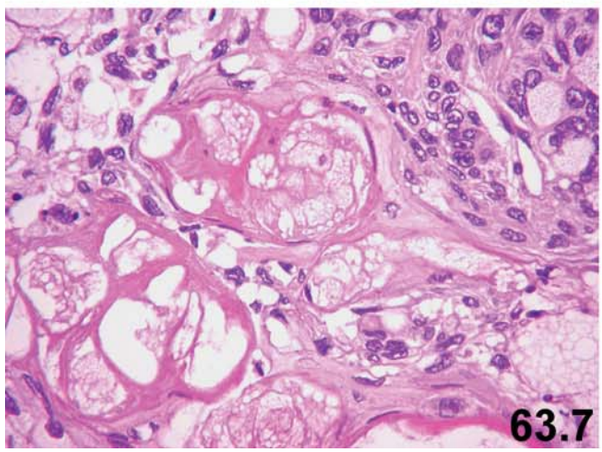
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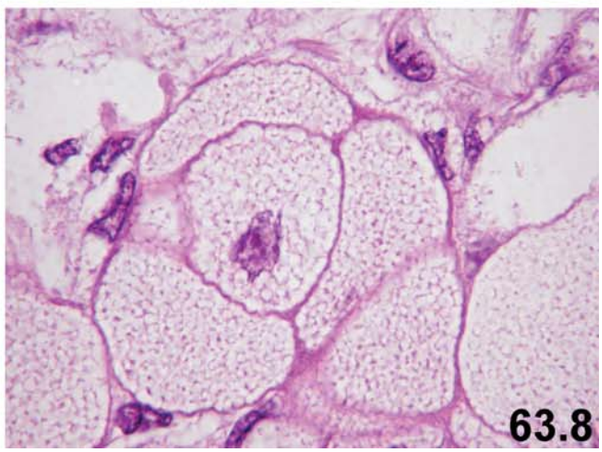
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Fig. 64: Invasive cribriform carcinoma.

Case history: A 41-year-old woman noticed a hard tumor in the lower inner quadrant of her right breast. By physical examination, the tumor was not mobile and measured about 2.5 cm in diameter. A needle core biopsy of the tumor showed a well-differentiated infiltrating ductal carcinoma.

Fig. 64.1: Excisional biopsy shows a tumor with infiltrating and irregular borders.

Fig. 64.2: Irregular arrangement of infiltrating tubules with glandular confluence.

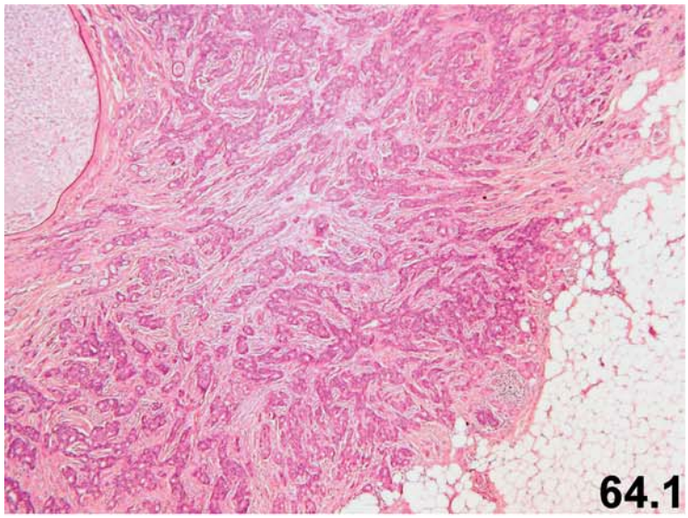
Fig. 64.3: Uniform tumor cells with glandular confluence forming a cribriform growth pattern. Some cribriform areas may closely resemble a cribriform DIN (DCIS).

Fig. 64.4: The tumor is composed of uniform cells without significant nuclear atypia. The invasive pattern of the tumor is clearly evident.

Figs. 64.5 and **64.6:** Clear-cut infiltrating growth pattern of a homogeneous epithelial cell population without association with a myoepithelial cell layer.

Fig. 64: Final remarks

- The differential diagnosis in this case is tubular carcinoma. Classic or pure tubular carcinoma does not have a significant cribriform growth pattern. Mixed type tubular carcinoma, however, often shows a cribriform component. Such well-differentiated invasive tumors have been designated as either mixed type tubular or as mixed type cribriform carcinomas. In this case, the cribriform growth pattern is dominant. The diagnosis of invasive cribriform carcinoma is, therefore, appropriate in this case.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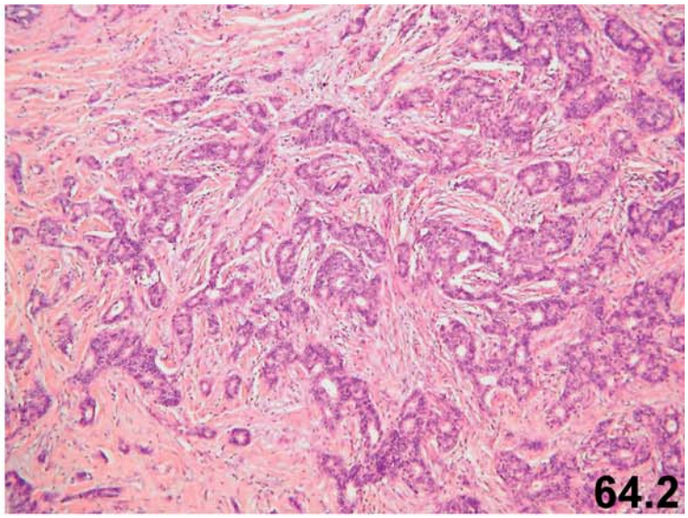
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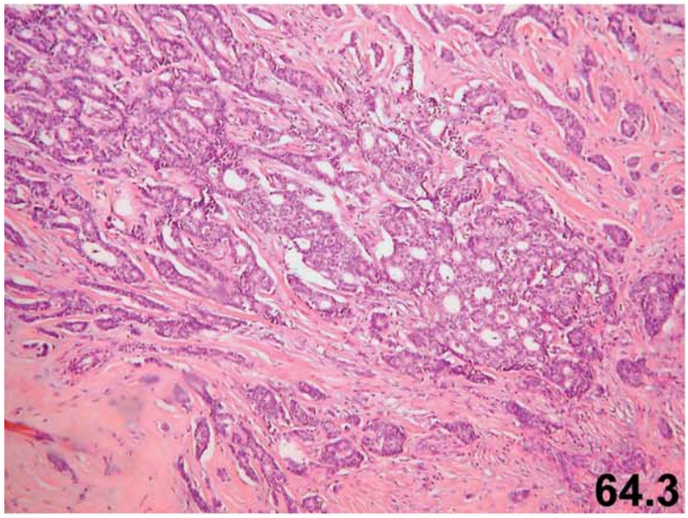
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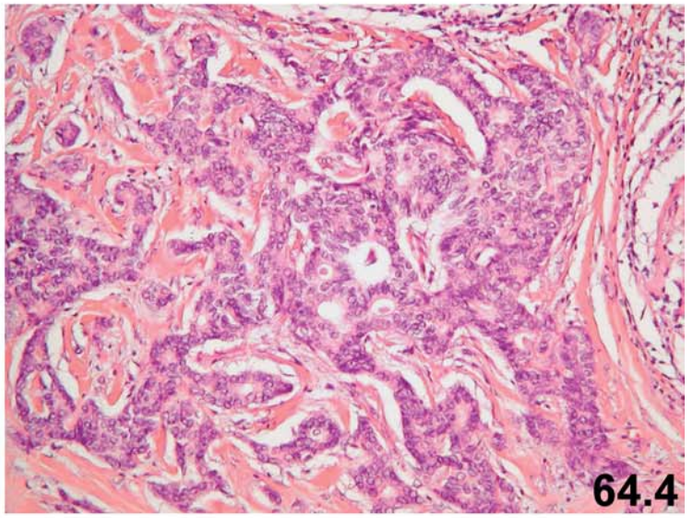
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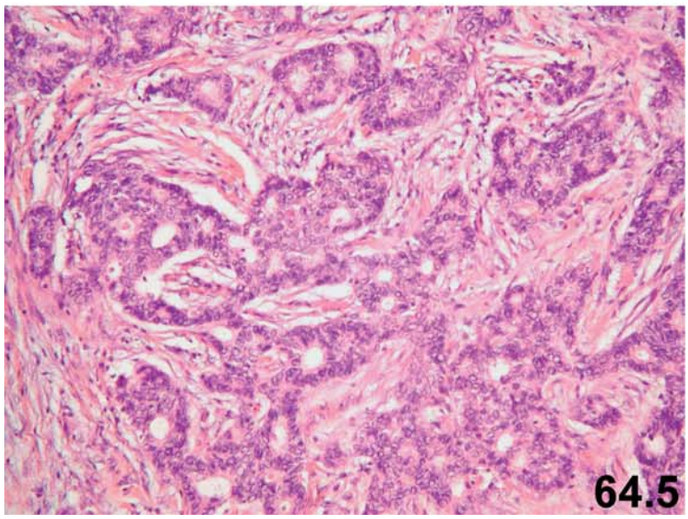
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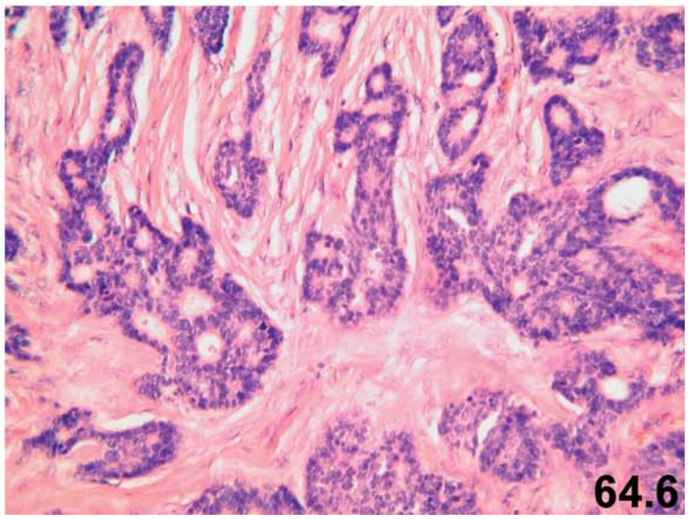
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Fig. 65: Medullary carcinoma.

Case history: A 25-year-old woman presented with a well-demarcated, mobile 2-cm left breast mass. The tumor showed a rubbery consistency simulating a fibroadenoma. Fine needle aspiration cytology was performed and, surprisingly, revealed numerous highly atypical and pleomorphic (anaplastic) epithelial tumor cells. Excisional biopsy of the tumor was done.

Fig. 65.1: The cut surface of the excisional biopsy shows a well-circumscribed yellow to pink tumor. The tumor was rubbery.

Fig. 65.2: The tumor shows solid epithelial aggregates with pushing margins.

Fig. 65.3: The tumor displays lobulated or pushing margins. The stroma adjacent to the carcinoma is infiltrated by numerous lymphocytes.

Fig. 65.4: Solid aggregates of highly atypical cells showing enlarged vesicular nuclei.

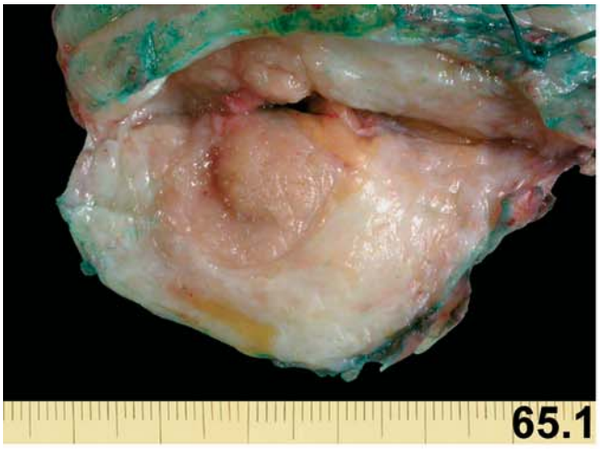
Fig. 65.5: Syncytial arrangement of highly pleomorphic or anaplastic tumor cells displaying very large vesicular nuclei with prominent nucleoli.

Figs. 65.6 and **65.7:** The tumor shows high mitotic activity, including several atypical mitotic figures.

Fig. 65.8: The cancerous cells exhibit a heterogeneous 1+ to 2+ immunoreactivity for HER2/neu. FISH was performed and did not show HER2/neu gene amplification (not shown).

Fig. 65: Final remarks

- This is an example of medullary carcinoma, which is, in the author's experience, extremely rare. As a matter of fact, the vast majority of breast cancers designated as medullary carcinomas represent poorly differentiated ductal carcinomas showing only some, but not all, of the medullary features. A search for breast carcinomas (cases diagnosed between 1975 and 2006) in the files of the Department of Pathology at Medical University Graz revealed about 30 cases that initially were diagnosed as medullary carcinoma. Reexamination of these cases, however, revealed only one case (the above case) of true medullary carcinoma. All other cases were reclassified as poorly differentiated ductal carcinoma.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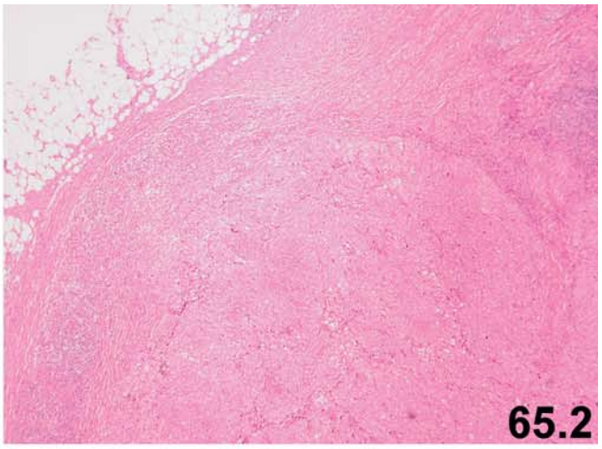
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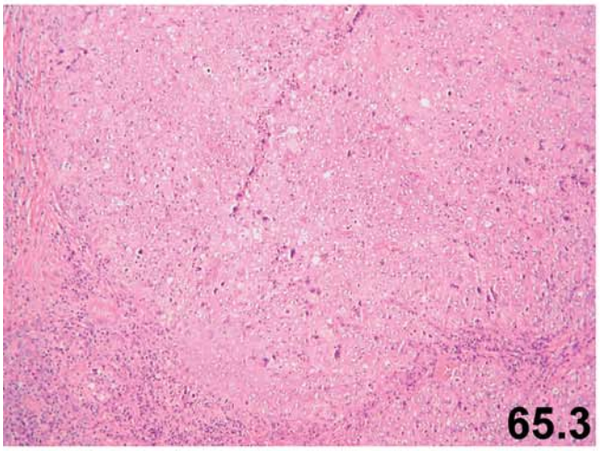
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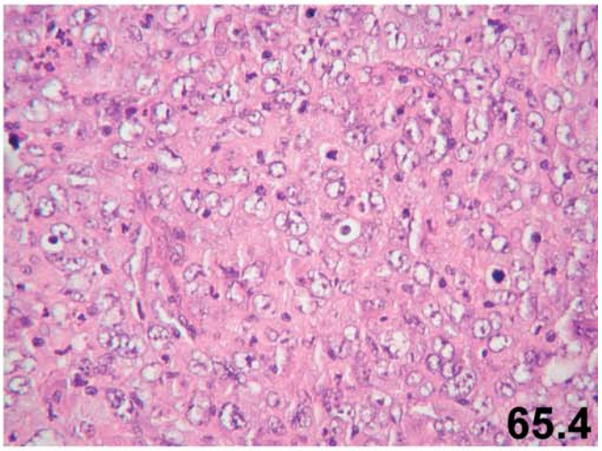
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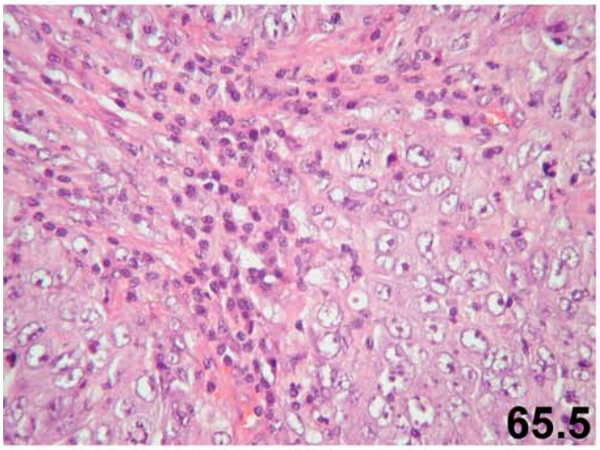
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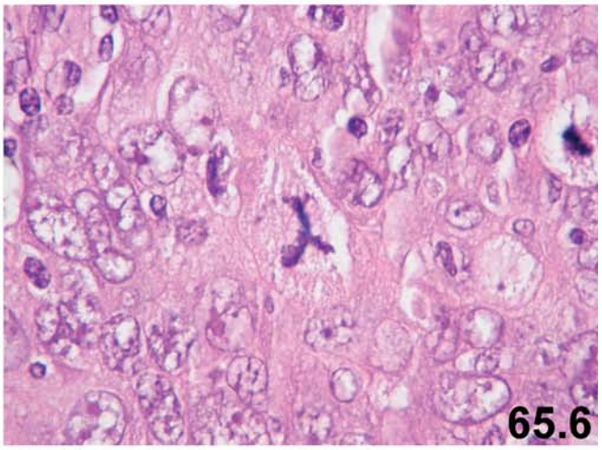
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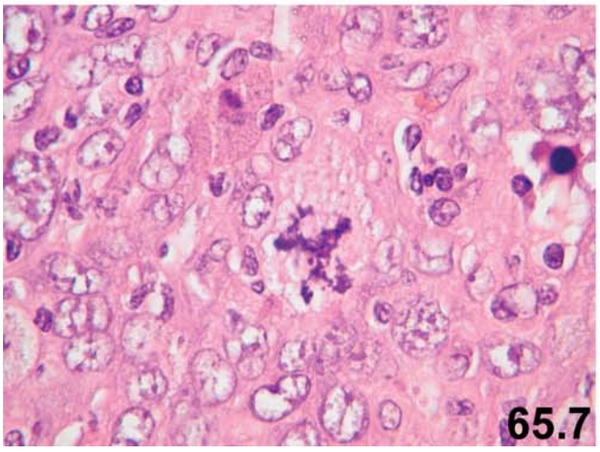
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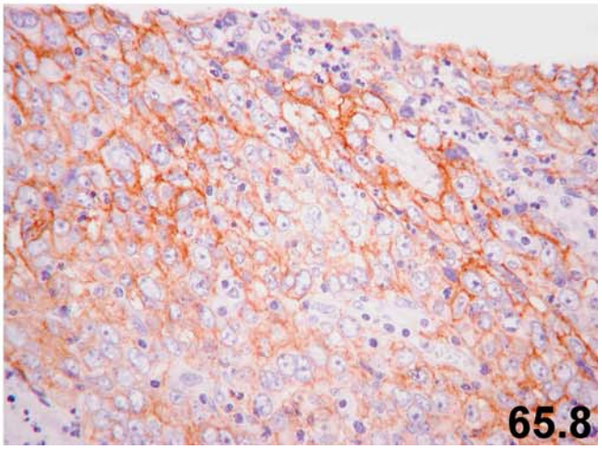
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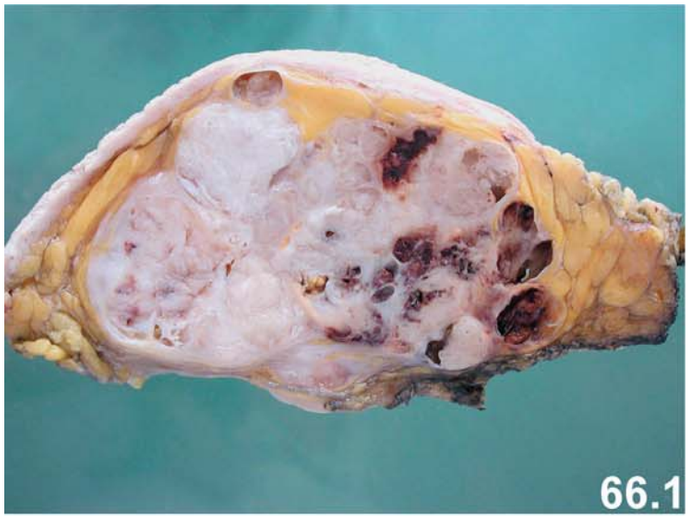
Fig. 66: Gross appearance of metaplastic carcinoma.

Fig. 66.1: Mastectomy specimen of a 14-cm metaplastic carcinoma showing solid and cystic areas associated with hemorrhage.

Fig. 66.2: A metaplastic breast carcinoma revealing a greyish-white cut surface. Note degenerative areas in the center of the tumor. The histology of this case revealed a primary squamous cell carcinoma.

Figs. 66.3 and **66.4:** Mastectomy specimen of a sarcomatoid breast carcinoma with infiltration of the pectoralis muscle (Fig. 66.3) and nipple (Fig. 66.4). The tumor was firm to rubbery.

Figs. 66.5 and **66.6:** A case with carcinosarcoma showing greyish-white firm, fleshy areas associated with hemorrhage and necrosis.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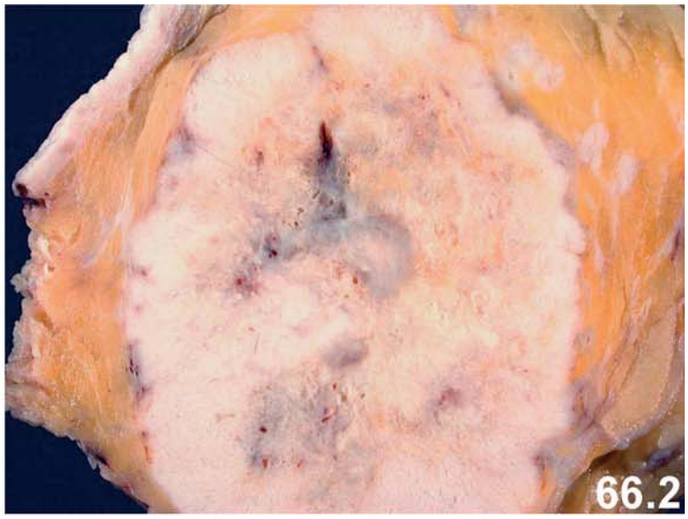
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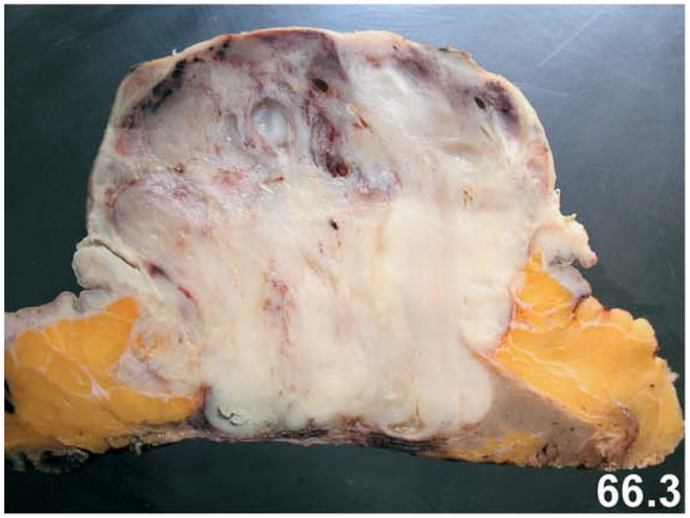
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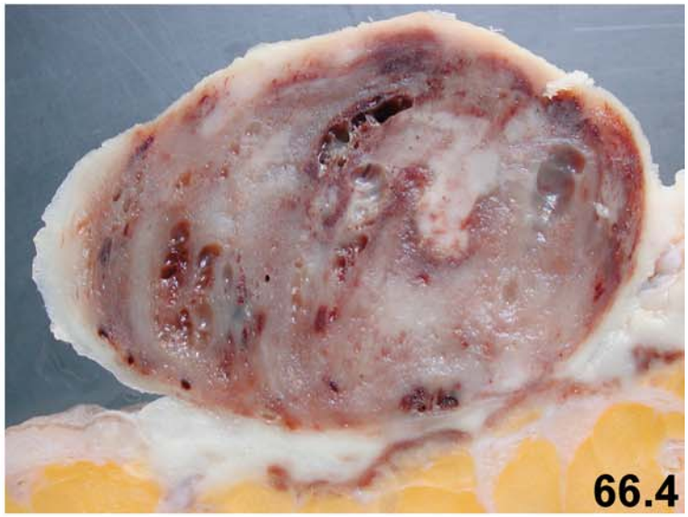
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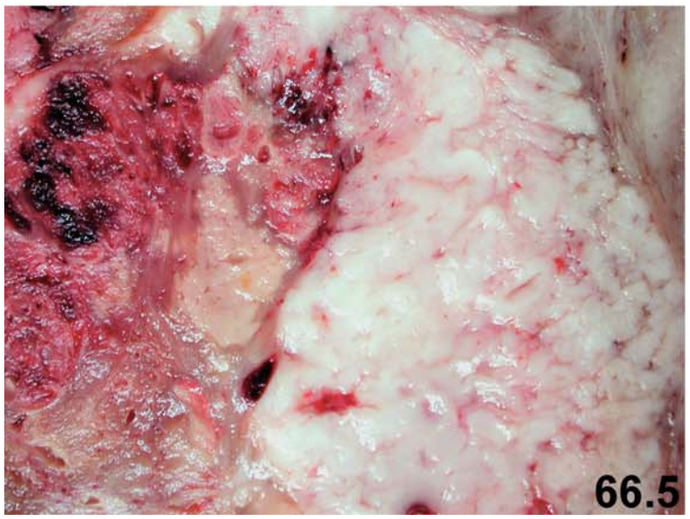
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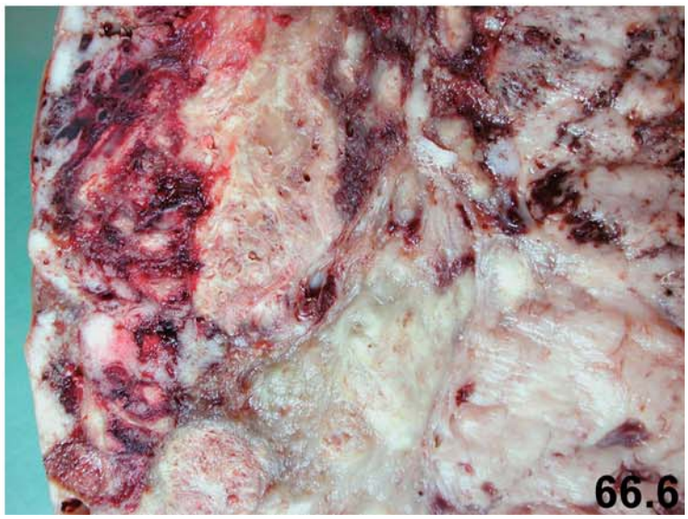
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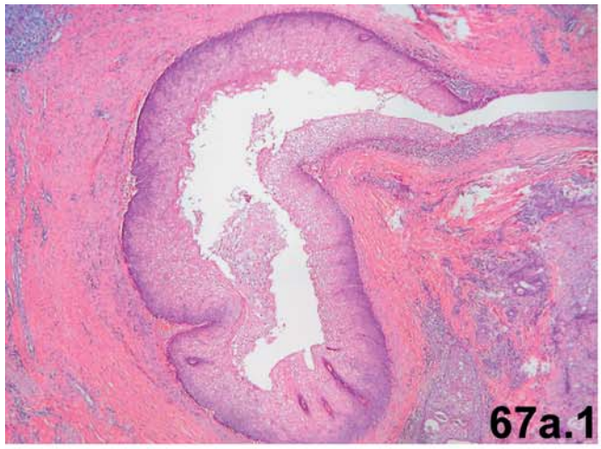
Fig. 67a: Adenosquamous carcinoma.

Case history: A 65-year-old woman presented with a palpable, firm mass in the lower, outer quadrant of her right breast. Mammography and ultrasonography showed a partly cystic tumor with a diameter of 3 cm. Excisional biopsy was performed.

Figs. 67a.1 and **67a.2:** At low magnification, the tumor shows multiple cystically dilated ducts which are lined by squamous cells. A periductal lymphocytic infiltration is present.

Figs. 67a.3 and **67a.4:** Higher magnification of the cysts reveals multiple layers of metaplastic squamous cells. Note the absence of cytological atypia within the squamous epithelium.

Figs. 67a.5, 67a.6, 67a.7, and **67a.8:** In addition to the cystically dilated ducts, several areas of early stromal invasion are present. These areas are <1 mm in diameter (multiple foci of microinvasion). Note the irregularity of infiltrating squamous cells. Small aggregates of invasive squamous carcinoma are characterized by deeply eosinophilic (keratinized) tumor cells.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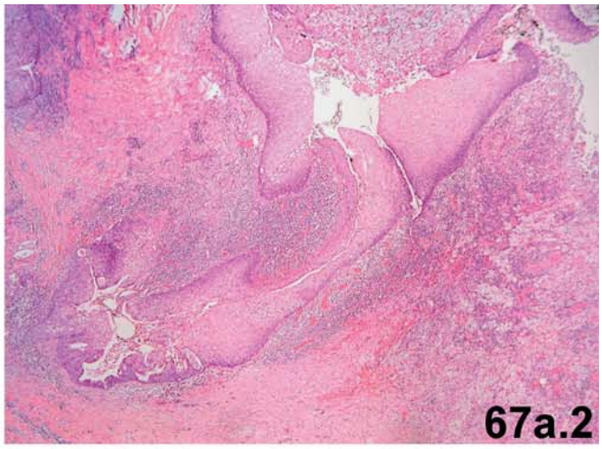
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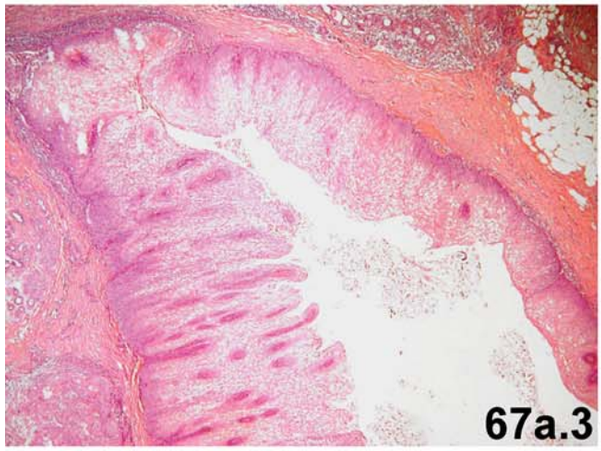
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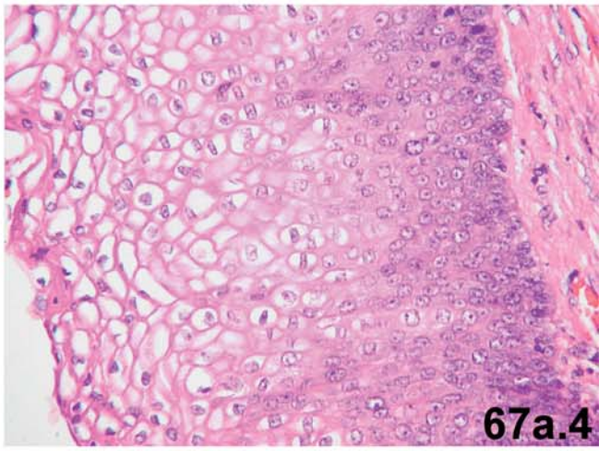
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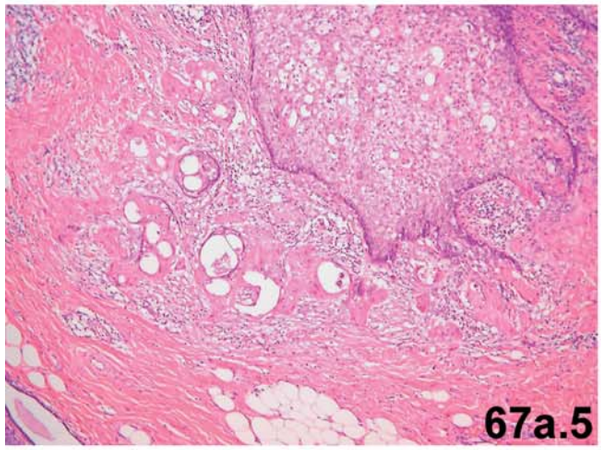
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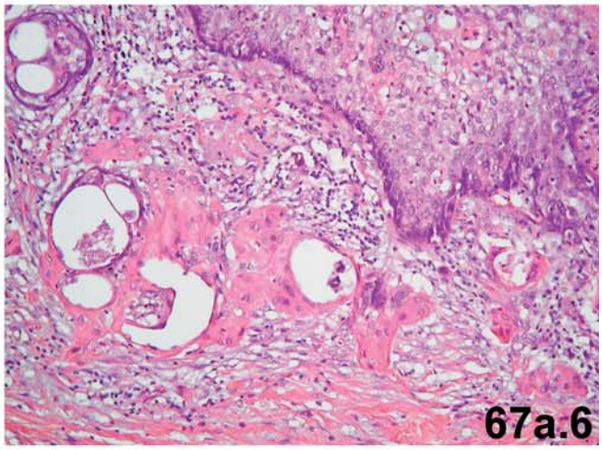
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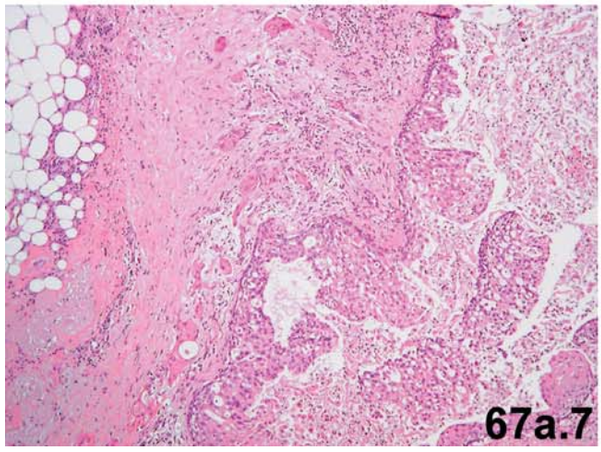
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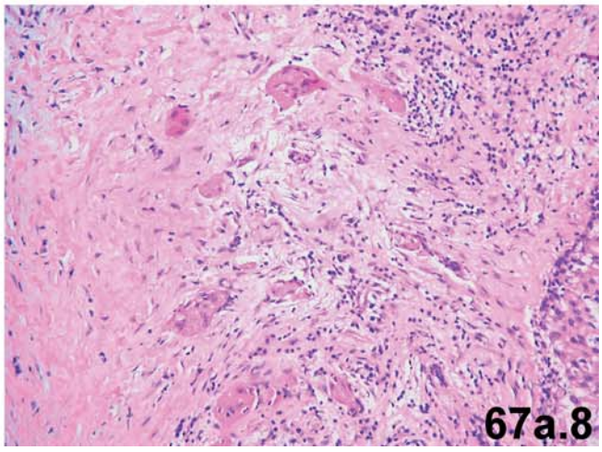
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Figs. 67a.9 and **67a.10:** In other areas of the tumor and in addition to the multiple foci of microinvasive carcinoma (invasion <1 mm in diameter), there are larger areas of infiltrating squamous cell carcinoma (with a maximum diameter of 1 cm).

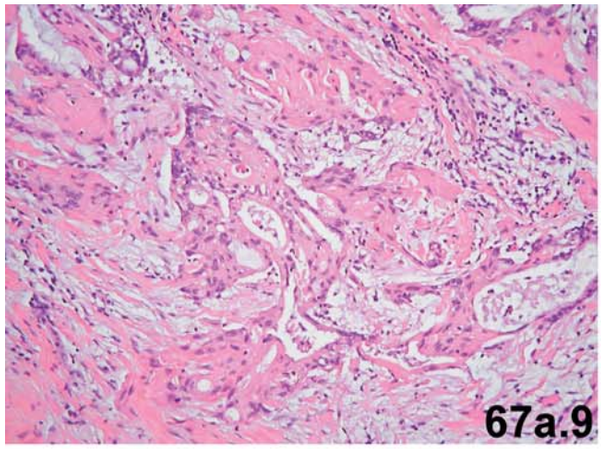
Figs. 67a.11 and **67a.12:** A close examination of the cystically dilated ducts with extensive squamous metaplasia reveals a second type of metaplastic cells that shows mucinous differentiation.

Figs. 67a.13 and **67a.14:** Another area of the tumor showing an infiltrating carcinoma composed of squamous and mucinous cells. Note the absence of cytological atypia and lack of mitotic activity. Some of the infiltrating adenosquamous structures, however, contain apoptotic bodies in the lumens. These areas with infiltrating growth pattern resemble a mucoepidermoid carcinoma of salivary glands.

Figs. 67a.15 and **67a.16:** Regular axillary lymph node dissection was performed in this case, revealing a total number of 23 lymph nodes. One lymph node of these 23 showed metastasis of adenosquamous carcinoma. Note the presence of benign-looking mucinous cells within the clusters of squamous epithelial cells (Fig. 67a.16).

Fig. 67a: Final remarks

- This case demonstrates an example of adenosquamous cell carcinoma of the breast. This is a variant of well-differentiated metaplastic carcinoma with prominent squamous cell differentiation.
- The intraepithelial or noninvasive component of mammary squamous cell carcinoma often shows cystically dilated ducts that are lined by metaplastic squamous cells without significant cytologic atypia or increased mitotic activity.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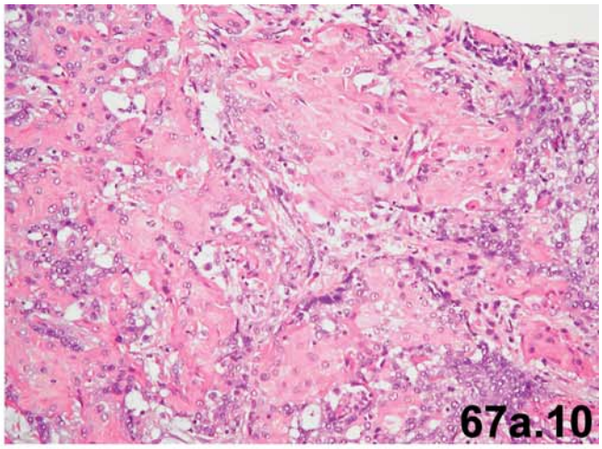
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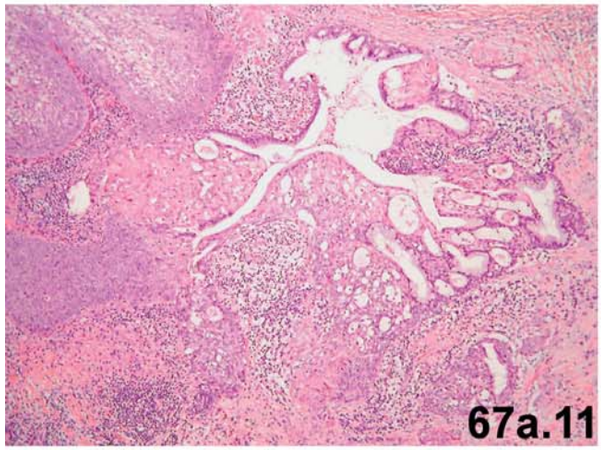
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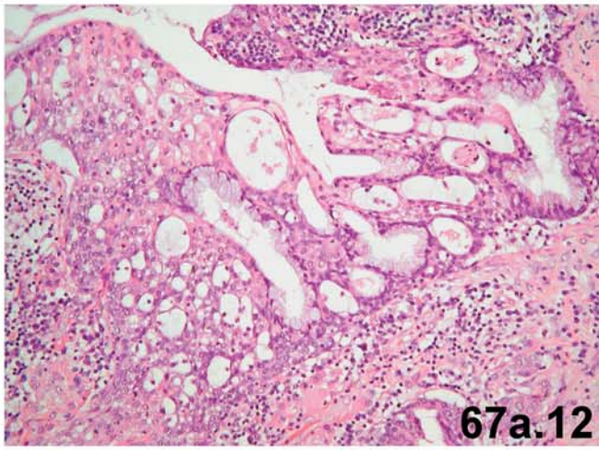
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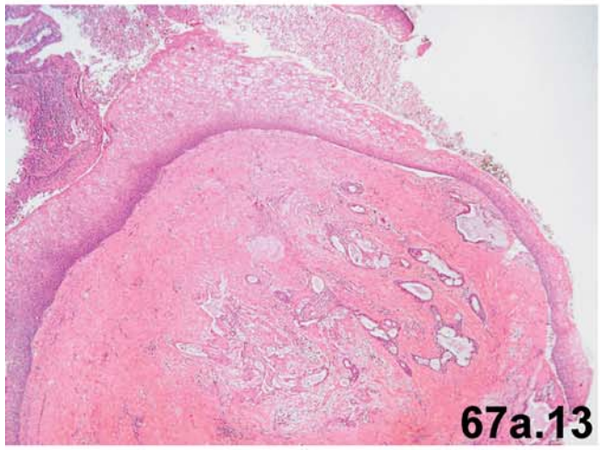
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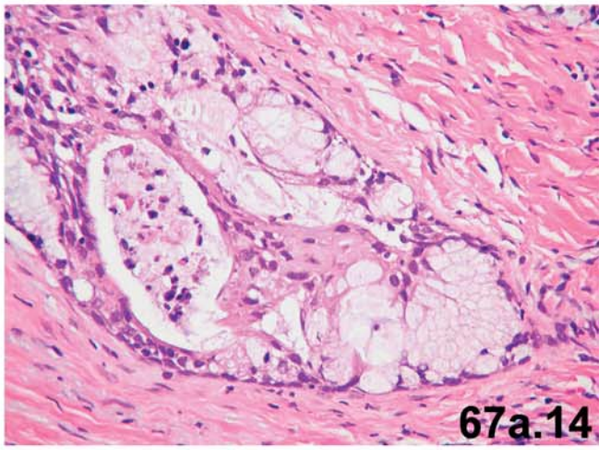
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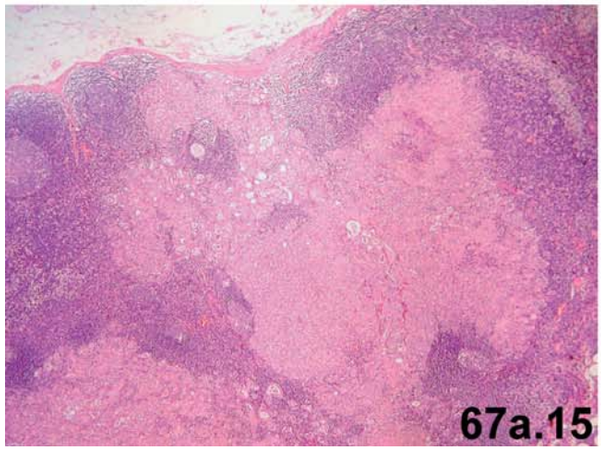
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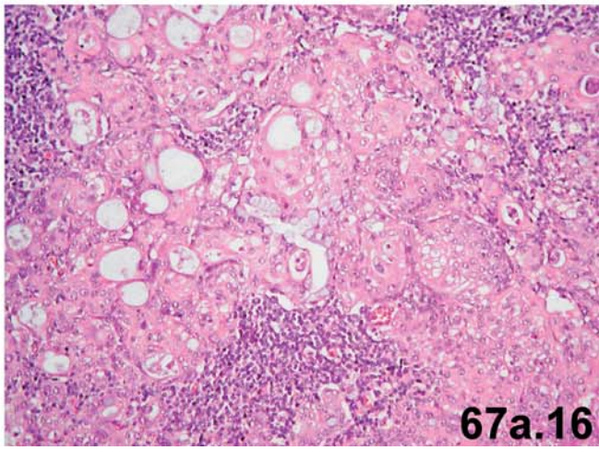
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Fig. 67b: Poorly differentiated squamous cell carcinoma.

Case history: A 53-year-old woman presented with a large (10 cm) well-circumscribed tumor in her left breast. Core needle biopsy showed a poorly differentiated infiltrating carcinoma. Modified radical mastectomy was performed.

Fig. 67b.1: The cut surface of the mastectomy specimen shows a well-circumscribed greyish-white solid tumor measuring 10 cm in greatest diameter.

Fig. 67b.2: The tumor is composed of irregular and infiltrating solid epithelial clusters.

Fig. 67b.3: Solid tumor aggregates showing cells with highly atypical nuclei.

Fig. 67b.4: Several other areas of the tumor show uniform cells without significant nuclear atypia. The tumor cells show large cytoplasm with distinct cytoplasmic borders. Several areas of the tumor show squamous cells with clear or pale cytoplasm.

Fig. 67b.5: Uniform tumor cells admixed with highly atypical epithelial cells with bizarre, hyperchromatic nuclei and abundant eosinophilic cytoplasm.

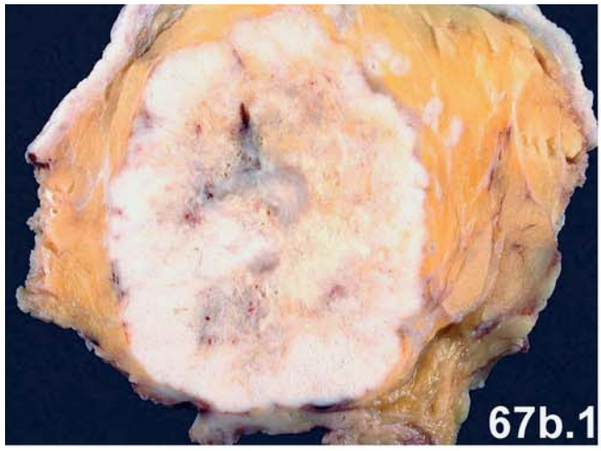
Fig. 67b.6: Immunohistochemistry for CK34BE12 shows a positive reaction in tumor cells with squamous differentiation.

Fig. 67b.7: Immunohistochemistry for CK5/6 reveals a positive reaction in the cell membrane of the tumor cells with squamous differentiation.

Fig. 67b.8: Immunohistochemistry for involucrin, a useful marker for squamous differentiation, shows tumor cells with positive cytoplasmic reaction.

Fig. 67: Final remarks

- This case represents an example of poorly differentiated, large-cell, nonkeratinizing squamous cell carcinoma of the breast. The results of immunohistochemistry in this case support the morphological impression of squamous cell carcinoma.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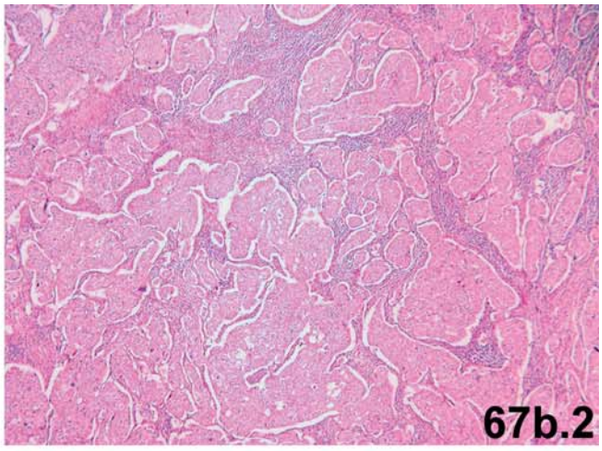
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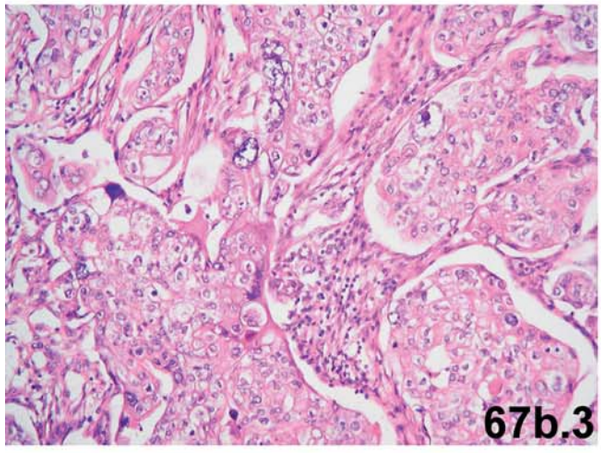
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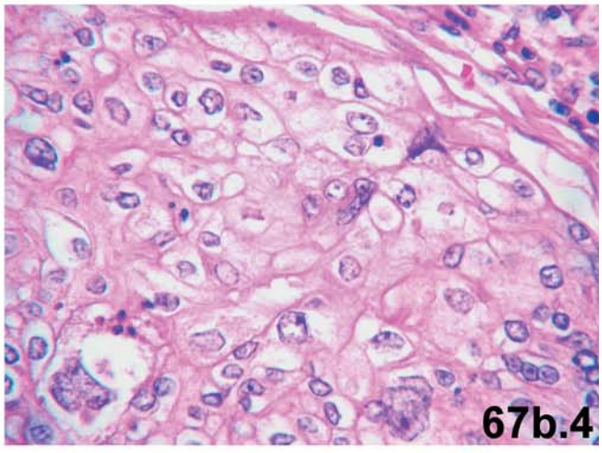
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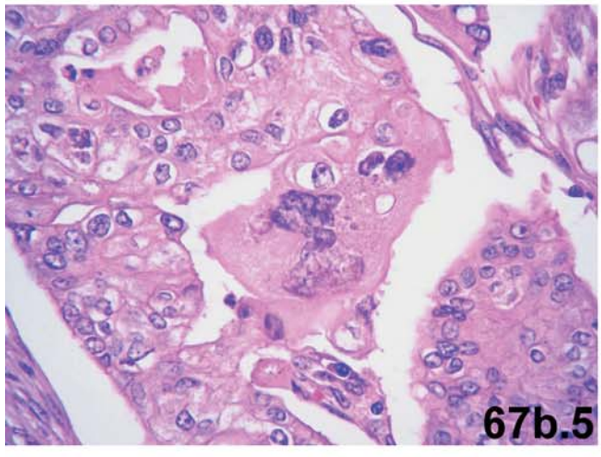
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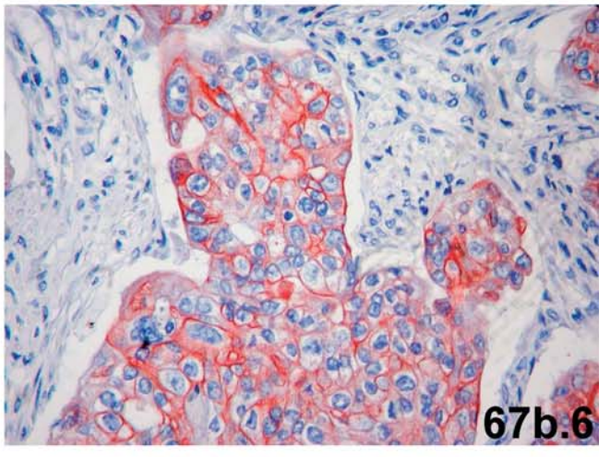
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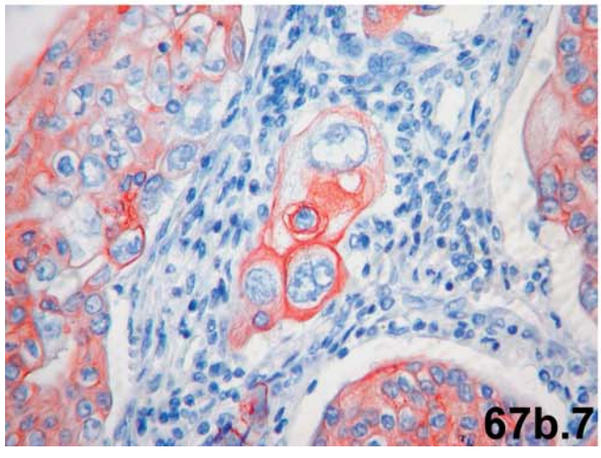
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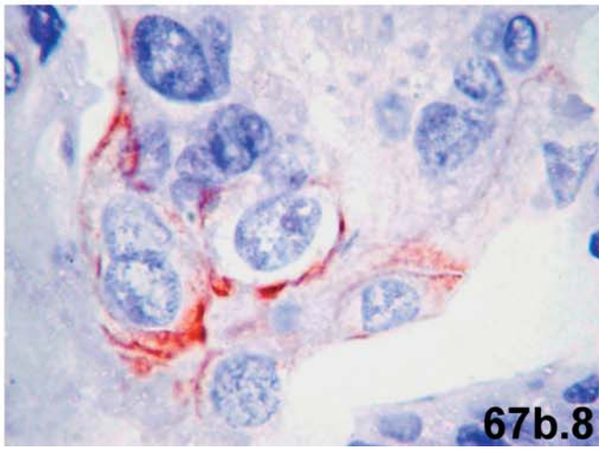

67b.8

Fig. 68: Squamous cell carcinoma, acantholytic variant.

Case history: A woman (80-year-old) presented with bloody nipple discharge and a very large tumor in her left breast.

Fig. 68.1: Gross appearance of the mastectomy specimen, showing solid and cystic areas with luminal projections.

Fig. 68.2: One of the cystic areas of the tumor lined by a few layers of epithelial cells.

Figs. 68.3 and **68.4:** Another cystic area lined by bland-looking squamous cells.

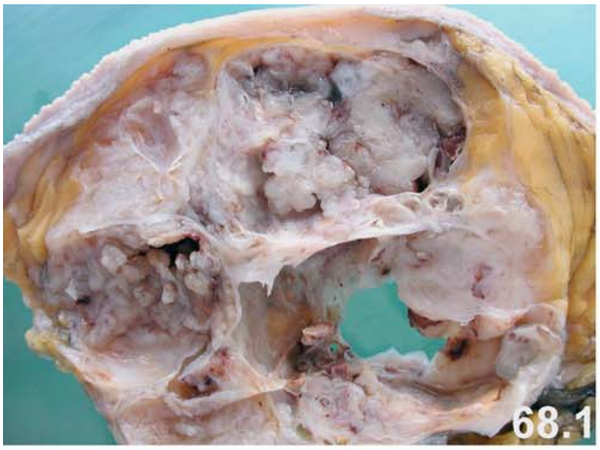
Figs. 68.5 and **68.6:** Several areas of the tumor display an admixture of spindle cells and empty spaces or spongiotic foci forming irregular channels. The anastomosing channels closely simulate a vascular tumor.

Fig. 68.7: The channels are either empty or show aggregates of squamous cells.

Fig. 68.8: The channels or empty spaces are lined by cells closely mimicking atypical endothelial cells (pseudoangiosarcomatous growth pattern).

Fig. 68: Final remarks

- This case shows an example of acantholytic variant of squamous cell carcinoma. The anastomosing channels and empty spaces in this variant of squamous cell carcinoma can easily be confused with a vascular neoplasm, particularly an angiosarcoma. A closer examination of empty spaces, however, reveals aggregates of squamous cells in many areas. The anastomosing channels are immunohistochemically negative for endothelial markers but typically positive for CK34BE12 or CK5/6.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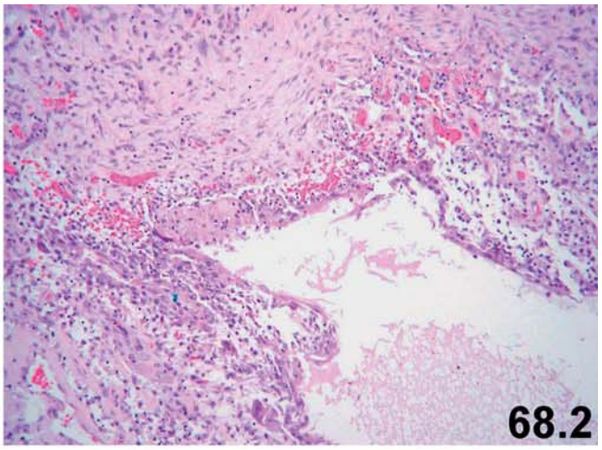
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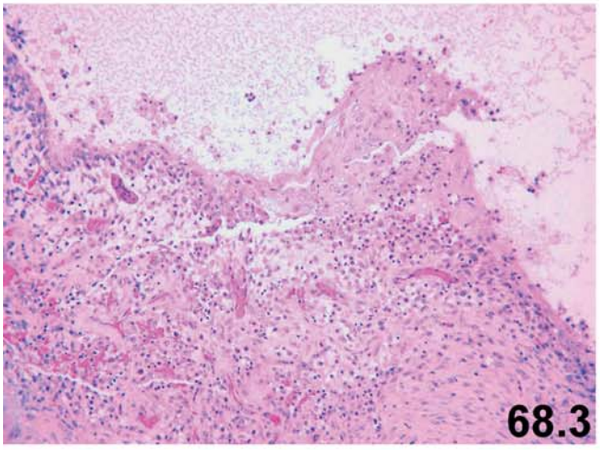
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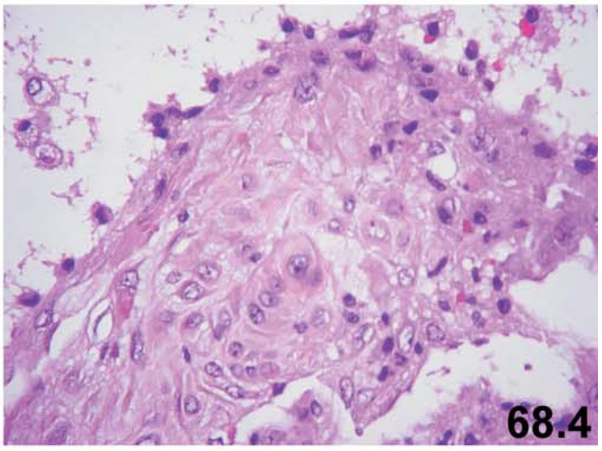
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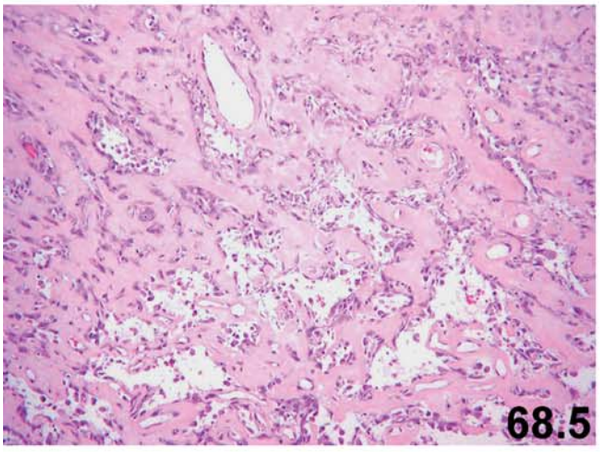
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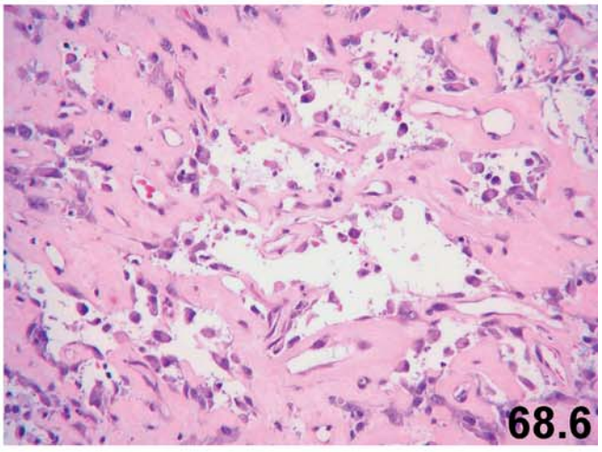
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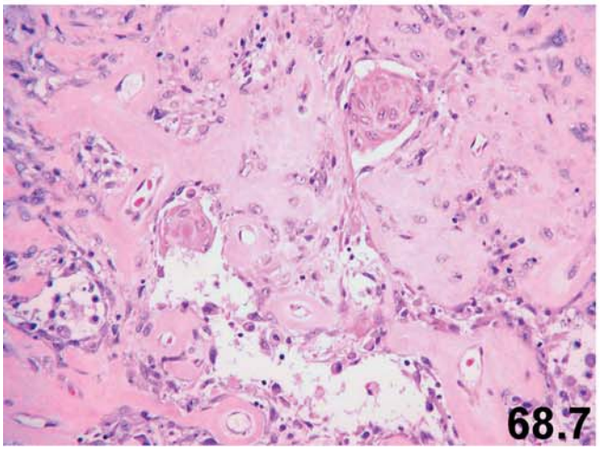
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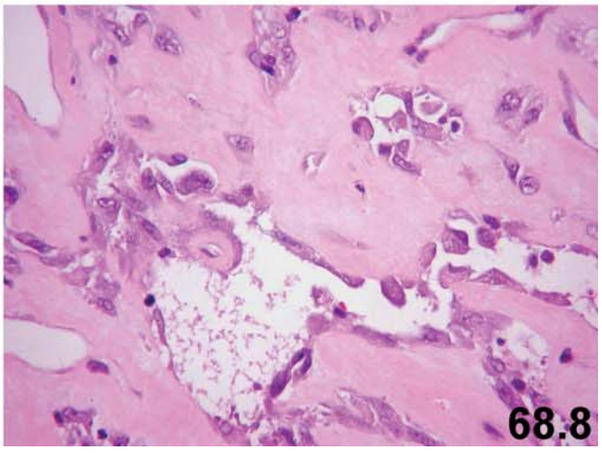

68.8

Fig. 69: Sarcomatoid (metaplastic) carcinoma.

Case history: A 30-year-old woman presented with a lobulated firm tumor in the lower inner quadrant of her left breast. Clinically and mammographically, the tumor was interpreted as fibroadenoma. However, its size increased significantly during 2 years of follow-up.

Fig. 69.1: The cut surface of the lesion shows a lobulated, well-circumscribed, greyish-white to yellow tumor.

Fig. 69.2: The tumor shows a pushing margin. In several sections of the tumor, no infiltrating tumor borders could be identified.

Fig. 69.3: The tumor is composed of spindle cells showing a plexiform growth pattern.

Fig. 69.4: Many areas of the tumor reveal spindle cells with fascicular arrangements.

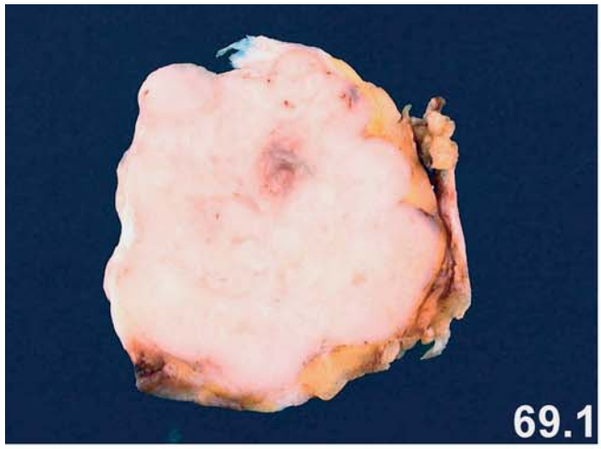
Figs. 69.5 and **69.6:** Higher magnification of the tumor exhibits tumor cells with elongated, hyperchromatic nuclei.

Fig. 69.7: Some areas of the tumor reveal spindle cells with significant nuclear atypia.

Fig. 69.8: Immunohistochemistry for CK5/6 shows a positive but heterogeneous reaction of spindle cells. Immunohistochemistry for smooth muscle actin and CD10 was also positive (not shown).

Fig. 69: Final remarks

- The differential diagnosis in this case should include stromal overgrowth of a phylloides tumor and sarcoma of NOS type. The positive immunoreaction for CK5/6 excludes the possibility of sarcoma. Even after extensive sampling of the tumor, no biphasic tumor could be identified (exclusion of stromal overgrowth of a phylloides tumor).
- This case demonstrates that sarcomatoid (metaplastic) carcinoma can be well circumscribed.
- Sarcomatoid (metaplastic) carcinoma often shows positive immunoreactions for basal type or high molecular weight cytokeratins (CK5/6, CK14, CK17, CK34BE12) and myoepithelial markers (smooth muscle actin, p63, CD10, CD29, etc.).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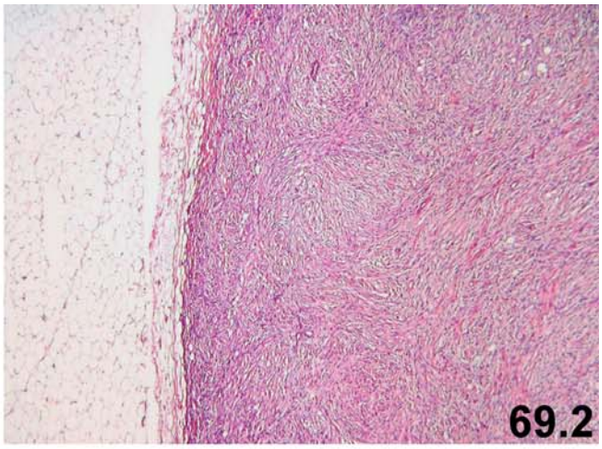
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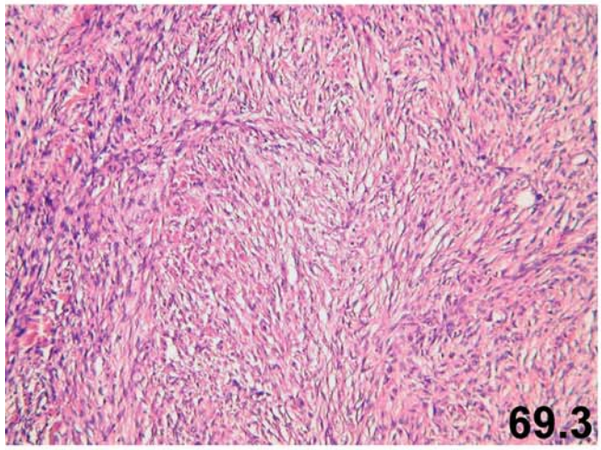
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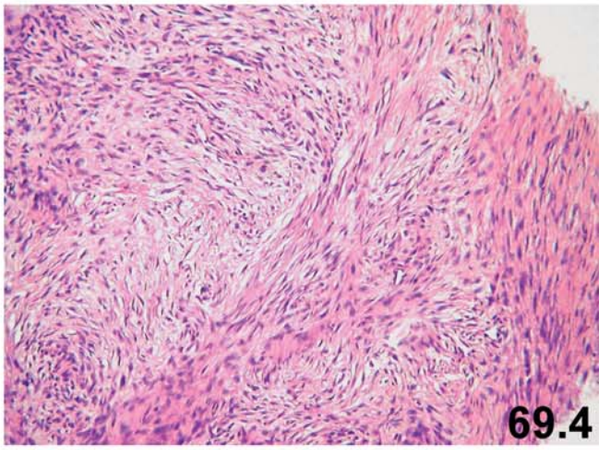
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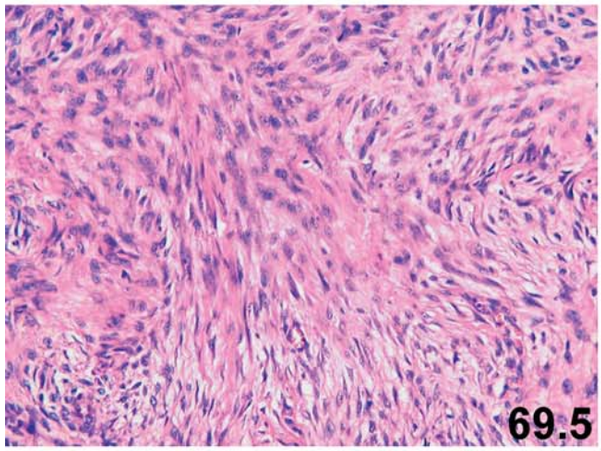
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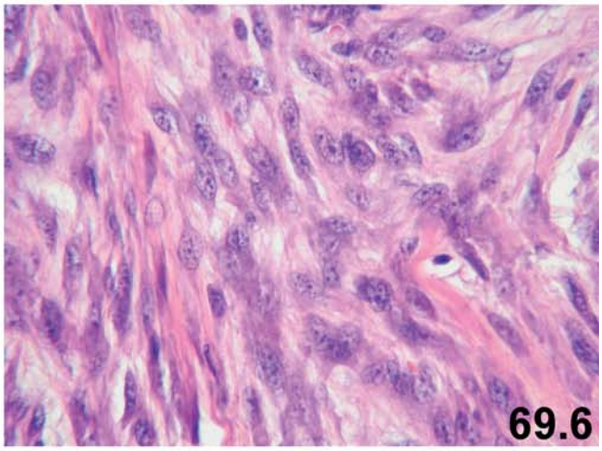
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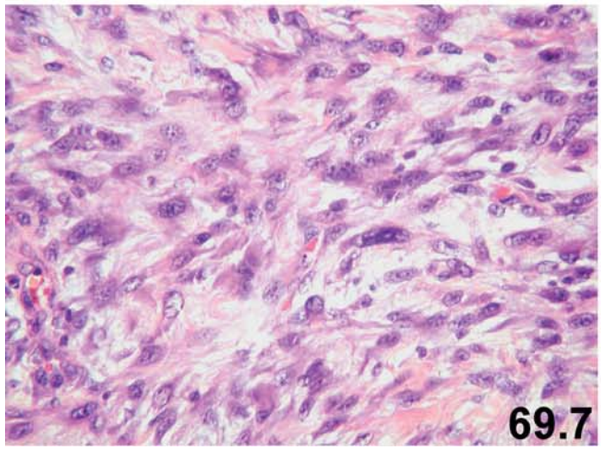
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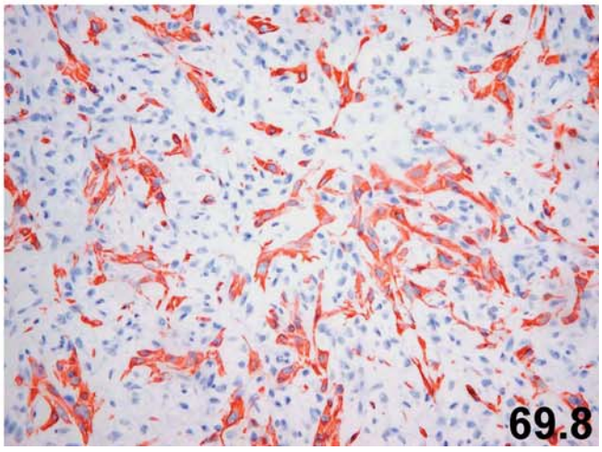

69.8

Fig. 70: Metaplastic carcinoma (with basal-like and myoepithelial differentiation).

Case history: A 74-year-old woman presented with a hard, irregular tumor in the upper outer quadrant of her left breast. The tumor was clinically and mammographically highly suspicious for malignancy.

Fig. 70.1: Excisional biopsy shows an infiltrating tumor with cordlike or trabecular structures.

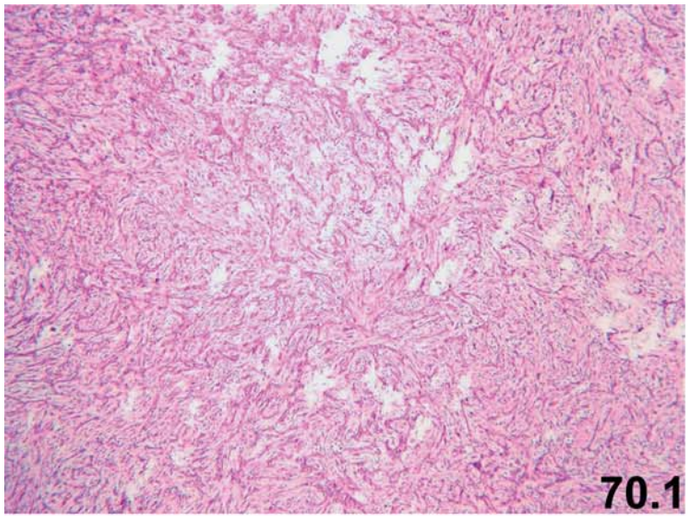
Fig. 70.2: The tumor is composed of epithelial cells showing a fascicular or trabecular growth pattern.

Fig. 70.3: Anastomosing fascicles showing uniform epithelial cells without significant nuclear atypia.

Fig. 70.4: Higher magnification of the tumor reveals cells with round-ovoid nuclei and scant eosinophilic cytoplasm.

Fig. 70.5: Immunohistochemistry for CD10 displays a diffuse and intense positive reaction of tumor cells.

Fig. 70.6: The tumor cells are positive for smooth muscle actin.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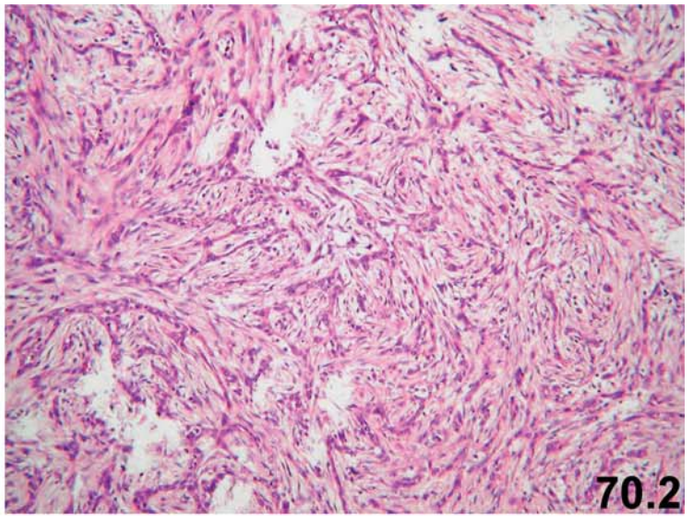
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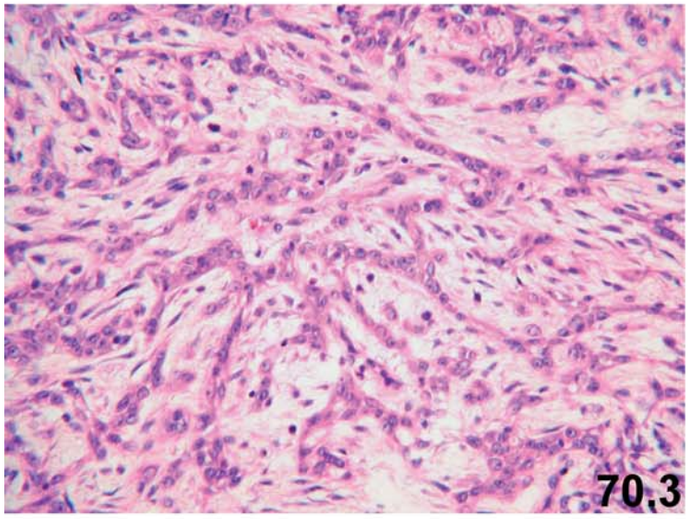
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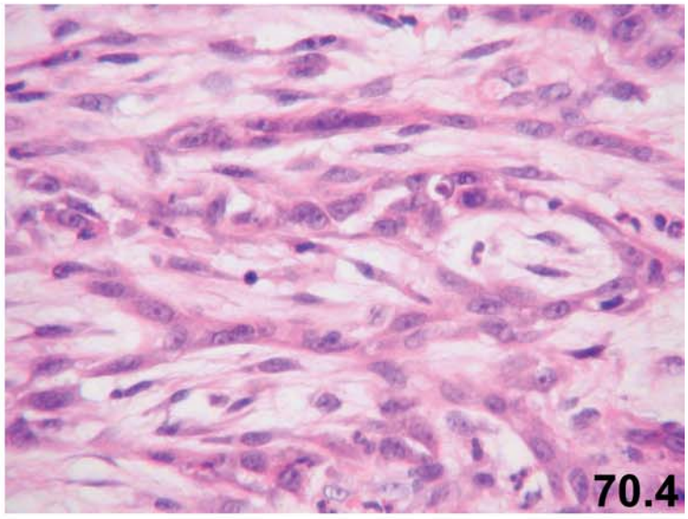
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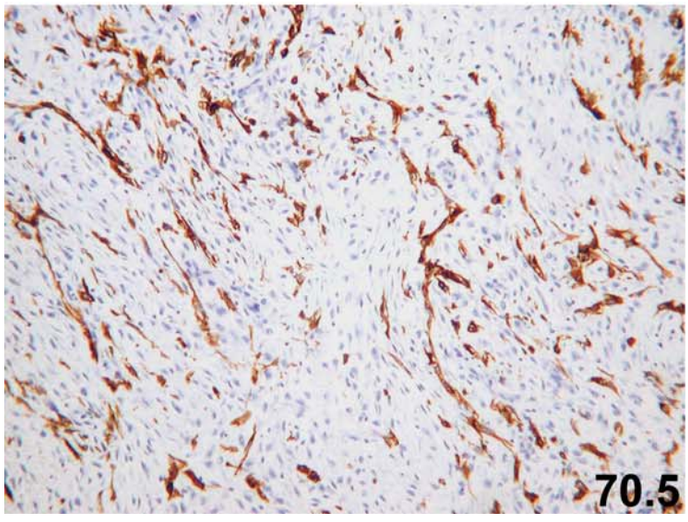
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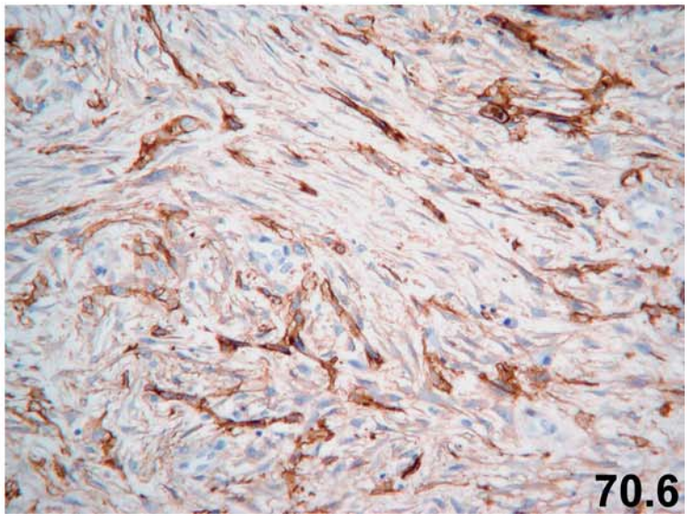

70.6

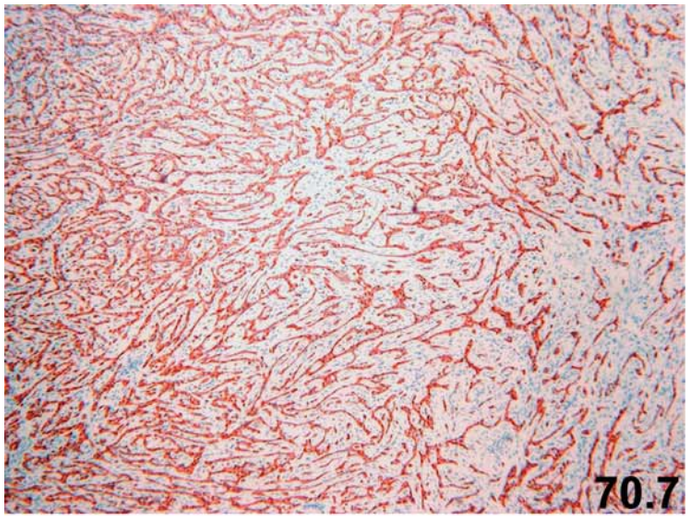
Figs. 70.7 and **70.8:** The tumor cells show a diffuse and intense immunoreaction for CK5/6.

Figs. 70.9 and **70.10:** Immunohistochemistry for S100 protein showing a diffuse reaction of tumor cells.

Figs. 70.11 and **70.12:** Many areas of the tumor also reveal a positive immunoreaction for CD29, which is a myoepithelial marker.

Fig. 70: Final remarks

- This case demonstrates metaplastic carcinoma with an unusual cordlike or fascicular growth pattern. As other variants of metaplastic or sarcomatoid breast carcinomas, the tumor cells in this case show positive immunoreaction for several myoepithelial and basal-type cytokeratins. Indeed, the vast majority of metaplastic or sarcomatoid carcinoma of the breast show myoepithelial differentiation. While some investigators would probably classify this case as myoepithelial carcinoma (malignant myoepithelioma), others may want to call it basal-like carcinoma.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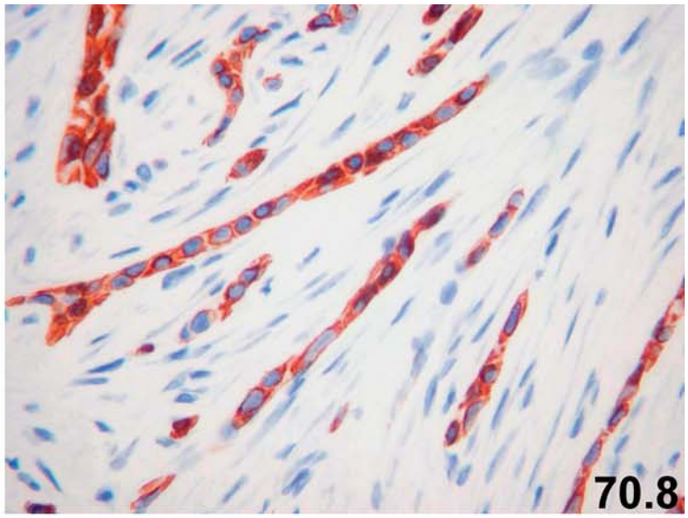
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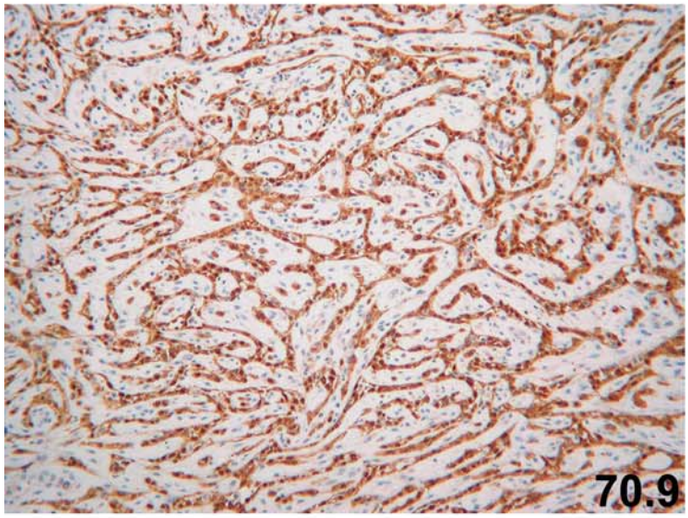
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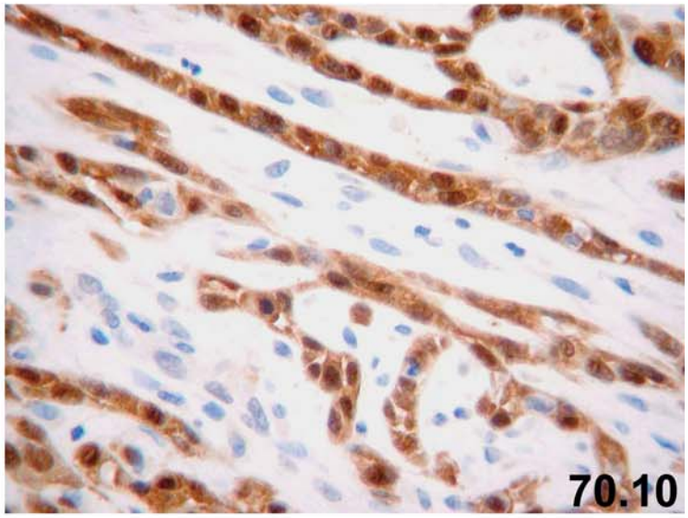
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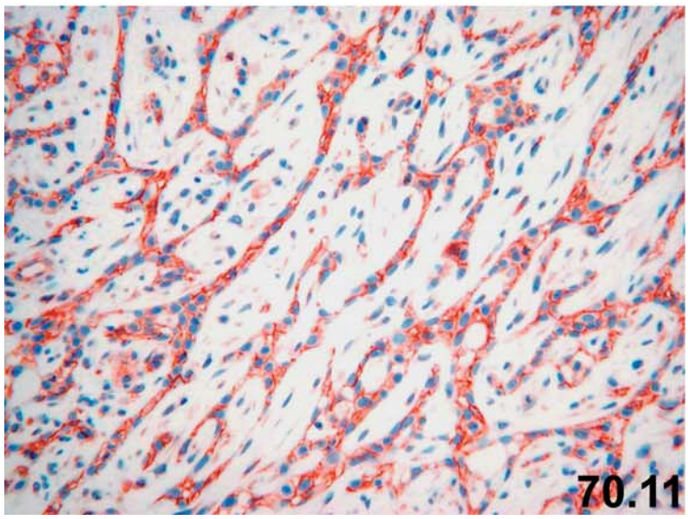
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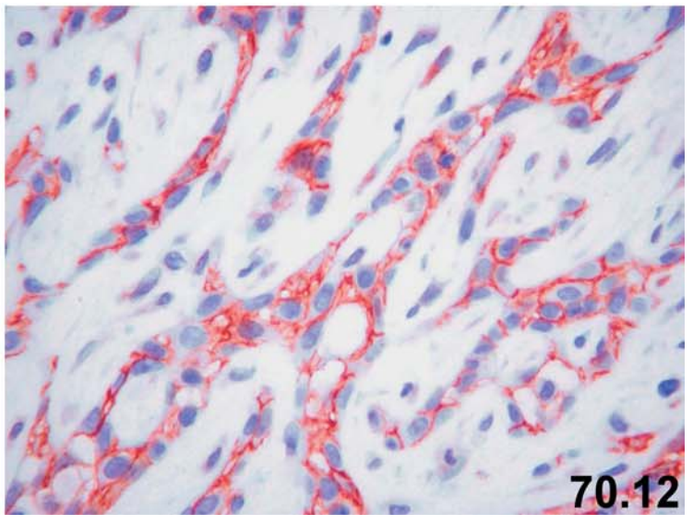

70.12

Fig. 71: Carcinosarcoma.

Case history: A 62-year-old woman presented with a right breast mass. Core needle biopsy revealed a poorly differentiated carcinoma. Because of the tumor's large size, a modified radical mastectomy was done.

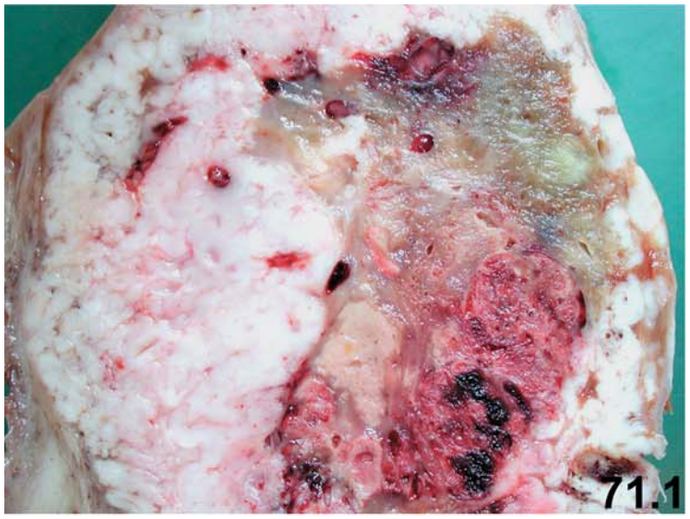
Fig. 71.1: The cut surface of the mastectomy specimen shows a tumor with greyish-white areas admixed with gelatinous or necrotic-hemorrhagic areas. The tumor was 14 cm in greatest diameter.

Fig. 71.2: Imprint cytology of the tumor reveals a cohesive cluster of cells with round to ovoid nuclei and scant cytoplasm (Papanicolaou stain).

Fig. 71.3: Imprint cytology showing highly atypical spindle cells with hyperchromatic nuclei (Papanicolaou stain).

Fig. 71.4: Imprint cytology displaying an anaplastic, multinucleated giant tumor cell. Note the irregularity of nuclear membrane and chromatin distribution.

Figs. 71.5 and **71.6:** Frozen section showing extremely atypical cells with bizarre nuclei.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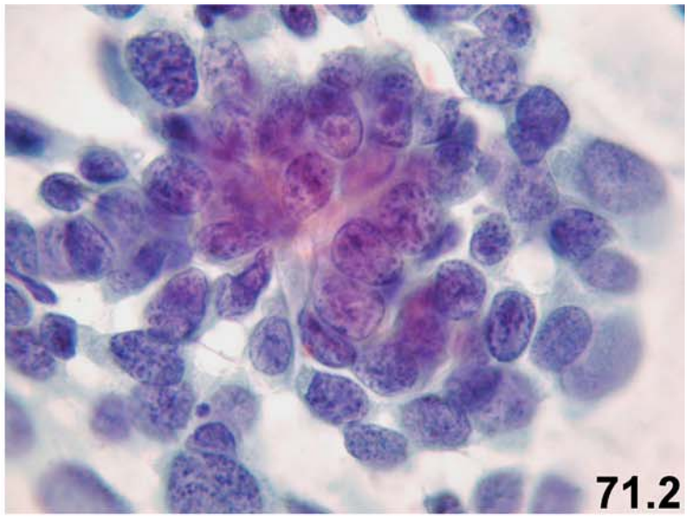
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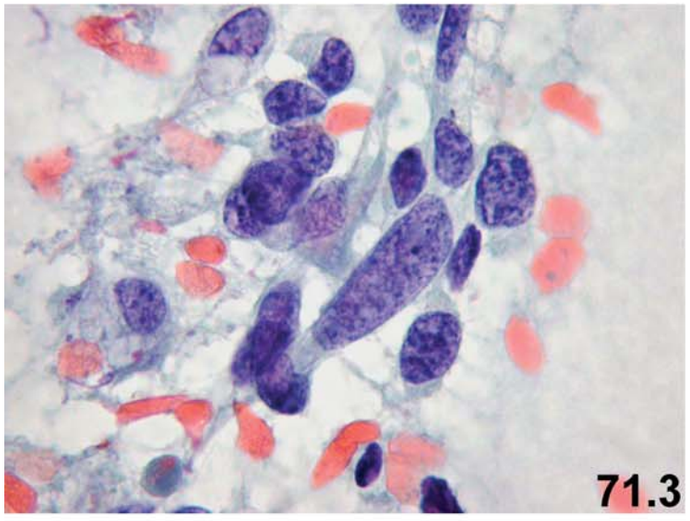
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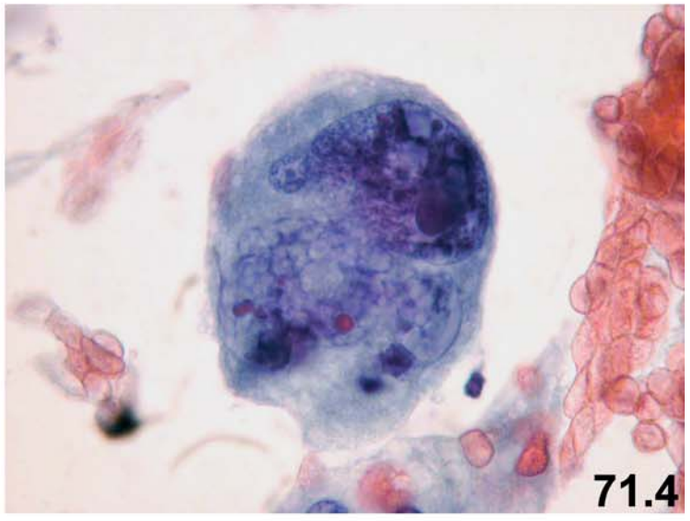
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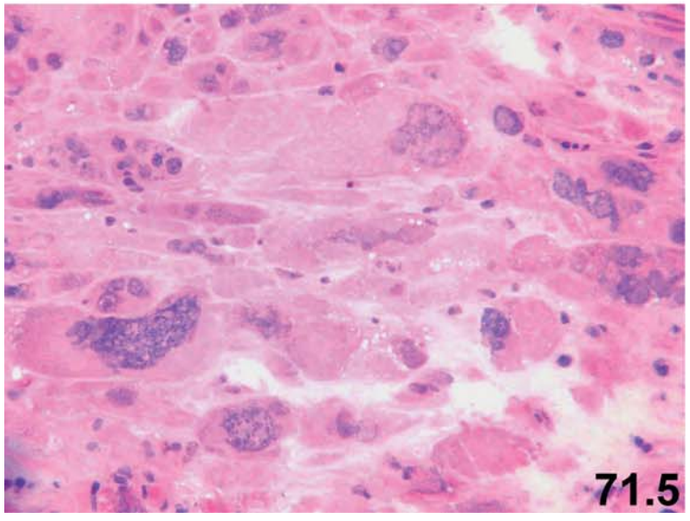
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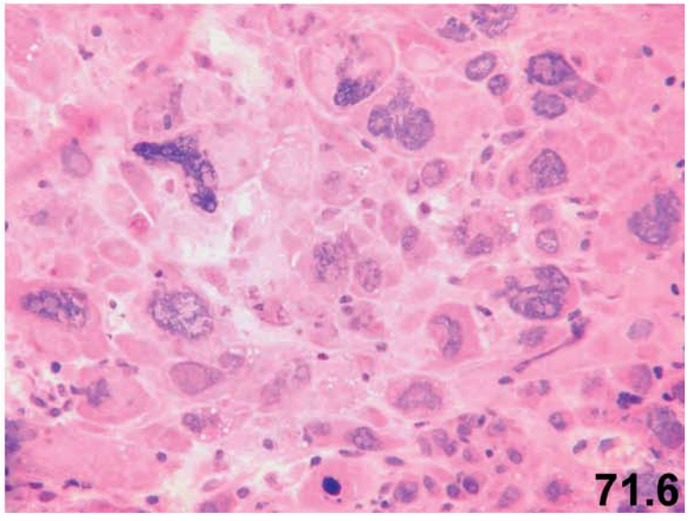
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Figs. 71.7, 71.8, and **71.9:** Permanent hematoxylin and eosin sections of the tumor showing a biphasic appearance composed of malignant epithelial and mesenchymal components

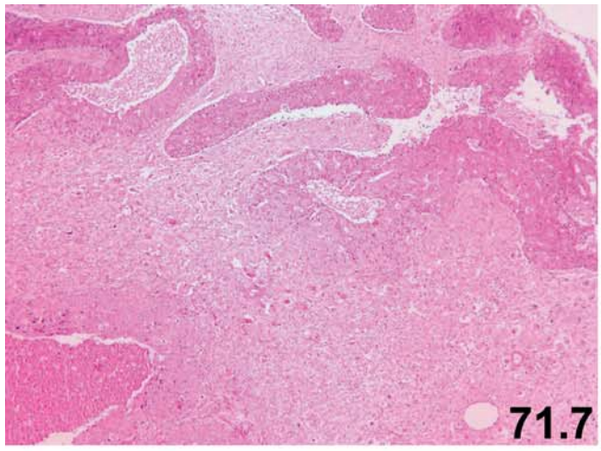
Fig. 71.10: The mesenchymal component of the tumor reveals highly atypical cells with bizarre nuclei.

Fig. 71.11: Highly atypical sarcomatoid tumor cells with hyperchromatic nuclei. Some of the tumor cells show intranuclear inclusions.

Fig. 71.12: Immunohistochemistry for pancytokeratin is positive in the carcinomatous component but negative in the sarcomatous component.

Fig. 71.13: Immunohistochemistry for smooth muscle actin displays a diffuse positivity in the sarcomatous tumor component. Note the negative reaction in the epithelial part of the tumor.

Fig. 71.14: Immunohistochemistry for CD10 shows an intense positive reaction in the sarcomatous part of the tumor.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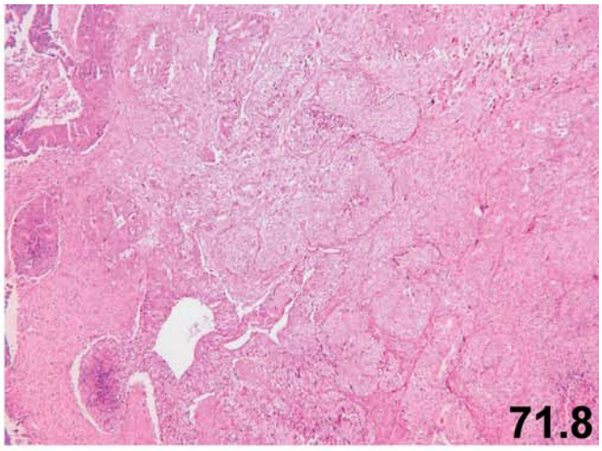
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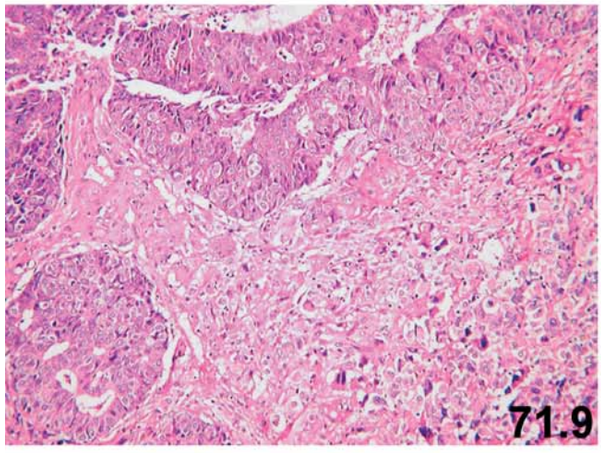
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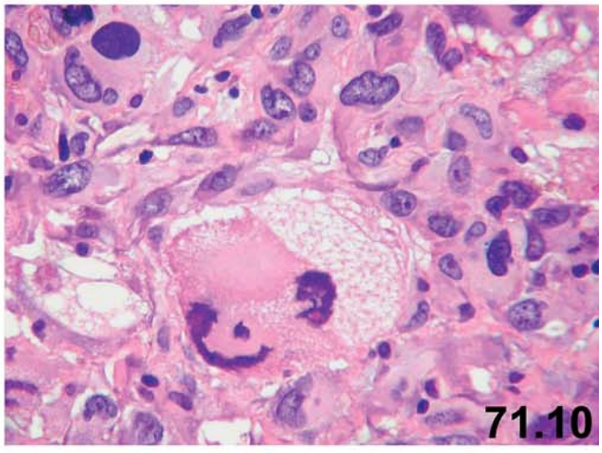
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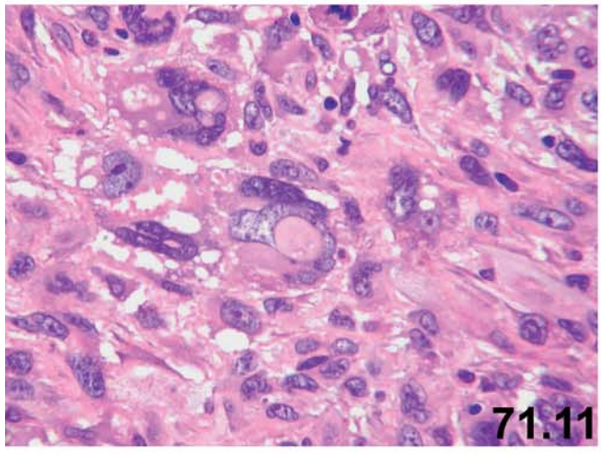
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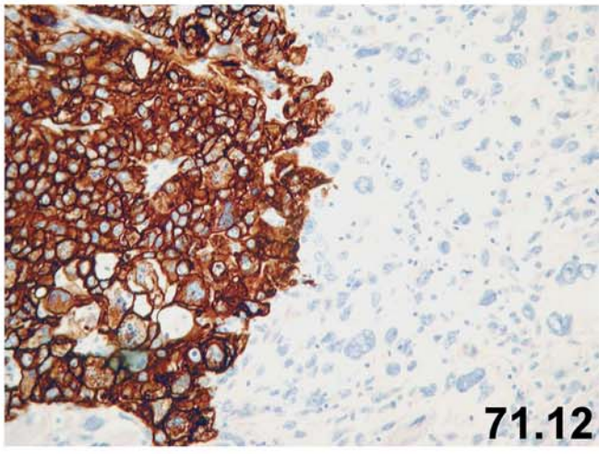
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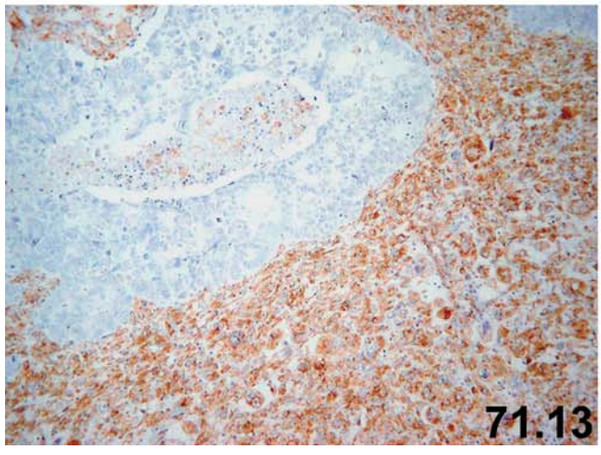
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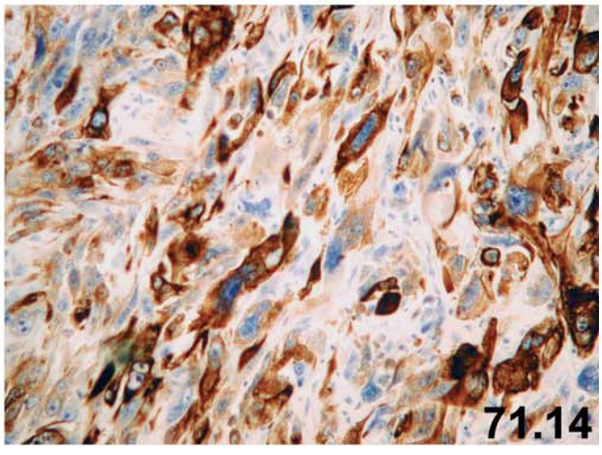
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Figs. 71.15 and **71.16:** Immunohistochemistry for EGFR (HER1) in the sarcomatous component of the tumor show a positive reaction (2+ to 3+). The immunoreaction for HER2/neu was, however, completely negative (not shown).

Fig. 71.17: Immunohistochemistry for p63 shows positive reactivity in the carcinomatous component.

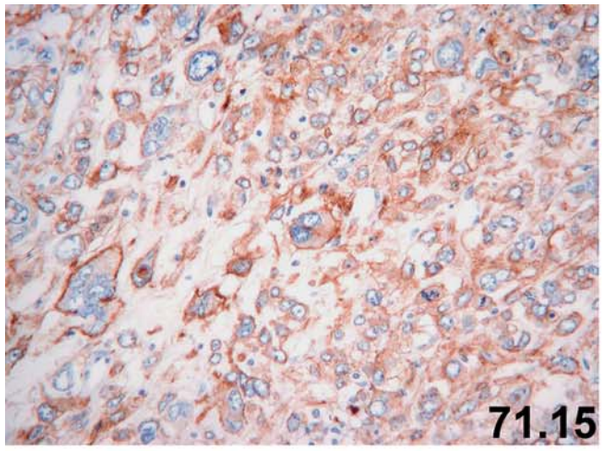
Fig. 71.18: Some areas with sarcomatous differentiation are also positive for p63.

Figs. 71.19 and **71.20:** Comparison between histology (Fig. 71.19) and imprint cytology (Fig. 71.20), demonstrating highly atypical or anaplastic tumor cells.

Figs. 71.21 and **71.22:** Comparison of highly atypical and pleomorphic tumor cells with irregular chromatin distribution in histologic sections (Fig. 71.21) and imprint cytology (Fig. 71.22).

Fig. 71: Final remarks

- This case shows an example of carcinosarcoma, another variant of metaplastic breast carcinoma. The highly malignant tumor cells show a divergent epithelial and mesenchymal differentiation. As other types of metaplastic or sarcomatoid breast carcinomas, the tumor cells in carcinosarcoma often show a myoepithelial cell differentiation. The epithelial cell component of the tumor may also be positive for basal-type cytokeratins such as CK5/6, CK14, or CK34BE12.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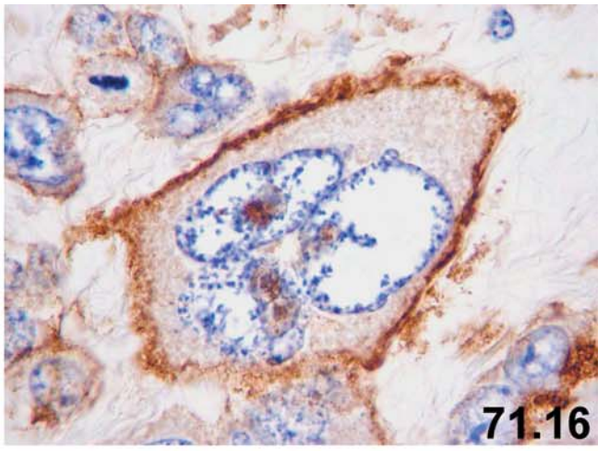
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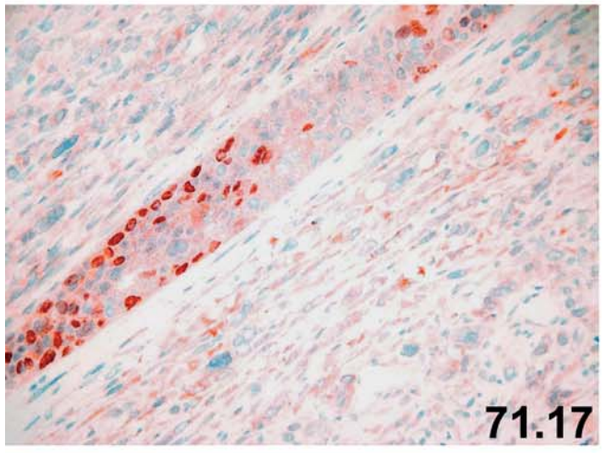
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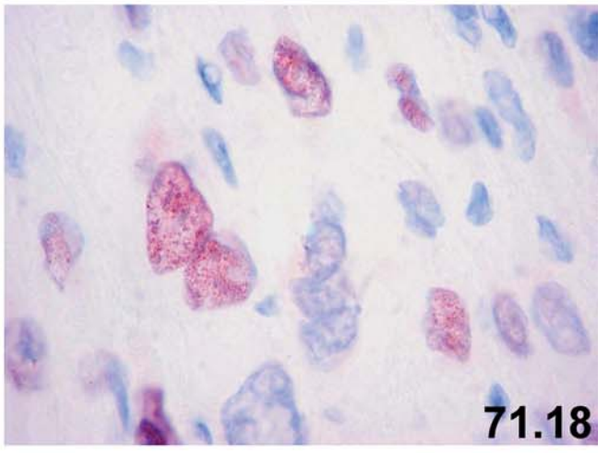
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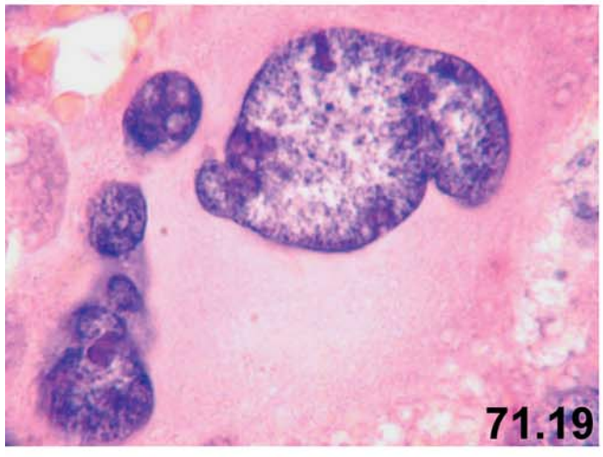
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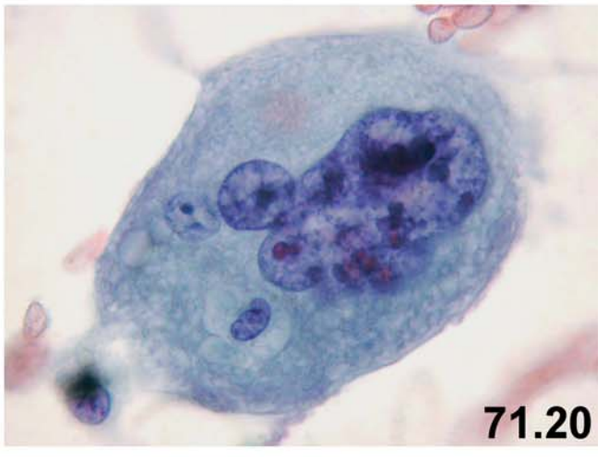
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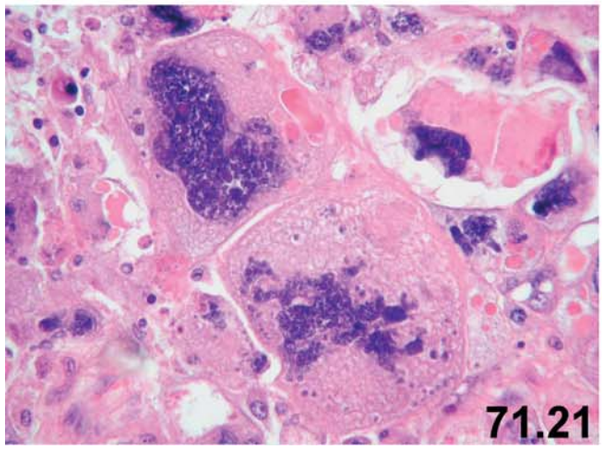
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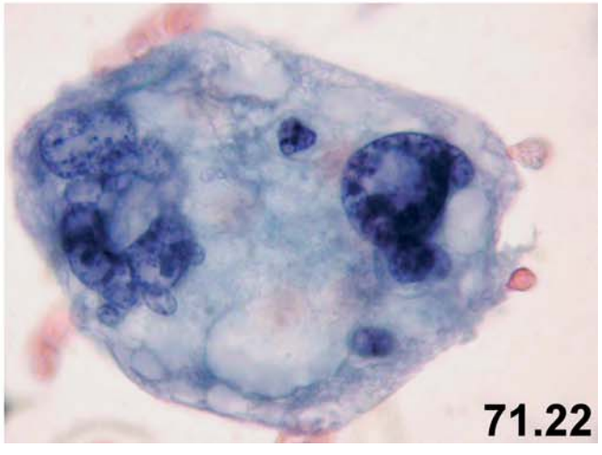

71.22

Fig. 72: Metaplastic carcinoma with prominent myxochondroid differentiation (matrix-producing carcinoma).

Case history: Routine screening mammogram was performed on a 58-year-old woman showing a well-circumscribed 2-cm tumor in her right breast. Excisional biopsy was performed.

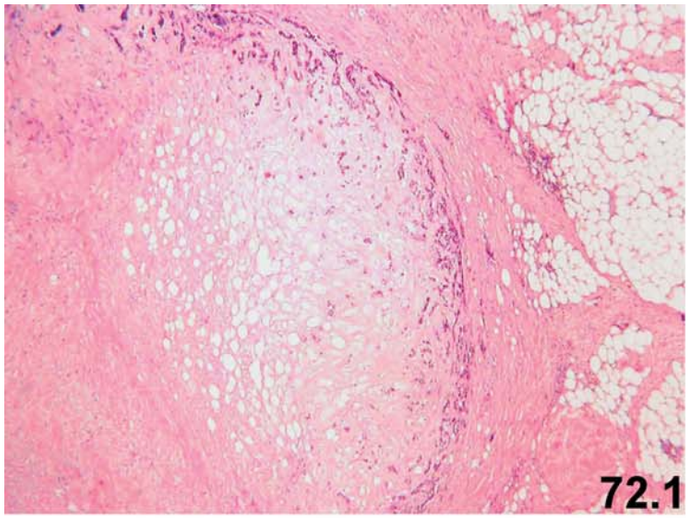
Fig. 72.1: Low magnification of the lesion shows a well-circumscribed tumor with a hypocellular central area.

Fig. 72.2: The periphery of the lesion is more cellular.

Fig. 72.3: The periphery of the tumor shows epithelial clusters with transition into more fibrotic and hypocellular central areas.

Fig. 72.4: Another area of the tumor showing irregular borders. The tumor cells are small and set in a myxoid stromal background.

Figs. 72.5 and **72.6:** Several areas of the tumor show a myxoid (myxochondroid) appearance.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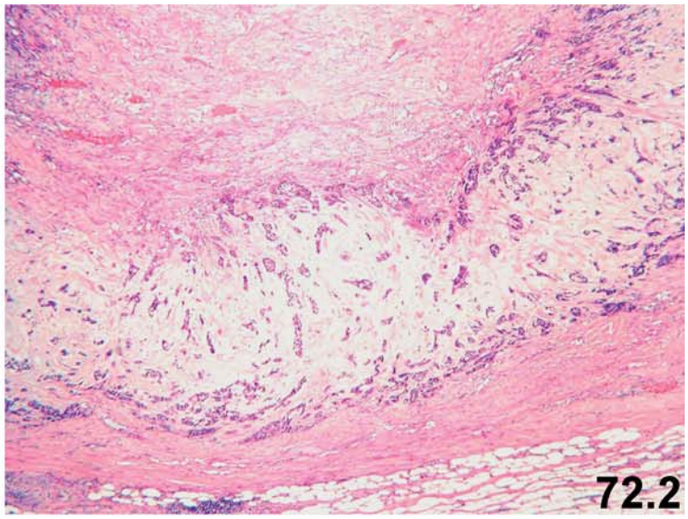
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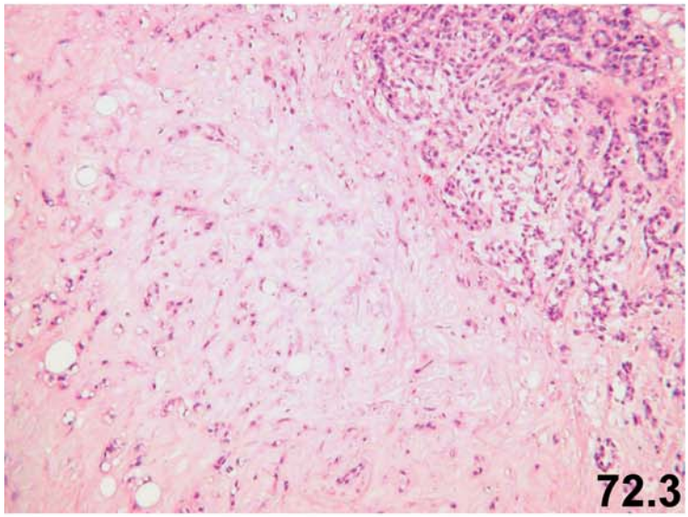
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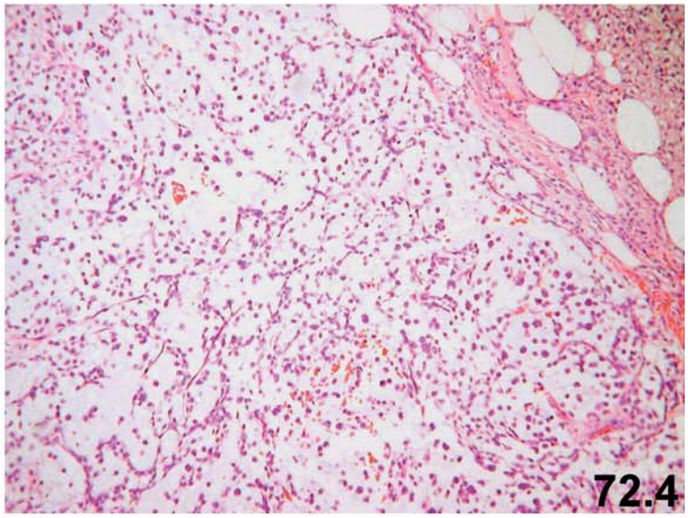
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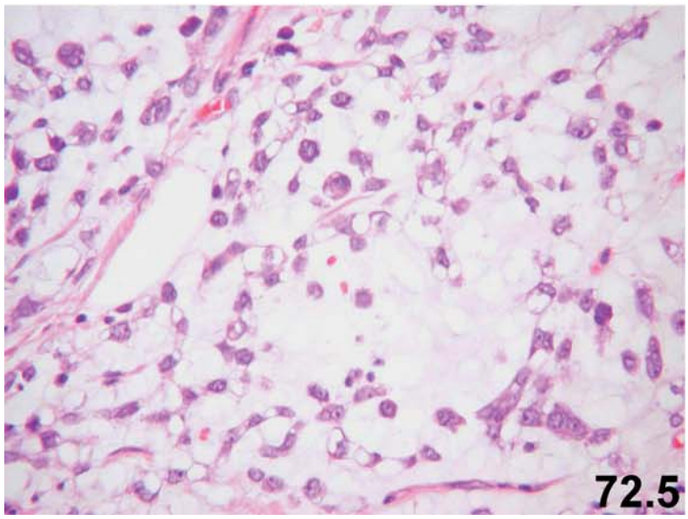
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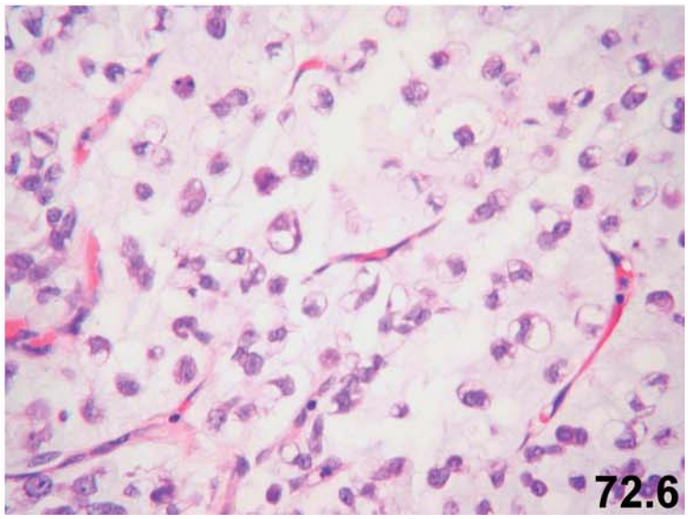

72.6

Figs. 72.7 and **72.8:** Higher magnification of tumor cells reveals isolated cells with large hyperchromatic nuclei and multivacuolated cytoplasm. The tumor cells clearly have a chondroblastic appearance. Note the myxoid stromal background.

Fig. 72.9: Immunohistochemically, the tumor cells are positive for pancytokeratin. Note the difference of positive immunoreaction in peripheral and central areas of the tumor.

Fig. 72.10: Immunohistochemistry for CK5/6 shows clusters of positive epithelial tumor cells, particularly at the periphery of the tumor.

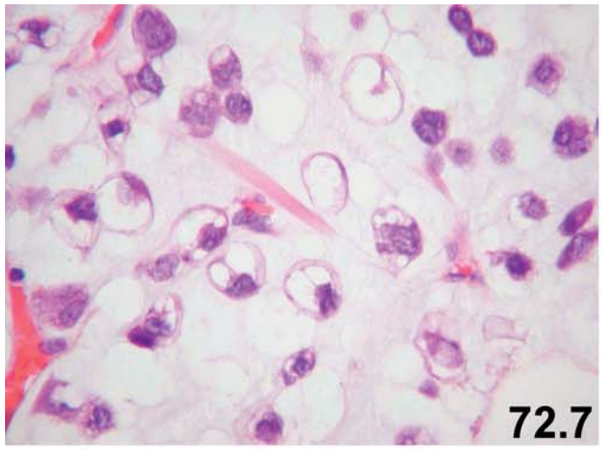
Fig. 72.11: In chondroid areas, the tumor cells also show a positive immunoreaction for CK5/6.

Fig. 72.12: Immunohistochemistry for S100 protein displays a positive reaction in tumor cells with chondroid differentiation.

Figs. 72.13 and **72.14:** The tumor cells show a heterogeneous positive immunoreaction for p63.

Fig. 72: Final remarks

- This case shows an example of so-called matrix-producing breast carcinoma. It represents a variant of metaplastic carcinoma with prominent myxochondroid differentiation.
- As in other variants of metaplastic carcinoma, this case demonstrates a close relationship between metaplastic (sarcomatoid) carcinoma and so-called basal-like carcinoma.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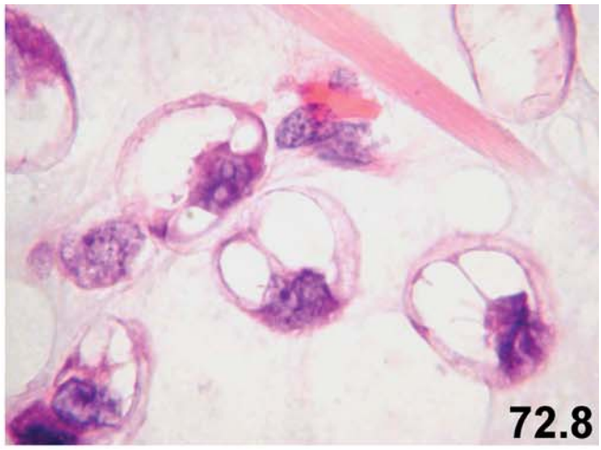
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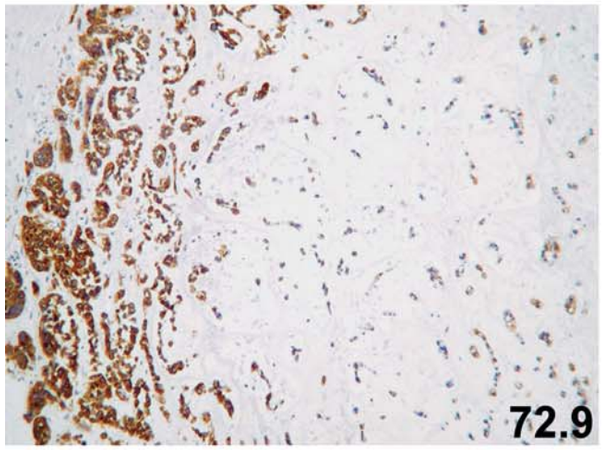
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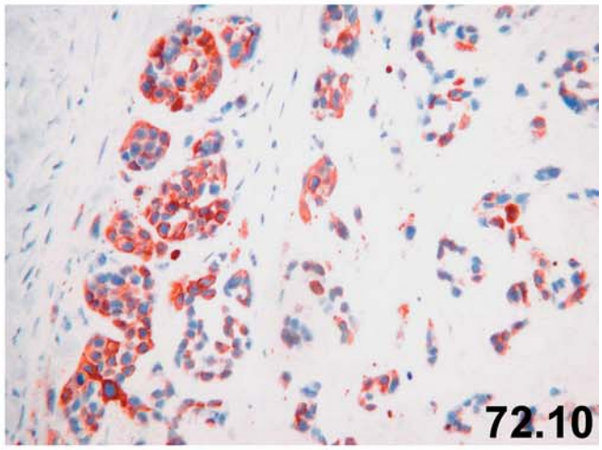
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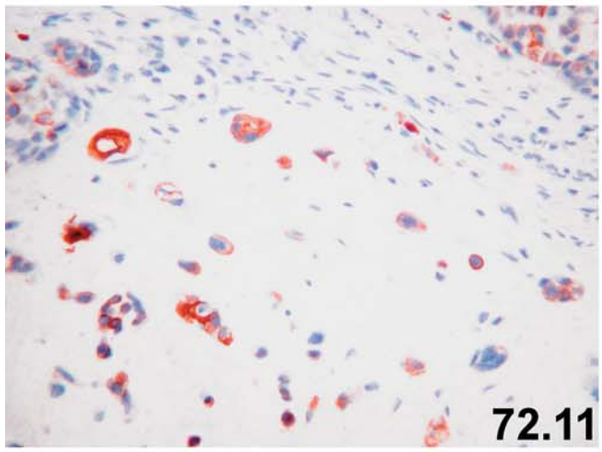
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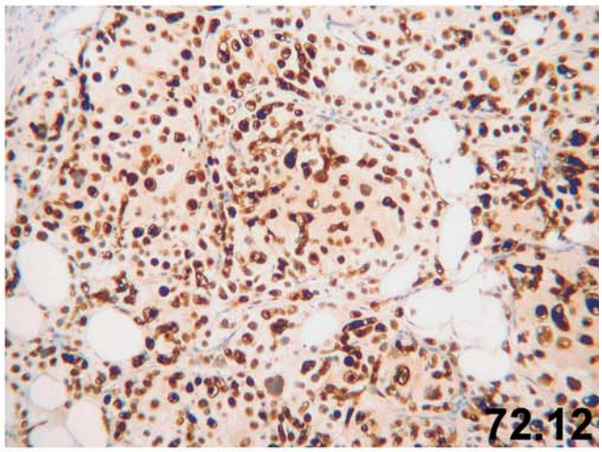
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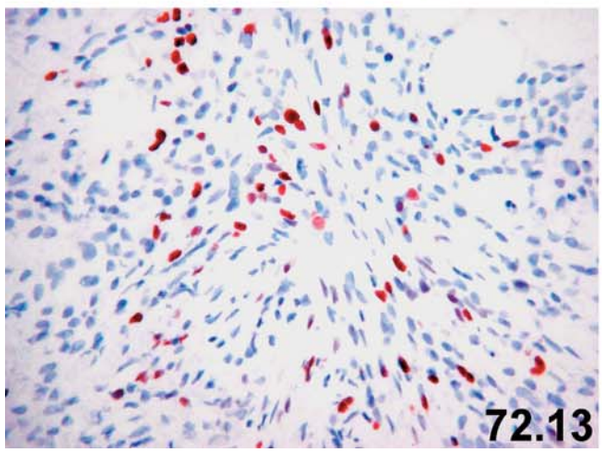
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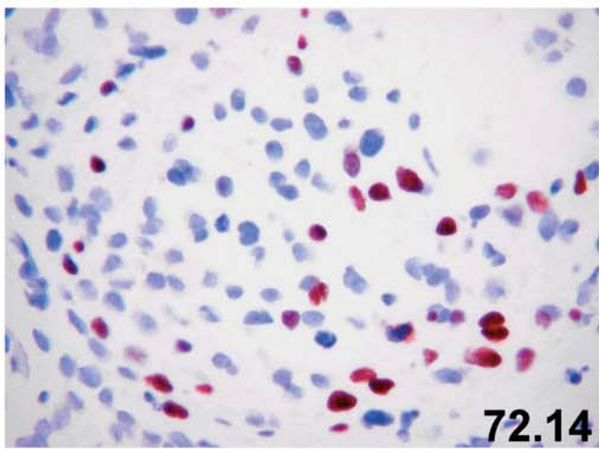

72.14

Fig. 73: Spindle cell, sarcomatoid carcinoma (with myoepithelial cell differentiation).

Case history: Routine screening mammogram was performed on a 45-year-old woman and showed an irregular, infiltrating lesion in the upper outer quadrant of her left breast.

Fig. 73.1: At low magnification, a very cellular tumor with irregular and infiltrating borders is evident.

Figs. 73.2 and **73.3:** The tumor is composed of spindle cells and lacks gland formations.

Fig. 73.4: Many areas of the tumor show interlacing fascicles of spindle cells (sarcomatoid appearance). The spindle tumor cells are uniform, lacking significant nuclear atypia.

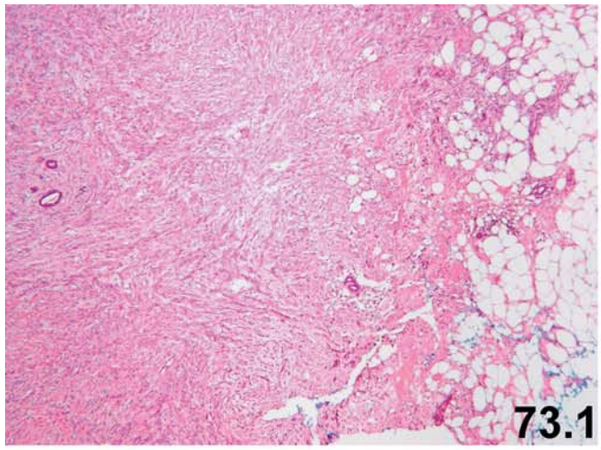
Fig. 73.5: Immunohistochemistry for p63 reveals numerous positive tumor cells.

Fig. 73.6: Interlacing fascicular growth pattern showing an intense positive immunoreaction for smooth muscle actin.

Figs. 73.7 and **73.8:** Several areas of the tumor show intense immunoreactivity for EGFR (HER1).

Fig. 73: Final remarks

- The sarcomatoid tumor cells in this case were also positive for pancytokeratin, CK5/6, and CK14 (not shown). Immunohistochemistry for a variety of cytokeratins is often necessary for distinguishing a sarcomatoid or spindle cell carcinoma from a true sarcoma of the breast.
- Sarcomatoid (metaplastic) breast carcinomas often coexpress some of the myoepithelial markers (smooth muscle actin, CD10, p63, S100 protein, CD29, etc.) and basal-type cytokeratins (CK34BE12, CK5/6, CK14, CK17).
- This case has been classified by different pathologists as sarcomatoid, metaplastic, basal-like, and myoepithelial carcinoma. It should be kept in mind that there is no sharp dividing line between all of these entities. Indeed, several cases of so-called basal-like carcinoma of the breast show myoepithelial differentiation if a combination of several myoepithelial markers is used.
- While HER2/neu is very often negative in sarcomatoid breast carcinoma, EGFR (HER1) is frequently positive in this tumor.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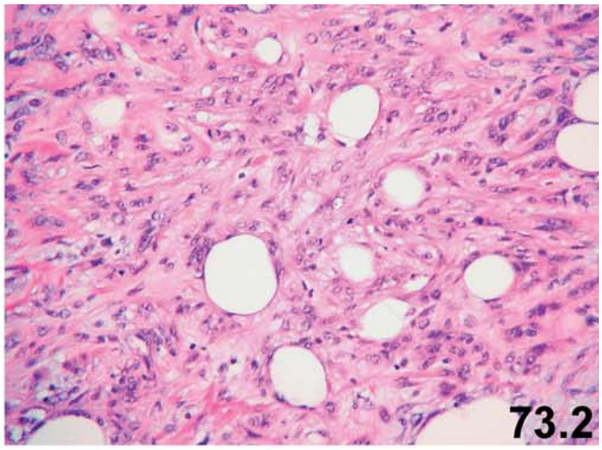
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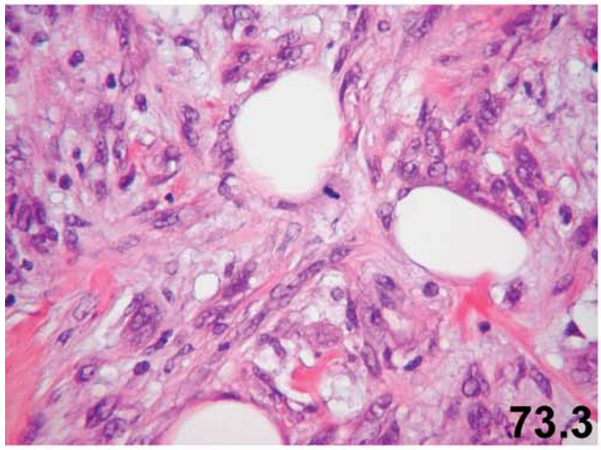
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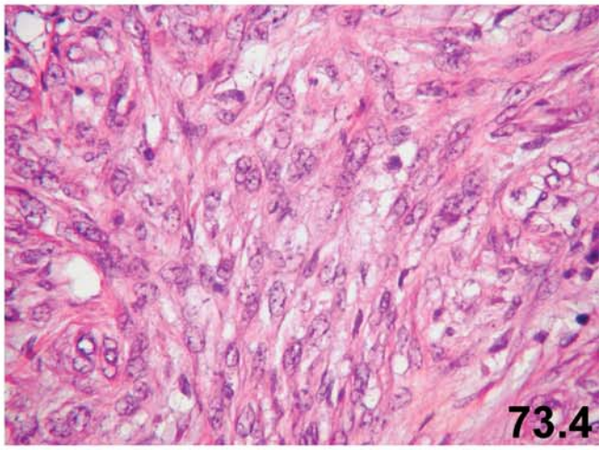
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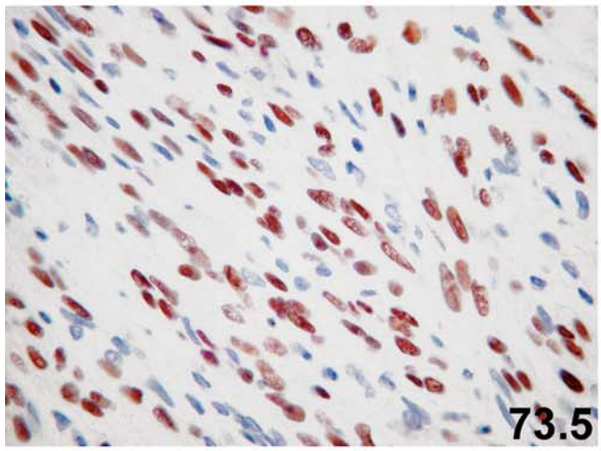
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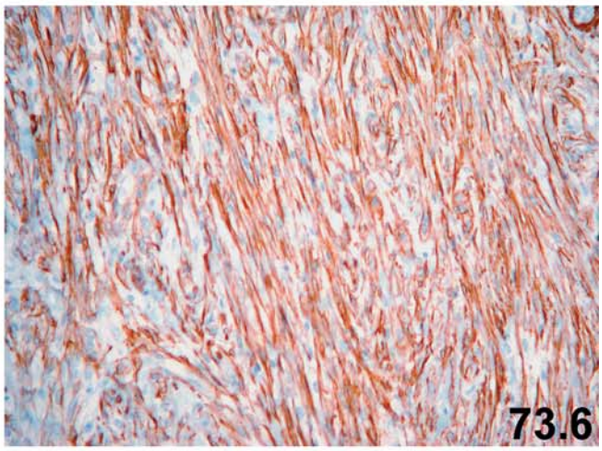
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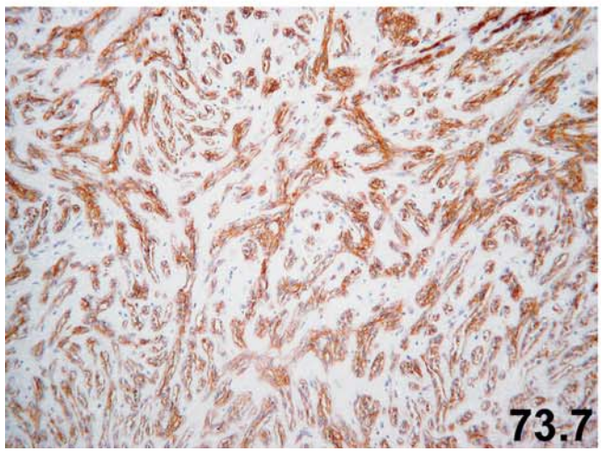
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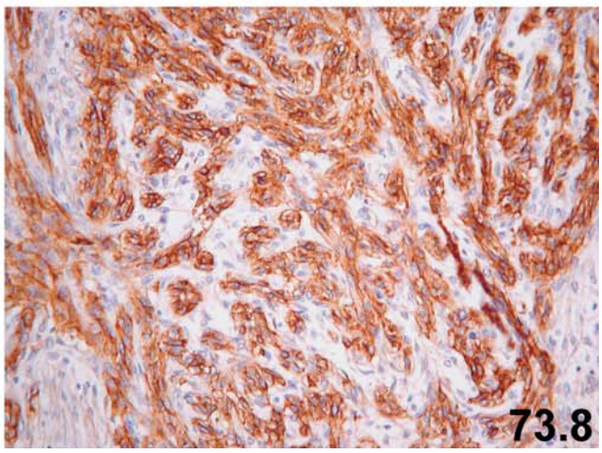

73.8

Fig. 74a: Glycogen-rich carcinoma.

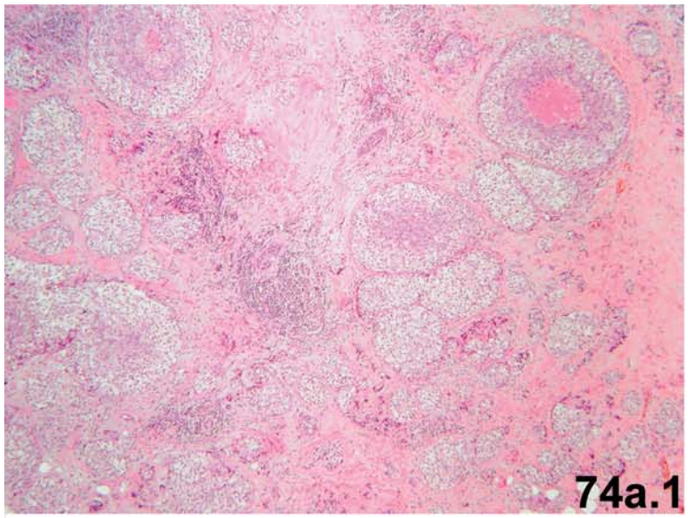
Case history: An 80-year-old woman presented with an ill-demarcated mass in her left breast. Excisional biopsy showed a tumor 3.7 cm in greatest diameter.

Fig. 74a.1 and **74a.2:** At low magnification, the tumor shows ducts with central comedo-type necrosis and numerous glands with irregular and infiltrating growth pattern.

Fig. 74a.3: Ducts with central necrosis, partially associated with luminal microcalcification. At higher magnification, the ducts show a myoepithelial cell layer (not shown). Note the clear cytoplasm of the intraductal neoplastic cells.

Fig. 74a.4: Other areas of tumor show a solid growth pattern. Note the clear cytoplasm of the tumor cells.

Figs. 74a.5 and **74a.6:** Irregular and infiltrating growth pattern of small glands and tubules demonstrating tumor cells with clear cytoplasm.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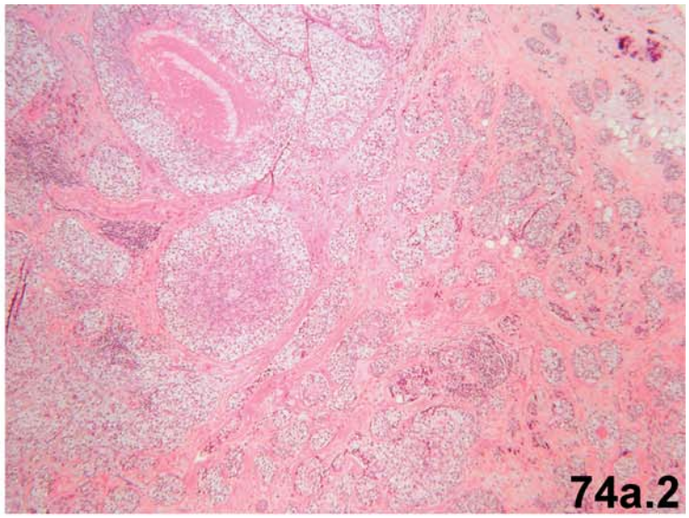
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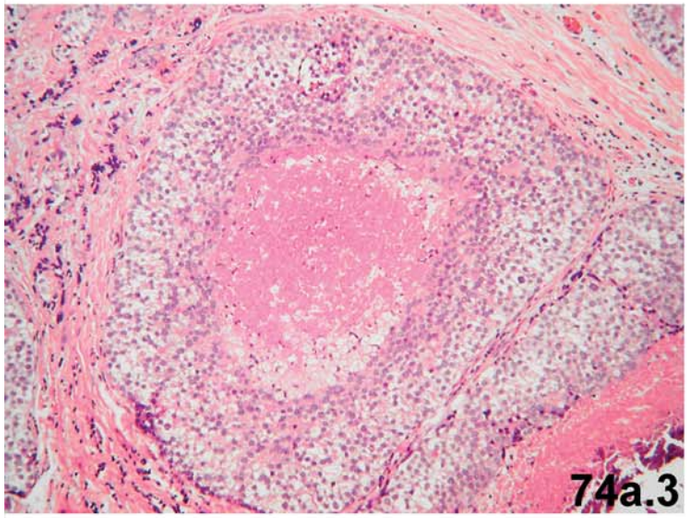
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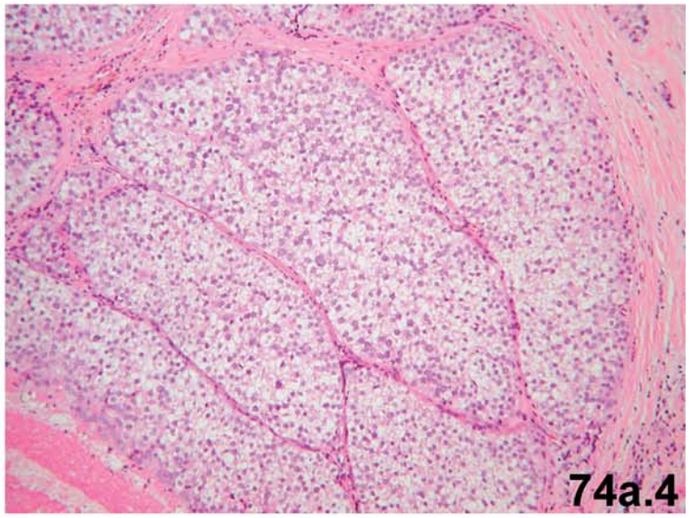
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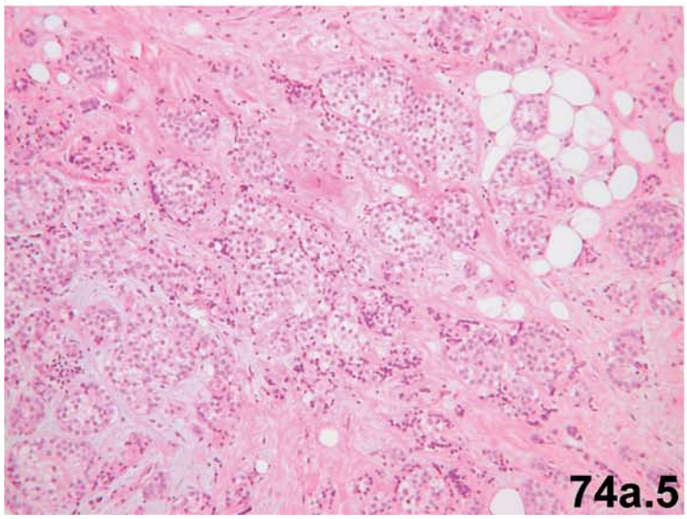
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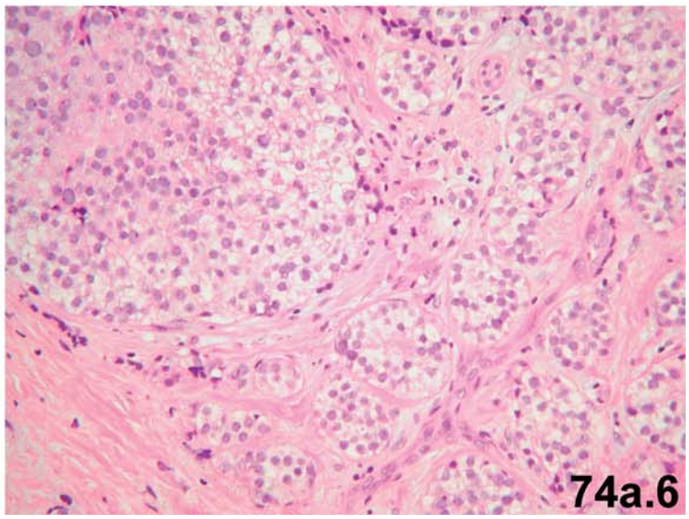

74a.6

Figs. 74a.7 and **74a.8:** Higher magnification of the carcinoma highlights tumor cells with abundant clear cytoplasm and distinct cytoplasmic borders.

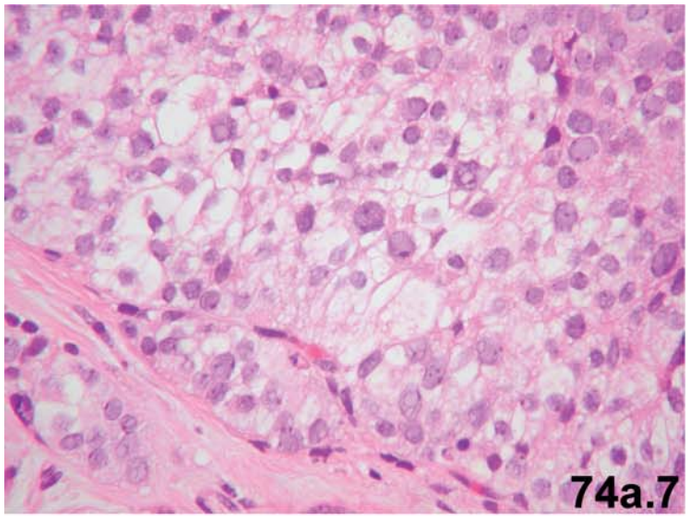
Figs. 74a.9 and **74a.10:** Special stain for PAS displays a positive granular cytoplasmic reaction.

Fig. 74a.11: The reaction for PAS after diastase is, however, negative indicating cytoplasmic glycogen in tumor cells with abundant clear cytoplasm.

Fig. 74a.12: Immunohistochemistry for estrogen receptors shows a diffuse positive reaction.

Fig. 74a: Final remarks

- Several breast carcinomas may have a minor component of tumor cells with clear (glycogen-rich) cell differentiation. The clear-cell morphology needs to be the predominant pattern (more than 80% of tumor cells) before the carcinoma is classified as clear cell carcinoma.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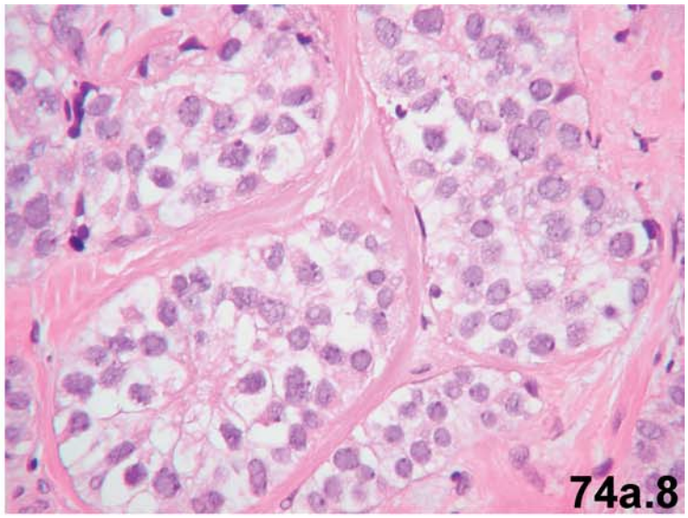
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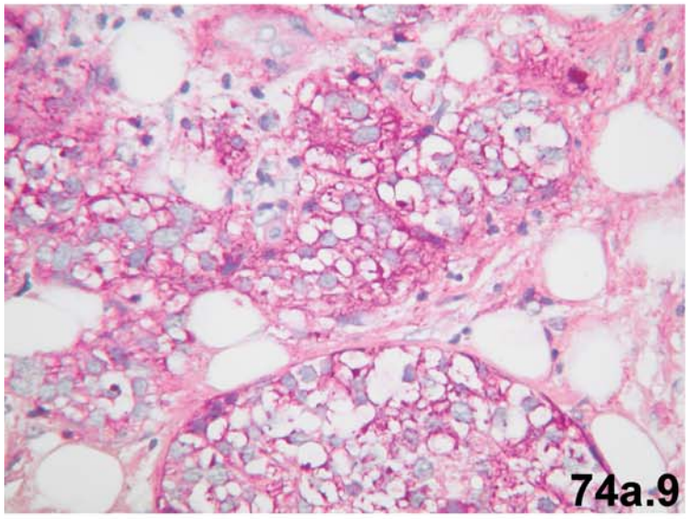
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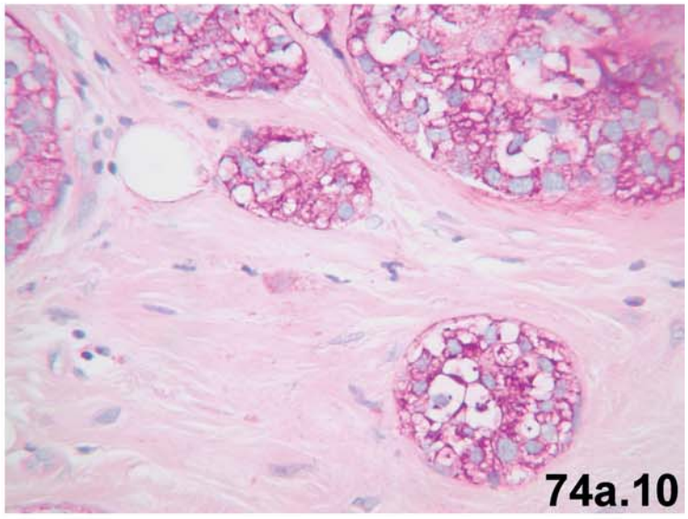
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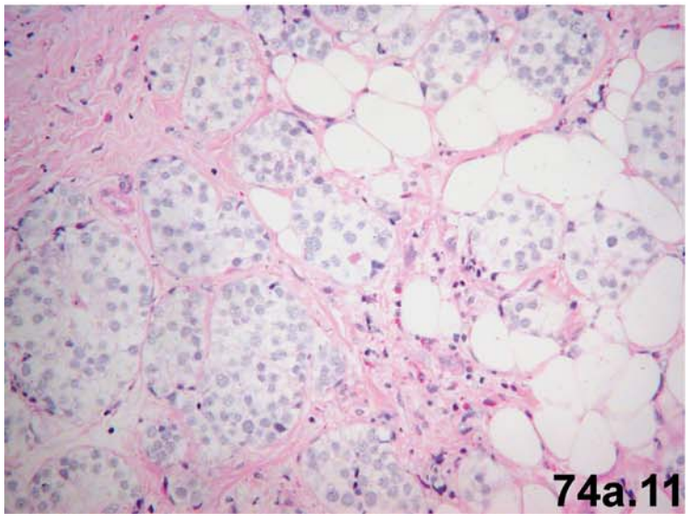
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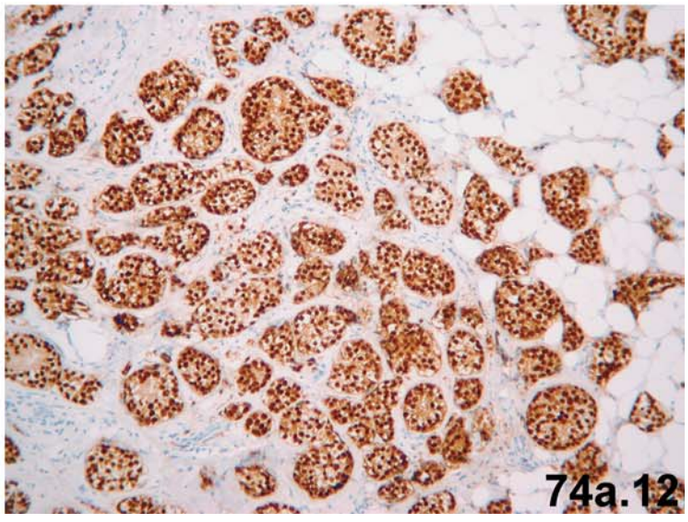

74a.12

Fig. 74b: Inflammatory breast carcinoma.

Case history: A 58-year-old woman presented with an ill-demarcated hard tumor in the upper outer quadrant of her left breast. The skin was diffusely red and warm. Clinically, the tumor was highly suspicious for an inflammatory carcinoma.

Fig. 74b.1: The skin over the surface of the breast is reddened and edematous. Note that the lesion is accompanied by peau d'orange. (Courtesy of Dr. G. Lushin, Graz, Austria.)

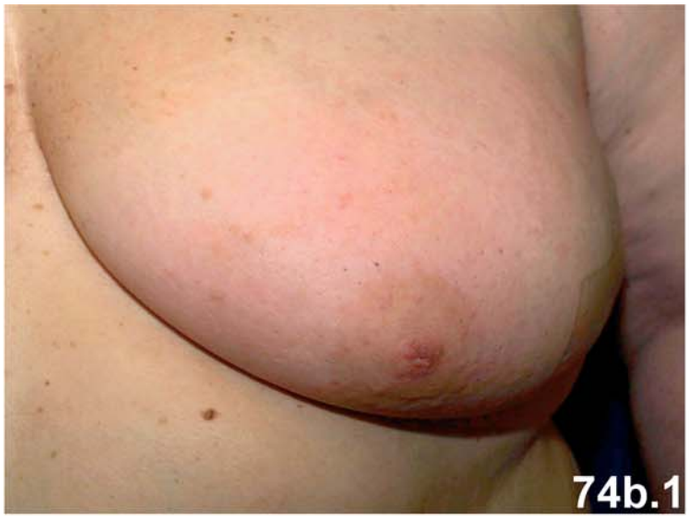
Fig. 74b.2: Invasive breast carcinoma showing infiltration of dermis.

Fig. 74b.3: Skin infiltration associated with marked edema.

Figs. 74b.4 and **74b.5:** Several areas show lymphangiosis carcinomatosa cutis as a hallmark of inflammatory carcinoma.

Fig. 74: Final remarks

- According to the TNM classification, inflammatory carcinoma is a clinical diagnosis. It is very often, but not always, associated with dermal lymphatic invasion. One needs to keep in mind that according to the TNM classification, a carcinoma without clinical signs of inflammatory carcinoma but with lymphangiosis carcinomatosa cutis should not be classified as inflammatory carcinoma or pT4d.
- Breast carcinoma infiltration of the skin does not automatically mean pT4! According to the TNM classification, a breast carcinoma with dermal infiltration but without edema, skin ulceration, satellite nodules in the skin, or inflammatory skin changes needs to be classified (T) according to its size.
- The presence of lymphangiosis carcinomatosa cutis should, however, be documented in the surgical pathology report.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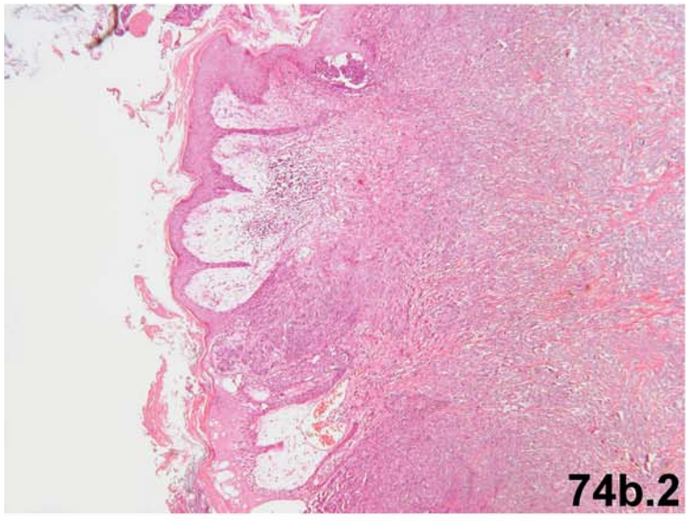
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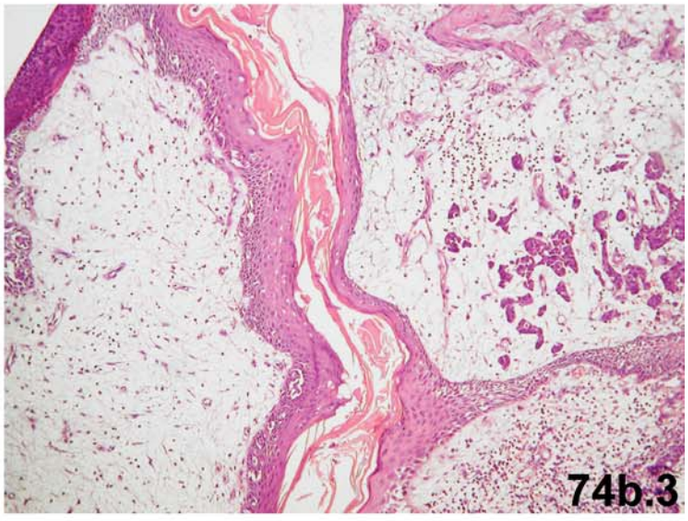
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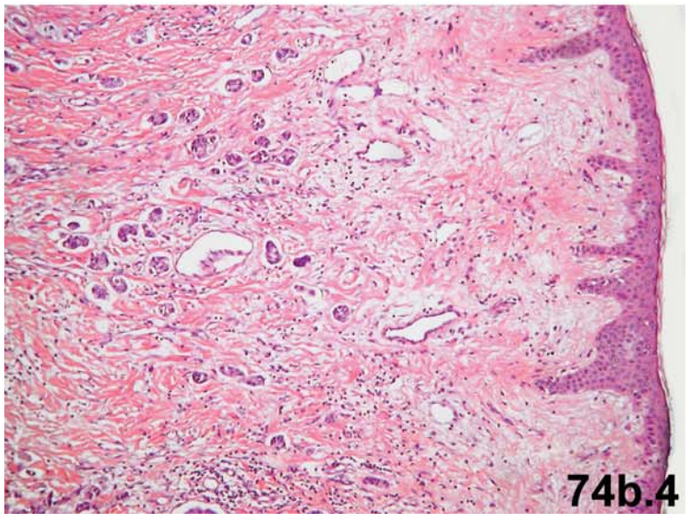
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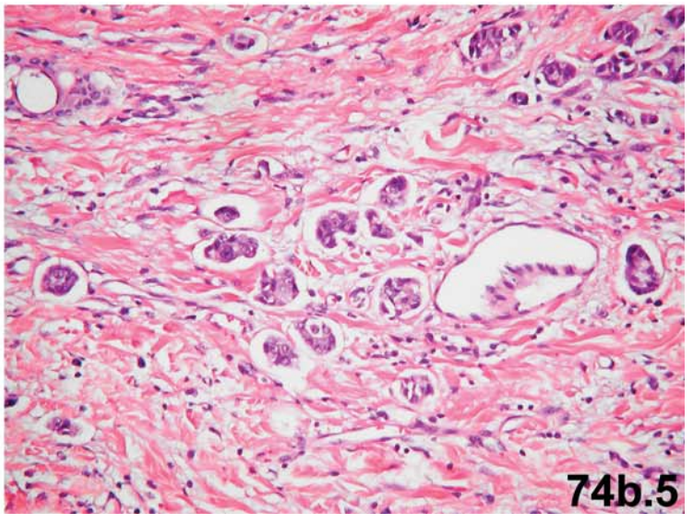
74b.5

Biphasic Tumors

Contents

CHAPTER 11 Biphasic Tumors

11.1 Fibroadenoma

11.1.1 Definition

A benign biphasic (fibroepithelial) tumor seen most frequently in women of childbearing age.

11.1.2 Macroscopy

Fibroadenoma (FA) is a sharply demarcated bulging and firm tumor with a greyish-white cut surface. It is generally 2–3 cm in size but may become very large (>10 cm, giant fibroadenoma). Myxoid change or calcification may occur.

11.1.3 Microscopic Features (Figs. 75–80)

- A well-circumscribed biphasic (fibroepithelial) neoplasm showing stromal proliferation around glands (pericanalicular pattern) or compressed cleft-like ducts (intracanalicular pattern).
- The ducts are lined by two cell layers: a luminal epithelial cell layer and an underlying layer of myoepithelial cells.
- A pushing growth margin is usually present. Focal irregularities are seen in some cases.
- Rarely, otherwise typical fibroadenomas develop a focal phylloides appearance, with the leaflike processes often protruding into dilated ductal spaces or cysts; the stroma in these areas is, however, not hypercellular.
- Squamous metaplasia and apocrine metaplasia can occur within the FA.
- The stromal component may show focal or diffuse hypercellularity or extensive myxoid or mucinous change, transforming the tumor to a gelatinous nodule. Atypical and bizarre multinucleated giant cells are occasionally present in the stroma. These may be identified focally or diffusely, but they are benign and have no prognostic significance.
- Chondroid, osseous, and smooth muscle metaplasia can very rarely occur in the stroma (the presence of these features is more suspicious for phylloides tumor).
- Epithelial prominence, proliferative changes, and intraepithelial neoplasias such as atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and lobular neoplasia are observed in a relatively small proportion of FAs.
- Some tumors can be combined with adenosis, which may be confused with an invasive carcinoma.
- Sometimes the myoepithelial cells become prominent or hyperplastic.
- Spontaneous infarction occasionally occurs, particularly during pregnancy and lactation.

Caution

- In a patient with myxoid FA, it is prudent to consider the possibility of Carney's syndrome (cardiac and/or cutaneous myxomas, abnormal skin pigmentation, and endocrine abnormality) [5].
- A myxoid FA can grossly and microscopically be mistaken for a mucinous (colloid) carcinoma!
- FAs with significant myxoid stroma occurring in women younger than 40 years of age are more likely to be associated with multiple recurrences [5].
- Atypical epithelial proliferations such as ductal intraepithelial neoplasia (DIN; ADH/DCIS) and lobular intraepithelial neoplasia (LIN; ALH/LCIS) can rarely be identified within the FA. Concerning the interpretation of such lesions, one should be more conservative as long as these neoplastic lesions are confined to the FA (with no evidence of intraepithelial neoplasia outside of the FA). Such FAs associated with DIN have an excellent prognosis without a significantly increased risk for recurrences or subsequent invasive carcinomas [10, 19].
- Epithelial proliferation with increased mitotic activity in a juvenile (cellular) fibroadenoma, when of a borderline nature, should be interpreted conservatively [6, 19].

11.1.4 Additional Comments

Some FAs can have a phylloides appearance with leaflike structures. The stromal component of such FAs, however, is not hypercellular; this variant of FA could be designated as fibroadenoma phylloides (or FA with some phylloides pattern).

Some FAs may show areas of closely packed tubules with minimal stromal components. This variant has been designated as combined FA and tubular adenoma.

Fibroadenomas with increased stromal cellularity and without leaflike processes are called cellular FA.

Juvenile FA is characterized by rapid growth, massive size, stretching of the overlying skin, and dilatation of superficial veins. It is more common in black females. Microscopic features are similar to those of regular FA. Juvenile FA not infrequently reveals epithelial hyperplasia, with irregular tufts overlying a stratified epithelium similar to that seen in gynecomastia (gynecomastoid hyperplasia). Follow-up of these patients (annual examination of the breasts by palpation) should be advised when the proliferation is atypical [2, 11, 19].

Fibroepithelial lesions with cellular stroma in core needle biopsy specimens of the breast may result in either FA or phylloides tumor at excision. Assessment of stromal cellularity,

mitoses, and proliferation indices might help determine the probability of phylloides tumor occurring and guide management of these cases [11, 12].

11.1.5 Further Reading

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11.2 Phylloides Tumor

11.2.1 Definition

A group of circumscribed biphasic fibroepithelial tumors characterized by an epithelial component arranged in clefts surrounded by a hypercellular mesenchymal component that is typically organized in a leaflike pattern.

11.2.2 Synonym

Phyllodes tumor

11.2.3 Macroscopy

Phylloides tumors (PTs) are highly variable in their gross appearance, but a majority display a solid, fleshy mass with cystic areas. The tumors may be small or very large, ranging in size from 1 to 45 cm. The characteristic whorled appearance with curved clefts resembling leaf buds is seen in large tumors. Some of the tumors appear solid with barely visible cysts. The majority of PTs are well circumscribed and greyish-white, yellow, or pink, with foci of necrosis and hemorrhage in the larger tumors. Mucoid changes can be present.

11.2.4 Microscopic Features (Figs. 81–85)

- Biphasic neoplasm composed of a benign epithelial component (two cell layers of epithelial and myoepithelial cells) and a cellular, spindle cell stroma.
- The hallmark of the tumor is formation of leaflike processes protruding into cystic (dilated) spaces.
- The margin can be either pushing or infiltrative.
- As a rule, the stroma is clearly more cellular than that of FAs: hypercellular stroma, often with a fibrosarcomatous appearance.
- Spindle-shaped fibroblastic and myofibroblastic cells generally constitute the stroma, but highly atypical and multinucleated mesenchymal cells also occur.
- Osseous and chondroid metaplasia (differentiation) may occur.
- Rhabdomyoblastic and smooth muscle differentiation rarely occur.
- Adipose differentiation ranging from mature fat to liposarcoma may occur.

- Mitotic figures are rare. They can, however, be numerous, particularly in high-grade tumors.
- Stromal overgrowth may be present, showing predominance of a pure mesenchymal component with minimal residual PT elements (epithelial component barely identifiable).

11.2.5 Correlation of Histologic Features with Clinical Behavior

It has been shown [25] that PTs smaller than 4 cm in diameter have a lower rate of recurrence than larger ones. Tumors with pushing margins recur rarely and are lethal on very rare occasions. Tumors with infiltrating margins have a significantly higher rate of recurrence and are more likely to be lethal [25]. It has been shown that the increasing degree of cytologic atypia is associated with increasing incidence of recurrence and fatal outcome [25, 36]. Tumors with increased mitotic activity (defined as three or four mitotic figures per 10 high-power fields [25]) in the stroma are more likely to be aggressive. However, it is important to note that the clinical course of PT cannot be accurately predicted based on histopathologic features.

Caution

- It is important to keep in mind that the behavior of phylloides tumors cannot be predicted in an absolute way. No single pathologic feature is wholly reliable in predicting the clinical behavior of PTs. However, a combination of pathologic features such as tumor size, margin, cellular atypia, presence of stromal overgrowth, and, most importantly, mitotic activity should be used as a guide in estimating the clinical course of these tumors.

11.2.6 Grading of Phylloides Tumors

Phylloides tumors can be divided into two major categories: low-grade and high-grade.

- *Low-grade:* A tumor with a "pushing" margin, mild cytologic atypia, and fewer than three mitotic figures per 10 hpf. Low-grade PT has a potential for local recurrence, but it is very unlikely to metastasize. A low-grade PT is a tumor with low malignant potential.
- *High-grade (synonyms include malignant phylloides tumor and cystosarcoma phylloides):* A tumor with either an infiltrating or pushing margin, moderate to severe nuclear atypia, and three or more mitotic figures per 10 hpf. Furthermore, the presence of stromal overgrowth is highly indicative of a high-grade tumor. A high-grade PT is a tumor with high malignant potential.

It should be noted that the current (2003) WHO classification of tumors of the breast and female genital organs separates phylloides (phyllodes) tumors into benign, borderline, and malignant categories, mainly based on the mitotic activity, type of margin, stromal overgrowth, and cellular pleomorphism [5]. For practical purposes, however, benign and borderline tumors can be viewed as low-grade PTs. Malignant tumors represent high-grade PTs.

11.2.7 Recurrence and Metastases

Approximately 30% of PTs develop recurrences, and a majority do so within 2–3 years after the diagnosis. Subsequent recurrences may show increased cellularity, significant nuclear atypia, and increased mitotic activity [1, 4, 5, 10, 15, 20, 24, 27, 35, 36].

Metastases are hematogenous (lung, bone, heart, liver, etc.) and occur in less than 10% of unselected cases. They usually occur within 2 years of the initial surgery. Lymph node metastases are very rare (less than 1% of high-grade PTs). The metastatic tumors are usually monophasic (mesenchymal) in appearance and lack an epithelial component [3–6, 8, 10, 13–17, 20, 21, 23, 25, 27, 36].

Caution

- A PT may show some edematous or myxoid stromal areas (hypocellular areas). The presence of leaflike structures should raise the possibility of a PT; deeper levels of sections should display more hypercellular stromal areas along with leaflike processes in a PT.
- Spindle-shaped fibroblastic and myofibroblastic cells in a PT may be compressed and simulate a single-file pattern of an invasive lobular carcinoma! Immunohistochemical examination with (pan)cytokeratin antibody would exclude this.
- Although the malignant stromal component of PT is often fibrosarcomatous in appearance, other types of sarcoma, such as liposarcoma, chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and "malignant fibrous histiocytoma," can also develop in a high-grade PT. The presence of such components should be specifically mentioned in the pathology report.
- Pure sarcomas (liposarcoma, chondrosarcoma, etc.) without relationship to a mammary PT are extremely rare; one needs to examine the mesenchymal tumor more carefully (deeper levels, additional sampling, at least one section for each centimeter of the tumor) to exclude the possibility of a PT.
- PTs with intermediate features occur occasionally; these should be called low-grade because local recurrence is the main concern for such tumors.
- The assessment of the resection margins is crucial in a PT. If the tumor is close to the margin or if it involves the margin, reexcision with a rim of uninvolved breast tissue needs to be done.

11.2.8 Additional Comments

Biphasic breast tumors with benign ductal structures and periductal sarcomatous stroma lacking a phylloides pattern are a source of diagnostic problems, particularly because of the lack of an appropriate designation. Periductal stromal tumor (periductal stromal sarcoma) is a useful descriptive designation for generally low-grade biphasic tumors with sarcomatous periductal stroma that do not have typical features of a PT. This rare tumor may evolve into a PT with time. This rare variant of biphasic breast tumor may show stromal mitotic activity of three or more per 10 hpf, stromal infiltration into surrounding breast tissue, and hypercellularity, sometimes with cytologic atypia

around the ducts. Complete excision of the tumor with a rim of uninvolved breast tissue is required [7, 26].

Many cases of PTs are now treated with wide local excision (with a rim of uninvolved breast tissue). Simple mastectomy should be reserved for large tumors or lesions with infiltrating margins and unfavorable histologic features. Axillary lymph node dissection is not indicated [3, 6, 17, 30, 32, 38].

11.2.9 Further Reading

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Fig. 75: Fibroadenoma.

Case history: Clinical examination of a 24-year-old woman revealed a lobulated, firm, and mobile tumor in the upper inner quadrant of her left breast. The tumor was 2.5 cm at its greatest diameter. The tumor was excised after 1 year of clinical follow-up.

Fig. 75.1: The cut surface of the excised lesion shows a well-circumscribed bulging whitish-grey to yellow tumor.

Fig. 75.2: At low magnification, a biphasic or fibroepithelial neoplasm is present. The tumor shows compressed cleft-like ducts (intracanalicular growth pattern). Other areas of the tumor also revealed stromal proliferation around glands (pericanalicular growth pattern; not shown).

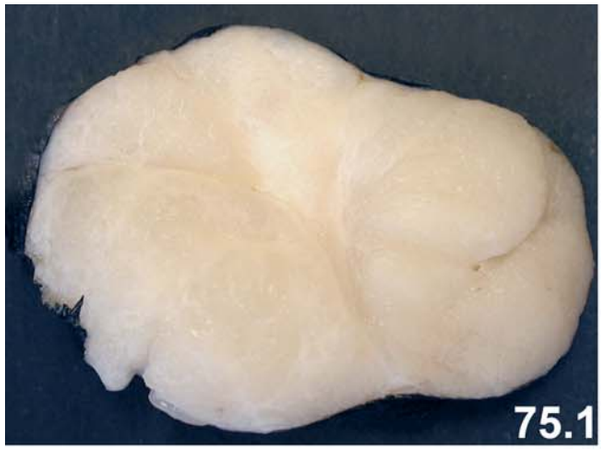
Fig. 75.3: The compressed or cleft-like ducts are lined by two cell layers: a luminal epithelial cell layer and an underlying layer of myoepithelial cells.

Fig. 75.4: The stromal component of the biphasic tumor shows cells with elongated or bipolar nuclei with barely visible cytoplasm.

Fig. 75.5: Imprint cytology (Papanicolaou stain) of the tumor shows numerous cohesive epithelial cell clusters.

Figs. 75.6 and **75.7:** The clusters in imprint cytology are composed of a heterogeneous cell population of epithelial cells (with round to oval nuclei) and myoepithelial cells (with bipolar or elongated hyperchromatic nuclei).

Fig. 75.8: The background of imprint cytology displays numerous bipolar naked nuclei. These cells represent proliferating intralobular stromal cells and/or myoepithelial cells.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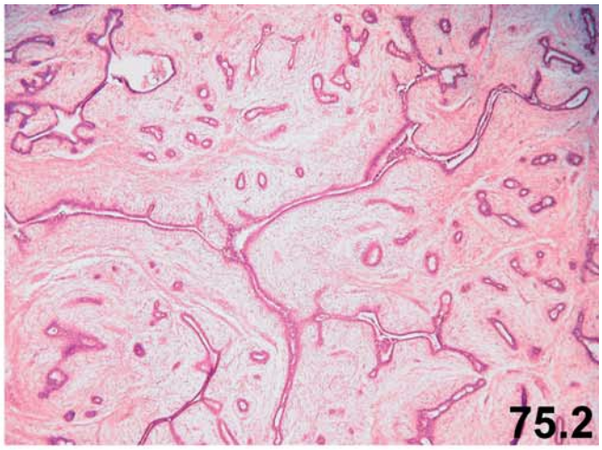
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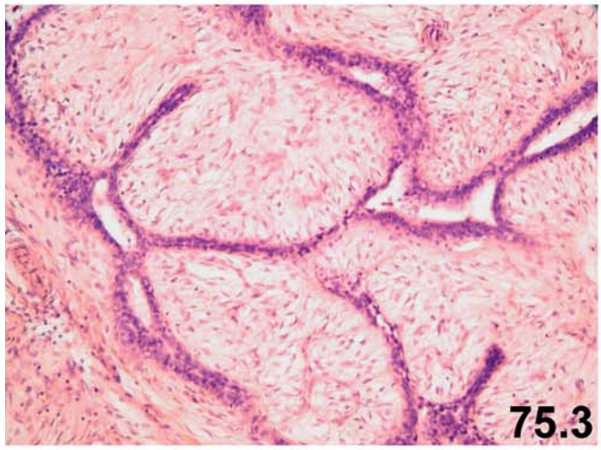
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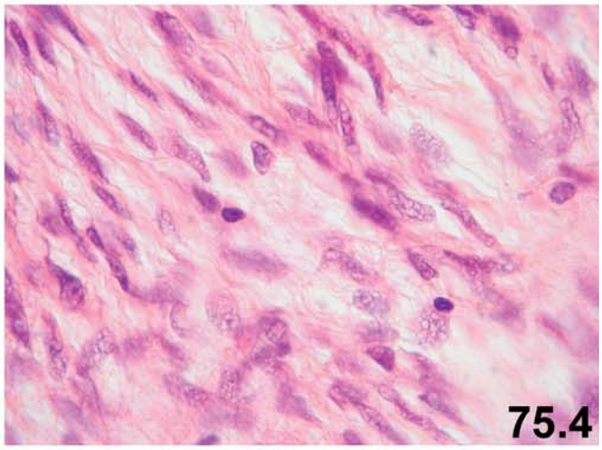
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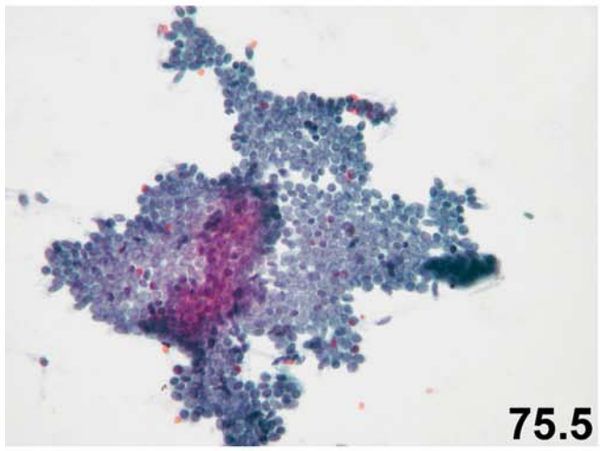
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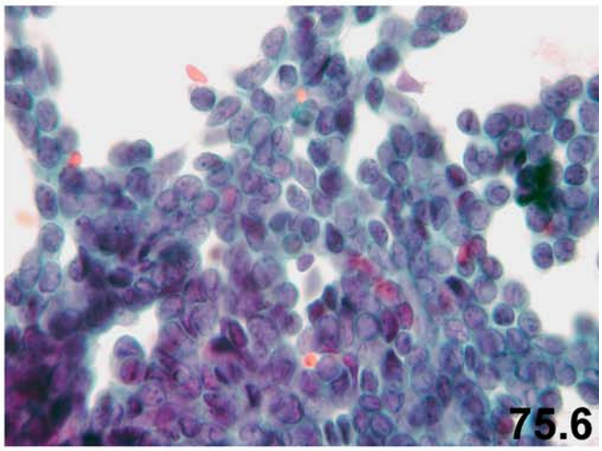
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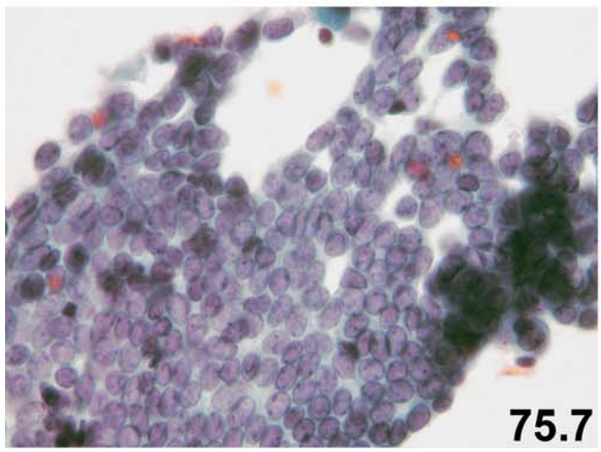
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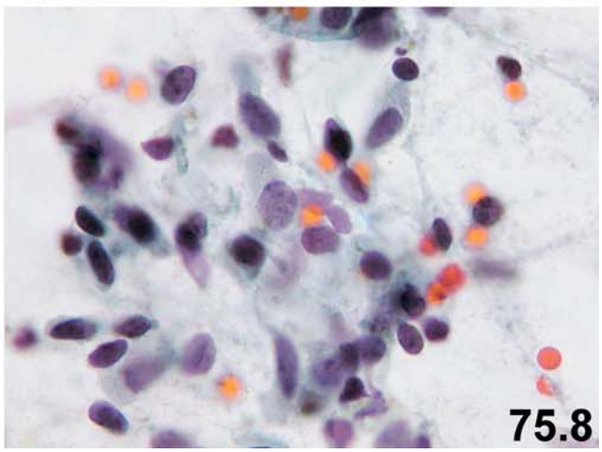
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Fig. 76: Juvenile fibroadenoma.

Case history: A 15-year-old girl presented with a rapidly growing mobile breast tumor with dilatation of superficial veins and stretching of the overlying skin. The tumor was well circumscribed and 4.5 cm in greatest diameter.

Fig. 76.1: Low magnification shows a biphasic or fibroepithelial neoplasm with intracanalicular growth pattern.

Figs. 76.2, 76.3, and **76.4:** Several ducts show epithelial hyperplasia with irregular tufts. In some areas, a micropapillary-like pattern is present, which closely mimics a micropapillary variant of DIN (DCIS).

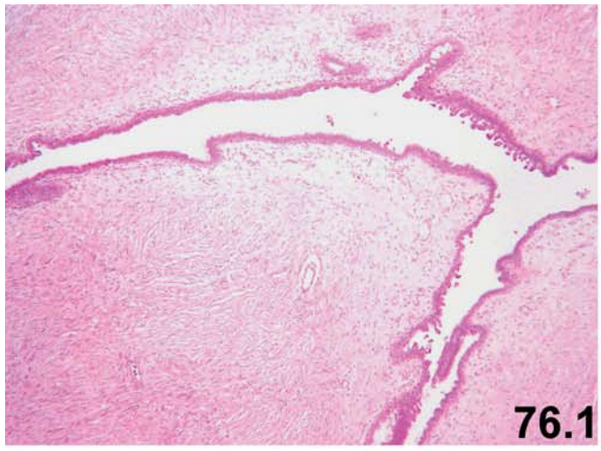
Figs. 76.5 and **76.6:** Epithelial tufts or florid-type intraluminal epithelial proliferations showing irregular secondary lumens. Note the heterogeneity of the proliferating cells consisting of epithelial and modified myoepithelial (progenitor) cells, which is characteristic of florid intraductal hyperplasia (usual ductal hyperplasia).

Fig. 76.7: Immunohistochemistry for high molecular weight cytokeratin (CK34BE12) shows intense positivity in the proliferating luminal cells.

Fig. 76.8: Immunohistochemistry for CK5/6 reveals a heterogeneous positive reaction of luminal cells.

Fig. 76: Final remarks

- The hyperplastic epithelial tufts within juvenile (cellular) fibroadenoma may be mistaken for micropapillary DIN (DCIS). The cell population in the proliferating luminal cells of juvenile fibroadenoma is, however, quite heterogeneous (mixture of epithelial and modified myoepithelial cells).
- While immunohistochemistry for high molecular weight cytokeratin (CK5/6 or CK34BE12) is always positive in ductal hyperplasia, the vast majority of DIN (DCIS), including micropapillary variant, is negative for it.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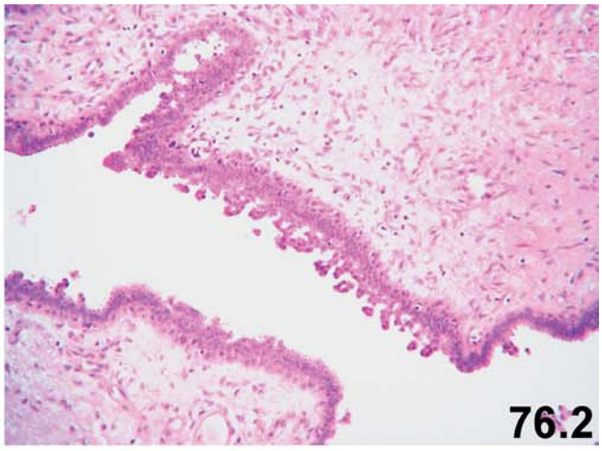
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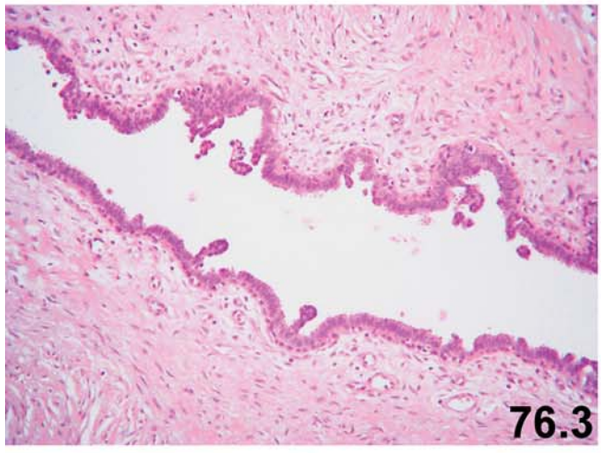
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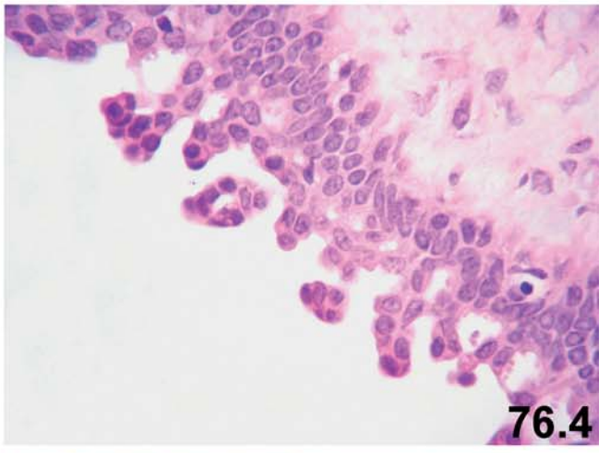
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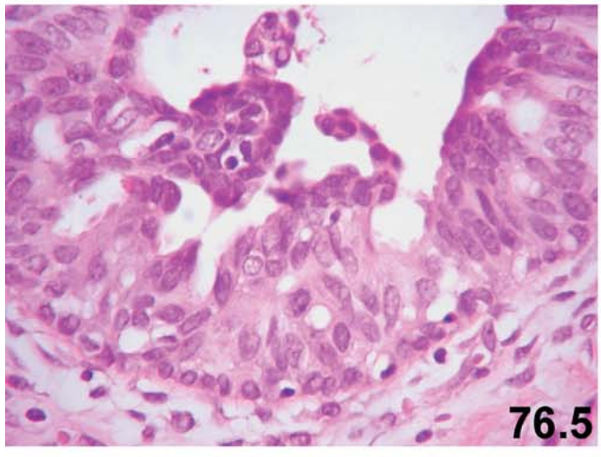
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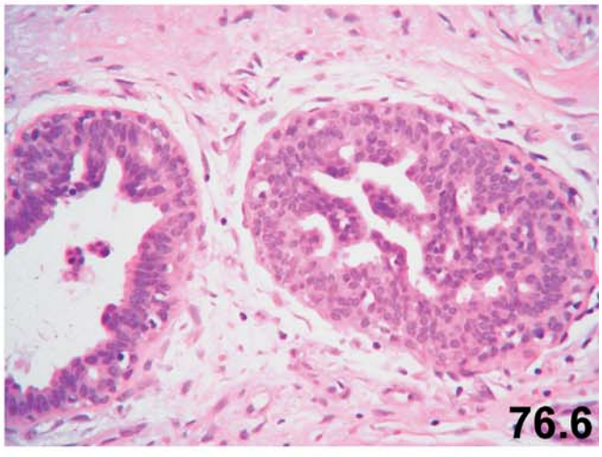
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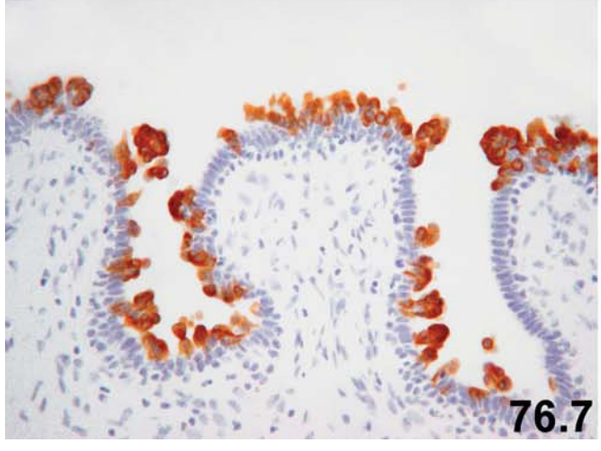
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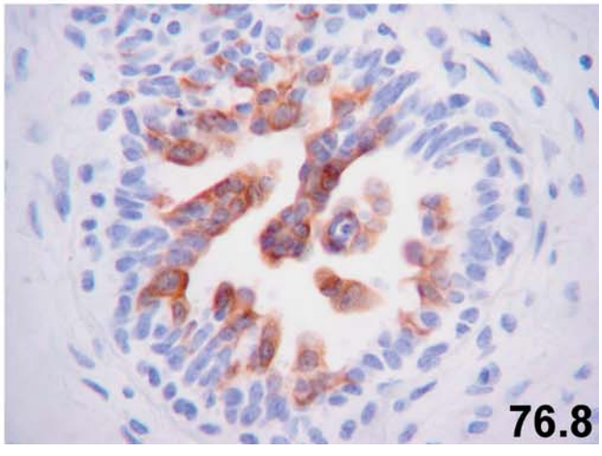
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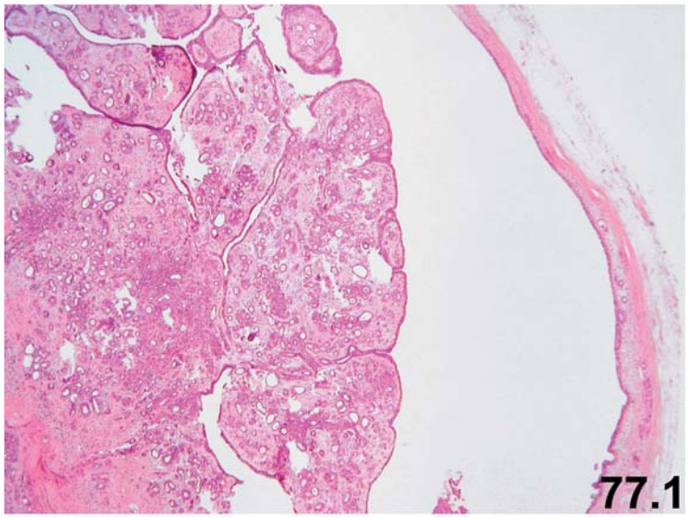
Fig. 77: Fibroadenoma associated with sclerosing adenosis.

Case history: A 29-year-old woman presented with a mobile firm mass in her left breast.

Fig. 77.1: Low magnification of the lesion shows a fibroepithelial neoplasm with an intracanalicular growth pattern.

Figs. 77.2 and **77.3:** Several areas of the fibroadenoma reveal closely packed tubules or acinar structures. Note the lobulated appearance of tubules or acini.

Fig. 77.4: Fibroadenoma with areas of sclerosing adenosis showing closely packed acini and areas with glands with some irregular arrangement.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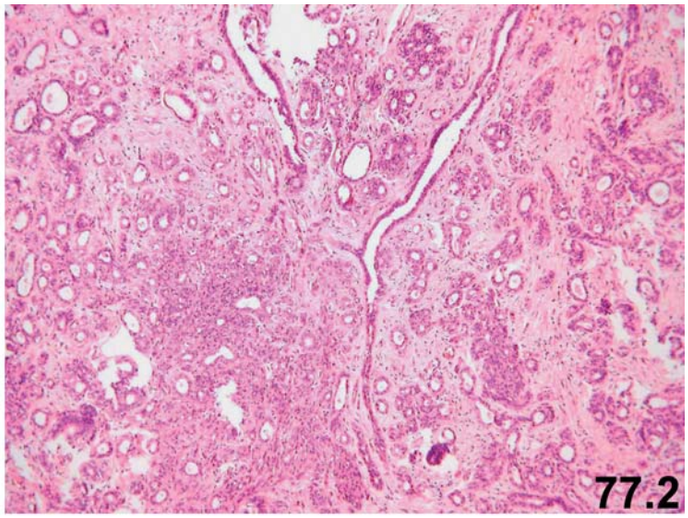
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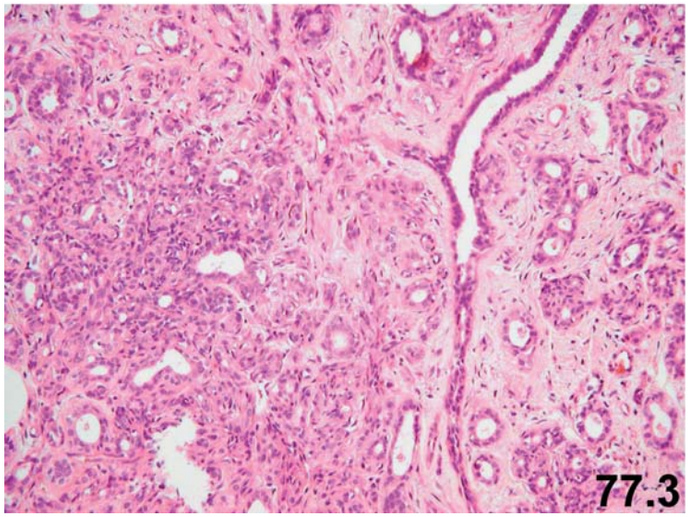
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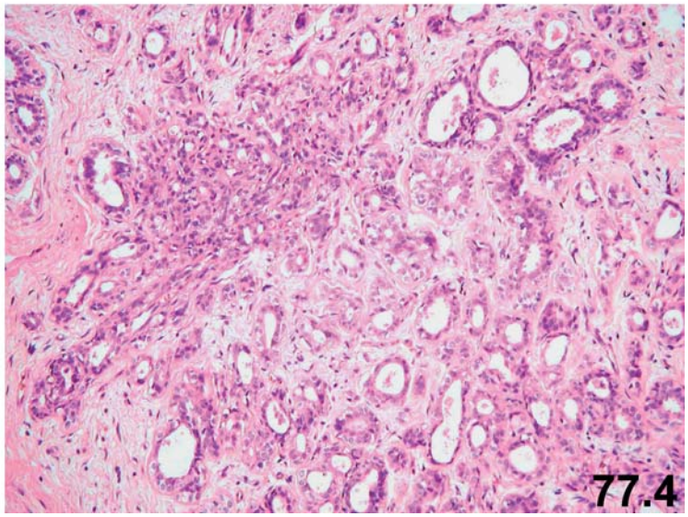
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Fig. 78: Myxoid fibroadenoma.

Case history: A 36-year-old woman presented with a lobulated mobile tumor in the upper outer quadrant of her right breast. Mammography showed a tumor with some irregular borders.

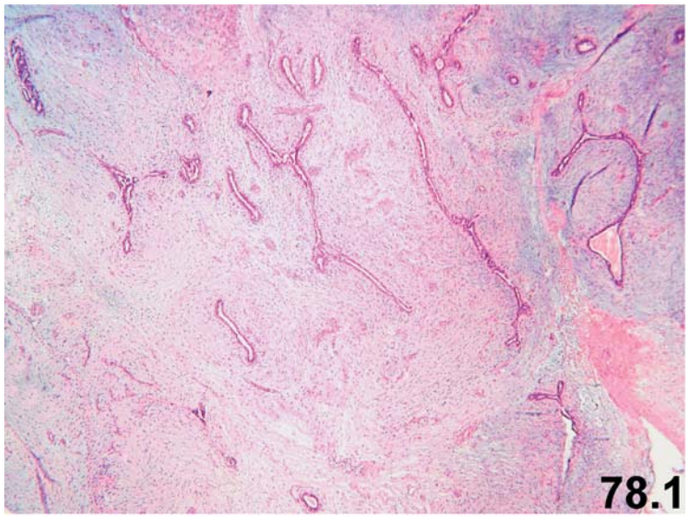
Fig. 78.1: The excisional biopsy shows a fibroadenoma with an intracanalicular growth pattern.

Fig. 78.2: Several areas of the tumor show prominent myxoid stromal changes.

Figs. 78.3 and **78.4:** Fibroadenoma with focal irregular borders. Note the prominent myxoid stromal changes.

Fig. 78: Final remarks

- Myxoid fibroadenoma can be associated with Carney's syndrome. Indeed, further examinations of the patient revealed cardiac myxoma and multiple skin lesions with abnormal pigmentation.
- One should be aware of the macroscopic appearance of myxoid fibroadenoma; it can grossly be mistaken for a mucinous carcinoma.
- Patients with myxoid fibroadenomas are more likely to develop multiple recurrences.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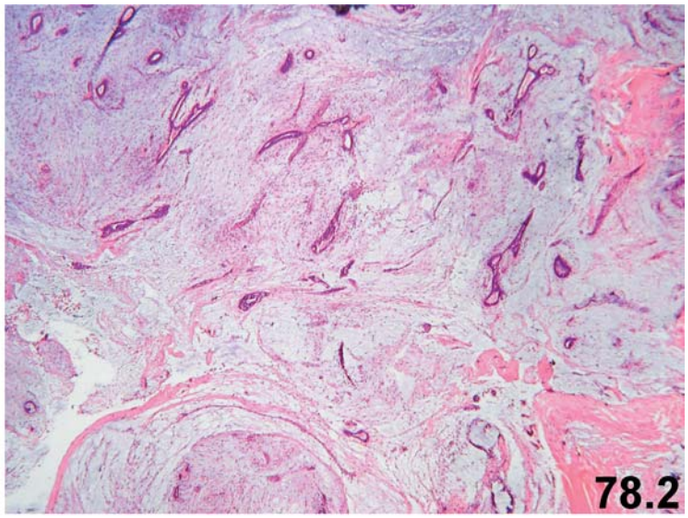
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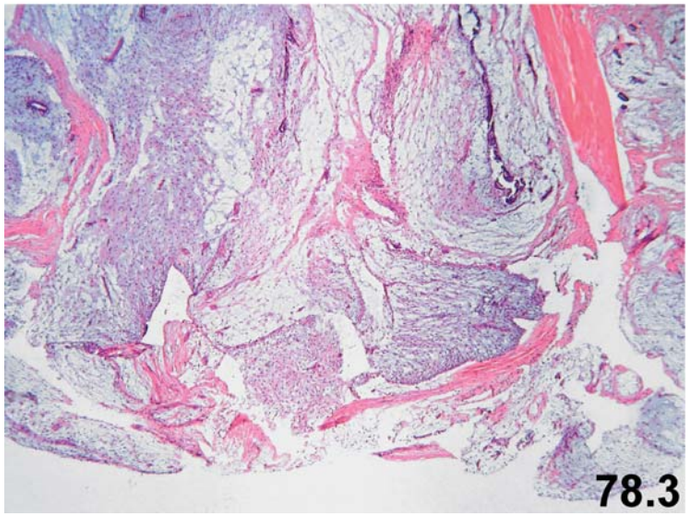
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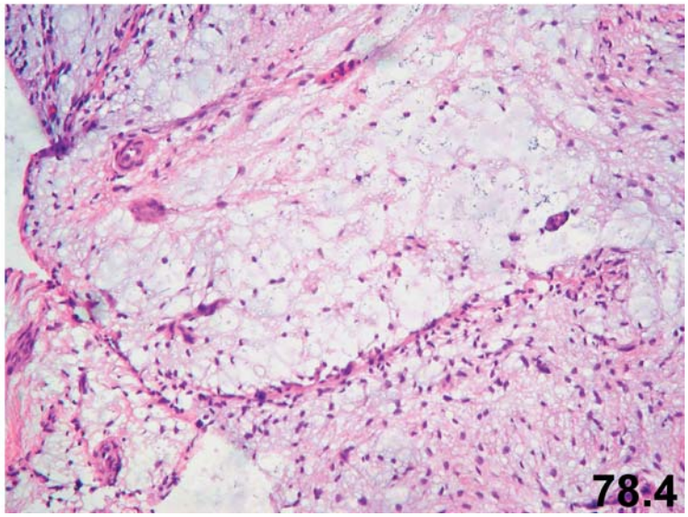
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Fig. 79: Fibroadenoma with some phylloides features associated with low-grade ductal intraepithelial neoplasia (DIN).

Case history: A 27-year-old woman presented with a lobulated firm and mobile tumor in her left breast. The excisional biopsy showed on the cut surface a well-demarcated, lobulated greyish-white tumor measuring 2.6 cm in greatest diameter.

Figs. 79.1 and **79.2:** Low magnification of the lesion shows a fibroepithelial neoplasm with leaflike structures. The stroma within the leaflike structures is, however, not hypercellular.

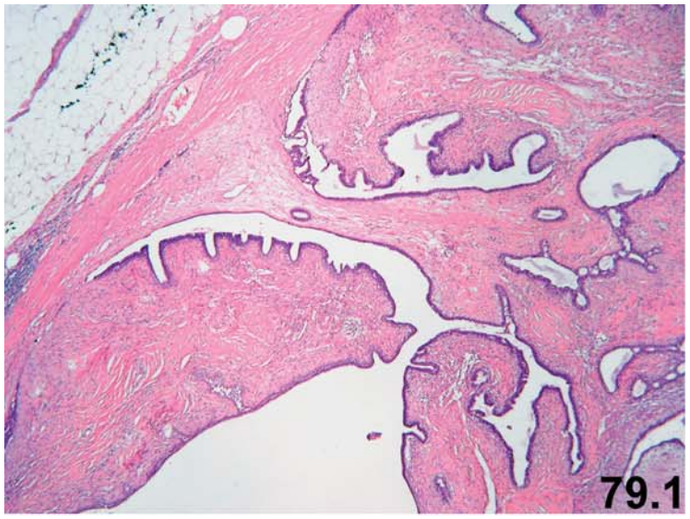
Fig. 79.3: Several areas of the tumor display a pericanalicular growth pattern.

Fig. 79.4: Several ducts within the biphasic tumor exhibit intraepithelial proliferation with a cribriform growth pattern.

Figs. 79.5 and **79.6:** Atypical intraductal proliferation characterized by proliferation of a monotonous cell population forming round secondary lumens. The neoplastic cells are qualitatively identical to those of low-grade DCIS. Immunohistochemistry for CK5/6 did not show a positive reaction in atypical cribriform areas (not shown). Note that while some pathologists favored ADH in this case, others called this tumor low-grade DCIS in a fibroadenoma.

Fig. 79: Final remarks

- This case differs from a typical phylloides tumor by lack of a hypercellular stroma in leaflike areas.
- The epithelial component of this tumor is atypical and is best classified as low-grade ductal intraepithelial neoplasia (DIN1). In such cases, extensive sampling of breast tissue outside of the fibroadenoma is required. The prognosis is excellent if the DIN is confined to fibroadenoma.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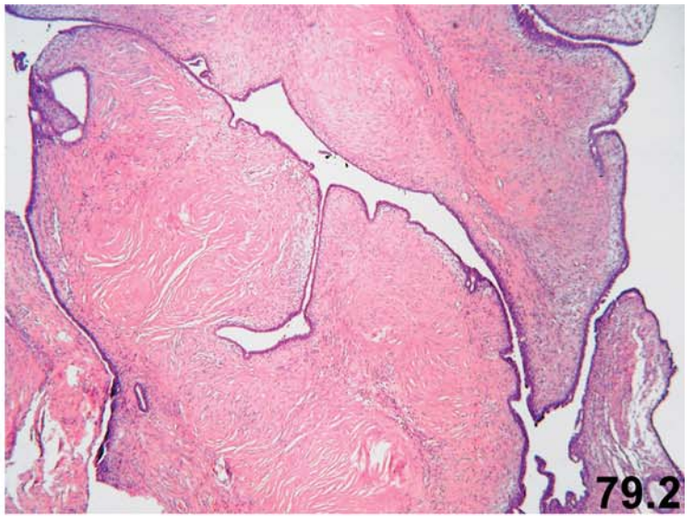
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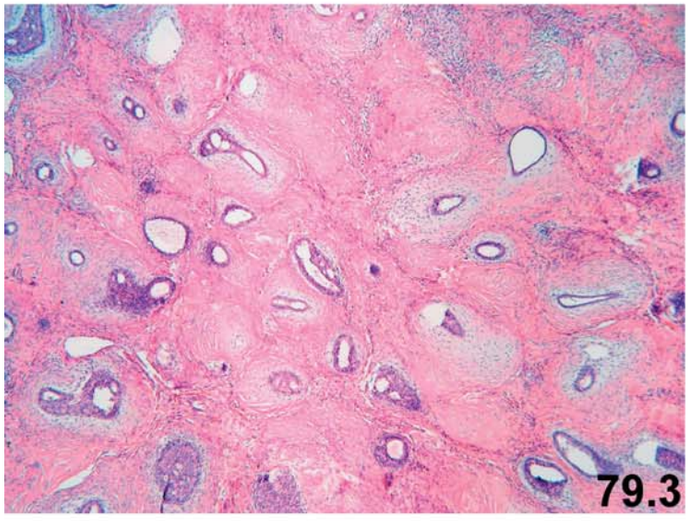
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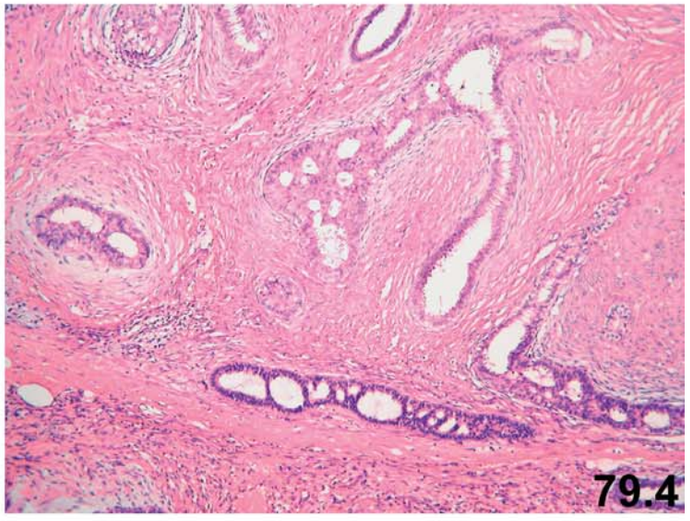
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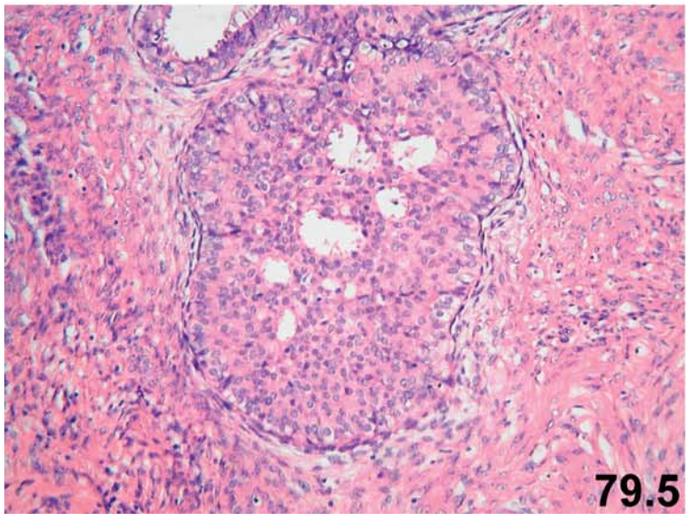
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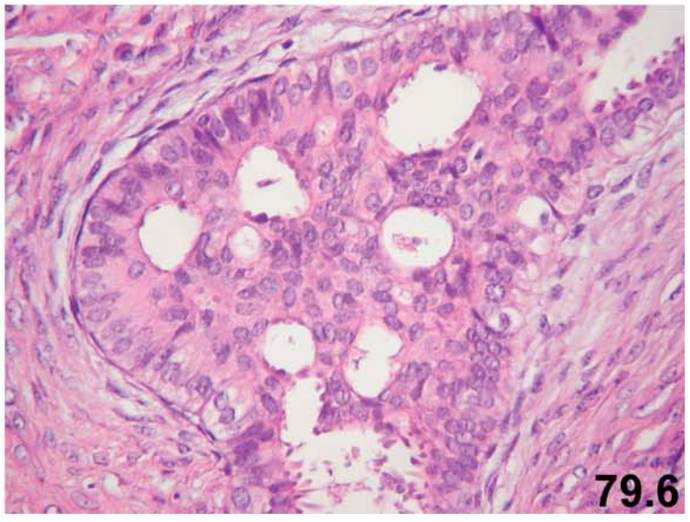
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Fig. 80: Fibroadenoma associated with lobular intraepithelial neoplasia.

Case history: A 37-year-old woman presented with a well-circumscribed mobile mass in the lower outer quadrant of her left breast.

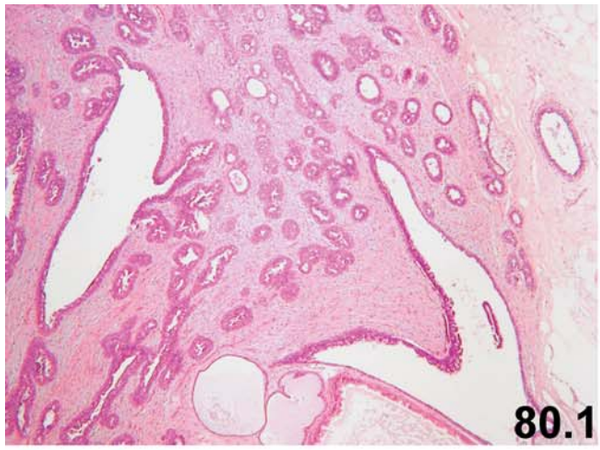
Fig. 80.1: Several areas of the tumor show a typical fibroadenoma with intracanalicular and pericanalicular growth patterns.

Fig. 80.2: The fibroadenoma also shows areas with intraepithelial proliferation.

Figs. 80.3 and **80.4:** Higher magnification of intraepithelial proliferative areas displaying loosely cohesive small and uniform tumor cells with typical features of lobular intraepithelial neoplasia.

Figs. 80.5 and **80.6:** The areas of lobular intraepithelial neoplasia within the fibroadenoma are immunoreactive for CK34BE12. Note the typical cap-like or perinuclear positive reaction of tumor cells.

Figs. 80.7 and **80.8:** Lobular intraepithelial neoplasia within fibroadenoma with a typical negative immunoreaction for E-cadherin.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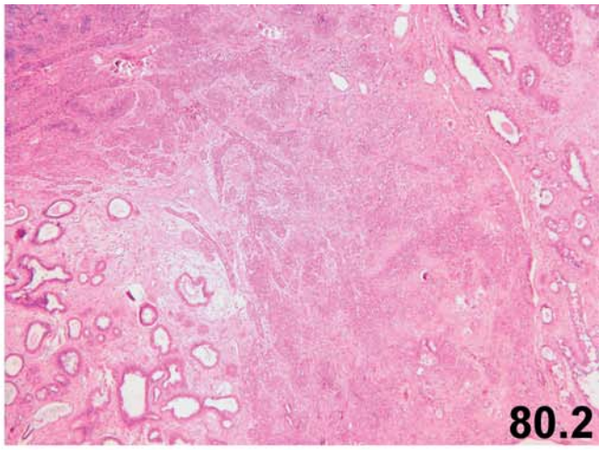
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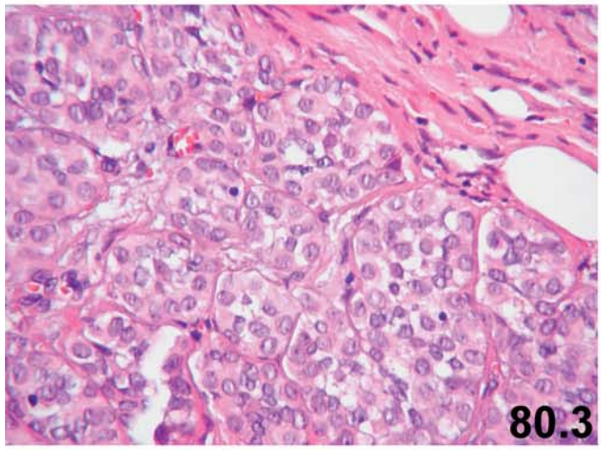
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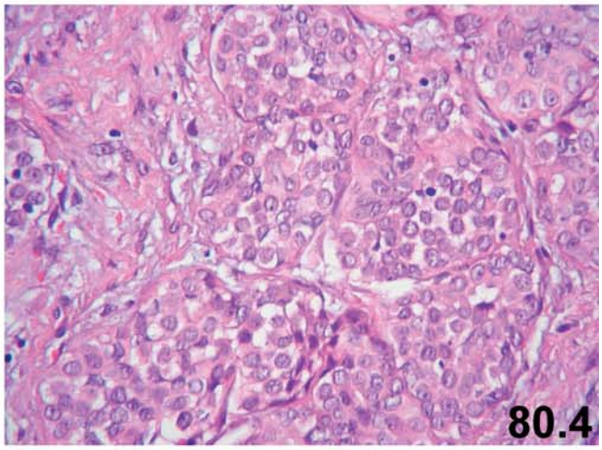
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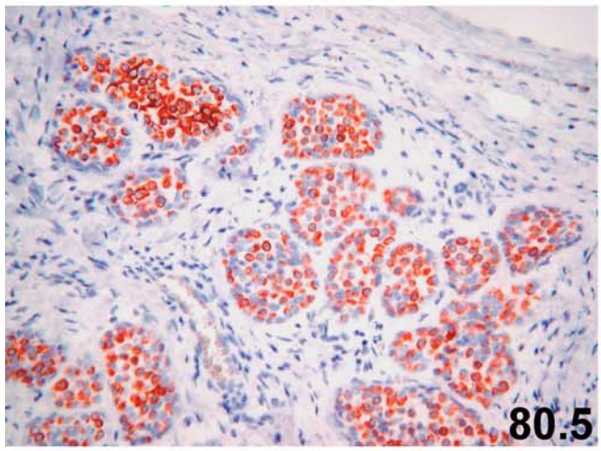
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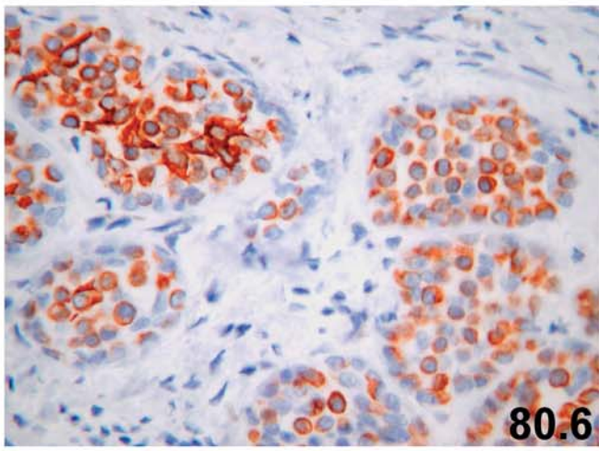
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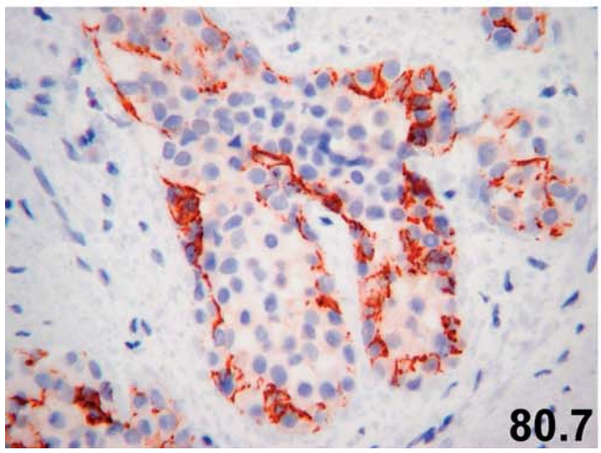
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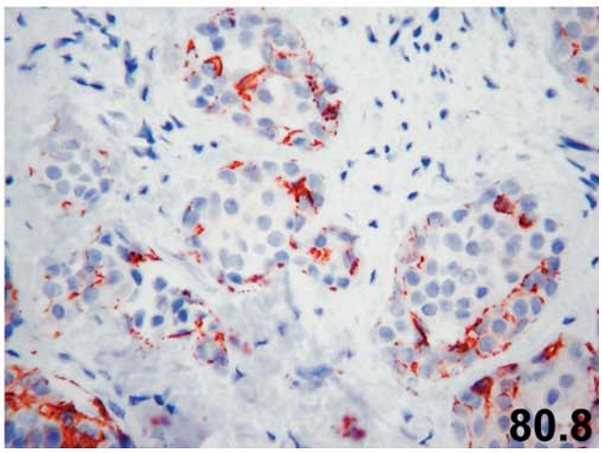
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Fig. 81: Low-grade phylloides tumor.

Case history: A 48-year-old woman presented with a well-circumscribed 3.5-cm firm tumor in her right breast. The cut surface of the excisional biopsy revealed a solid, fleshy, greyish-white tumor with a whorled appearance.

Figs. 81.1 and **81.2:** The tumor is biphasic, showing formation of leaflike processes protruding into dilated spaces.

Fig. 81.3: The tumor is composed of a benign epithelial component and a cellular stroma.

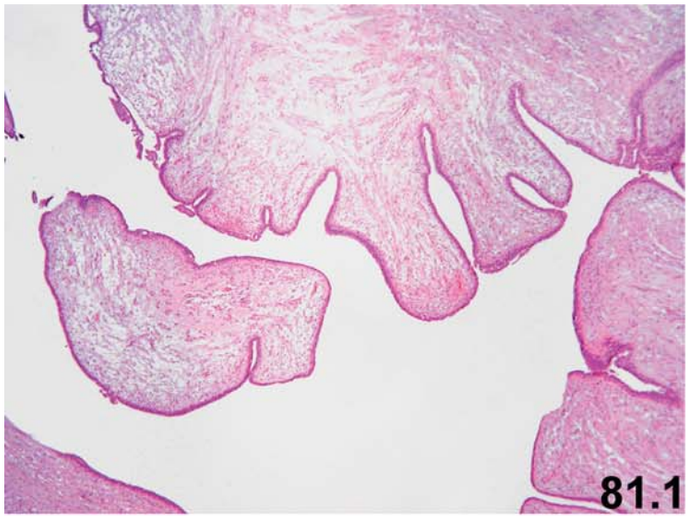
Fig. 81.4: The stroma of the tumor is more cellular than that of a fibroadenoma.

Fig. 81.5: Some areas of the tumor reveal a more periductal or pericanalicular appearance showing hypercellular stromal component.

Fig. 81.6: The mesenchymal tumor cells in hypercellular areas represent spindle-shaped fibroblasts with mild nuclear atypia. The stromal component of the tumor focally shows increased mitotic activity (up to two mitotic figures per 10 high-power fields).

Fig. 81: Final remarks

- This biphasic tumor differs from a fibroadenoma by having a hypercellular stromal component and leaflike processes. This tumor is a low-grade phylloides tumor based on mild nuclear atypia and low mitotic activity.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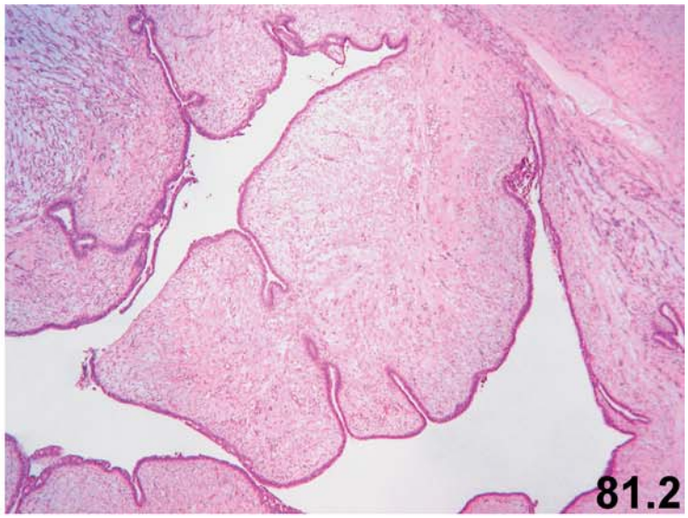
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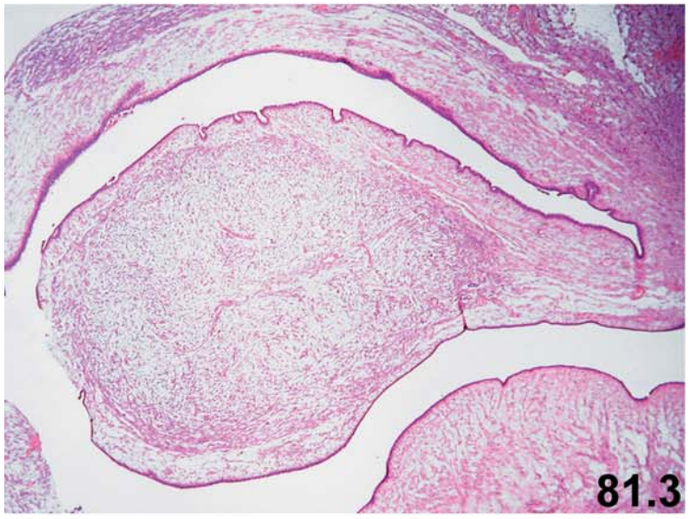
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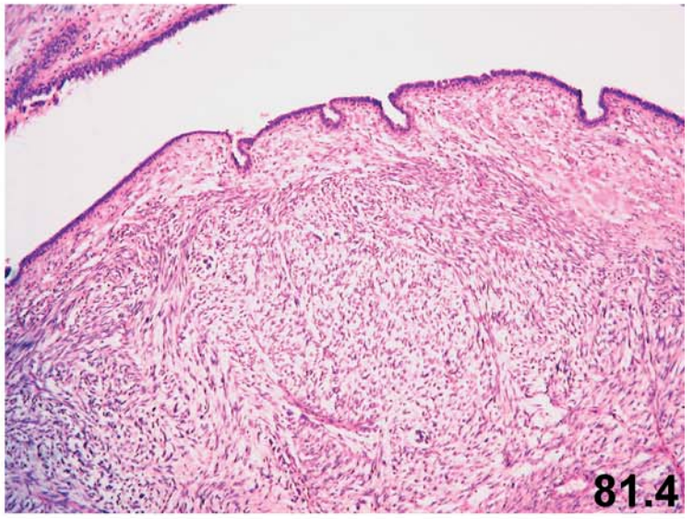
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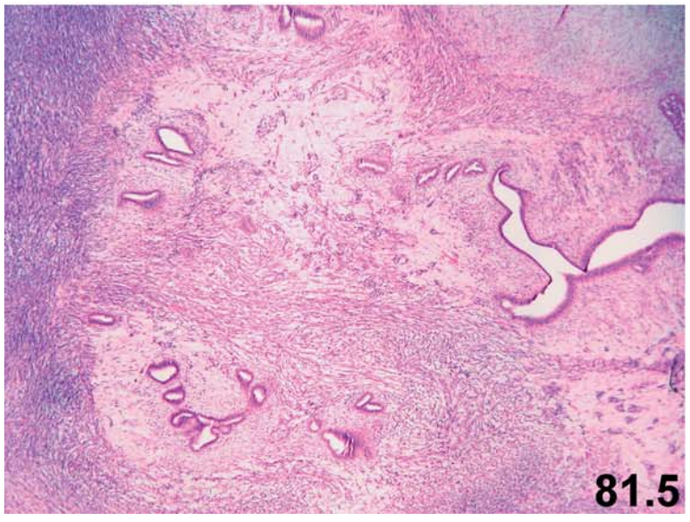
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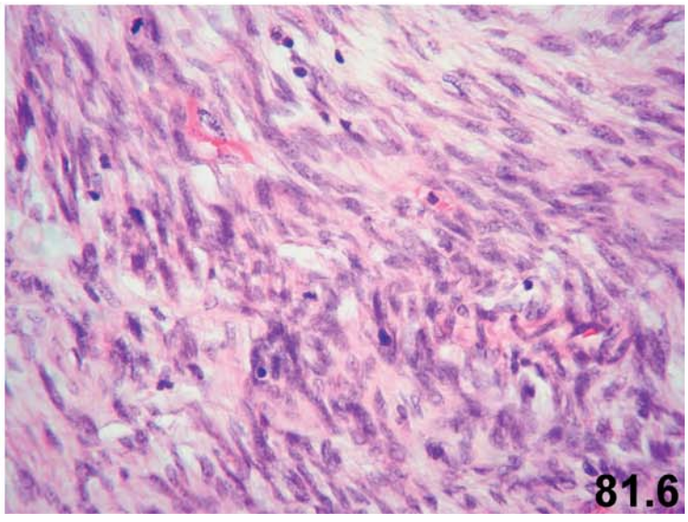
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Fig. 82: High-grade phylloides tumor.

Case history: A 33-year-old woman felt a palpable mass in the upper inner quadrant of her right breast. Clinical examination of the mass revealed a well-demarcated, mobile firm tumor consistent with a fibroadenoma. After 1 year, excisional biopsy of the lesion was performed and revealed a 3-cm greyish-white, fleshy tumor. The tumor was sharply circumscribed.

Figs. 82.1 and **82.2:** Excisional biopsy revealed a biphasic tumor with pushing margins.

Fig. 82.3: The tumor displays several leaflike structures associated with hypercellular stroma.

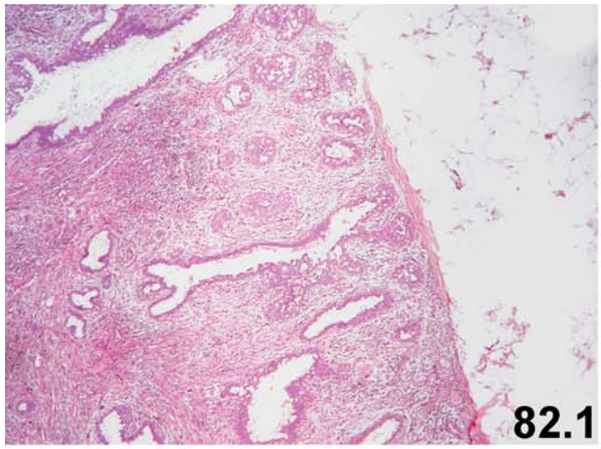
Fig. 82.4: The hypercellular stromal component of the tumor shows significant nuclear atypia.

Figs. 82.5, 82.6, and **82.7:** Higher magnification of the tumor revealing stromal cells with high-grade nuclear atypia.

Fig. 82.8: The tumor has up to six mitotic figures per 10 high-power fields (hpf) in the most mitotically active areas.

Fig. 82: Final remarks

- While the tumor is well-circumscribed and lacks any infiltrative growth pattern, it represents an example of high-grade phylloides tumor. It must be kept in mind that high-grade phylloides tumor of the breast can be very well-circumscribed. The grading of this tumor is based on the presence of high-grade nuclear atypia and significant mitotic activity (more than three mitoses per 10 hpf).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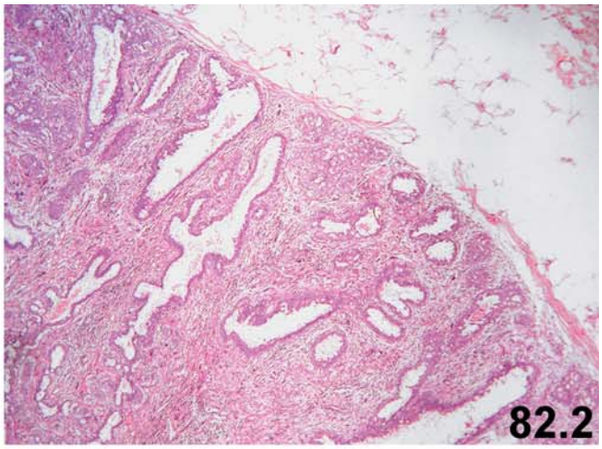
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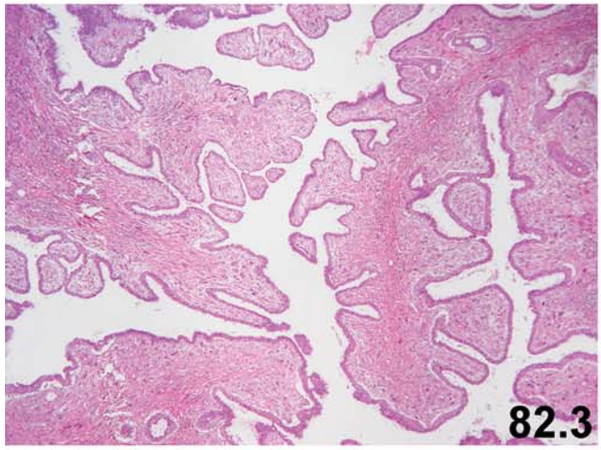
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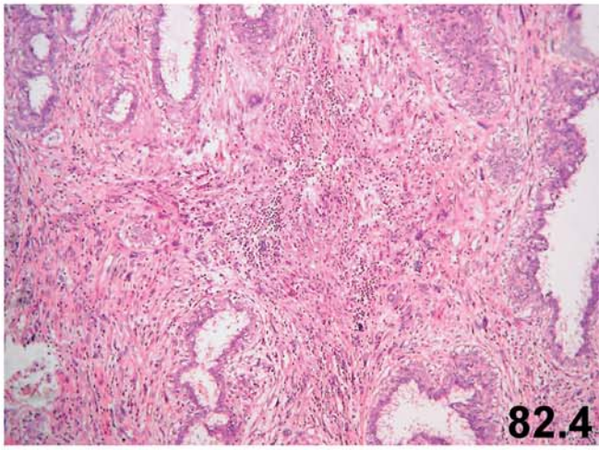
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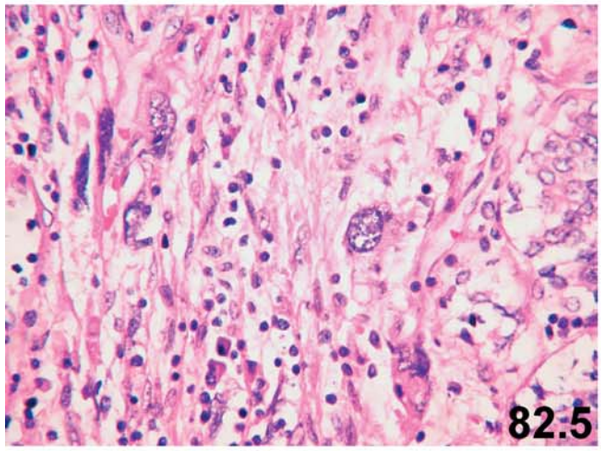
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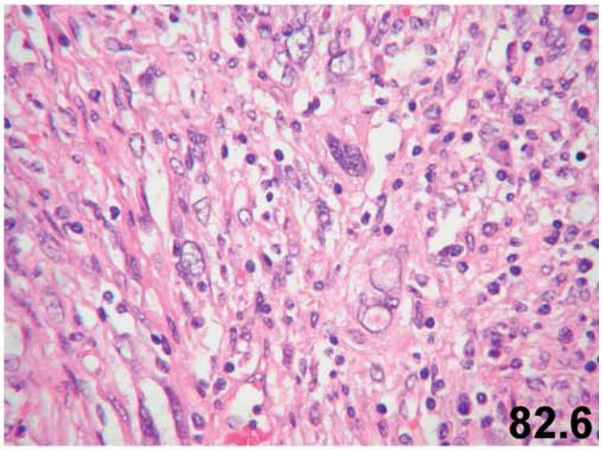
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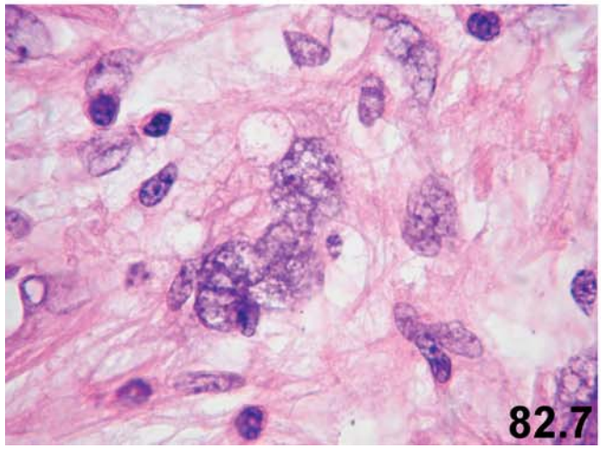
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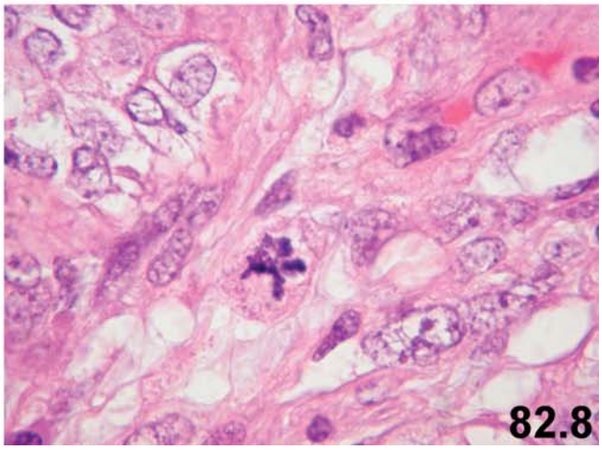

82.8

Fig. 83: Stromal overgrowth of a high-grade phylloides tumor.

Case history: A 49-year-old woman presented with a solid, firm tumor in her left breast. Mammographic and ultrasonographic examinations revealed a predominantly well-circumscribed tumor. The cut surface of the surgical specimen showed a solid, greyish-white, fleshy tumor (4.8 cm) with pushing margins.

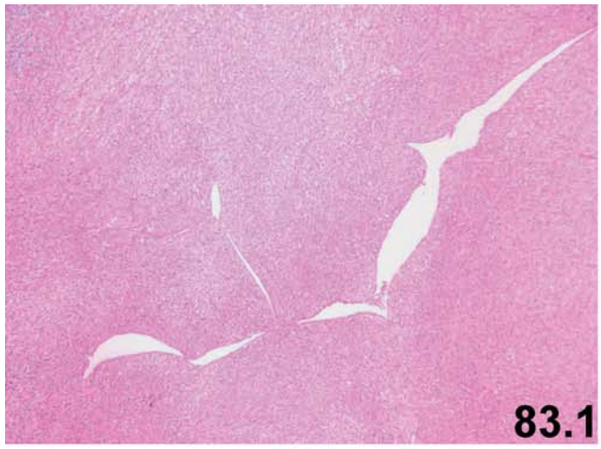
Figs. 83.1, 83.2, and **83.3:** Some areas of the tumor show a biphasic fibroepithelial neoplasm with a predominant stromal component. Note the leaflike processes protruding into ducts.

Figs. 83.4 and **83.5:** Several sections of the tumor display only mesenchymal elements.

Figs. 83.6, 83.7, and **83.8:** Several sections of the tumor show stromal overgrowth with numerous mitotic figures and moderate to severe cytologic atypia.

Fig. 83: Final remarks

- The minor epithelial component of this phylloides tumor could be identified after extensive sampling and serial sectioning of the tumor. The presence of stromal overgrowth, moderate to severe nuclear atypia, and high mitotic activity (more than eight mitoses per 10 hpf) in this case justify the diagnosis of high-grade phylloides tumor with stromal overgrowth.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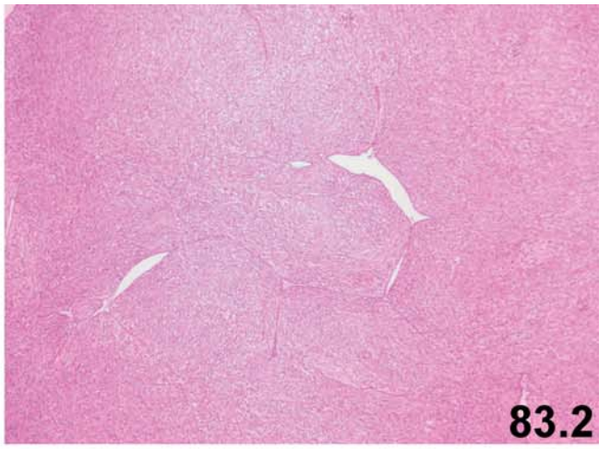
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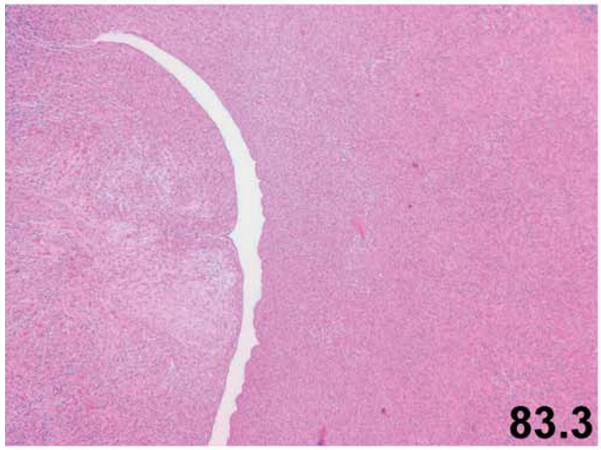
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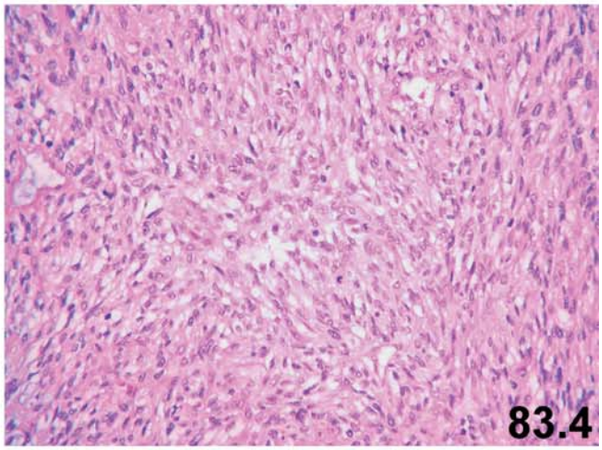
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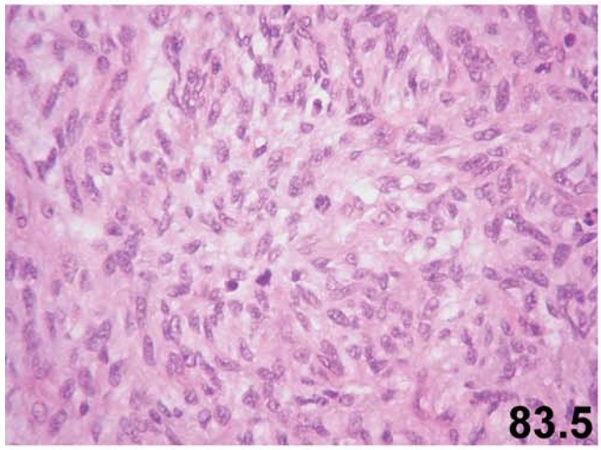
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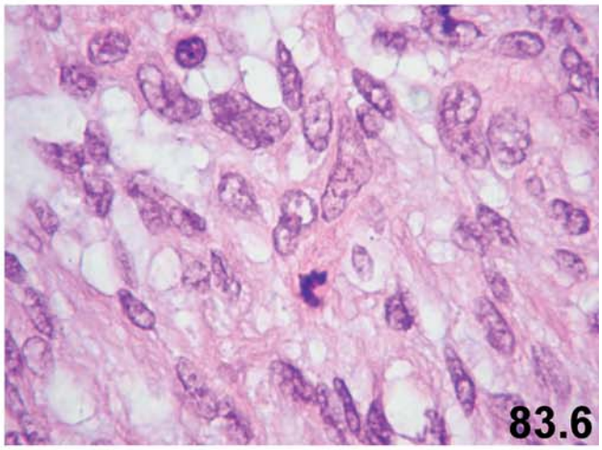
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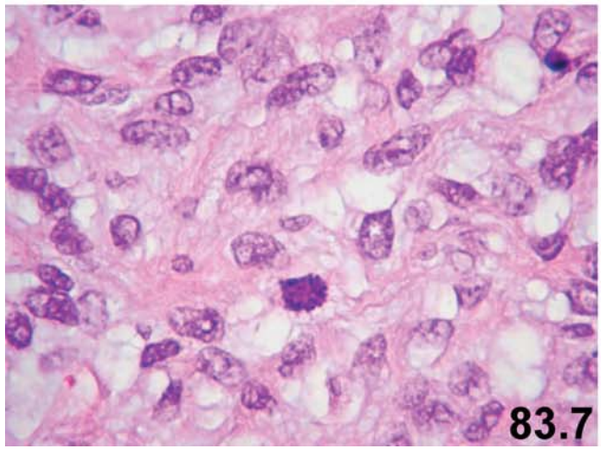
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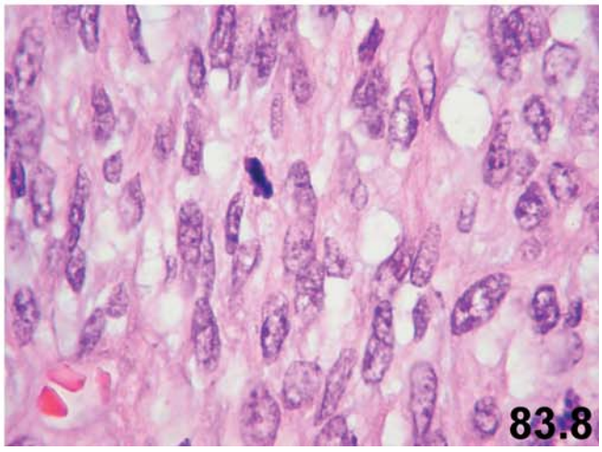

83.8

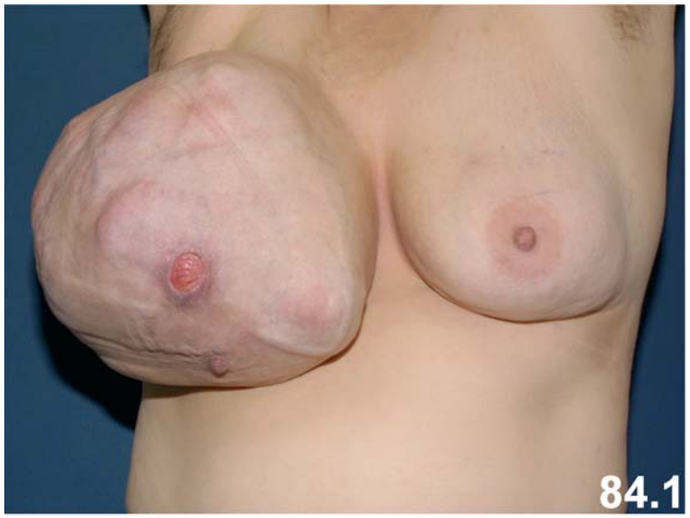
Fig. 84: High-grade phylloides tumor.

Case history: A 44-year-old woman presented with a huge right breast tumor measuring 29 cm at its greatest diameter. She had a slowly growing tumor over the past 18 years. However, she noticed rapid tumor enlargement during the previous year before she visited her physician.

Figs. 84.1 and **84.2:** A huge right breast tumor showing dilation of superficial skin veins. Note the centrally located skin ulceration. (Courtesy of Dr. G. Lushin, Graz, Austria.)

Fig. 84.3: Gross appearance of the tumor shows a solid, fleshy mass with a whorled appearance.

Fig. 84.4: The cut surface of the tumor with characteristic whorled appearance shows curved clefts.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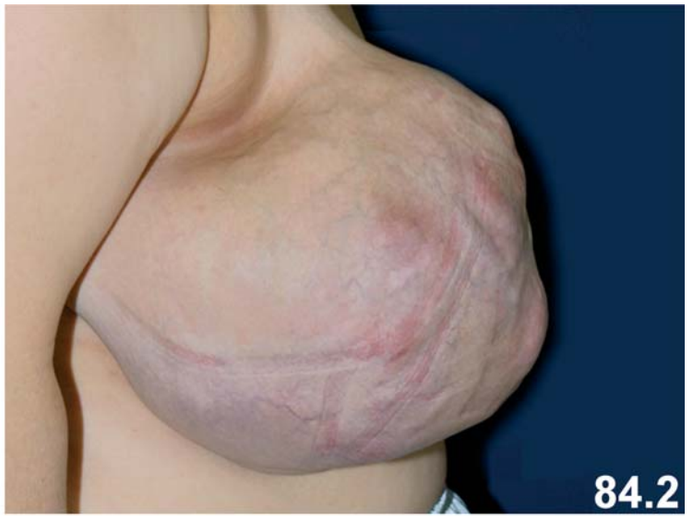
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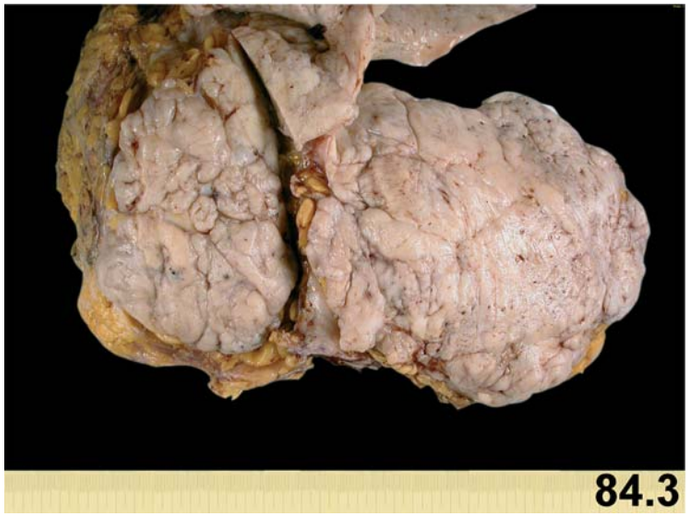
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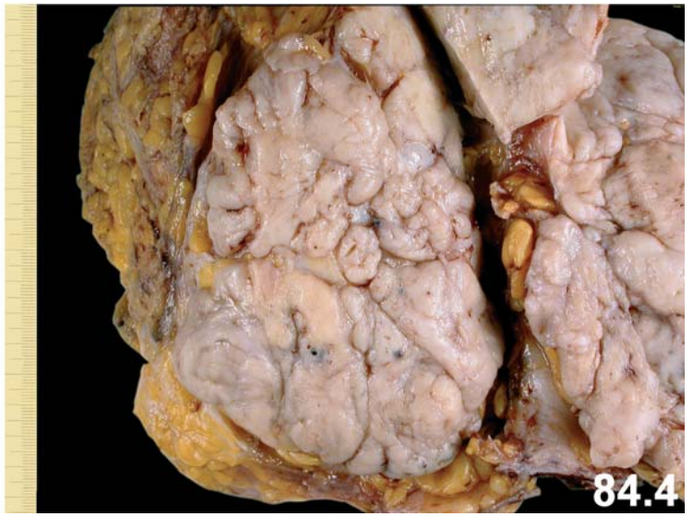
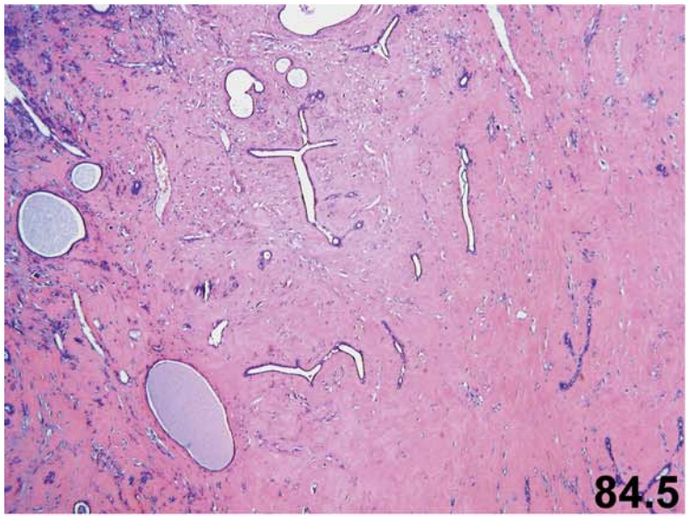

84.4

Figs. 84.5 and **84.6:** Some sections of the tumor show a biphasic tumor with hypocellular stroma closely mimicking an intracanalicular growth pattern of a fibroadenoma.

Figs. 84.7 and **84.8:** Several other sections of the tumor display a very cellular stromal component with periductal (Fig. 85.7) or leaflike (Fig. 85.8) arrangements.

Fig. 84.9: Periductal growth pattern of the tumor showing hypercellular stromal component.

Fig. 84.10: Several sections show hypocellular and more fibrous areas with an abrupt transition into the hypercellular stromal zones.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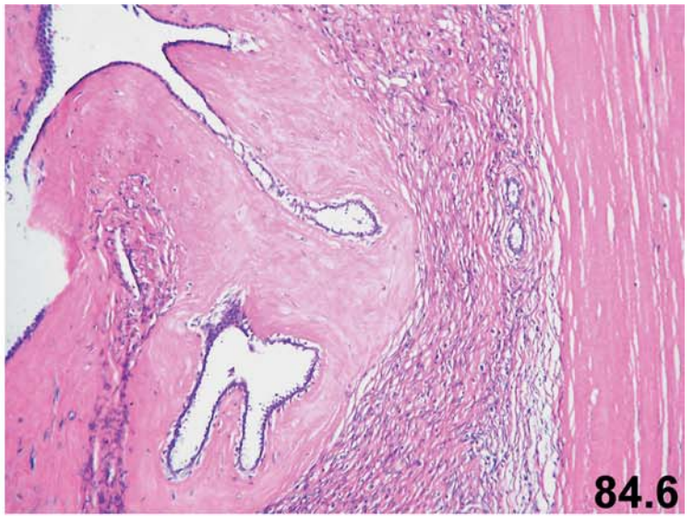
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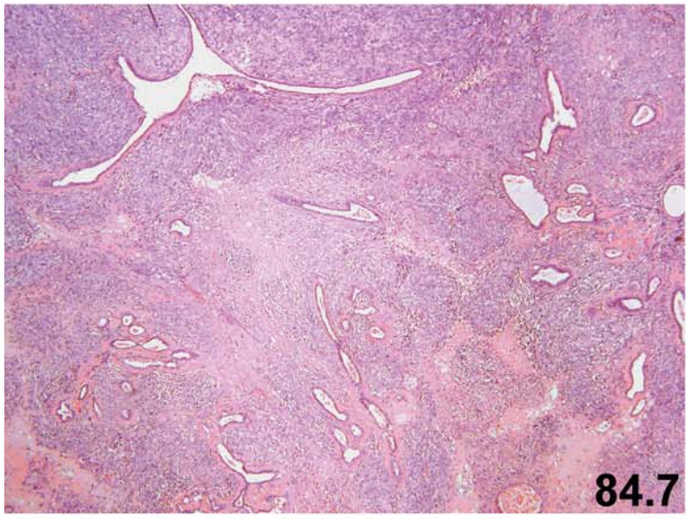
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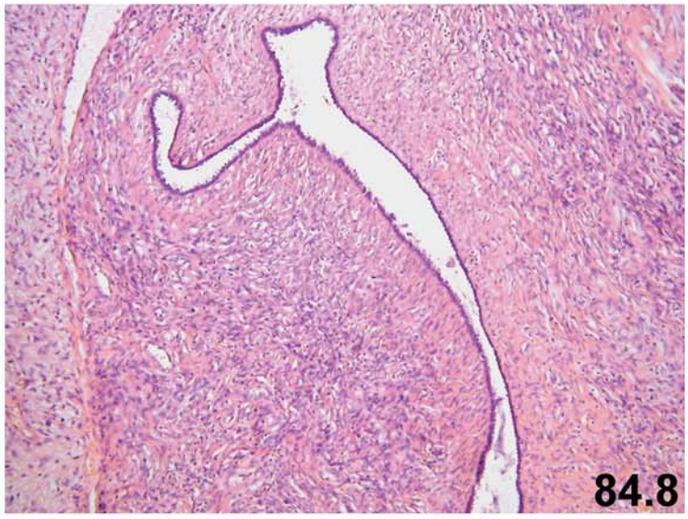
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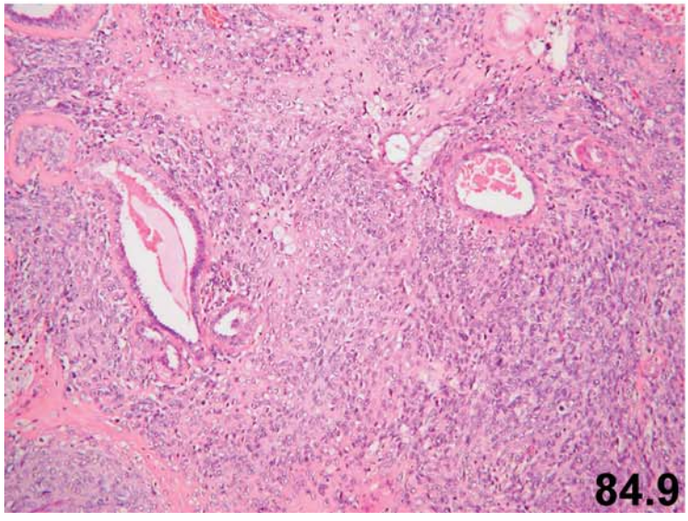
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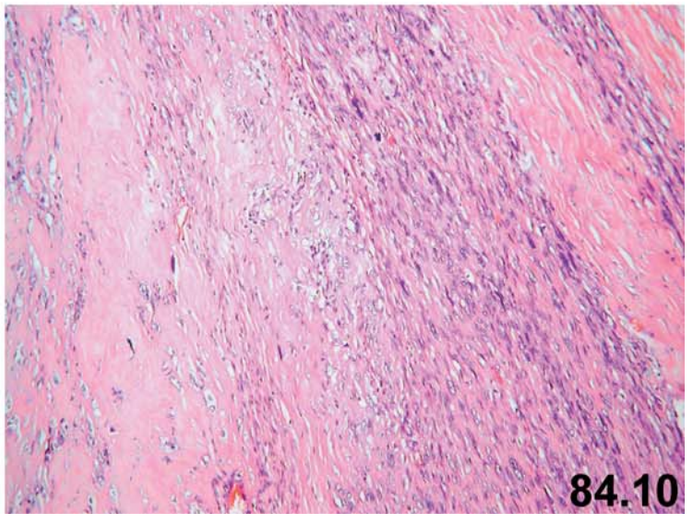

84.10

Fig. 84.11: Hypercellular stromal areas of the tumor showing atypical spindle cells. Several mitotic figures are present.

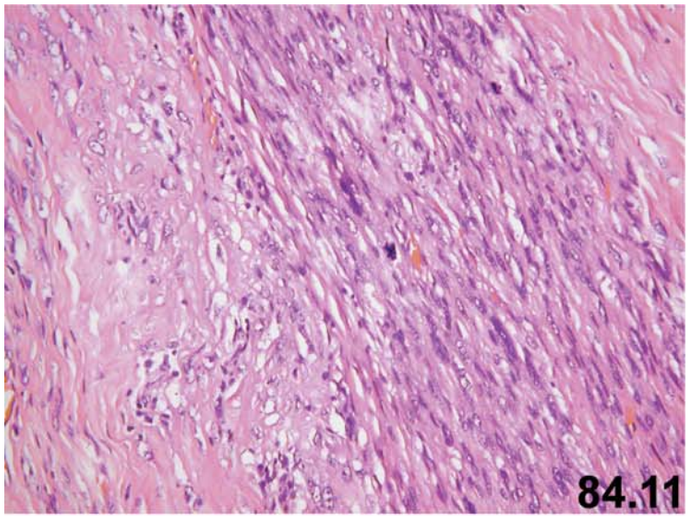
Fig. 84.12: Several sections of the tumor are highly cellular and show spindle cells with a fibrosarcomatous growth pattern.

Fig. 84.13: The tumor shows numerous mitotic figures. Indeed, there were up to 34 mitotic figures per 10 hpf in the most mitotically active areas.

Figs. 84.14, 84.15, and **84.16:** Several sections show stromal overgrowth revealing extremely atypical tumor cells with hyperchromatic and bizarre nuclei.

Fig. 84: Final remarks

- Concerning the cellularity, this tumor is heterogeneous in appearance. While some areas are hypocellular and closely simulate a (giant) fibroadenoma, other areas are extremely cellular and reveal extremely atypical stromal cells with high mitotic activity. Extensive sampling of such biphasic tumors (at least one section per 1 cm of the tumor) is necessary in order to identify and appropriately grade a phylloides tumor.
- The presence of highly atypical spindle cells or bizarre-looking tumor cells within the stroma should raise the possibility of a sarcomatoid (metaplastic) carcinoma in the background of a high-grade phylloides tumor. Immunohistochemistry for cytokeratin (CK) was performed on several sections in this case; the highly atypical cells were negative for CK (not shown).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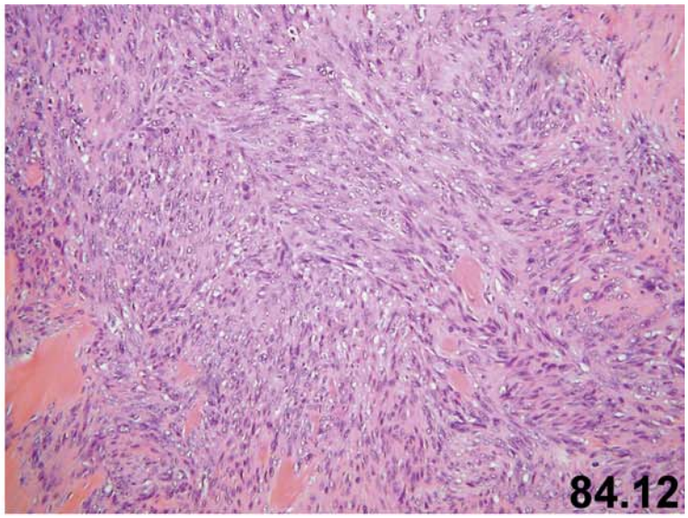
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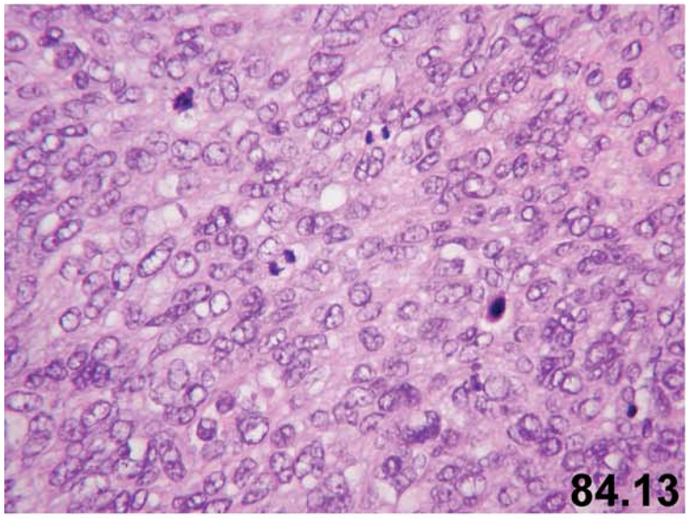
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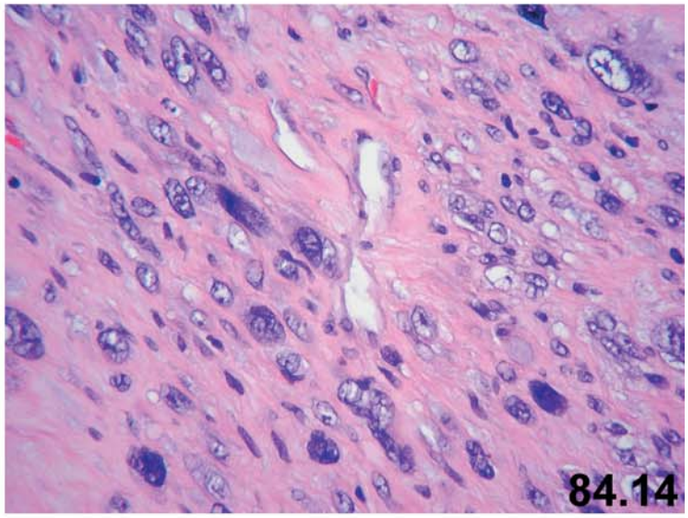
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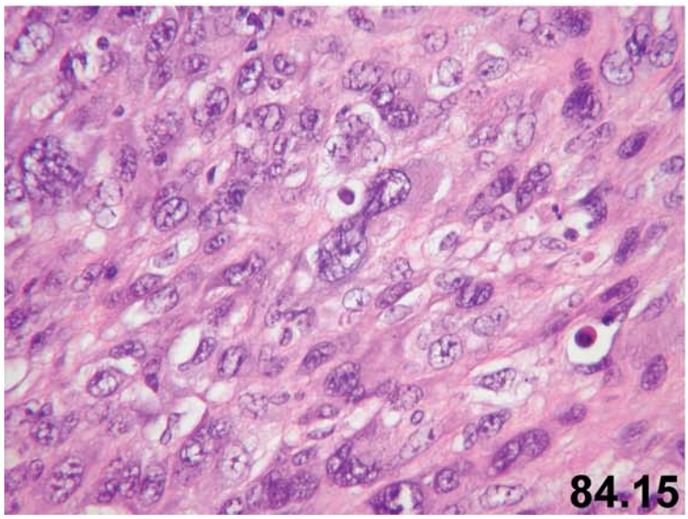
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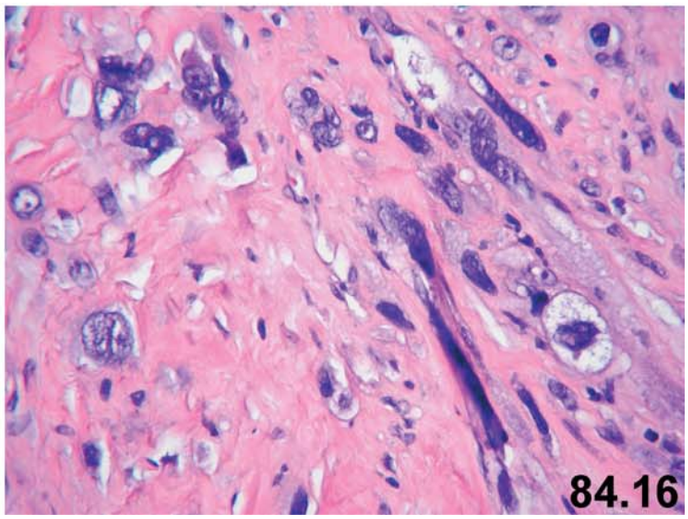
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Fig. 85: Osteosarcoma arising in a high-grade phylloides tumor.

Case history: 85-year-old woman presented with a giant tumor of her left breast. The tumor measured 20 cm in greatest diameter. A needle core biopsy showed a biphasic, fibroepithelial neoplasm with atypical stromal cells, suggestive of a phylloides tumor. Because of the tumor's size, a modified radical mastectomy was performed.

Fig. 85.1 and **85.2:** Cut surface of the mastectomy specimen revealing a predominantly solid tumor with areas of necrosis and hemorrhage. Note the fleshy, greyish-white appearance and the cystic component of the tumor.

Fig. 85.3: Low magnification of the tumor shows a biphasic, fibroepithelial neoplasm with several leaflike structures.

Fig. 85.4: The cellularity of the stromal component of the tumor varies significantly ranging from hypocellular to very hypercellular zones. The hypercellular stromal areas showed up to 10 mitotic figures per 10 high-power fields (not shown).

Fig. 85.5: Hypercellular stroma with numerous multinucleated giant cells or osteoclastic-type stromal cells.

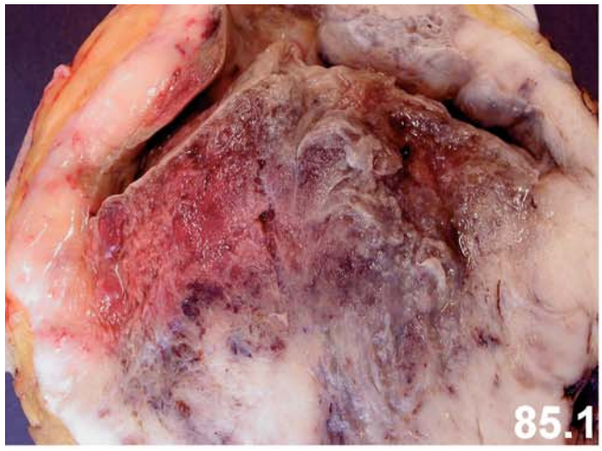
Fig. 85.6: Other areas of the tumor show numerous spindle cells set in a homogeneous, osteoid background.

Fig. 85.7: High magnification reveals atypical stromal cells and osteoid material.

Fig. 85.8: High magnification shows atypical mononuclear stromal cells and multinucleated osteoclasts surrounding osteoid material.

Fig. 85: Final remarks

- In this case, the gross appearance of the tumor is highly suggestive of a phylloides tumor (formerly called cystosarcoma phylloides). Because the cellularity of the stromal component in a phylloides tumor can vary significantly, extensive sampling (at least one section per 1 cm of the tumor) is recommended.
- This case represents an osteosarcoma arising in the background of a high-grade phylloides tumor. The osteosarcomatous component of this tumor metastasized to the lungs 3 years after the breast surgery.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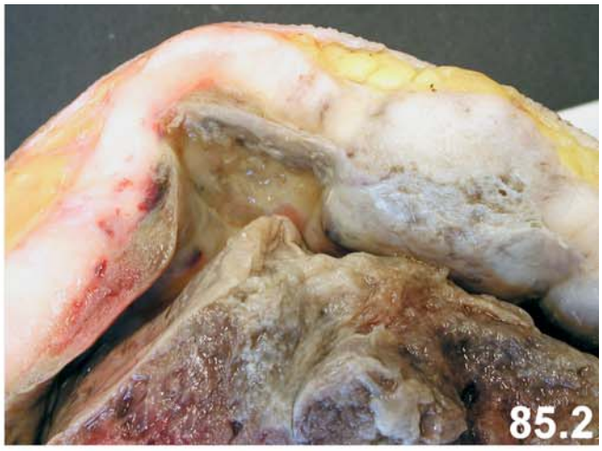
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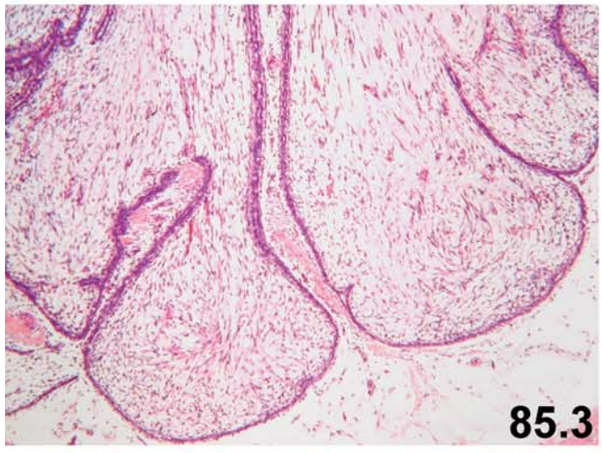
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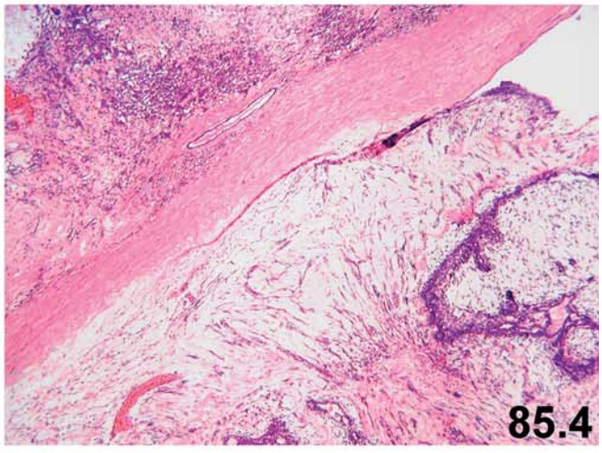
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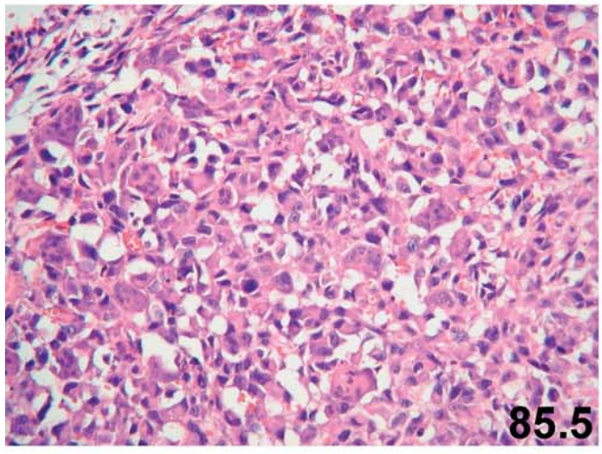
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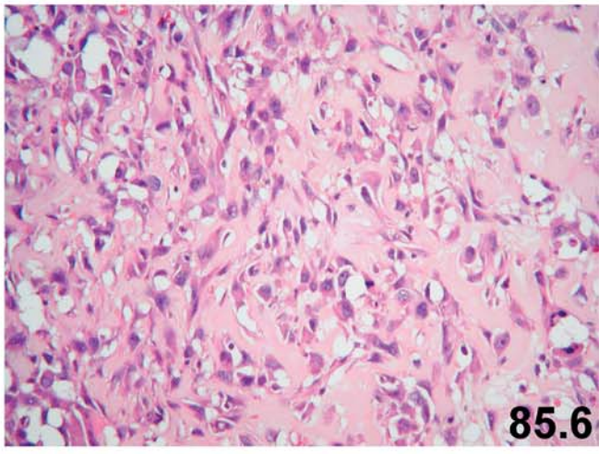
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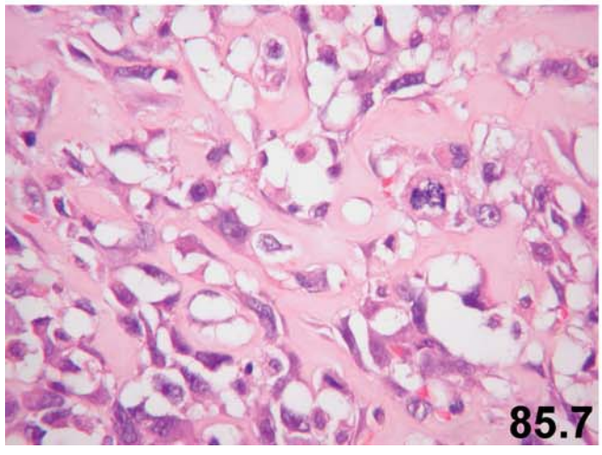
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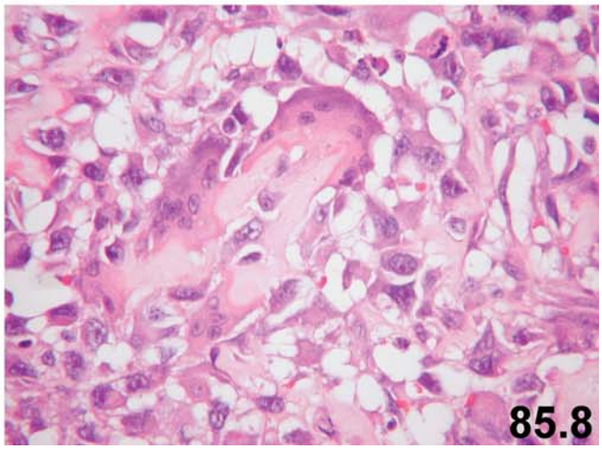
85.8

Diseases of the Nipple

Contents

CHAPTER 12 Disease of the Nipple

12.1 Paget's Disease

12.1.1 Definition

Presence of highly atypical, large cells with abundant cytoplasm and prominent nucleoli within the epidermis (mostly nipple), almost always associated with underlying ductal intraepithelial neoplasia (high-grade ductal intraepithelial neoplasia [DIN; DCIS]).

12.1.2 Macroscopic (Clinical) Features

Often eczematoid itching and a unilateral change of the nipple, eventually associated with erosion. Ulceration, crusting, and serous or bloody discharge often occur in more advanced cases. In about 50% of cases, a painless mass is palpable in the underlying breast tissue. There is sometimes retraction of the nipple. Occasionally, it may be bilateral [1, 4, 11, 15].

12.1.3 Microscopic Features (Fig. 86)

- Isolated cells or clusters of atypical round or oval cells are present within the squamous epithelium. The neoplastic cells show round, large, hyperchromatic nuclei; prominent nucleoli; and clear pale, eosinophilic, or amphophilic cytoplasm.
- In the vast majority of cases (more than 95%), high-grade DIN (DCIS) within the lactiferous duct is present (intraepidermal spread of the tumor cells).
- A variant of Paget's disease resembling Bowen's disease with full-thickness epidermal atypia and severe nuclear atypia can occur.
- Intracytoplasmic mucin can be present.
- Paget's disease can be associated with infiltrating carcinoma of various types (mostly infiltrating ductal carcinoma, NOS type).
- Very rarely, there is an association with infiltrating lobular carcinoma or lobular intraepithelial neoplasia (LIN, high-grade or pleomorphic variant).

12.1.4 Differential Diagnosis

- *Clear cell changes of keratinocytes:* Occasionally, normal squamous cells of the nipple show clear cytoplasm; the cells lack nuclear atypia and are smaller and uniform.
- *Malignant melanoma:* Often associated with clear-cut underlying malignant melanoma. No underlying DIN (DCIS) or invasive carcinoma. The cells are typically cytokeratin (CK)-negative but HMB45-positive. One should keep in mind that some melanomas are devoid of pigment, while Paget cells can incorporate melanin from epidermal cells [19, 21].
- *Bowen's disease (squamous carcinoma in situ):* The neoplastic cells usually involve the entire layers of epidermis, with morphological evidence of squamous cells usually lacking large clear or eosinophilic cytoplasm. There is no association with underlying breast carcinoma or DIN (DCIS) [8, 13, 23, 26]. The neoplastic cells in Bowen's disease are typically positive for HMW-CK such as CK5/6 and CK34BE12. (See Table 12.1.)

Table 12.1. Immunohistochemical profile of Paget's disease (PD), malignant melanoma (MM), and Bowen's disease (BD)

	PD	MM	BD
LMW-CK (CK8/18)	+	–	–
HMW-CK (CK34BE12)	–	–	+
HMW-CK (CK5/6)	–	–	+
CK7	+	–	–
EMA	+	–	–
CEA	+ (polyclonal) – (monoclonal)	–	–
MUC1	+	–	–

Caution

- The most useful combination markers in difficult cases are low molecular weight cytokeratins (LMW-CKs) that are always positive in Paget's disease (such as CK7 and CK8/18) and high molecular weight cytokeratins (HMW-CKs, either CK5/6 or CK34BE12) that are always negative in Paget's disease. MUC1 is another reliable marker that is always positive in Paget's cells.

12.1.5 Additional Comments

Diagnostic problems particularly arise when fixation and tissue preparation are not optimal or when the biopsy was taken from a degenerative area. Poor fixation of the tissue makes it difficult to distinguish Paget cells from melanocytic cell population.

Paget cells are very often negative for estrogen receptors and progesterone receptors. Androgen receptors, however, are commonly positive in Paget cells [14].

HER2/neu is almost always positive in mammary Paget's disease [5, 10, 14].

The Paget cells are usually negative for S100 and HMB45.

The glandular nature of the neoplastic cells in Paget's disease is confirmed by electron microscopic features. Immunohistochemical studies have confirmed that Paget cells have the same phenotype as the underlying DIN (DCIS). However, a few reports suggest that a minority of cases of Paget's disease develop independently from the underlying carcinoma (primary intraepidermal neoplasia of glandular type) [17].

12.1.6 Further Reading

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12.2 Nipple Duct Adenoma

12.2.1 Definition

A benign tumor of the nipple with compact proliferation of small tubules lined by epithelial and myoepithelial cells, with or without intraepithelial proliferation, around the collecting ducts.

12.2.2 Synonyms

Nipple adenoma, adenoma of the nipple, florid papillomatosis of the nipple, subareolar duct papillomatosis, papillomatosis of the nipple.

12.2.3 Macroscopy

Nipple duct adenoma (NDA) is a solitary tumor with well-delineated margins and greyish-white cut surface. Cystic dilatation of the underlying ducts can be present. Erosion or ulceration of the epidermis in advanced disease can occur.

12.2.4 Microscopic Features (Fig. 87)

- Although grossly the tumor appears well circumscribed, histologically the margins are often ill defined.
- Compact aggregates of tubules proliferate within and replacing the nipple stroma.
- Often, there are prominent sclerotic changes of the stroma, causing distortion of the tubules (sclerosing adenosis pattern).
- Ducts usually exhibit florid ductal hyperplasia with or without a mild degree of cytologic atypia.
- Papillary structures are often present; these can be a prominent feature (papillomatosis pattern).
- The tubules, compressed glands, and papillary structures display a two-cell layer of epithelial and myoepithelial cells.
- Necrosis as well as surface (epidermis) erosion can occur.
- Increased mitotic activity is a common finding in the epithelial cells.
- Squamous or apocrine metaplasia may occur.
- Some areas of the stroma may show edematous or myxoid changes. Elastosis can also be present. Areas of the stroma can be cellular (desmoplastic appearance).

Caution

- NDA can be mistaken for invasive carcinoma or Paget's disease clinically. The adenosis pattern with significant stromal sclerosing (pseudoinfiltrative pattern) can easily be misinterpreted as invasive carcinoma. The presence of a myoepithelial cell layer and the heterogeneity of cell population exclude the possibility of cancer.
- The epithelial cells may show nuclear enlargement, higher nuclear-cytoplasmic ratio, vesicular or hyperchromatic nuclei, and prominent nucleoli. These changes are mostly reactive. One should always pay attention to the heterogeneity of cell population in the proliferating areas, a feature characteristic of florid intraductal hyperplasia (UDH).
- The presence of intraluminal necrosis, increased mitotic activity, or surface erosion should not lead to the diagnosis of cancer. If there is any doubt about the nature of the tumor, immunohistochemistry should be performed.

12.2.5 Immunoprofile

The presence of a myoepithelial cell layer can be confirmed by smooth muscle actin or other myoepithelial markers (such as p63, CD10, and calponin). The heterogeneity of the cell population can be demonstrated by staining for HMW-CK (CK5/6 or CK34BE12).

12.2.6 Malignant Changes Associated with NDA

Rarely, high-grade DIN (DCIS) can arise in the background of NDA. An invasive ductal carcinoma may rarely be associated with NDA.

12.2.7 Histopathology

- Infiltrating glands and solid aggregates of tumor cells without a myoepithelial cell component.
- The DIN (DCIS) or invasive carcinoma is typically composed of a homogeneous epithelial cell population negative for HMW-CK (such as CK5/6).

Caution

- It is always best to be conservative when the diagnosis of malignancy is in any doubt, particularly when the consideration is DCIS arising in NDA. Necrosis in ductal hyperplasia may occur and should not lead to the diagnosis of in situ ductal carcinoma. In a difficult case, immunohistochemistry for CK5/6 and myoepithelial markers can be very helpful.

12.2.8 Further Reading

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12.3 (Infiltrating) Syringomatous Adenoma

12.3.1 Definition

A rare, nonmetastasizing, locally infiltrative tumor of the nipple/areolar region showing some sweat duct differentiation.

12.3.2 Synonym

Infiltrating syringomatous adenoma

12.3.3 Macroscopy

A firm greyish-white mass usually with ill-defined borders simulating an invasive carcinoma.

12.3.4 Microscopic Features (Fig. 88)

- Angulated or small curved (comma-like) tubules are evident.
- Compressed, cordlike glands or strands are present.
- The tubules (glands) show haphazard and infiltrating arrangements with permeation of the nipple stroma.
- The tubules and compressed glands are lined by two cell layers: a luminal layer of epithelial cells and a basally located myoepithelial cell layer.
- As a rule, there is no nuclear atypia or increased mitotic activity.

- Squamous metaplasia within the glands is a very common finding.
- Some of the glands may show usual ductal hyperplasia.
- Small keratinous cysts are often present.
- The stroma is either unaltered or, in some cases, can show reactive cellular areas (desmoplasia).
- Myxochondroid stromal changes may also occur.
- Invasion into the smooth muscle bundles of the nipple is common.
- Perineural invasion can rarely be identified.

12.3.5 Differential Diagnosis

Well-differentiated ductal carcinoma or tubular carcinoma; well-differentiated adenosquamous carcinoma.

Caution

- The most important feature for distinguishing syringomatous adenoma from a well-differentiated ductal or tubular carcinoma is the presence of epithelial and myoepithelial cells in the tubules of the syringomatous adenoma. While squamous metaplasia within the glands frequently occurs in syringomatous adenoma, it is not a feature of tubular carcinoma.

12.3.6 Additional Comments

Syringomatous adenoma also occurs deep within the breast proper.

All reported cases have been unilateral, and none has been associated with axillary lymph node metastasis. There is no hematogenic metastasis.

Because of its infiltrating pattern and local recurrences, this type of tumor has been considered by some dermatopathologists as microcystic adnexal carcinoma [2, 3] or sclerosing sweat duct (syringomatous) carcinoma. The reported recurrences are most likely because of incomplete excision of this frequently ill-defined tumor, which often extends beyond the grossly apparent margins.

Optimal treatment is complete excision with free margins [1, 5, 6, 8].

12.3.7 Further Reading

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Fig. 86: Paget's disease.

Case history: A 63-year-old woman presented with an itching, eczematoid nipple of her left breast. Although there was a bloody nipple discharge, no palpable tumor could be identified in the breast.

Fig. 86.1: Clinical aspect of Paget's disease shows a sharply demarcated eczematoid change of the nipple and areolar region. (Courtesy of Dr. G. Lushin, Graz, Austria.)

Fig. 86.2: Epidermis of the nipple showing isolated or small clusters of atypical cells. The atypical cells show hyperchromatic or vesicular nuclei.

Fig. 86.3: Highly atypical cells within the squamous epithelium of the nipple. The atypical cells reveal pale eosinophilic or amphophilic cytoplasm.

Fig. 86.4: Immunohistochemically, the tumor cells are characteristically positive for CK8/18 (low molecular weight cytokeratin). The tumor cells are also typically positive for CK7 (not shown).

Fig. 86.5: The neoplastic epithelial cells in Paget's disease are completely negative for high molecular weight cytokeratins such as CK34BE12 or CK5/6.

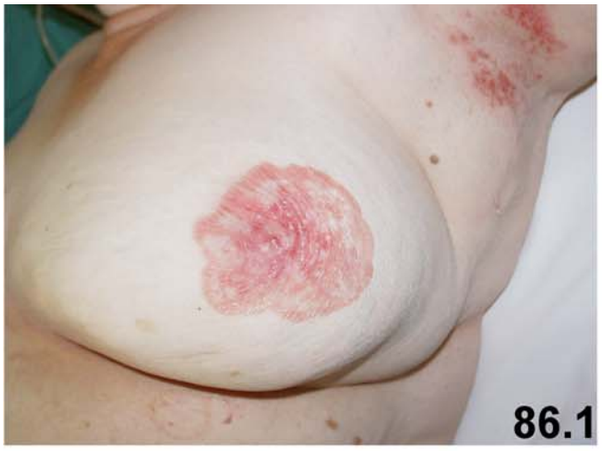
Fig. 86. 6: The tumor cells in Paget's disease are very often negative for estrogen receptors and progesterone receptors.

Fig. 86.7: In contrast to estrogen receptors and progesterone receptors, neoplastic cells in Paget's disease frequently express androgen receptors.

Fig. 86.8: The neoplastic cells almost always overexpress HER2/neu.

Fig. 86: Final remarks

- In a difficult case, the most useful markers in order to identify Paget's cells are LMW-CK (CK8/18, CK7) in combination with high molecular weight cytokeratin (CK34BE12, CK5/6). While the tumor cells in Paget's disease are positive for LMW-CK, they are typically negative for high molecular weight cytokeratin.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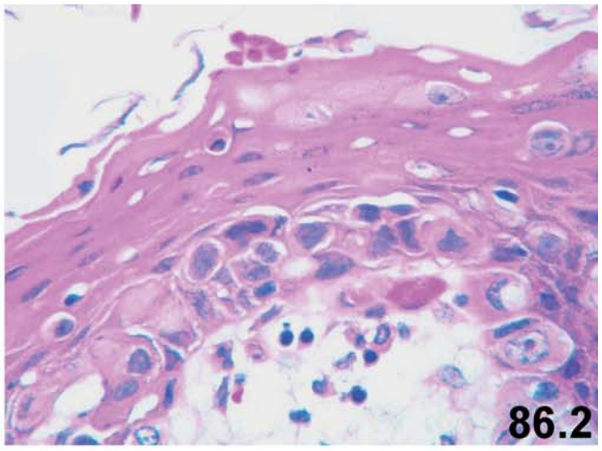
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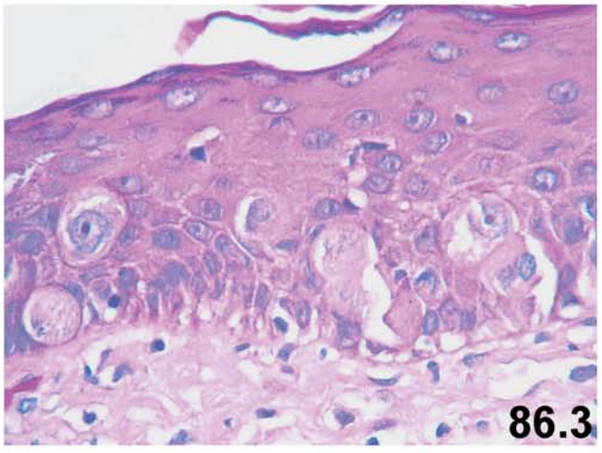
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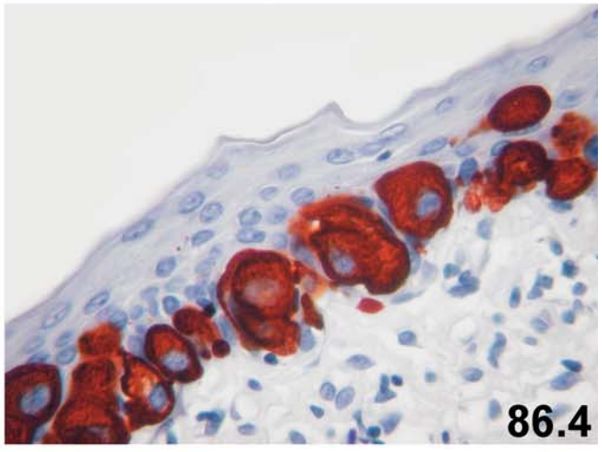
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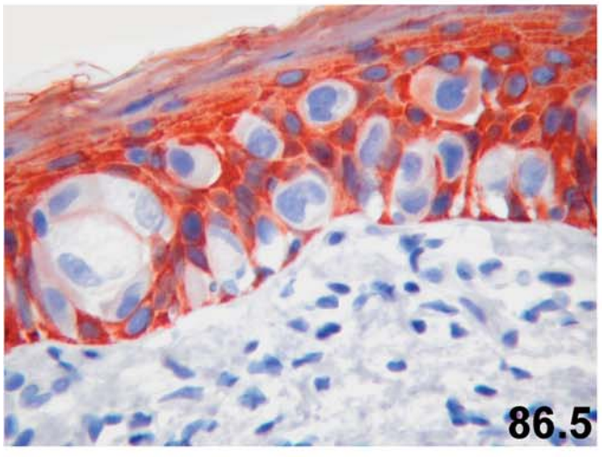
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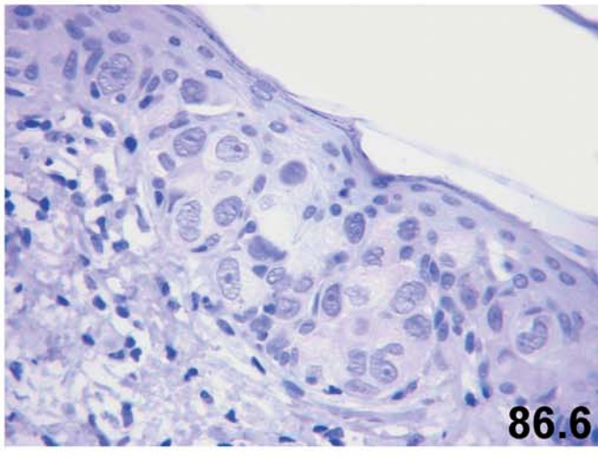
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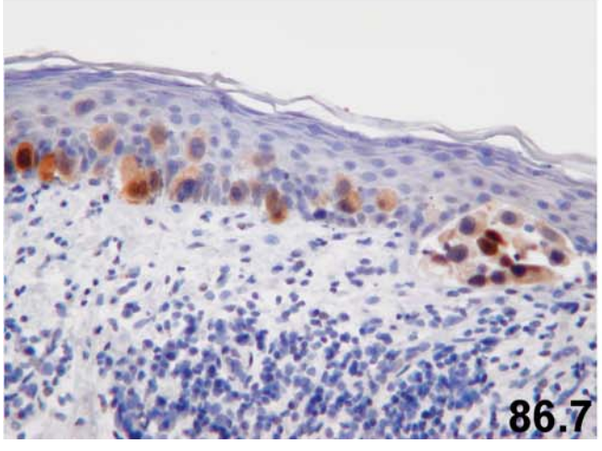
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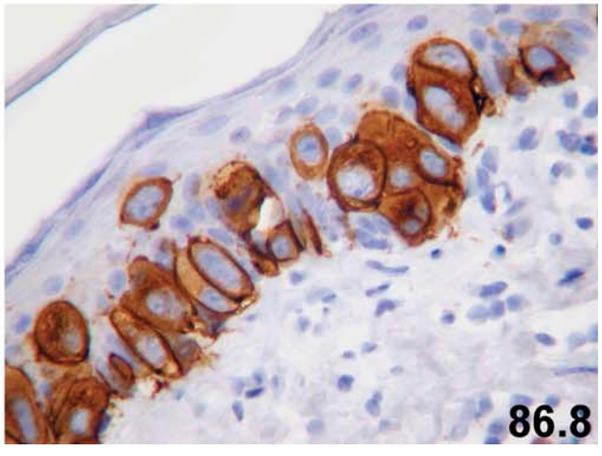
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Fig. 87: Nipple duct adenoma.

Case history: A 50-year-old woman presented with bloody nipple discharge and a firm tumor located in the left nipple. The overlying skin was ulcerated. The tumor was clinically and mammographically interpreted as malignant. A needle core biopsy of the tumor was performed, and the lesion was erroneously interpreted as DCIS associated with foci of infiltrating ductal carcinoma. The patient was treated by modified radical mastectomy.

Fig. 87.1: The cut surface of the mastectomy specimen shows a solid tumor, greyish-white to yellow in color, with well-defined margins.

Fig. 87.2: At low magnification, the tumor exhibits compact aggregates of tubules proliferating within and replacing the nipple stroma. Sclerotic changes of the stroma are also present, which cause distortion of the tubules.

Fig. 87.3: Some areas of the tumor with elongated and irregularly distributed tubules (sclerosing adenosis pattern).

Fig. 87.4: Several ducts reveal florid-type intraductal proliferations with tufting growth pattern.

Fig. 87.5: Intraductal hyperplasia of usual type demonstrating several irregular and slit-like secondary lumens.

Fig. 87.6: Higher magnification of the intraductal proliferating cells showing a heterogeneous cell population consisting of epithelial and modified myoepithelial (progenitor) cells. While the proliferating epithelial cells show round nuclei, the modified myoepithelial (progenitor) cells display a small spindle shaped or bipolar dark nuclei and scant cytoplasm. The cytology (cell population) and the architecture of the involved ducts are typical of usual ductal hyperplasia.

Figs. 87.7 and **87.8:** Immunohistochemistry for CK5/6 showing the heterogeneous positive reaction of the proliferating cells (mosaic positive pattern) that is typical for usual ductal hyperplasia.

Fig. 87: Final remarks

- Nipple duct adenoma (or florid papillomatosis of the nipple) can easily be mistaken for invasive carcinoma or Paget's disease, clinically. As unfortunately happened in this case, needle core biopsy of the nipple duct adenoma can be misinterpreted as carcinoma. Skin erosion or ulceration, increased mitotic activity, and luminal necrosis can occur in nipple duct adenoma and should not mislead to the diagnosis of cancer. The morphologic (and eventually immunohistochemical) analysis of the proliferating cells (recognition of epithelial and modified myoepithelial cells) and identification of basally located myoepithelial cells in the glands with pseudoinvasion are the most helpful clues for appropriately classifying this rare, benign neoplasm.


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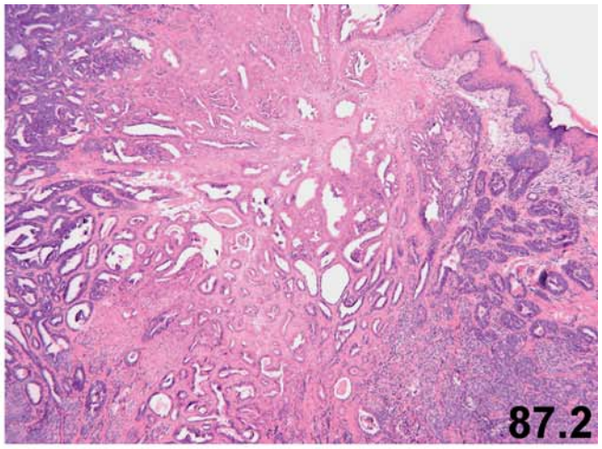
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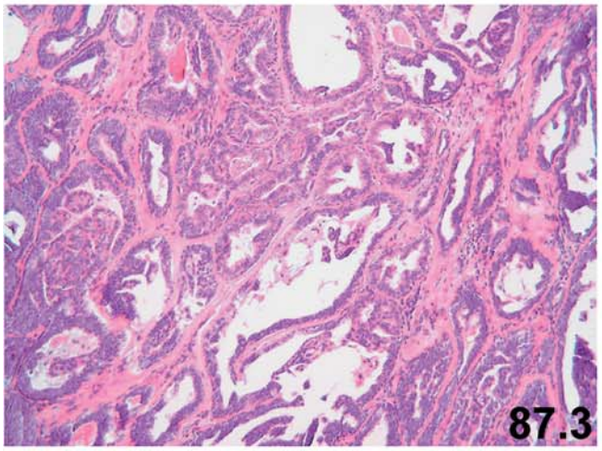
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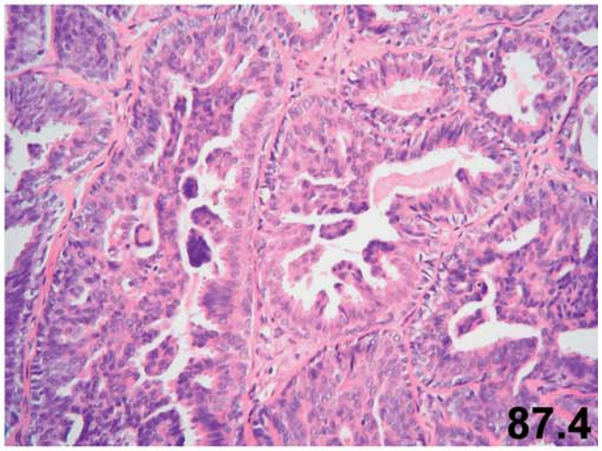
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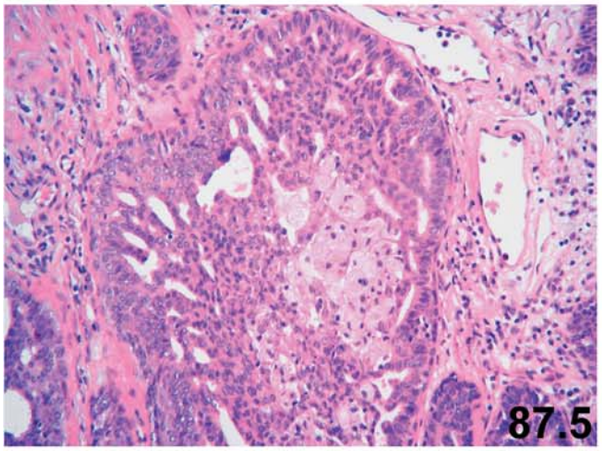
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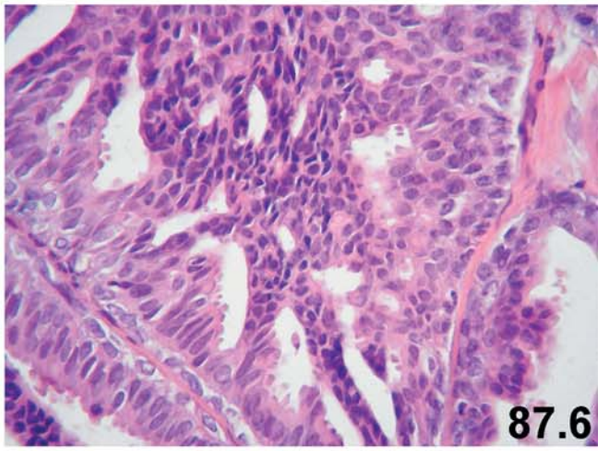
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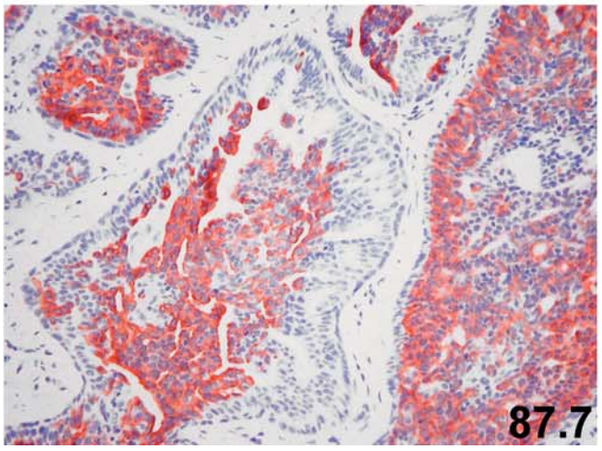
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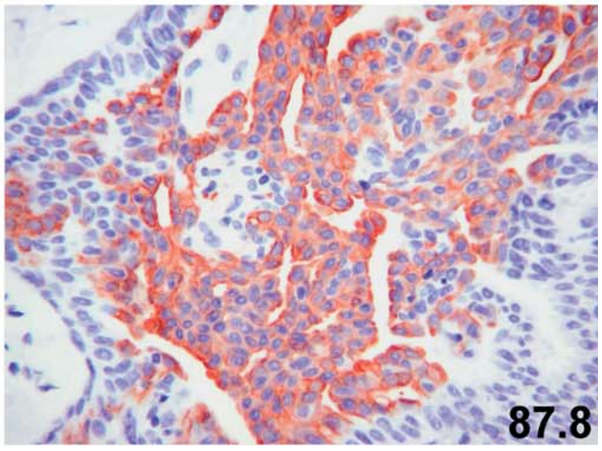
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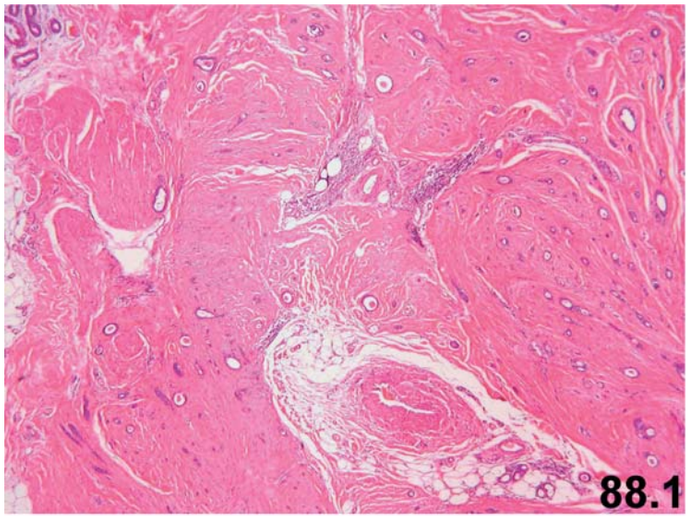
Fig. 88: (Infiltrating) syringomatous adenoma.

Case history: A 43-year-old woman presented with a firm tumor of the areolar region of the right breast. Clinical and mammographic examinations of the tumor revealed a tumor with ill-defined borders, highly suspicious for malignancy.

Figs. 88.1 and **88.2:** Excisional biopsy of the tumor showing numerous open glands or tubules with haphazard and infiltrating arrangements.

Figs. 88.3 and **88.4:** Several angulated tubules with irregular and infiltrating arrangements are present.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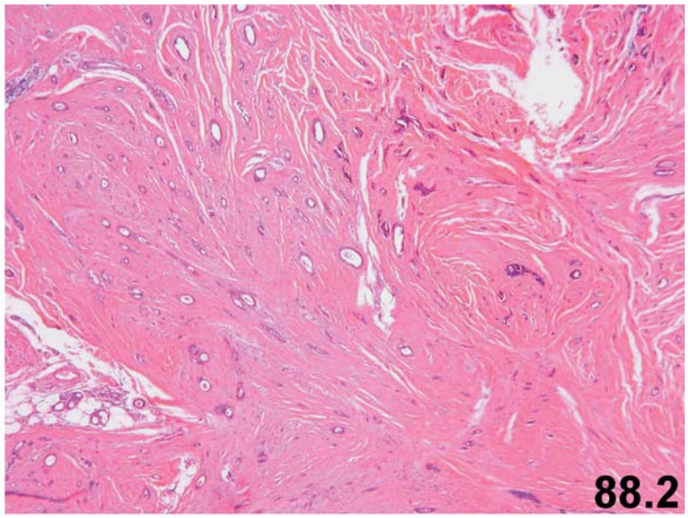
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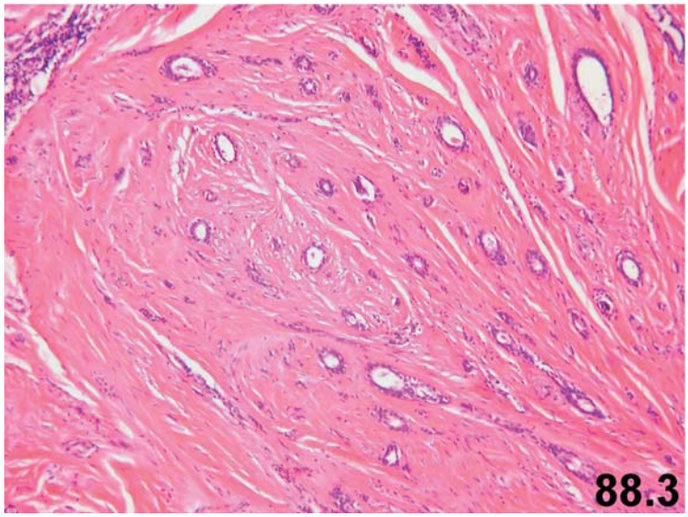
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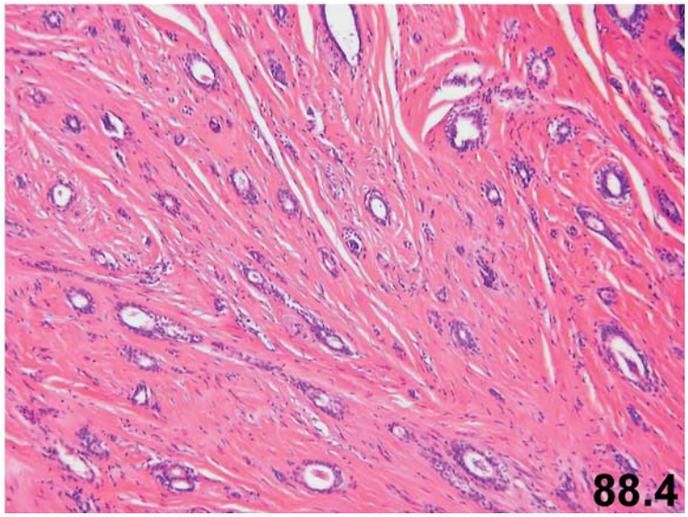
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Fig. 88.5: In addition, several areas of the tumor show compressed, cordlike glands or strands.

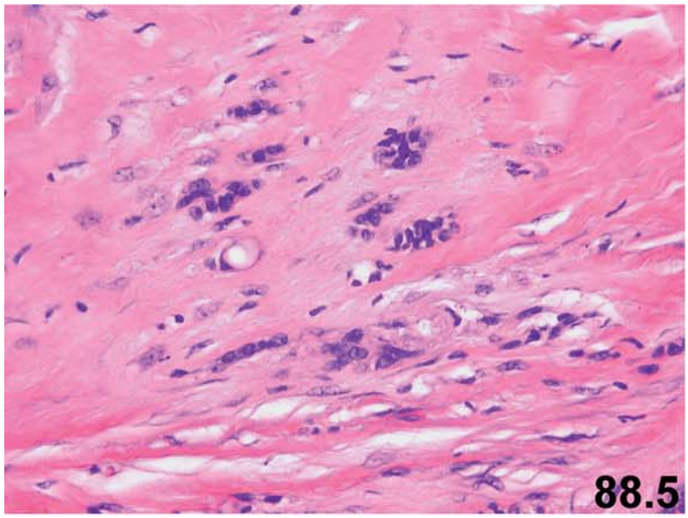
Fig. 88.6: Infiltrating glands showing angulated tubules and cordlike compressed structures.

Figs. 88.7 and **88.8:** At higher magnification, the tubules and cordlike structures clearly reveal a basally located myoepithelial cell layer.

Figs. 88.9 and **88.10:** Angulated or small curved (comma-like) tubules with infiltrating growth pattern containing a myoepithelial cell layer.

Fig. 88: Final remarks

- The syringomatous adenoma of the nipple has a true infiltrating growth pattern with invasion into smooth muscle bundles of the nipple. The stroma can be either unaltered or, in some instances, can show reactive, cellular (desmoplastic) areas.
- The main differential diagnosis in this case is a well-differentiated ductal or tubular carcinoma. The presence of two cell types within the tubules in this case excludes the possibility of an infiltrating carcinoma.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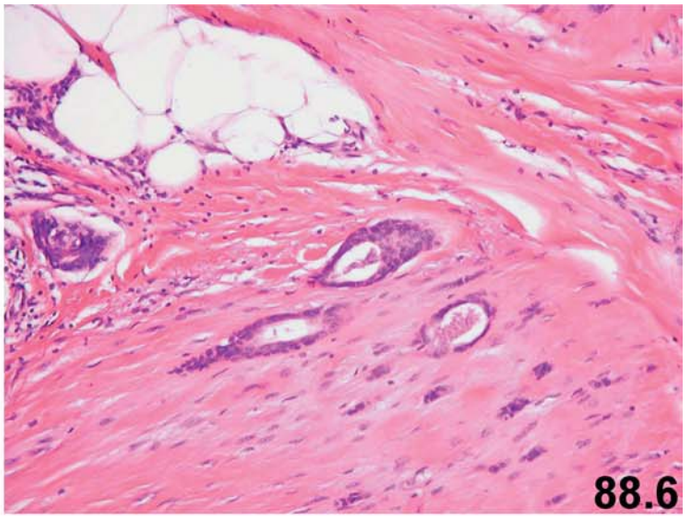
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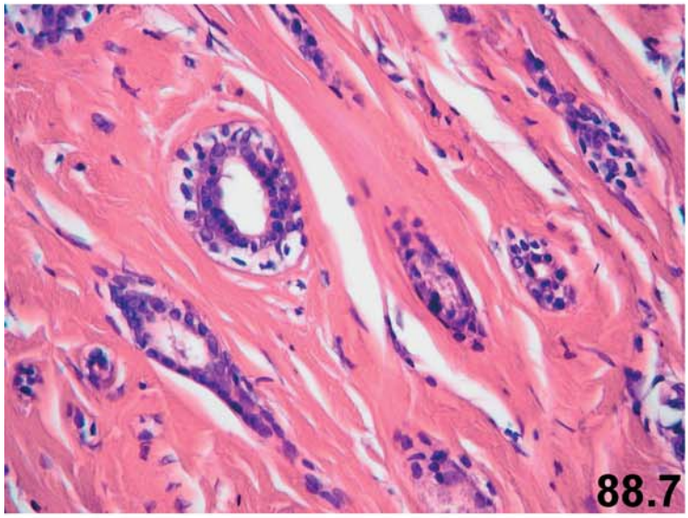
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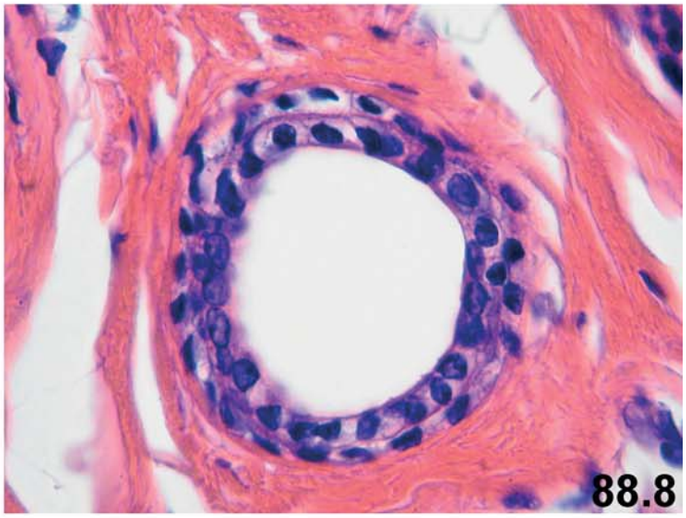
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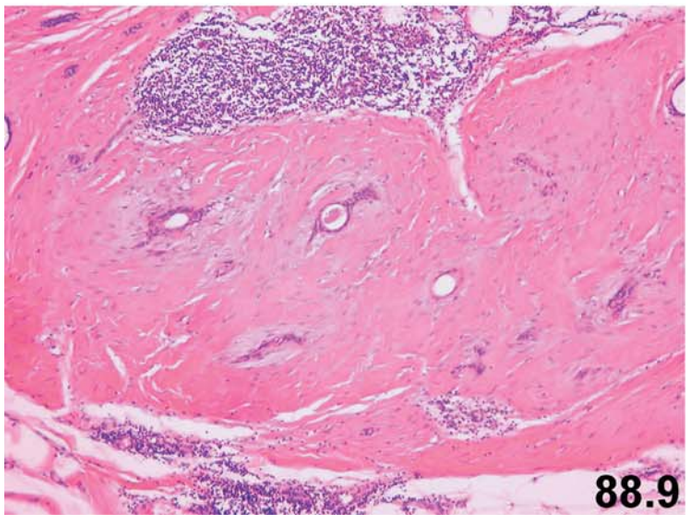
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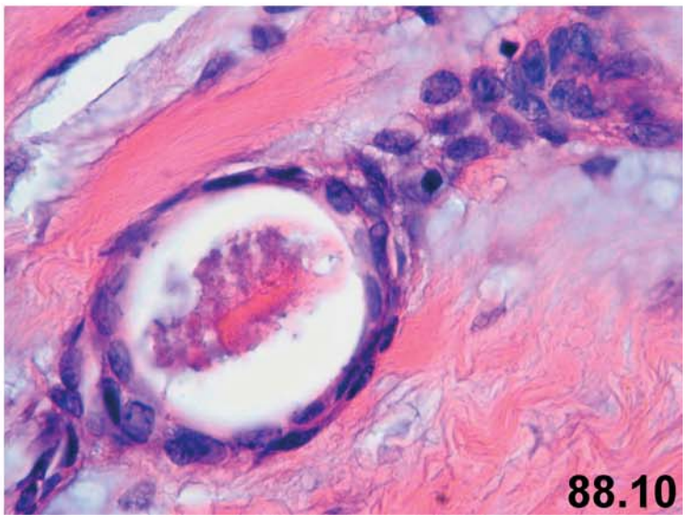
88.10

Male Breast Lesions

Contents

CHAPTER 13 Male Breast Lesions

13.1 Gynecomastia

13.1.1 Definition

A non-neoplastic, potentially reversible enlargement of the male breast with proliferation of ductal epithelial and mesenchymal components. The lesion usually presents as a bilateral, diffuse enlargement of the breasts.

13.1.2 Macroscopy

When diffuse, gynecomastia appears ill defined. In the discrete form, the hyperplastic tissue is well circumscribed. Rubbery or firm consistency and a greyish-white cut surface are typical.

13.1.3 Microscopic Features (Figs. 89 and 90a)

- Proliferation of ductal epithelial cells and mesenchymal components resembling fibroadenomatous hyperplasia or "pericanalicular" type of fibroadenoma of the female breast.
- The florid phase is characterized by prominent ductal hyperplasia, usually with a tufting pattern. Periductal stroma is often cellular; it can also be edematous.
- The fibrous or inactive phase occurs in late stages, showing mild epithelial proliferation. But the stroma is more collagenous, with less edema and vascularity.
- The intermediate phase has both florid and fibrous changes.
- The proliferating epithelial cells in the florid phase may show enlarged hyperchromatic nuclei with an increased nuclear-cytoplasmic ratio. Numerous mitotic figures may be present.

Caution

- The cytologic features and growth pattern of intraepithelial proliferation may appear atypical, particularly in the florid phase. The micropapillary-like proliferation (tufting pattern) can be pronounced in such cases and should not be mistaken for DIN (DCIS).
- The cell population of intraepithelial proliferation in the florid phase is always heterogeneous, composed of epithelial and modified myoepithelial cells. If one is in doubt, immunostains for CK5/6 or CK34BE12 can be very helpful; these are always positive in ductal hyperplasia.
- On rare occasions, DIN (DCIS) may occur in the background of gynecomastia. The neoplastic cells of DIN lack a modified myoepithelial cell component and, therefore, are negative for CK5/6 in the vast majority of DIN (DCIS) cases associated with gynecomastia.
- Some cases of gynecomastia may be associated with prominent pseudoangiomatous stromal hyperplasia (PASH). This should not be mistaken for vascular neoplasia (angiosarcoma).
- In gynecomastia induced by antiandrogen therapy, there may be strong focal prostate-specific antigen (PSA) immunoreactivity in normal or hyperplastic ductal epithelium. This finding should not be mistaken for metastasis from a prostatic adenocarcinoma.

13.1.4 Additional Comments

Gynecomastia is generally a transient disease in the adolescent male. In patients older than 25 years, symptomatic gynecomastia is often a manifestation of underlying disease (hepatic disease, renal disease, hyperthyroidism, etc.), or it reflects a hormonal imbalance (such as gonadal dysfunction, Klinefelter's syndrome, and hyperprolactinemia) or the use of a variety of drugs (including spironolactone, digitalis, and cimetidine) [1, 3, 7, 9, 10]. Gynecomastia is a significant problem in men undergoing hormonal therapy for prostate cancer. It requires prompt recognition, evaluation, and management [3, 10]. Rarely, unilateral gynecomastia can occur.

13.1.5 Further Reading

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13.2 Papilloma

The macroscopic and microscopic features are the same as those of papilloma in females.

Caution

- Because of the high proportion of papillary lesions among carcinomas of the male breast, all male papillary tumors should be carefully evaluated.

13.3 Primary Male Breast Carcinoma (Fig. 90b)

Papillary carcinomas, often with a prominent intracystic component, are more common among men than women. Most papillary carcinomas in men are noninvasive and intracystic (intracystic papillary carcinomas) [14].

Male breast carcinoma represents only 1% of all mammary cancers. In Egypt, the incidence of male breast cancer is 5% that of the female population; this high percentage is related to hyperestrogenism secondary to bilharzial disease [2, 3, 11, 15].

The varieties of carcinoma that occur in the male breast are morphologically indistinguishable from their female counterparts. Invasive lobular carcinoma is extremely rare in men, even in those exposed to endogenous or exogenous hormonal stimulation.

Men develop breast carcinoma at an older age than women. Skin ulceration is more common in men, and male breast carcinomas have a slightly worse prognosis than carcinomas in women [1].

Occasionally, the distinction between a primary carcinoma of the breast and metastatic prostatic carcinoma may be difficult, particularly when ductal intraepithelial neoplasia (DIN; ductal carcinoma in situ [DCIS]) is lacking. The immunohistochemical demonstration of both PSA and prostatic acid phosphatase (PAP) is almost diagnostic of metastatic prostatic carcinoma. It is, however, important to note that in gynecomastia induced by antiandrogen therapy, immunoreaction for PSA in normal or hyperplastic duct epithelium can be positive, whereas PAP immunoreactivity is negative [12, 16, 27].

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Fig. 89: Gynecomastia.

Case history: A 36-year-old man presented with bilateral diffuse enlargement of his breasts. There was no palpable mass.

Figs. 89.1 and **892:** Excisional biopsy showing proliferation of ductal epithelial cells and periglandular mesenchymal cells resembling fibroadenomatous hyperplasia or pericanalicular growth pattern of fibroadenoma.

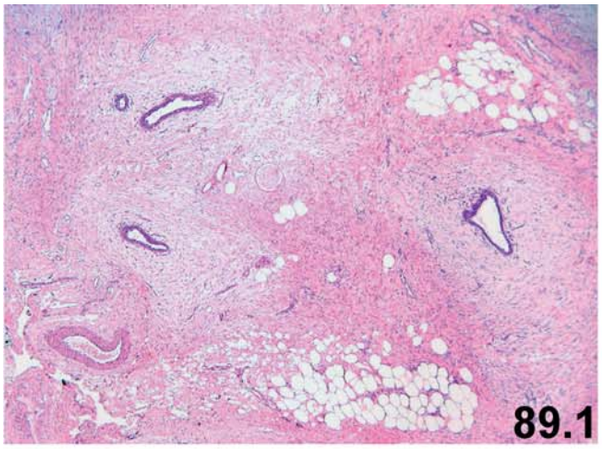
Figs. 89.3 and **89.4:** The florid phase of proliferation showing ductal hyperplasia with tufting growth pattern.

Fig. 89.5: Ductal hyperplasia with intraluminal tufts mimicking micropapillary growth pattern of DIN (DCIS). In contrast to DIN (DCIS), however, the cell population of proliferating cells in gynecomastia is heterogeneous.

Figs. 89.6, 89.7, and **89.8:** Immunohistochemistry for CK5/6 reveals in several ducts a heterogeneous positive reaction, which is typical for usual ductal hyperplasia.

Fig. 89: Final remarks

- The cytologic features and growth pattern of intraductal proliferation in gynecomastia may appear to be atypical. The tufting growth pattern of gynecomastia should not be confused with micropapillary DIN (DCIS). In a difficult case of gynecomastia, immunostaining for high molecular weight cytokeratin (such as CK5/6) can be helpful for identifying the benign nature of proliferating luminal cells.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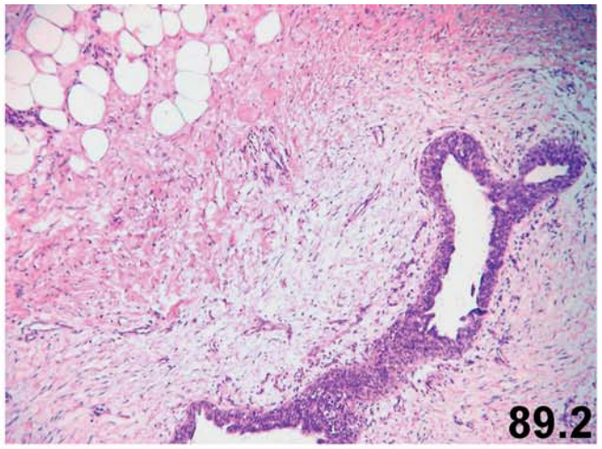
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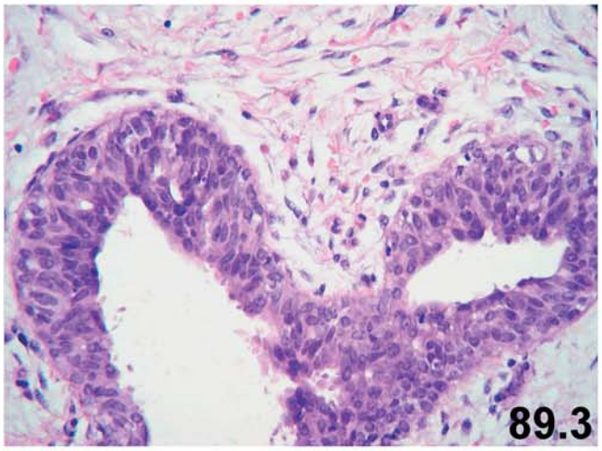
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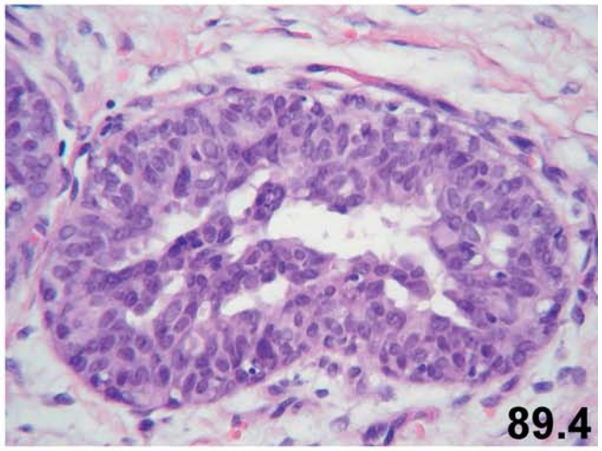
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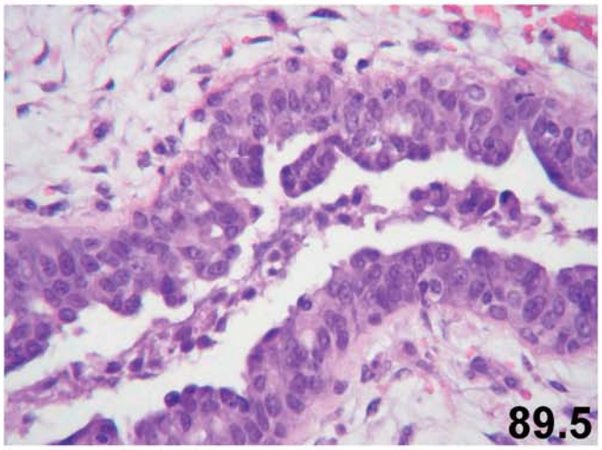
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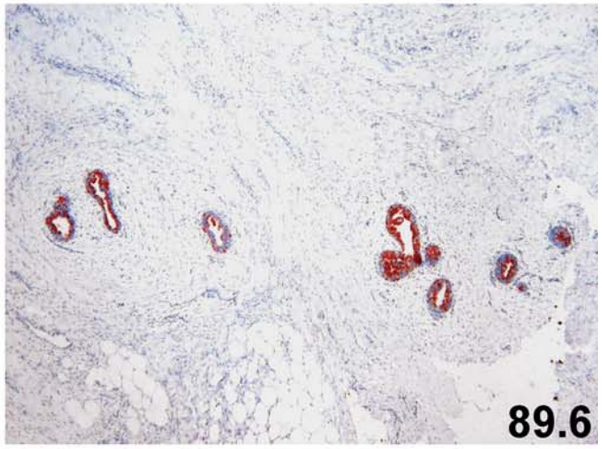
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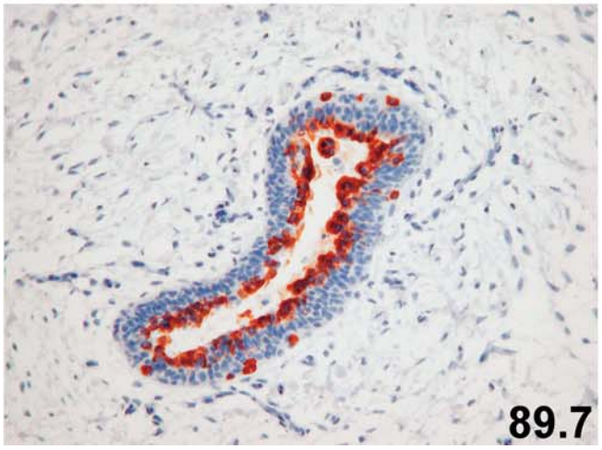
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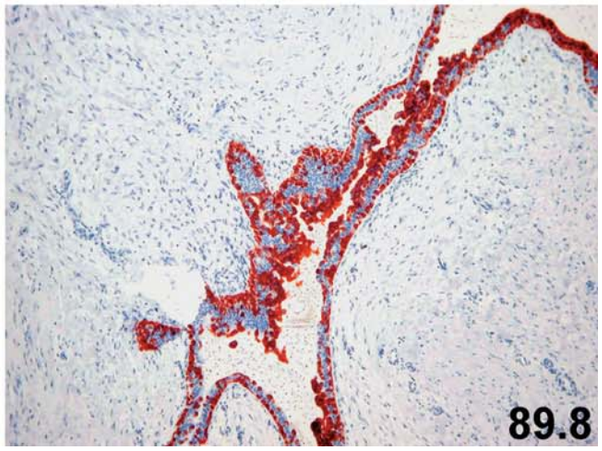

89.8

Fig. 90a: Gynecomastia associated with pseudoangiomatous stromal hyperplasia (PASH).

Case history: A 70-year-old man presented with a unilateral right breast tumor. He had a history of prostate cancer and antiandrogen hormonal treatment. The breast tumor was firm and clinically suspicious for malignancy (breast cancer? metastatic prostate cancer?).

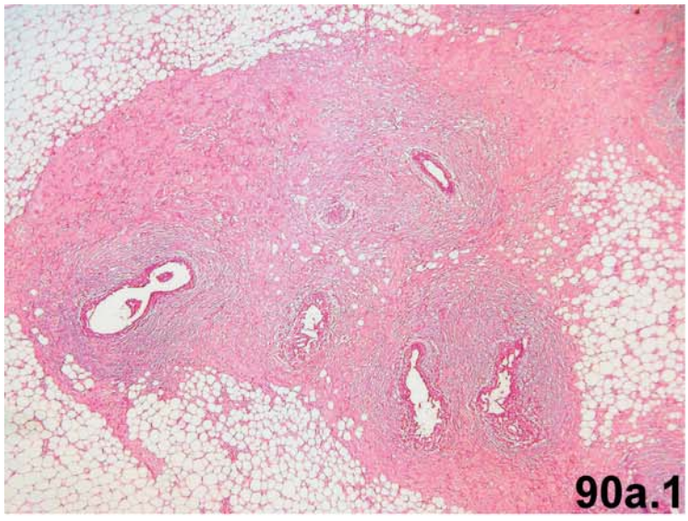
Figs. 90a.1 and **90a.2:** Excisional biopsy of the breast shows gynecomastia with periductal stromal proliferation (pericanalicular growth pattern). Some ducts reveal intraluminal proliferation with typical features of intraductal hyperplasia.

Figs. 90a.3 and **90a.4:** In addition, several sections show periductal empty spaces or vascular-like channels.

Figs. 90a.5 and **90a.6:** The anastomosing spaces are lined by spindle cells closely mimicking endothelial cells. The immunohistochemistry of the spindle cells was negative for endothelial markers (CD31, CD34; not shown). Note significant stromal fibrosis associated with some edematous/myxoid changes.

Fig. 90a: Final remarks

- This is a typical example of pseudoangiomatous stromal hyperplasia (PASH). which is a benign proliferation of fibroblasts and myofibroblasts. The clinical impression of malignancy in this case was due to gynecomastia associated with PASH.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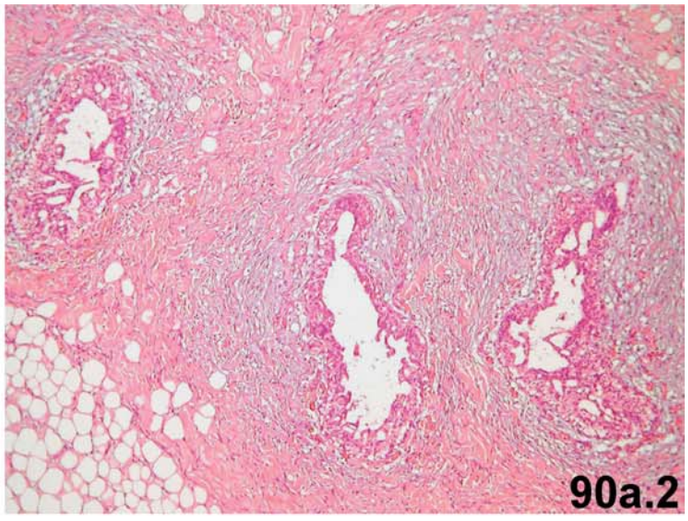
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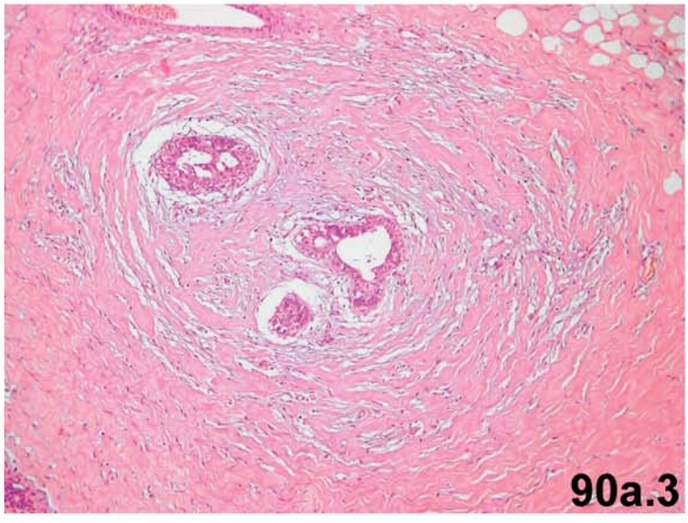
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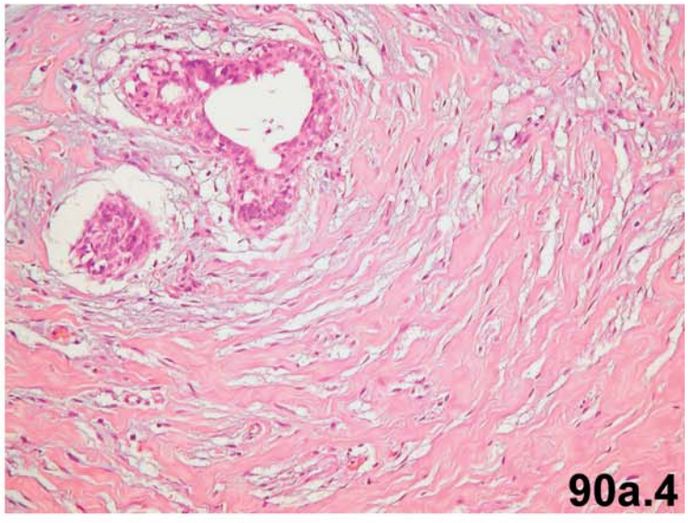
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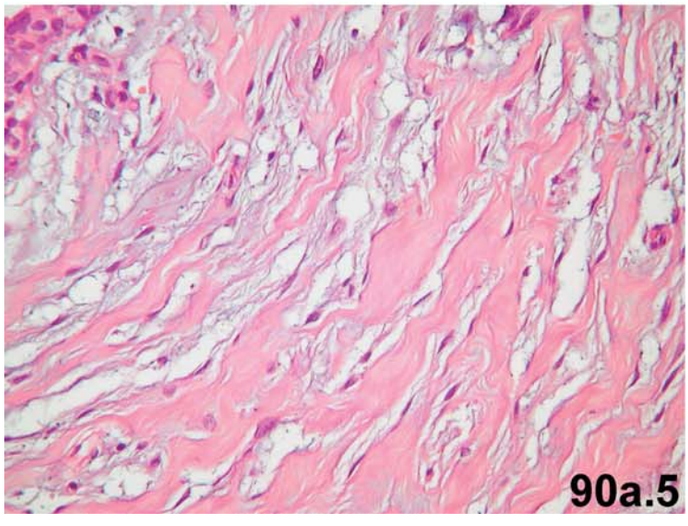
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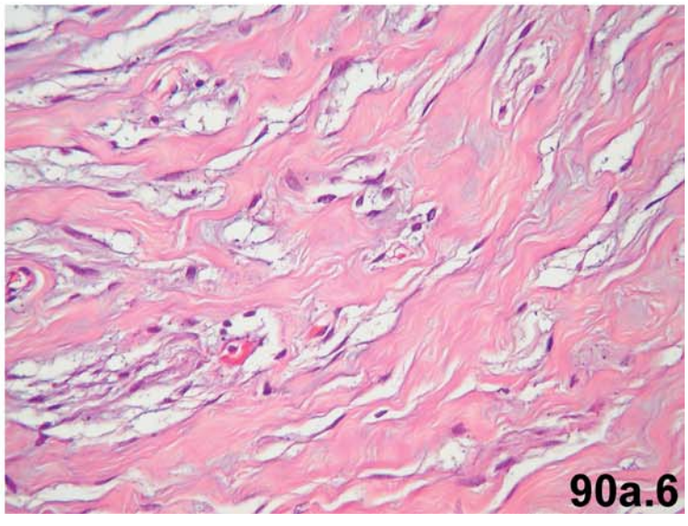

90a.6

Fig. 90b: Male breast carcinoma (infiltrating ductal carcinoma) associated with intraductal papillary carcinoma.

Case history: A 23-year-old man with a history of bloody nipple discharge presented with a firm tumor close to the nipple of his left breast. There was a positive family history of ovarian and breast carcinoma (mother). Excisional biopsy of the tumor was performed.

Fig. 90b.1: Low magnification shows an intraductal papillary tumor. The tumor is within 1.5 mm of the inked margin.

Figs. 90b.2 and **90b.3:** Several areas of the papillary tumor show a monotonous cell population of mildly atypical cells with cribriform growth pattern.

Fig. 90b.4: In addition to the intraductal papillary carcinoma, there is a focus of infiltrating carcinoma.

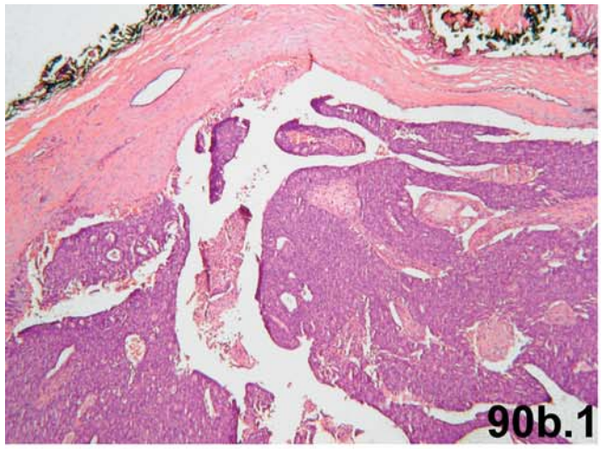
Figs. 90b.5 and **90b.6:** Higher magnification reveals invasive ductal carcinoma that is characterized by solid and cordlike epithelial clusters with haphazard arrangement. The tumor cells show mild to moderate nuclear atypia.

Fig. 90b.7: The neoplastic cells of intraductal papillary carcinoma are positive for estrogen receptors.

Fig. 90b.8: Infiltrating carcinoma showing positive reaction for estrogen receptors.

Fig. 90b: Final remarks

- This is a remarkable case of breast carcinoma occurring in a young man. While the invasive component of the tumor is 3 mm in diameter (pT1a), the lesion is predominantly a low-grade intraductal papillary carcinoma (low-grade papillary DIN).
- Note that intraductal papillary carcinoma is the most common type or growth pattern of male breast cancer.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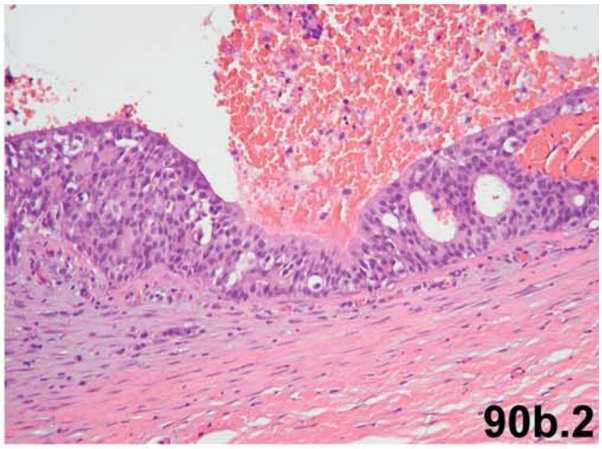
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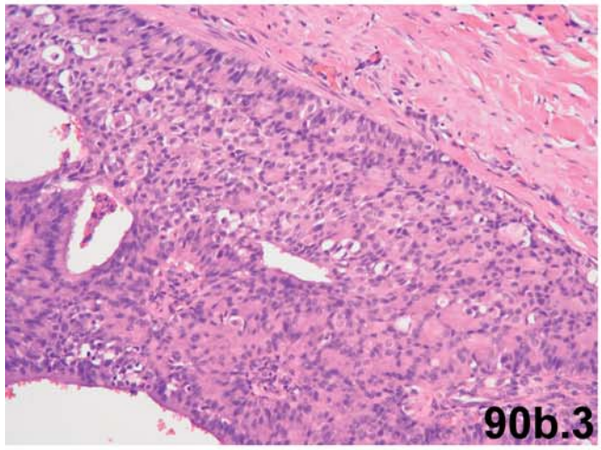
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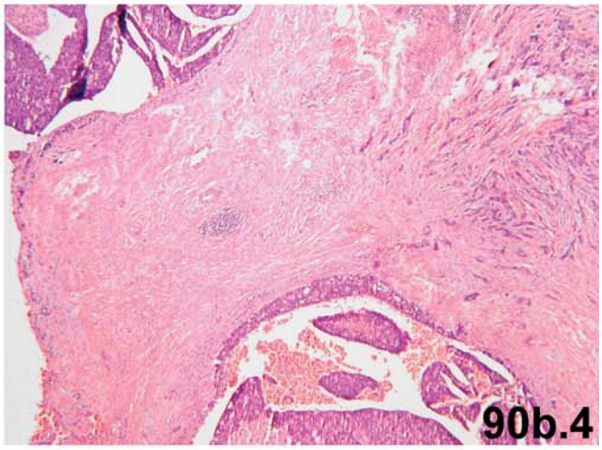
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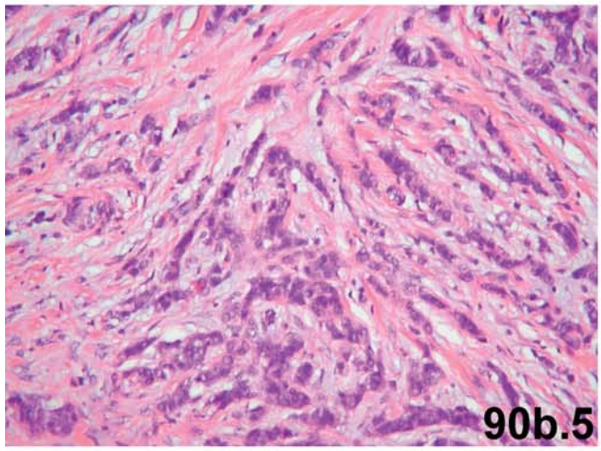
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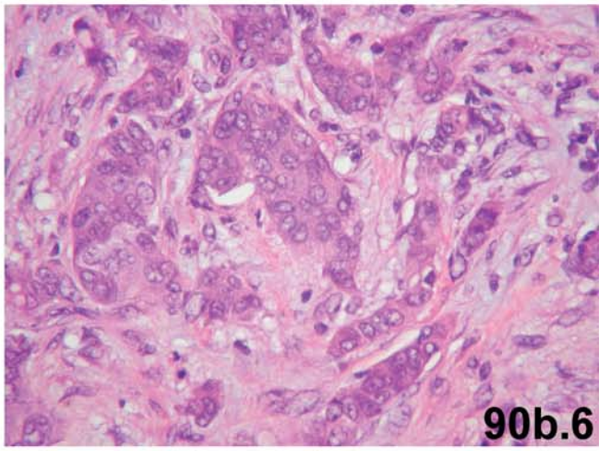
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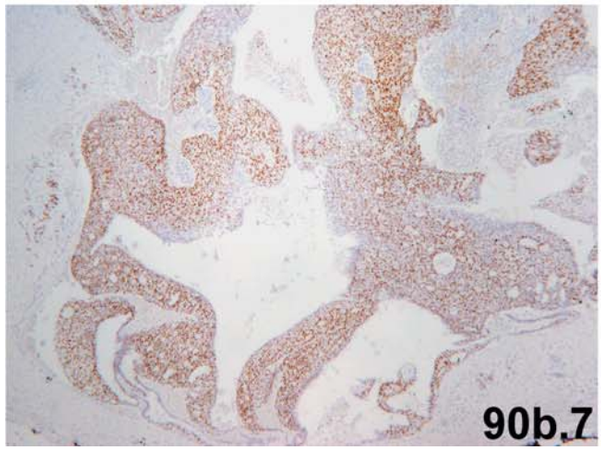
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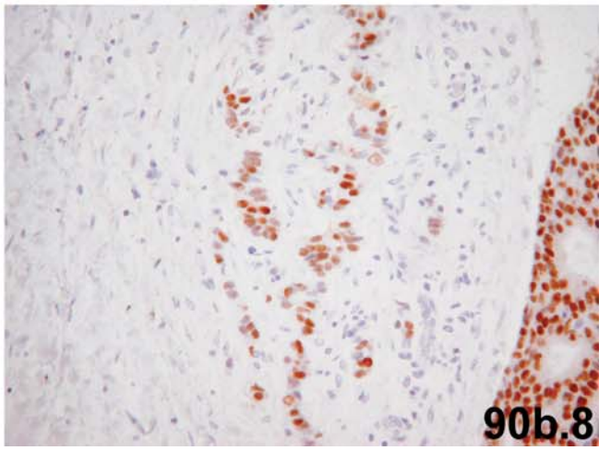
90b.8

Mesenchymal Lesions/Tumors

Contents

Contents

CHAPTER 14 Mesenchymal Lesions/Tumors

14.1 Stromal Elastosis

14.1.1 Definition

Degeneration of elastic fibers showing a homogeneous amyloid-like material within the connective tissue, seen in the normal breast as well as in both benign and malignant lesions.

14.1.2 Macroscopy

The cut surface may show yellow streaks due to the elastosis.

14.1.3 Microscopic Features

- Aggregates of a homogeneous eosinophilic, amyloid-like material around the ducts.
- Common association with stromal fibrosis (fibroelastosis).
- Common association with duct ectasia (periductal mastitis) and central part of radial scar/complex sclerosing lesion.

14.1.4 Further Reading

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14.2 Fat Necrosis

14.2.1 Macroscopy

The early lesion has the appearance of hemorrhage in indurated fat. After several weeks, it appears as a firm nodule with a well-delineated round border. Areas of necrosis (yellow) and hemorrhage are present. The end stage of the lesion may show a dense scar. Cystic degeneration may develop in the center, showing oily fluid or necrotic fat. Calcifications are not infrequently present in the cyst wall.

14.2.2 Microscopic Features

- Multiple small cysts resulting from fusion of necrotic fat cells surrounded by aggregates of lipid-laden, foamy macrophages and foreign-body-type giant cells.
- Chronic inflammatory cells, including lymphocytes, plasma cells, and eosinophils, are present. Acute inflammatory cells may be present.
- Hypercellular areas of mesenchymal cells composed of fibroblasts with activated nuclei (granulation tissue) are present.
- At late stage, macrocystic changes are surrounded by dense fibrous tissue.
- Calcifications occur in the wall of cysts.
- Long-standing fat necrosis may be associated with focal or extensive areas of squamous metaplasia.

Caution

- Fat necrosis may clinically and mammographically simulate a carcinoma, particularly when fixed to the skin and associated with retraction.
- The presence of numerous fibroblasts and myofibroblasts with activated nuclei and irregular arrangement of cell clusters should not lead to a misinterpretation of sarcomatoid (metaplastic) carcinoma.
- Among patients who develop fat necrosis after radiation therapy, cytologic alterations (atypia) attributable to this treatment may be found in ducts and lobules.

14.2.3 Additional Comments

It is believed that most cases of fat necrosis have a traumatic origin, although a history of trauma is obtained in only about 40% of patients.

Fat necrosis commonly occurs after surgery (excisional biopsy) and core needle biopsy, as well as following radiation therapy for carcinoma.

14.2.4 Further Reading

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14.3 Metaplasias

14.3.1 Smooth Muscle Metaplasia

Sometimes occurs within normal mammary stroma. Occasionally, it occurs in biphasic fibroepithelial tumors such as fibroadenoma or phylloides tumor. Pseudoangiomatous stromal hyperplasia (PASH) may also be associated with smooth muscle metaplasia (differentiation).

14.3.2 Osseous and Cartilaginous Metaplasia

Rare occurrence in phylloides tumors; very rarely, within the stroma of benign complex sclerosing lesion and adenosis tumor.

14.4 Pseudoangiomatous Stromal Hyperplasia

14.4.1 Definition

A benign mesenchymal proliferation with numerous slit-like structures mimicking a vasoformative tumor.

14.4.2 Macroscopy

A well-demarcated tumor with a smooth external surface and a homogeneous fibrous tan, grey, or white cut surface. Nodular pseudoangiomatous stromal hyperplasia (PASH) is usually similar to fibroadenoma and can be as large as 15 cm. The tumors occasionally contain cysts up to 1 cm in diameter. As a rule, there is no necrosis or hemorrhage. The cut surface can be inconspicuous (incidental or microscopic finding).

14.4.3 Microscopic Features (Fig. 91)

- Numerous slit-like, anastomosing empty spaces in the dense collagenous stroma are present.
- The changes affect the intralobular and interlobular stroma.
- The spaces are almost empty, only rarely containing a few red blood cells.
- Spindle cells (myofibroblasts) are present at the margins of the spaces, resembling endothelial cells.
- Mitosis, tufting, atypia, and pleomorphism are absent.
- There is no destruction of normal breast tissue, no necrosis, and no infiltration of adipose tissue.
- A periductal pattern, particularly in gynecomastia, can be found.
- Nonspecific proliferative epithelial changes such as mild ductal hyperplasia , often with some accentuation of myoepithelial cells and apocrine metaplasia, can be found.
- The lesion can be very focal (incidental microscopic finding).

14.4.4 Immunoprofile

The spindle cells show intense immunoreactivity for vimentin but are negative for endothelial markers such as factor VIII-related antigen, Ulex europaeus agglutinin, and CD31. The spindle cells adjacent to the clefts are positive for CD34, actin, and calponin. Low and high molecular weight cytokeratins are negative. Actin and/or desmin can be positive. While estrogen receptor is usually negative, the stromal cells are frequently positive for progesterone receptor [8].

Caution

- A tumorous (nodular) PASH may be misinterpreted as a low-grade angiosarcoma.

14.4.5 Additional Comments

Microscopic, nontumorous PASH can be found in about 20% of breast specimens obtained for benign or malignant conditions. PASH is not infrequently associated with gynecomastia [1, 2, 8].

The spaces in PASH are not fixation artifact because they can be identified in frozen section as well.

PASH represents a proliferation of myofibroblasts [8].

The lesion may recur after incomplete excision. The recommended treatment is wide local excision [8].

14.4.6 Further Reading

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14.5 Fibromatosis

14.5.1 Definition

A locally aggressive fibroblastic/myofibroblastic tumor with infiltrating pattern without metastatic potential.

14.5.2 Synonym

Desmoid tumor

14.5.3 Macroscopy

Ill-defined tumor with a firm white, tan, or grey fibrous cut surface, sometimes with a stellate configuration.

14.5.4 Microscopic Features

- Fascicle of proliferating spindle cells (myofibroblasts) with fingerlike infiltrating projections into mammary ducts, lobules, and fat tissue.
- Uniform, plump, spindle-shaped stromal cells with varying degree of cellularity, ranging from relatively cellular lesions to predominantly collagenized tumors. Many tumors are more cellular at the periphery with a tendency to collagenization centrally.
- Uniform bland fibroblasts and myofibroblasts are loosely arranged in long fascicles.
- The mesenchymal cells are set within a collagenous to myxoid matrix.
- The tumor has low mitotic activity; mitotic figures rarely exceed four per 10 high-power fields (hpf).
- Occasionally, a part of the tumor displays rounded and well-circumscribed margins.
- Deep fibromatosis may show infiltration of skeletal muscle. The muscle fibers at the muscle-tumor interface often show atrophy or signs of cell injury displaying multinucleated cells with enlarged hyperchromatic nuclei.
- Perivascular microhemorrhages and extravasation of red blood cells are seen in some tumors.
- Rarely, juxtanuclear intracytoplasmic inclusions similar to those described in infantile digital fibromatosis can be seen.

Caution

- Wide local excision of the lesion is necessary. Careful examination of the margins of resection is important for this lesion; intraoperative assessment of the margins may require multiple frozen sections. This benign tumor does not metastasize, but it is locally aggressive and has the potential for recurrence [2, 6, 11, 14].

14.5.5 Immunoprofile

The tumor cells are positive for vimentin but negative for cytokeratin and S100 protein. A minor component of spindle cells is actin-positive. The intracytoplasmic inclusions are positive for cytokeratin and desmin. In contrast to one-third of extramammary desmoid tumors, fibromatoses in the breast are negative for estrogen (ER), progesterone (PR), and androgen receptors (AR) [3–5].

14.5.6 Differential Diagnosis

Fibrosarcoma: Highly cellular tumor, mostly with significant cytologic atypia and pleomorphism. Usually numerous mitotic figures. The tumor shows long fascicles with a herringbone pattern.

Sarcomatoid (metaplastic or spindle cell) carcinoma: Positive immunoreactivity for epithelial markers. Usually significant cytologic atypia and more mitosis.

Infiltrating myoepithelioma (myoepithelial carcinoma): Myoepithelial lesions are often positive for smooth muscle actin, p63, S100 protein, CD10, and so on. The tumor cells can be positive for CK5/6 or CK34BE12 (HMW-CK) but are usually negative for CK8/18 (LMW-CK). Myoepithelial lesions are generally negative for ER, PR, and AR.

Infiltrating type of myofibroblastoma: Fingerlike infiltrating pattern closely similar to that of fibromatosis. The tumor cells, however, are positive for ER, PR, and AR in most reported cases.

Nodular fascitis: Nodular fascitis tends to be more circumscribed and often shows a higher mitotic activity. It often shows a prominent inflammatory infiltrate that is distributed throughout the lesion.

14.5.7 Additional Comments

Mammary fibromatosis can be manifested as a complication of familial adenomatous polyposis coli (FAP) in 10% of patients with FAP.

Unlike abdominal desmoid tumor, mammary fibromatosis has not been associated with pregnancy. It has been also observed in nulliparous women and in the male breast.

Several patients have developed mammary or chest wall fibromatosis after receiving silicone breast implants [1, 2, 13].

14.5.8 Further Reading

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14.6 Myofibroblastoma

14.6.1 Definition

A benign mammary stromal tumor composed of myofibroblasts.

14.6.2 Macroscopy

A well-demarcated, firm, and rubbery tumor with a lobulated external surface, closely resembling fibroadenoma. Greyish-white or pink whorled cut surface.

14.6.3 Microscopic Features (Fig. 92)

- A well-circumscribed expansile tumor, often compressing the surrounding stroma.
- Occasionally, the tumor shows a partial infiltrating growth pattern.
- It is composed of uniform, ovoid to spindle-shaped (bipolar) cells arranged in short, haphazardly intersecting fascicles.
- The short fascicles are interrupted by thick and brightly eosinophilic collagen bands.
- There is no entrapment of mammary ducts or lobules within the tumor.
- The cells display pale to deeply eosinophilic cytoplasm with a round to oval nucleus. The nuclei commonly display grooves.
- Mitotic figures are rare (0–2 per 10 hpf).
- Most cases show numerous mast cells.
- Some cases may show increased cellularity (cellular variant), but these are not associated with cytologic atypia or significant mitotic activity.
- Extensive myxoid changes may occur.
- Occasionally, smooth muscle, cartilaginous or osseous metaplasia may occur.
- Admixture with adipose tissue may occur, particularly when multiple tumors are present.
- Rarely, aggregates of myofibroblasts form epithelioid cell clusters (epithelioid cell variant); these are immunoreactive for actin and desmin.
- Rarely, an infiltrative variant of myofibroblastoma occurs, which is characterized by an entirely invasive pattern. In this unusual variant, the spindle cells incorporate fat, ducts, and lobules (see differential diagnosis).
- Rarely, a cellular variant of myofibroblastoma occurs, which shows a dense proliferation of spindle-shaped myofibroblasts. Collagenous bands may be absent in some areas of the tumor.

14.6.4 Immunoprofile

The myofibroblastic tumor cells react positively for vimentin. The tumor cells are usually positive for desmin and CD34. Positive reaction for smooth muscle actin and CD99 is variable. ER, PR, and AR are variably positive. The tumor cells are negative for cytokeratin [1, 6, 8, 9, 11, 17].

Caution

- A myofibroblastic tumor with high cellularity, moderate to severe nuclear atypia, irregular and infiltrating margins, and high mitotic activity (more than four mitoses per 10 hpf) should be diagnosed as myofibrosarcoma or myofibroblastic sarcoma. A myofibroblastic tumor with some (but not all) of the atypical features should be classified as myofibroblastic tumor of uncertain malignant potential (limited experience) [7, 10, 16].

14.6.5 Differential Diagnosis

Nodular fascitis, fibromatosis, and leiomyoma: The differential diagnosis is not infrequently based on immunophenotype, but even so, may be difficult in some cases. The infiltrating variant of myofibroblastoma should not be misinterpreted as sarcoma. In contrast to myofibroblastic sarcoma, the infiltrating variant of myofibroblastoma has no cytologic atypia and increased mitotic activity.

14.6.6 Additional Comments

The tumor is more common in the male breast. Local excision with a free resection margin is the adequate treatment for myofibroblastoma.

14.6.7 Further Reading

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14.7 Lipoma

14.7.1 Definition

A benign, well-circumscribed tumor with a delicate capsule consisting of fat cells without atypia.

14.7.2 Macroscopy

Solitary soft and well-delineated tumor with lobulated yellow cut surface.

14.7.3 Microscopic Features

- Expansile tumor with a delicate capsule around it.
- Mature adipocytes; no lipoblasts, no nuclear atypia.
- Rarely, uniform spindle cells and bundles of mature collagen (spindle cell lipoma).
- Occasionally, mucoid matrix alteration.
- When the lesion is composed of brown fat, the designation of hibernoma is used (hibernoma occurs in the axillary tail of the breast or in the axilla).
- Rarely, bundles of smooth muscle are admixed with adipose tissue; this variant is designated myolipoma.

14.7.4 Further Reading

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14.8 Angiolipoma

14.8.1 Definition

A mesenchymal tumor, clinically and grossly closely resembling lipoma.

14.8.2 Macroscopy

The same as for lipoma.

14.8.3 Microscopic Features

- A well-circumscribed tumor with no infiltration into the surrounding tissue.

- Branching vascular network distributed diffusely among the mature lipocytes.
- Vascular clustering in the subcapsular region.
- Scattered microthrombi in small vessels.
- Vascular areas may become prominent and simulate a cavernous hemangioma.
- Mature lipocytes are the dominant component (no cytologic atypia, no adipoblasts).

14.8.4 Additional Comments

Angiolipoma presents as solitary unilateral or multiple bilateral tumors. Simple excision is the adequate treatment.

14.8.4 Further Reading

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14.9 Granular Cell Tumor

14.9.1 Definition

A mesenchymal tumor, probably of Schwannian origin, with tumor cells showing abundant eosinophilic granular cytoplasm.

14.9.2 Macroscopy

Either well-circumscribed or infiltrative firm or hard mass with a greyish-white to yellow or tan cut surface.

14.9.3 Microscopic Features (Fig. 93)

- Often an infiltrating growth pattern is evident, even in tumors that appear well circumscribed grossly.
- The tumor cells may infiltrate into the dermis of the skin.
- The margin can, however, be lobulated and well defined.
- Solid nests, clusters, or cords of uniformly round to polygonal cells with coarse, granular, eosinophilic cytoplasm are present. Cytoplasmic vacuolization and clearing may be seen.
- The tumor cells show small centrally located round nuclei. Some tumors may show mild nuclear pleomorphism. Nucleoli tend to be prominent.
- In some cases, tumor cells partially show cytoplasmic vacuolization or clearing.
- In some cases, rare mitoses may be found.
- Adjacent stroma is either unaltered, collagenized, or desmoplastic.
- The cytoplasmic granules of the tumor cells are diastase-resistant and PAS-positive.

14.9.4 Immunoprofile

The tumor cells of granular cell tumor are characteristically positive for S100 protein. They are negative for pancytokeratin but may be positive for CEA. The tumor cells are negative for histiocyte-associated antigens, such as alpha1-antitrypsin and alpha1-antichymotrypsin. Positivity for CD68, however, has been reported [1, 2, 5, 10, 12].

Caution

- The typical infiltrating growth pattern of granular cell tumor can be misinterpreted as invasive carcinoma (lobular carcinoma, histiocytic carcinoma, apocrine carcinoma). Immunohistochemical examination (cytokeratin) is recommended to confirm the diagnosis.
- This mesenchymal tumor must be distinguished from metastatic neoplasms (carcinoma with oncocytic or clear cell features, renal carcinoma and malignant melanoma).

14.9.5 Additional Comments

As a rule, the clinical behavior of granular cell tumor is benign following complete surgical excision. Incomplete excision may result in local recurrence. It is of note that less than 1% of granular cell tumors are malignant (lymph node, pulmonary, liver, and bone metastases). A malignant course should be expected in the extremely rare malignant granular cell tumor that displays marked nuclear atypia, high mitotic activity, and necrosis. However, some tumors without these atypical features may also behave in a malignant fashion. Long-term follow-up of the patients is therefore prudent [1, 3, 5, 6].

14.9.6 Further Reading

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14.10 Hamartoma

14.10.1 Definition
A well-circumscribed, usually encapsulated nodule consisting of all breast tissue components, often with an abnormal proportion (malformation).

14.10.2 Synonym
Fibroadenolipoma

14.10.3 Macroscopy
A well-demarcated, sometimes lobulated mass, often rubbery greyish-white to yellow cut surface, resembling fibroadenoma or lipoma.

14.10.4 Microscopic Features
- The morphology varies depending on the proportion of fibroadipose and glandular components within the lesion.
- The lesion often gives the impression of "breast within breast."
- There is a pseudocapsule of compressed breast tissue.
- There are normal ducts and lobular structures within the lesion.
- Some areas of the mass may show fibrocystic changes, sclerosing adenosis, or PASH.
- Very rarely, an intracystic papillary hamartoma admixed with mature fat tissue may occur.

14.10.5 Additional Comments
Adenohibernoma, myoid hamartoma, and chondrolipoma represent rare variants of hamartoma.

Usual ductal hyperplasia, apocrine metaplasia, calcification, stromal giant cells, and adenosis may be associated with hamartoma. Lobular intraepithelial neoplasia (LIN) and ductal intraepithelial neoplasia (DIN; DCIS) may rarely occur within the hamartoma [10].

The lesion is benign. Rarely, it can recur [5, 6, 9].

14.10.6 Further Reading
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14.11 Perilobular Hemangioma

14.11.1 Definition
A microscopic, incidental finding of benign vascular lesion involving perilobular, intralobular, or periductal stroma.

14.11.2 Synonym
Microscopic hemangioma

14.11.3 Macroscopy
No grossly identifiable changes.

14.11.4 Microscopic Features
- Solitary or multiple microscopic areas composed of congested capillaries located in perilobular, intralobular, or extralobular stroma.
- Sharply defined aggregates of small, distinct vascular channels arranged in a meshwork fashion. Anastomosing vascular channels may be found.
- Rarely, this lesion may show extension into the adjacent adipose and fibrous tissue.
- Endothelial papillary proliferation or mitotic activity are not present. A mild degree of cytologic atypia with hyperchromatic nuclei of endothelial cells may be present.

14.11.5 Additional Comments
This lesion is completely benign and requires no treatment. Endothelial papillary proliferation, mitotic activity, and extensive vascular anastomoses are not observed in a typical perilobular hemangioma.

14.11.6 Further Reading
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14.12 Hemangioma

14.12.1 Definition

A benign vascular neoplasm large enough to be clinically palpable or detected by mammography.

14.12.2 Macroscopy

Well-circumscribed soft tumor with reddish to dark blue or brown spongy cut surface.

14.12.3 Microscopic Features

- Low magnification shows an expansile vascular tumor with well-defined margins.
- Cavernous hemangioma displays a lobular pattern with dilated, blood-filled vessels lined by flattened endothelium. Focally, anastomosing channels may be present, but there is no cytologic atypia or mitotic activity.
- Cavernous hemangioma may show areas of thrombosis and focal papillary endothelial hyperplasia.
- Capillary hemangioma exhibits capillary-sized vessels lined by flattened endothelium. An immature form of capillary hemangioma represents the juvenile hemangioma, displaying a combination of vascular spaces with inconspicuous lumens lined by plump endothelial cells and spaces lined by flattened endothelial cells.
- The arteriovenous and venous hemangiomas show clusters of thick-walled, muscular vessels with an elastic layer in the vessel wall of those with an arterial component.

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Caution

- Any type of hemangioma may show irregularities in its margins, a focal anastomosing pattern, variation in the caliber of vascular spaces, sclerosis, focal endothelial hyperplasia, and mild cytologic atypia of endothelial cells. These tumors should not be misinterpreted as low-grade angiosarcoma. The term "atypical hemangioma" has been used for this variant, but there is no evidence that it predisposes to the development of angiosarcoma [4, 8].
- Intravascular papillary endothelial hyperplasia is a rare vascular lesion with a complex papillary configuration of proliferating endothelial cells easily mistaken for an angiosarcoma. The lack of irregular infiltrating margin and significant cytologic atypia, the absence of a solid growth pattern, and the presence of muscle and elastic tissue in the vessel often unmask the lesion's benign nature [1].

14.12.4 Additional Comments

A transition from benign hemangioma to angiosarcoma has not been described. Atypical hemangiomas are clinically benign vascular tumors without a tendency to local recurrence.

Breast hemangioma may simulate an inflammatory carcinoma [3].

Complete excision of all benign vascular lesions of the breast is necessary to exclude the possibility of angiosarcoma.

14.12.5 Further Reading

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14.13 Angiomatosis

14.13.1 Definition

A very rare benign vascular neoplasm composed of hemangiomatous and lymphangiomatous channels with a diffuse infiltrating pattern.

14.13.2 Macroscopy

Generally a large tumor (15–22 cm) with a cystic and spongy cut surface. The tumor appears hemorrhagic and often closely resembles an angiosarcoma.

14.13.3 Microscopic Features

- Anastomosing, large vascular spaces with diffuse infiltration of the breast parenchyma are evident.
- The vascular channels surround lobules and ducts; however, they do not invade into the lobular stroma.
- The tumor consists of hemangiomatous erythrocyte-containing spaces or lymphangiomatous empty channels, or a mixture of these.
- The vessels are lined by flat endothelium with no cytologic atypia. The vessels are usually thin-walled or at best contain a few poorly formed fascicles of smooth muscle.
- There is no necrosis or increased mitotic activity.

Caution

- The histologic distinction between angiomatosis and low-grade angiosarcoma may be difficult, particularly in a small biopsy. It is important to note that anastomosing channels occur in both lesions.

- In contrast to low-grade angiosarcoma, invasion and destruction of lobules does not occur in angiomatosis. Even in low-grade angiosarcoma, the endothelial cells show nuclear atypia with hyperchromasia and an increased nuclear-cytoplasmic (N/C) ratio, whereas the endothelial cells in angiomatosis are quite bland-looking or attenuated.

14.13.4 Additional Comments

Angiomatosis may recur, particularly when incompletely excised. There is no risk of malignant transformation [1, 2].

14.13.5 Further Reading

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14.14 Angiosarcoma

14.14.1 Definition

A malignant vascular neoplasm of the breast, usually with highly aggressive clinical behavior.

14.14.2 Synonyms

Hemangiosarcoma, hemangioblastoma, (malignant) hemangioendothelioma, metastasizing hemangioma.

14.14.3 Macroscopy

Almost always a palpable and grossly visible tumor with ill-defined margins. Tumor size varies between 1 cm and 20 cm (average 5 cm). The cut surface has a spongy appearance, often with irregular hemorrhagic areas. Cystic or necrotic areas may be present in large high-grade sarcomas. Some tumors show poorly defined areas of thickening or induration.

14.14.4 Microscopic Features (Fig. 94)

- Low magnification shows ill-defined margins with infiltration into the surrounding tissue.
- There is infiltration around and into lobular stroma.
- Irregular anastomosing vascular channels are evident, which are lined by one or more layers of endothelial cells.
- Tufts, papillary formations, and solid nests of spindled endothelial cells may be present.
- Endothelial cells often show hyperchromatic and enlarged nuclei. Nucleoli may or may not be prominent.
- Mitotic figures are rare or absent in low-grade angiosarcoma. Numerous mitoses are present in high-grade sarcoma.

14.14.5 Grading

Angiosarcomas of the breast are graded based on the nuclear atypia, mitotic activity, and proportion of solid aggregates of spindle cells:

Low-grade (well-differentiated, grade I) angiosarcoma:

- Anastomosing, open vascular spaces with diffuse infiltration around and into lobular stroma as well as fat tissue.
- The vascular channels are lined by a single layer of flat endothelial cells; these, however, often display hyperchromatic nuclei with slightly increased N/C ratio.
- Papillary formations or solid nests are absent.
- Mitotic figures are rarely observed in the endothelial cells.
- Necrosis and "blood lakes" are absent.

Intermediate-grade (moderately differentiated, grade II) angiosarcoma:

- At least 75% of the tumor's bulk is formed by the low-grade (well-differentiated) pattern, but solid cellular foci and papillary configurations are also scattered throughout the tumor.
- Mitoses are usually present in the papillary or solid structures.
- Sometimes, numerous spindle cell nodules with a swirling pattern are present.
- Necrosis and "blood lakes" are absent.

High-grade (poorly differentiated, grade III) angiosarcoma:

- Admixture of interanastomosing vascular channels with solid areas of spindle cells with high-grade nuclear atypia and numerous mitotic figures.
- Necrosis is usually present, as are areas of hemorrhage, often accompanied by necrosis ("blood lakes").
- More than 50% of the total neoplastic area is composed of solid and spindle cell components without evidence of vascular spaces.
- Prominent endothelial tufting and papillary configuration reveal high-grade nuclear atypia of endothelial cells.

Caution

- Benign-appearing areas may be found in a high-grade (poorly differentiated) angiosarcoma. To avoid underdiagnosing angiosarcoma, it is crucial to use a generous sampling (at least one block per 1 cm of the tumor diameter) of large tumors and to process small tumors in their entirety.
- Low-grade angiosarcoma may easily be misdiagnosed as hemangioma. One should always pay attention to the margin of the tumor and its invasive, destructive nature, with infiltration into lobular stroma and adipose tissue as a hallmark of angiosarcoma.
- An unusual variant with epithelioid transformation of the mesenchymal tumor cells may occur and could lead to misinterpretation as an invasive ductal carcinoma.
- The spectrum of postradiation vascular lesions of the breast is wide and ranges from atypical vascular proliferations with benign clinical behavior to angiosarcoma. There is, however, significant clinical and histological overlap.

14.14.6 Immunoprofile

The neoplastic endothelial cells in low-grade and intermediate-grade angiosarcomas are positive for CD31, CD34, and factor VIII. These markers, however, may be lost in solid areas of a high-grade tumor. The tumor cells are negative for cytokeratin [1, 10].

14.14.7 Additional Comments

Angiosarcoma can be subdivided into (1) de novo (primary) forms, (2) secondary forms in the skin and soft tissues of the arm after ipsilateral radical mastectomy and subsequent lymphedema (Stewart–Treves syndrome), and (3) secondary forms in the skin and chest wall following breast surgery (conservative tumorectomy or radical mastectomy) and local radiotherapy [2–4, 13, 15].

Most of the tumors are intermediately or poorly differentiated and are highly lethal. The prognosis of low-grade (well-differentiated) angiosarcoma is much better than that of intermediate-grade and high-grade tumors [8, 10, 14, 18].

The tumor is generally present in pure form, so unlike other breast sarcomas, it is very unusual to find angiosarcoma as a component of a high-grade phylloides tumor (malignant phylloides tumor).

Axillary lymph node metastases are very uncommon; axillary node dissection should not be considered part of the surgical treatment of angiosarcoma! Metastases are mainly to lungs, skin, bone, and liver. Radiotherapy and chemotherapy seem to be ineffective.

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14.14.8 Further Reading

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14.15 Leiomyosarcoma

14.15.1 Definition

A very rare malignant mesenchymal tumor of the breast with smooth muscle differentiation.

14.15.2 Macroscopy

A well-defined soft to firm lobulated tumor with a greyish-white cut surface. Areas of necrosis or hemorrhage may be present.

14.15.3 Microscopic Features

- Interlacing bundles of fusiform smooth muscle tumor cells.
- Irregular and infiltrating margins, at least in some areas of the tumor.
- Often, moderate to severe cytologic (nuclear) atypia and numerous mitotic figures.
- Tumor cell necrosis.

14.15.4 Immunoprofile

The tumor cells are positive for smooth muscle actin and desmin. They are often positive for h-caldesmon and smooth muscle myosin. The tumor cells can also focally be positive for cytokeratin (weak cytoplasmic reaction).

Caution

- Primary smooth muscle tumors of the breast are extremely rare and should be diagnosed cautiously. A leiomyoma of the breast should not show any cytologic atypia or increased mitotic activity; more than three mitotic figures per 10 hpf is highly suggestive of malignancy (Fig. 95).

- A metaplastic (sarcomatoid) carcinoma or carcinoma with myoepithelial differentiation (malignant myoepithelioma) may share many morphological and immunohistochemical similarities with leiomyosarcoma. It is likely that some of the reported mammary leiomyosarcomas represent a metaplasic or sarcomatoid carcinoma. If a sarcomatoid tumor is positive for some additional myoepithelial markers such as p63, CD10, or S100 protein and also shows positive reaction for cytokeratins such as CK5/6 or CK14, a metaplastic or sarcomatoid carcinoma should be diagnosed.

14.15.5 Further Reading

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14.16 Liposarcoma

14.16.1 Definition

A malignant lipomatous tumor containing lipoblasts.

14.16.2 Macroscopy

A well-circumscribed or encapsulated soft to firm tumor with a yellow cut surface. Gelatinous (myxoid) areas may be found. Hemorrhage, necrosis, or both may be present. Rarely, the tumor may show irregular and infiltrating margins.

14.16.3 Microscopic Features

- Similar histomorphology as that of liposarcoma at other sites.
- *Pleomorphic variant:* Highly cellular tumor with numerous lipoblasts and numerous mitotic figures. Numerous tumor cells with bizarre nuclei resembling malignant fibrous histiocytoma.
- *Myxoid variant:* Typical features include a myxoid matrix, uniform tumor cells, and a characteristic delicate capillary pattern of stroma. A few lipoblasts are always present.
- *Well-differentiated or lipoma-like liposarcoma:* Mature lipocytes without nuclear atypia, caliber variation of tumor cells, and a few lipoblasts are typical features.

14.16.4 Additional Comments

Liposarcoma is among the rarest malignant breast tumors. It can be a component of high-grade phylloides (malignant phylloides) tumor or may arise directly from the mammary adipose tissue. It may also be a component of carcinosarcoma (metaplastic carcinoma). Rarely, liposarcoma develops following radiation therapy for breast cancer.

Because of the high frequency of marginal irregularity, complete excision of the tumor with free margins is mandatory. Axillary lymph node metastases are extremely rare.

14.16.5 Further Reading

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14.17 Rhabdomyosarcoma

14.17.1 Definition

A malignant mesenchymal tumor showing varying degrees of skeletal muscle differentiation.

14.17.2 Macroscopy

A well-circumscribed soft to rubbery tumor with some areas of necrosis on the cut surface.

14.17.3 Microscopic Features

- The same morphology as that of rhabdomyosarcoma at other sites (pleomorphic, alveolar, and embryonal subtypes).
- Primary rhabdomyosarcoma is usually highly cellular with a highly atypical spindle to round cell population associated with numerous mitotic figures.
- Rhabdomyoblasts are scattered throughout the tumor but tend to concentrate in some areas.
- The malignant tumor cells can be small with eosinophilic cytoplasm. At higher magnification, some of the tumor cells may clearly display cross-striation.

14.17.4 Immunoprofile

The tumor cells are variably positive for actin, desmin, myoglobin, MyoD1, and myogenin.

Caution

- Pure, primary rhabdomyosarcomas of the breast are exceedingly rare. Most cases of mammary rhabdomyosarcomas represent metastatic sarcomas to the breast, a sarcomatous component of a high-grade (malignant) phylloides tumor, or a rhabdomyosarcomatous component of a metaplastic carcinoma (carcinosarcoma).

14.17.5 Additional Comments

This is a highly aggressive malignant tumor with general dissemination by the time it manifests in the breast.

14.17.6 Further Reading

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14.18 Malignant Fibrous Histiocytoma

14.18.1 Definition

A malignant mesenchymal tumor composed of varying proportions of fibroblasts, myofibroblasts, histiocyte-like cells, and undifferentiated cells.

14.18.2 Macroscopy

A fleshy, often multilobulated tumor with necrosis and hemorrhage and a greyish-white to tan cut surface. A mucoid appearance may also be present.

14.18.3 Microscopic Features

- All variants of malignant fibrous histiocytoma (MFH), including pleomorphic, giant cell, myxoid, and inflammatory types, may occur.
- Most of the spindle cells are randomly arranged, but focal areas with small fascicles and bundles can be present. An organized long fascicular arrangement is usually absent.
- The most common tumor is composed of spindle cells with numerous mitotic figures, and inflammatory cells.
- The histiocyte-like cells tend to be round with abundant cytoplasm ranging from relatively uniform cells to cells that are huge and pleomorphic, often with bizarre nuclei and eosinophilic cytoplasm.
- A storiform pattern in spindle cell areas is often evident.

Caution

- Several recent immunohistochemical and electron microscopic examinations have raised serious questions regarding the existence of MFH as a distinct entity. There is convincing evidence that most MFHs are not related to histiocytes; rather, they are fibroblasts, myofibroblasts, and primitive undifferentiated stromal cells. In fact, the vast majority of MFH cases are the result of dedifferentiation of mesenchymal cells.
- MFH of the breast is extremely rare. It should be diagnosed cautiously after excluding sarcomatoid (metaplastic) carcinoma.

14.18.4 Immunoprofile

Positive reaction for lysozyme, alpha1-antitrypsin, and factor VIII. Actin and desmin may be positive. A few MFHs contain tumor cells that express cytokeratin; this is usually focal and weak. S100 protein, CD34, and CD45 are typically negative.

14.18.5 Additional Comments

MFH may occur as a component of high-grade phylloides tumor (cystosarcoma phyllodes). Rare cases of mammary MFH have been reported to be related to radiation therapy for breast carcinoma.

In the breast, MFH behaves aggressively, with a high rate of local recurrence. The most frequent sites of metastases are lung and bone.

14.18.6 Further Reading

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14.19 Osteosarcoma

14.19.1 Definition
A malignant mesenchymal tumor composed of spindle cells that produce osteoid and/or bone together with cartilage in some cases.

14.19.2 Synonym
Osteogenic sarcoma

14.19.3 Macroscopy
Sharply defined and lobulated tumor, often described as gritty under the knife. Variation of consistency from firm to hard. The cut surface varies from soft and gelatinous to firm or hard greyish-white. Cavitation and necrosis are seen in larger tumors. Gross calcification may be visible and palpable.

14.19.4 Microscopic Features (Fig. 96)
- Despite its grossly well-demarcated appearance, the tumor shows at least focally infiltrative margins.
- The tumor cells are composed of spindle to oval cells with variable amounts of osteoid (osseous) tissue; cartilage is present in over a third of cases.
- In the fibroblastic type, the tumor cells are predominantly monomorphic. In the osteoblastic variant, the tumor cells are larger and polygonal, proliferating among branching trabeculae of bone and osteoid. The tumor cells in the osteoclastic variant are very large and form aggregates of osteoclastic giant cells admixed with atypical plump cells.
- Some areas of the tumor can be bland-looking with layers of osseous tissue alternating with uniform spindle cells.

Caution
- In rare cases, mammary osteosarcoma can be extremely bland in appearance and may easily be underestimated as a benign metaplastic change or myositis ossificans, even by experienced bone pathologists. Focal infiltrative pattern and increased mitotic activity in an osteogenic mammary tumor should, however, raise the possibility of malignancy.
- Extensive sampling of the tumor is crucial; an origin in a high-grade (malignant) phylloides tumor or metaplastic carcinoma (carcinosarcoma) should always be considered and excluded.

14.19.5 Additional Comments
Osteosarcoma is a highly aggressive tumor with an overall 5-year survival of less than 40%. Metastases to the lungs are common. Axillary lymph node metastases are extremely rare.

Osteoclastoma: Most of the tumors probably reflect variants of osteosarcoma with minimal osteoid production.

Chondrosarcoma: Pure chondrosarcoma of the breast is extremely rare. However, it can occur as a malignant mesenchymal component of a high-grade (malignant) phylloides tumor or as part of a metaplastic carcinoma with chondroid differentiation (carcinosarcoma, matrix-producing carcinoma).

14.19.6 Further Reading
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14.20 Spindle Cell Sarcoma, Not Otherwise Specified (NOS-Type Mammary Sarcoma)

14.20.1 Definition
Rare primary sarcoma of the breast with no specific differentiation; a sarcoma that cannot be subclassified based on morphology and immunohistochemistry.

14.20.2 Synonym
Stromal sarcoma

14.20.3 Macroscopy
Well-demarcated, lobulated fleshy tumor with greyish-white to tan cut surface with or without necrosis.

14.20.4 Microscopic Features (Fig. 97)
- Despite grossly sharp circumscription, irregular and infiltrating borders are present in some areas of the tumor.
- Sarcomatoid appearance of tumor cells shows spindle cells with no recognizable specific mesenchymal differentiation. Interlacing spindle cell fascicles with varying amounts of interspersed collagen bundles are evident.
- Infiltration of the ducts and lobules is a common finding.
- Significant cytologic (nuclear) atypia and numerous and often atypical mitoses are often present.
- A biphasic (phylloides) tumor component is absent.
- There is no association with malignant epithelial cells (carcinoma).

14.20.5 Immunoprofile

The tumor cells are negative for several epithelial markers. Whereas cytokeratins (pancytokeratin, CK5/6, CK14, CK34BE12), CD34, desmin, and h-caldesmon are not expressed, the tumors almost always show a positive reaction for CD10. Some of the myoepithelial markers such as CD29, SM actin, p63, and calponin may show positive immunoreaction in the tumor cells (focal positivity). ER, PR, and AR are negative. Most cases are positive for EGFR (HER1) [3].

Caution

- Spindle cell sarcoma, NOS type, should be distinguished from fibromatosis, metaplastic (sarcomatoid) carcinoma, and sarcomatous overgrowth in a high-grade phylloides tumor. Extensive sampling is crucial in order to exclude a biphasic fibroepithelial pattern (phylloides tumor) or a more recognizable epithelial component in a metaplastic (sarcomatoid) carcinoma. Spindle cell sarcoma, NOS type should not be diagnosed without adequate sampling and immunohistochemistry.
- Because some NOS-type sarcomas with CD10 expression and most metaplastic (sarcomatoid) carcinomas show positivity for CD29, SMA, and p63, differential diagnosis can be extremely difficult and requires extensive immunohistochemical evaluation. The immunophenotype of NOS-type sarcoma suggests that this malignant neoplasm represents a mammary sarcoma variant with myoepithelial features (differentiation) [3].

14.20.6 Additional Comments

Using the above-mentioned definition and after excluding other more common spindle cell tumors of the breast, primary NOS-type sarcomas of the breast are very rare. In the past, several examples of fibrosarcoma or liposarcoma have been reported as stromal sarcoma. It is likely that most examples of primary MFH in the breast actually represent undifferentiated spindle cell sarcoma that cannot be subclassified further.

14.20.7 Further Reading

1. Berg JW, De Cosse JJ, Fracchia AA, et al. Stromal sarcoma of the breast. Cancer 1962;15:418–424.
2. Callery CD, Rosen PP, Kinne DW. Sarcoma of the breast. A study of 32 patients with reappraisal of classification and therapy. Ann Surg 1985;201:527–532.
3. Leibl S, Moinfar F. Mammary NOS-type sarcoma with CD10 expression. A rare entity with features of myoepithelial differentiation. Am J Surg Pathol 2006;30:450–456.
4. Pollard SG, Marks, Temple LN, et al. Breast sarcoma. A clinicopathologic review of 25 cases. Cancer 1990;66:941–944.
5. Terrier PH, Terrier-Lacombe MJ, Mouriesse H, et al. Primary breast sarcoma: a review of 33 cases with immunohistochemistry and prognostic factors. Breast Cancer Res Treat 1989;13:39–48.

Fig. 91: Nodular (tumorous) pseudoangiomatous stromal hyperplasia.

Case history: A 45-year-old woman presented with a well-demarcated firm tumor in her right breast.

Fig. 91.1: Cut surface of the excised tumor showing a well-demarcated, fibrous yellow to greyish-white tumor. The gross appearance of the tumor is similar to that of a fibroadenoma.

Fig. 91.2: Low magnification of the nodule reveals numerous slit-like, anastomosing empty spaces in a dense collagenous stroma.

Fig. 91.3: The spaces are empty and lined by spindle cells.

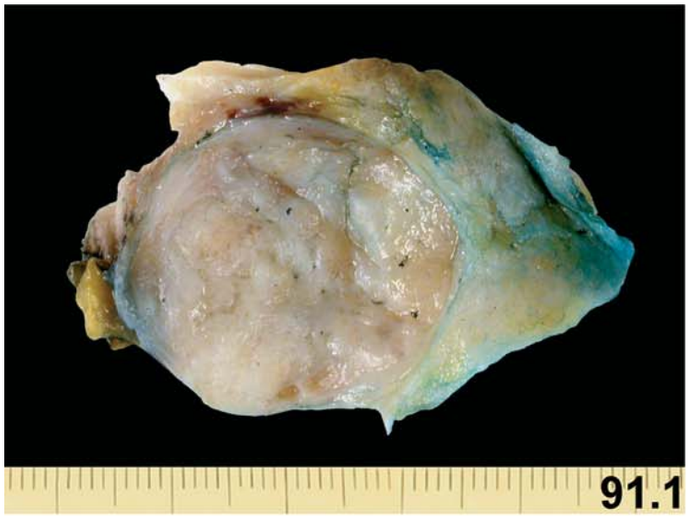
Fig. 91.4: Higher magnification displaying spindle cells at the margins of the spaces closely resembling endothelial cells.

Fig. 91.5: A few areas of the nodule show a more epithelioid appearance of the stromal cells (epithelioid myofibroblasts) with vacuolated or pale cytoplasm.

Fig. 91.6: Higher magnification of fibroblasts/myofibroblasts showing elongated nuclei. The tumor cells do not show increased mitotic activity.

Fig. 91: Final remarks

- This is an example of nodular or tumorous pseudoangiomatous stromal hyperplasia that represents a benign myofibroblastic proliferation with pseudovascular stromal alteration. The spindle cells at the margins of the anastomosing spaces are negative for endothelial markers such as CD31 and factor VIII-related antigen. The spindle cells are positive, however, for smooth muscle actin.
- The main differential diagnosis in this case is a low-grade angiosarcoma. The negative reaction for endothelial markers and lack of any destructive growth pattern or infiltration of lobules exclude the possibility of angiosarcoma.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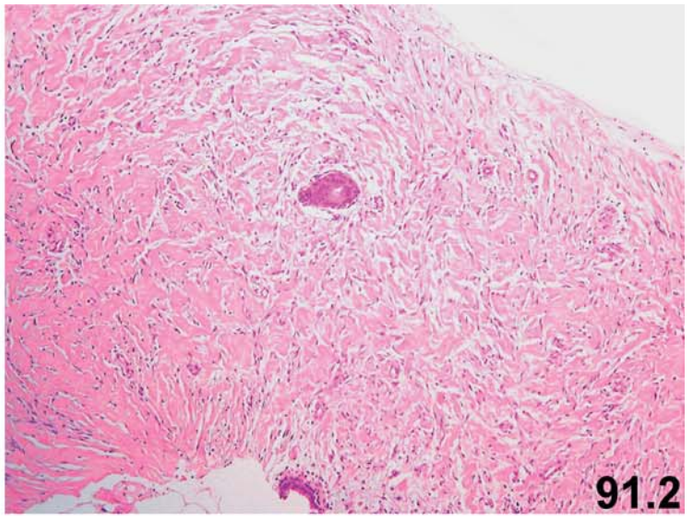
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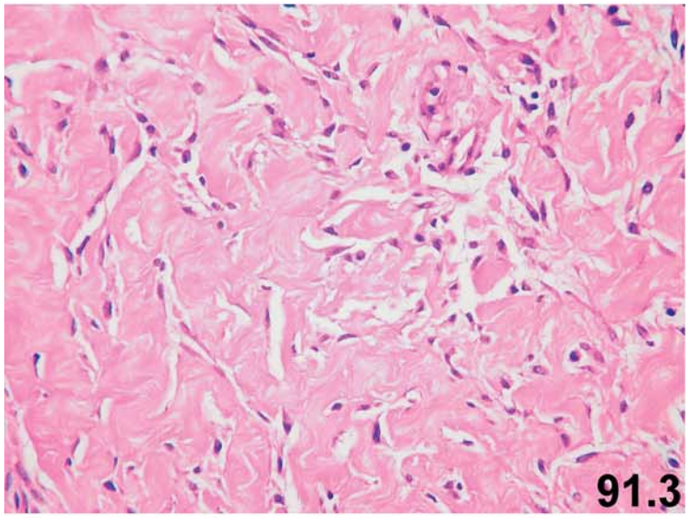
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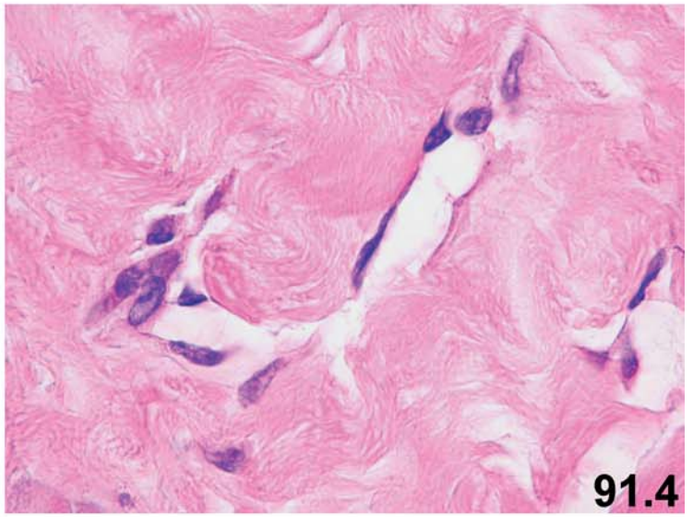
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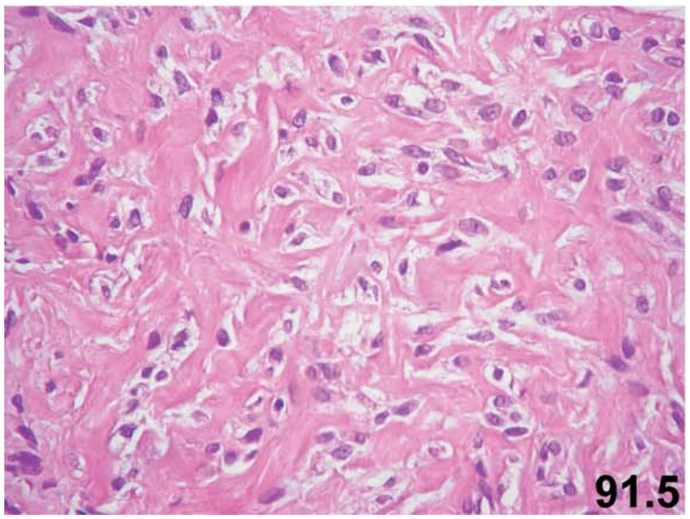
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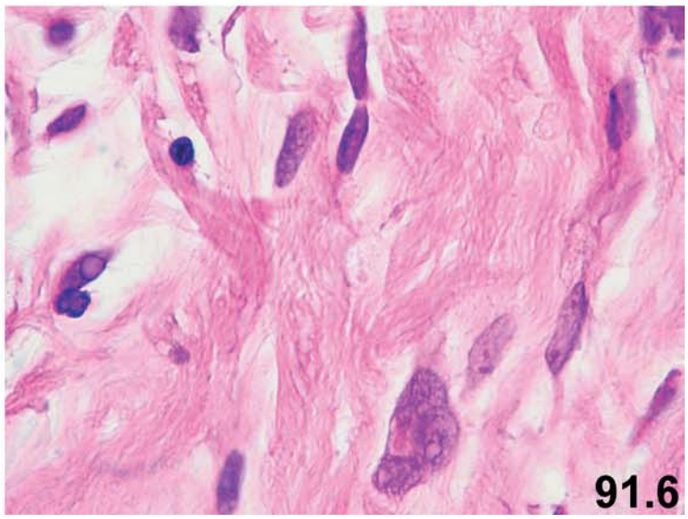
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Fig. 92: Myofibroblastoma.

Case history: A 41-year-old man with a well-circumscribed firm and mobile tumor in his left breast.

Fig. 92.1: The excisional biopsy shows a well-demarcated firm and rubbery, greyish-white tumor with lobulated external surface.

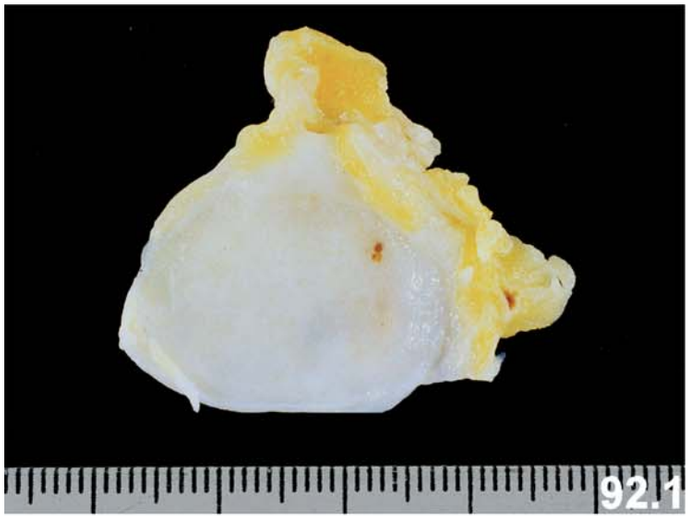
Fig. 92.2: Low magnification of the tumor displaying a well-circumscribed expansile tumor.

Fig. 92.3: and **Fig. 92.4:** The tumor is composed of uniform, ovoid to spindle-shaped cells arranged in short intersecting fascicles.

Figs. 92.5 and **92.6:** The tumor cells show pale to eosinophilic cytoplasm with round to elongated nuclei. The short fascicles are interrupted by thick and brightly eosinophilic collagen bands. There is no significant nuclear atypia or increased mitotic activity.

Fig. 92: Final remarks

- The main differential diagnosis in this case is a sarcomatoid (metaplastic) carcinoma with myoepithelial differentiation (malignant myoepithelioma). While the tumor cells in this case were positive for vimentin and focally expressed desmin and CD34, they were completely negative for several cytokeratins (pancytokeratin, CK34BE12, CK5/6, and CK14). The results of immunohistochemistry in this case (not shown) confirmed the diagnosis of myofibroblastoma.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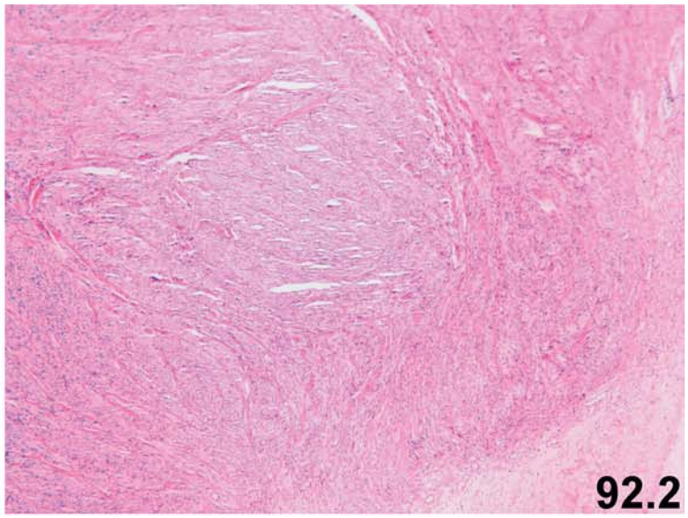
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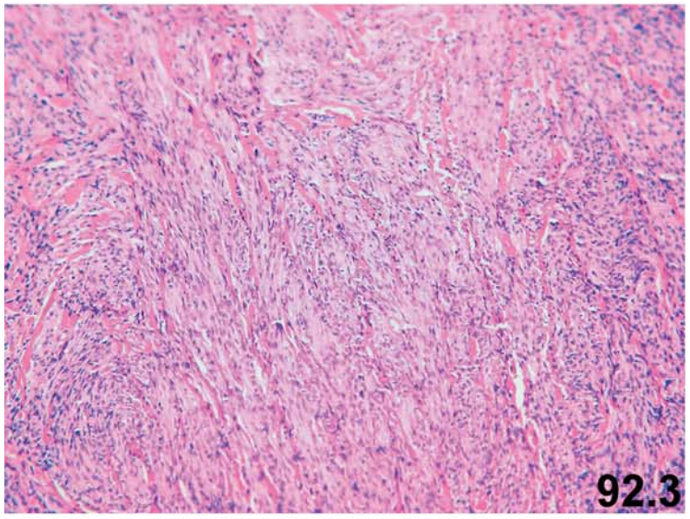
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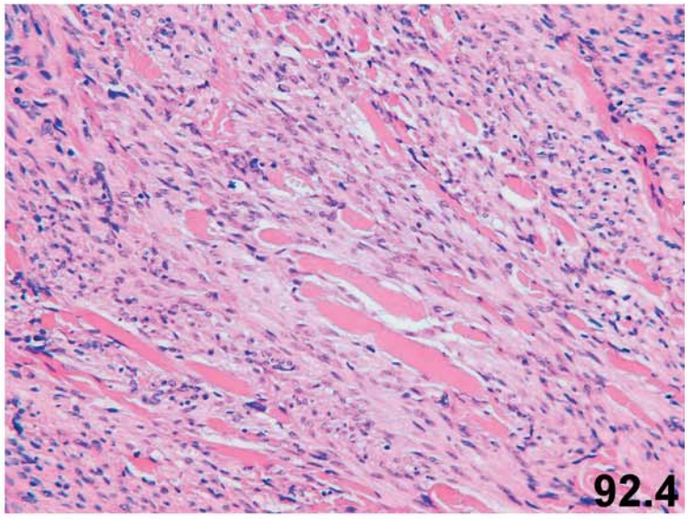
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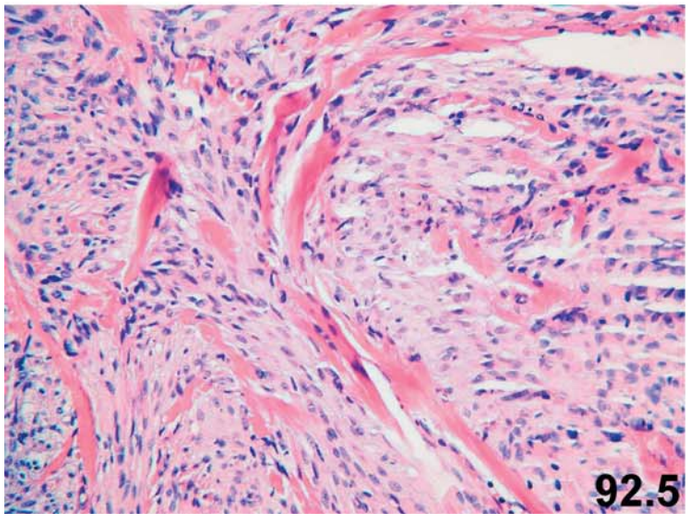
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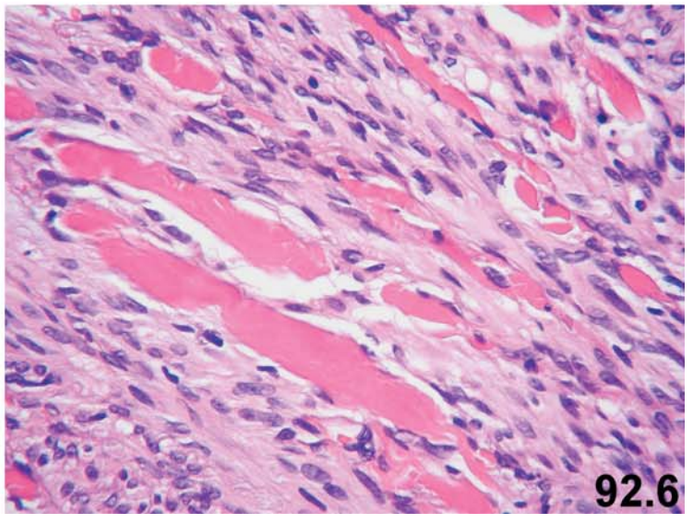
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Fig. 93: Granular cell tumor.

Case history: A 37-year-old woman presented with an ill-defined firm tumor in the upper outer quadrant of her right breast. Mammography revealed a tumor with infiltrative borders. Excisional biopsy showed a greyish-white to yellow tumor (1.7 cm).

Figs. 93.1 and **93.2:** Excisional biopsy of the lesion showing a tumor with irregular and infiltrative borders.

Figs. 93.3 and **93.4:** The tumor is composed of solid nests, clusters, or cords of uniform round to polygonal cells.

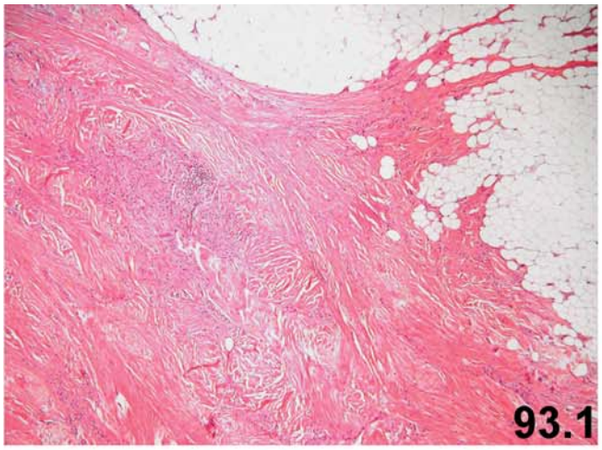
Fig. 93.5: Uniform round to polygonal cells with granular eosinophilic cytoplasm. The tumor cells show small round nuclei.

Fig. 93.6: Focally, there are a few cells with hyperchromatic and large nuclei.

Figs. 93.7 and **93.8:** Immunohistochemistry for S100 protein displays a diffuse positivity of tumor cells. Note the infiltrative pattern of the tumor cells. The tumor cells were negative for pancytokeratin (not shown).

Fig. 93: Final remarks

- The differential diagnoses in this case should include infiltrating lobular carcinoma, histiocytoid carcinoma, and apocrine carcinoma. Note that granular cell tumors are negative for cytokeratin but positive for S100 protein.
- The vast majority of granular cell tumors of the breast are clinically benign. After incomplete excision of this mesenchymal tumor, local recurrence may occur. In very rare cases, granular cell tumors may be associated with high-grade nuclear atypia, high mitotic activity, and tumor necrosis. These atypical features suggest an aggressive clinical behavior and therefore should be documented in a surgical pathology report.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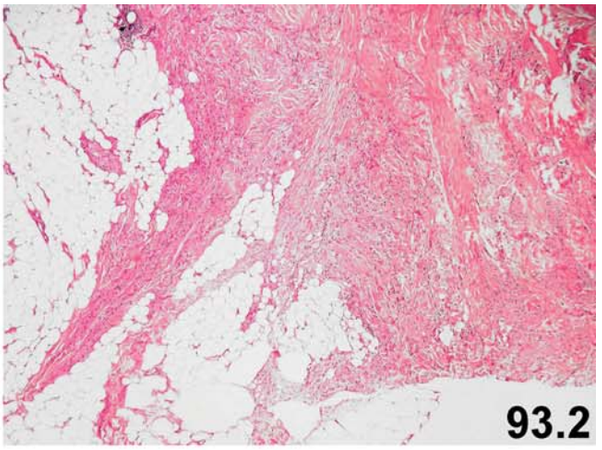
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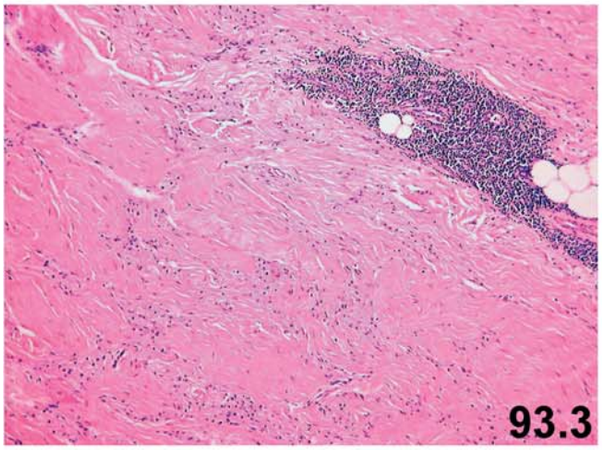
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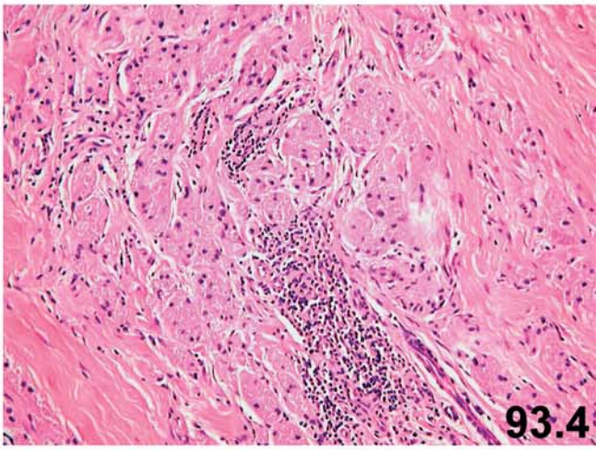
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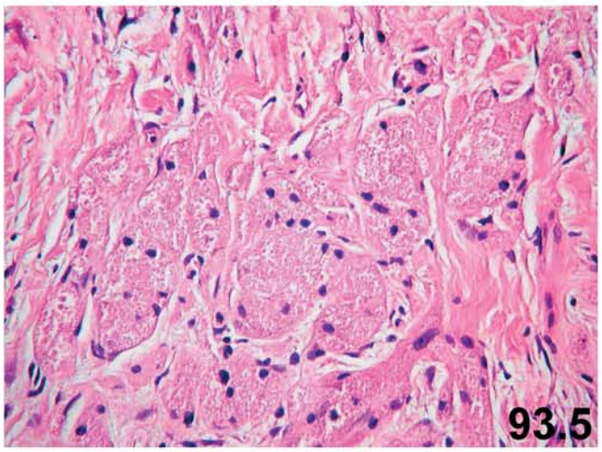
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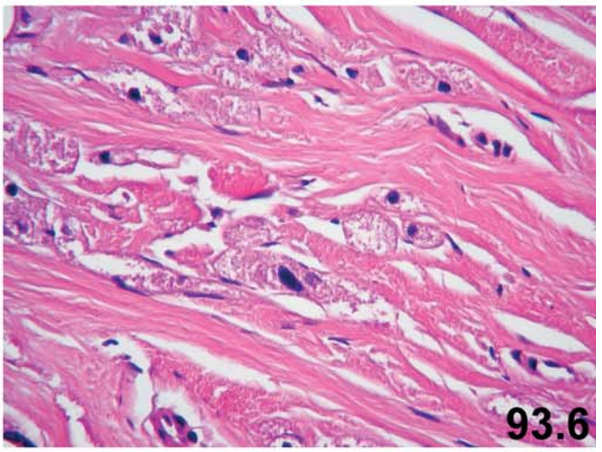
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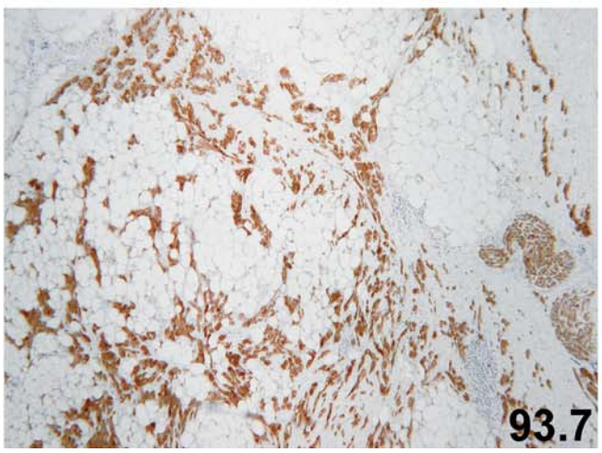
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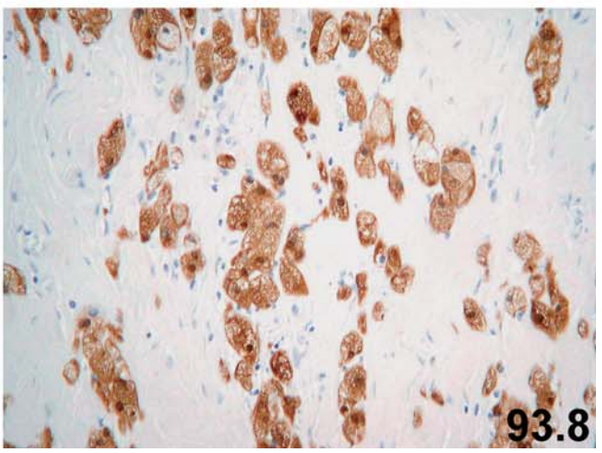
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Fig. 94: Angiosarcoma.

Case history: A 55-year-old woman with a history of invasive ductal carcinoma (pT1c, G2) of the left breast was treated by wide local excision and postoperative radiation therapy. Four years later, she presented with a palpable ill-defined tumor of her left breast. The skin of the breast showed several red to blue papules. A needle core biopsy showed a vascular neoplasm with highly atypical endothelial cells, consistent with an angiosarcoma. A modified radical mastectomy was finally performed.

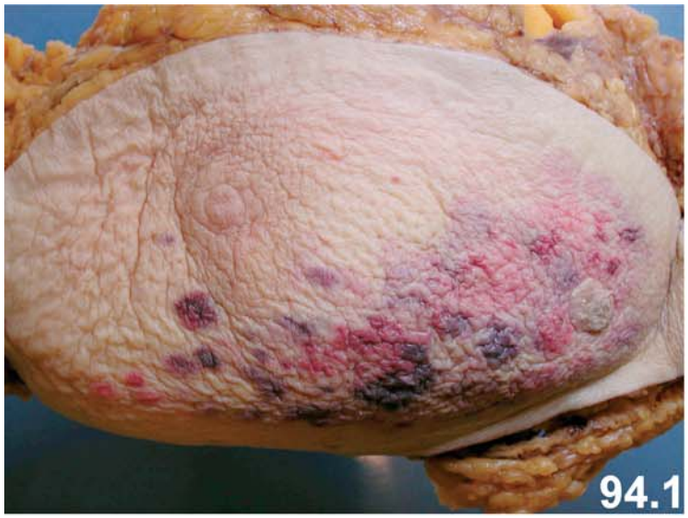
Figs. 94.1 and **94.2:** The skin of the mastectomy specimen shows numerous red to blue or brown papules that are partly well-circumscribed and partly ill-defined.

Fig. 94.3: Cut surface of the tumor showing nodules and hemorrhagic areas under the skin.

Fig. 94.4: Low magnification of the tumor shows a vascular proliferation with hemorrhagic areas.

Fig. 94.5: Several irregular anastomosing vascular channels lined by endothelial cells.

Fig. 94.6: A vascular tumor with infiltration of adipose tissue. Note the solid aggregates of tumor cells with hyperchromatic nuclei.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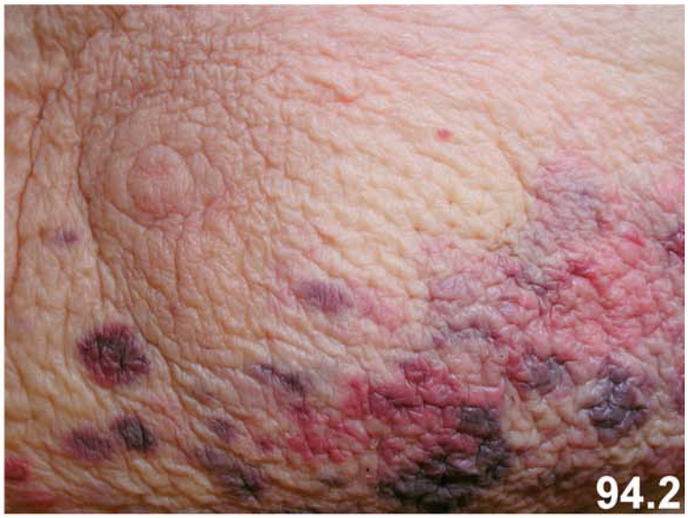
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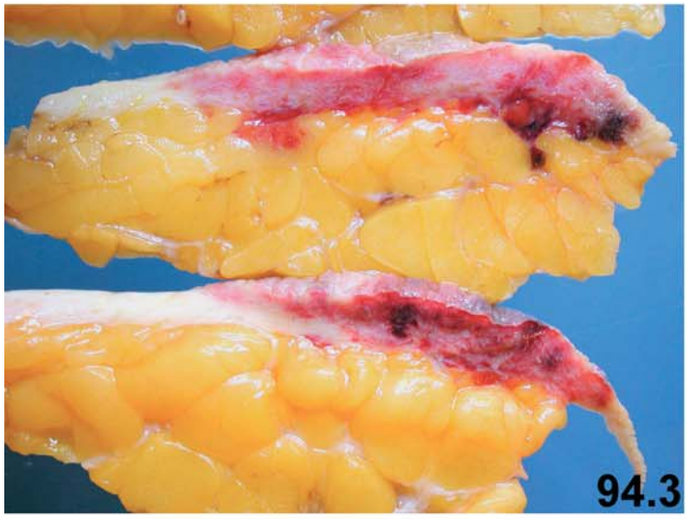
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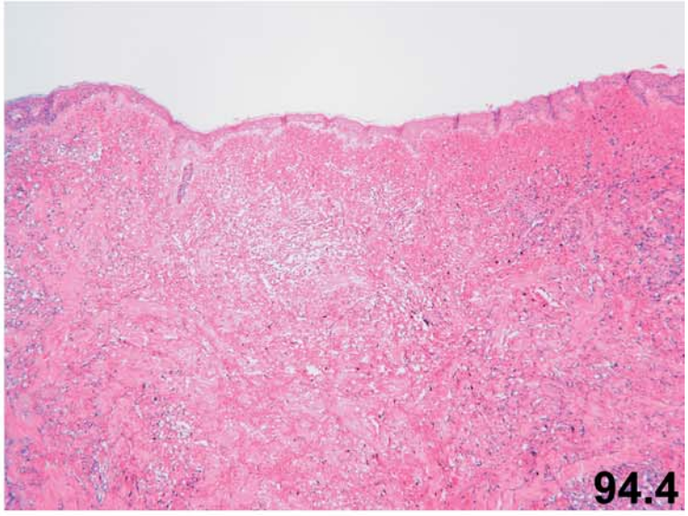
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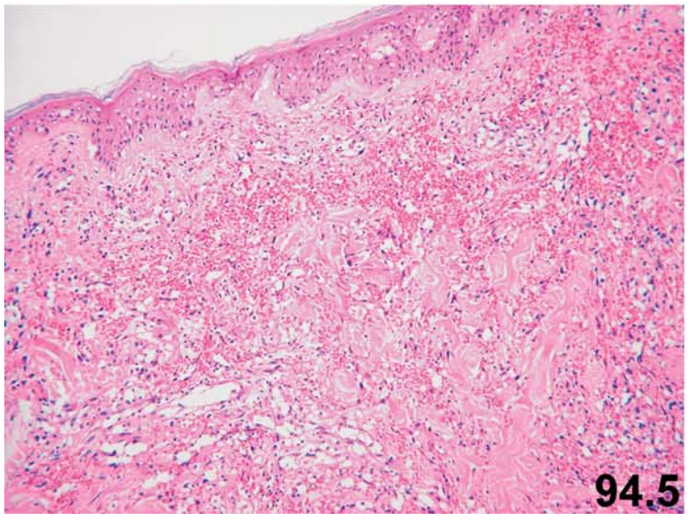
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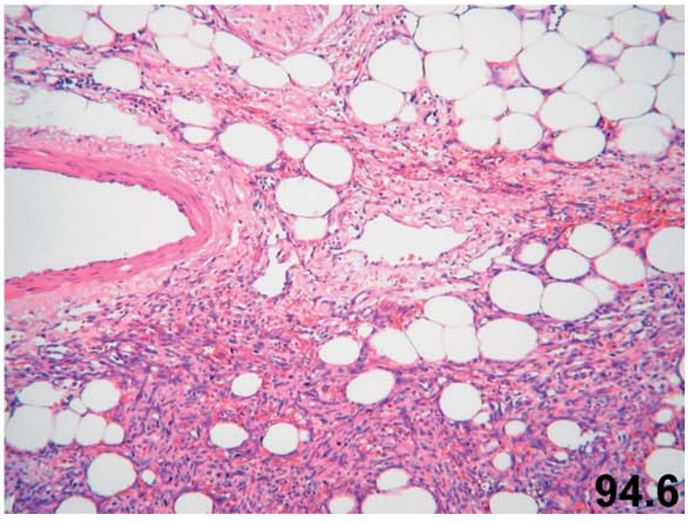
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Fig. 94.7: Several areas of the tumor show infiltration around and into lobular stroma. Note irregular, anastomosing channels lined by one or more layers of atypical endothelial cells.

Fig. 94.8: Some areas of the tumor display tufts of atypical endothelial cells.

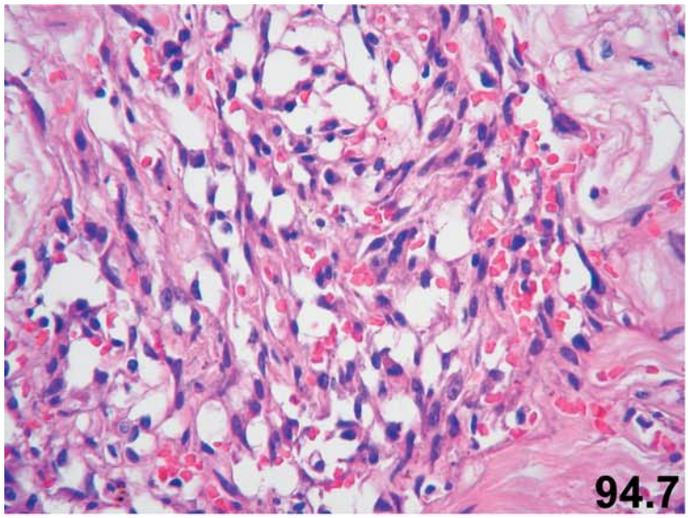
Fig. 94.9: Several areas of the tumor show solid aggregates of spindle cells with enlarged and hyperchromatic nuclei.

Figs. 94.10 and **94.11:** Higher magnification of the tumor displays spindle (endothelial) cells with high-grade nuclear atypia. Note the irregular chromatin distribution and nuclear pleomorphism.

Fig. 94.12: Immunohistochemistry for CD31 decorating endothelial cells of angiosarcoma with anastomosing channels and irregular arrangements of vascular spaces.

Fig. 94: Final remarks

- This is an example of angiosarcoma occurring years after breast surgery and local radiotherapy. Based on the degree of nuclear atypia and admixture of interanastomosing vascular channels with solid areas of spindle cells, this tumor is classified as high-grade angiosarcoma.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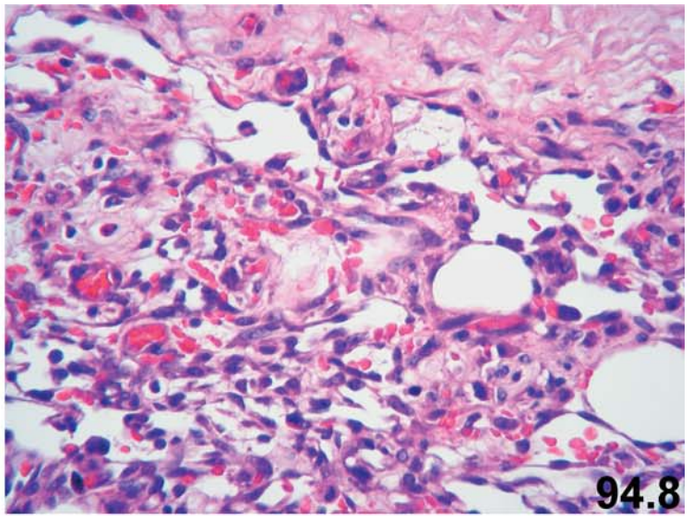
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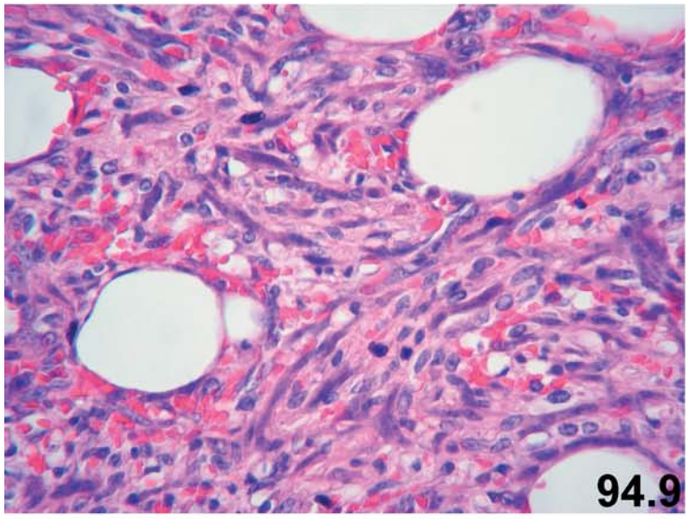
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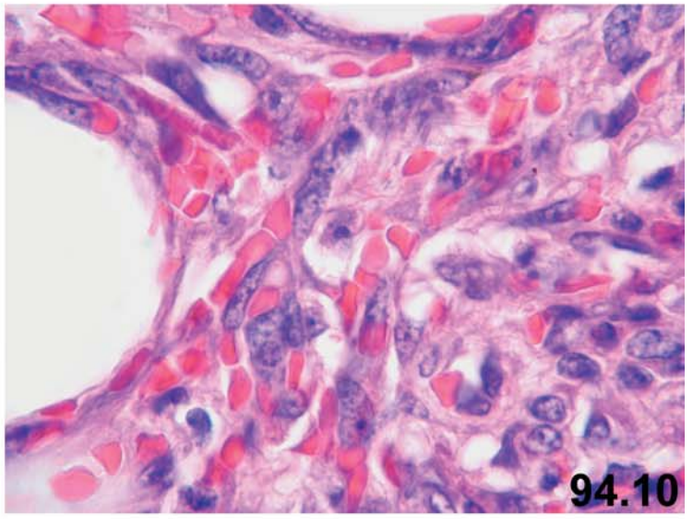
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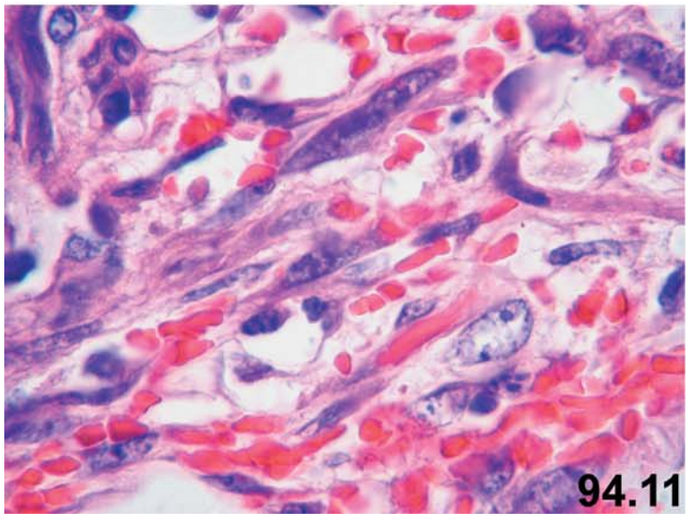
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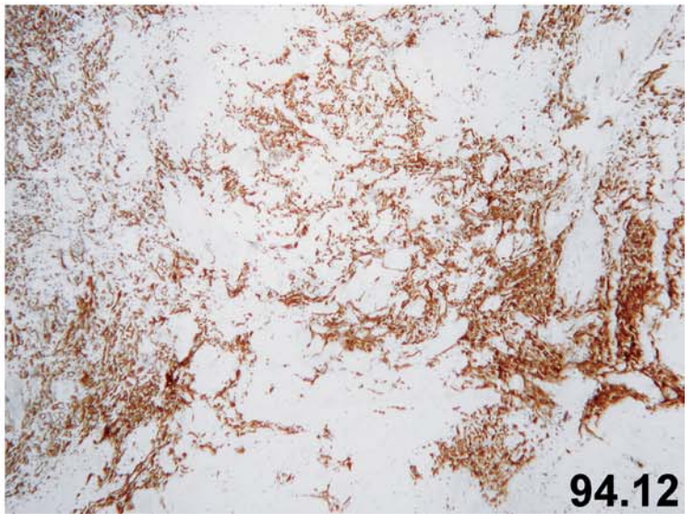
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Fig. 95: Leiomyoma of the breast.

Case history: A 61-year-old woman presented with a well-defined soft to firm tumor in the upper inner quadrant of her left breast. The tumor was 7 cm in greatest diameter. A needle core biopsy of the tumor revealed a mesenchymal tumor with smooth muscle differentiation (leiomyoma?).

Fig. 95.1: The tumor shows a greyish-white cut surface with focal areas of hemorrhage (core needle biopsy!).

Figs. 95.2 and **95.3:** Low magnification of the tumor displays interlacing bundles of fusiform mesenchymal tumor cells.

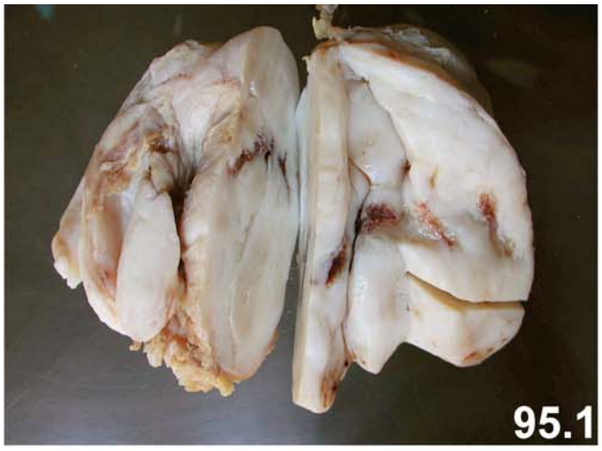
Figs. 95.4 and **95.5:** Higher magnification shows bundles of smooth muscle cells. Note the fibrillar and eosinophilic cytoplasm and the lack of nuclear atypia.

Fig. 95.6: Focally, the tumor shows aggregates of epithelioid cells. There is no cytologic atypia, mitotic activity, or tumor necrosis.

Figs. 95.7 and **95.8:** Immunohistochemistry for smooth muscle actin shows an intense and diffuse positive reaction in the tumor cells. Other markers such as smooth muscle myosin (heavy-chain) and h-caldesmon were also positive (not shown).

Fig. 95: Final remarks

- Primary smooth muscle tumors of the breast are very rare and should be diagnosed cautiously. As in this case, a mammary leiomyoma should show no cytologic atypia or increased mitotic activity.
- Sarcomatoid (metaplastic) carcinoma should be included in the differential diagnosis. Immunohistochemistry for cytokeratins (pancytokeratin, CK34BE12, CK5/6, CK14) needs to be done to exclude the possibility of a sarcomatoid carcinoma. It is of note, however, that mammary and extramammary smooth muscle tumors often show a weak, granular cytoplasmic reaction for pancytokeratin. In contrast, the immunoreaction for pancytokeratin in sarcomatoid (metaplastic) carcinoma is intense and membranous. Furthermore, as apposed to sarcomatoid carcinomas, smooth muscle tumors are negative for high molecular weight cytokeratin or basal-type cytokeratins such as CK5/6, CK14, and CK34BE12.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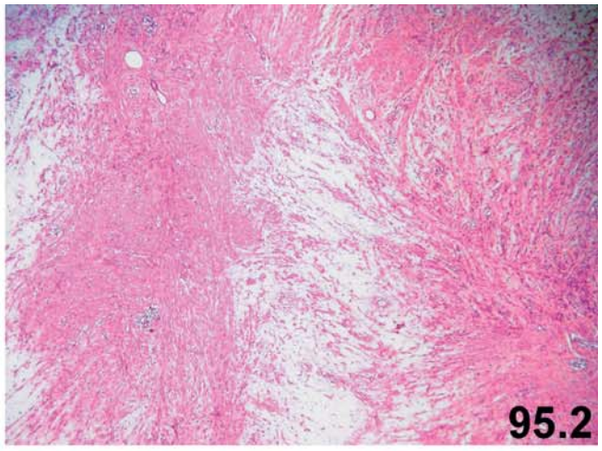
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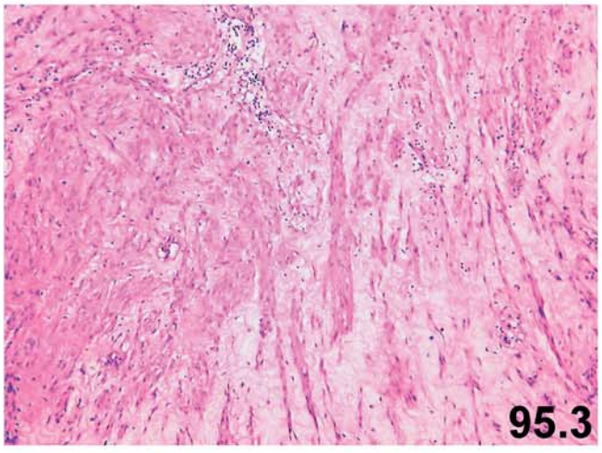
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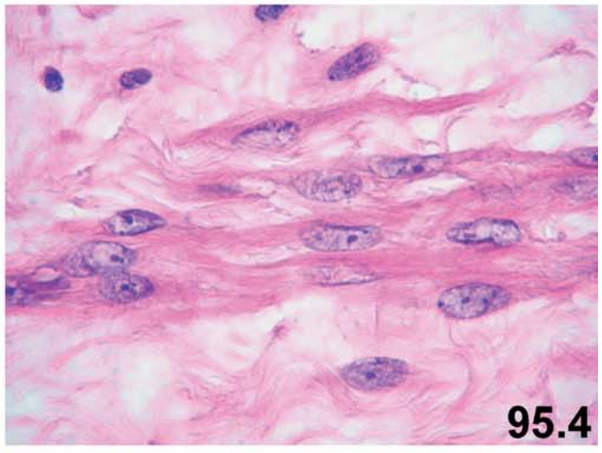
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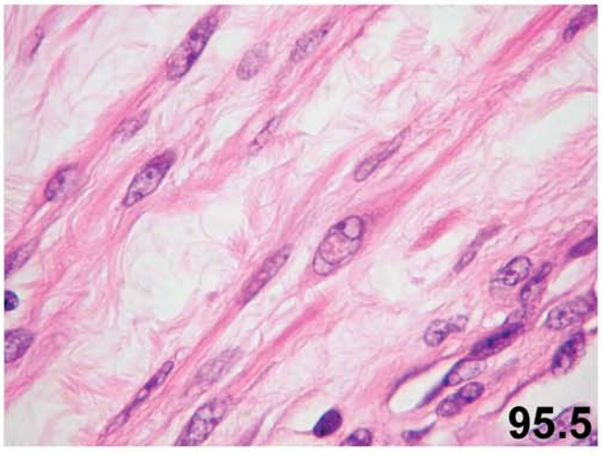
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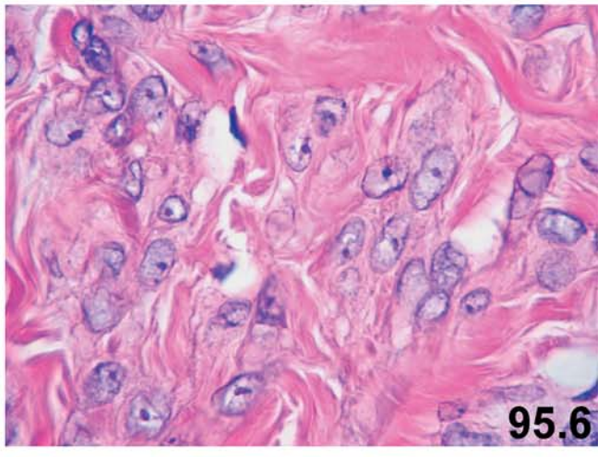
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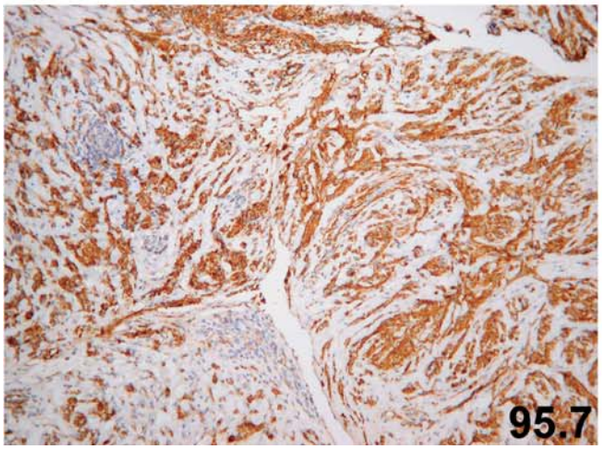
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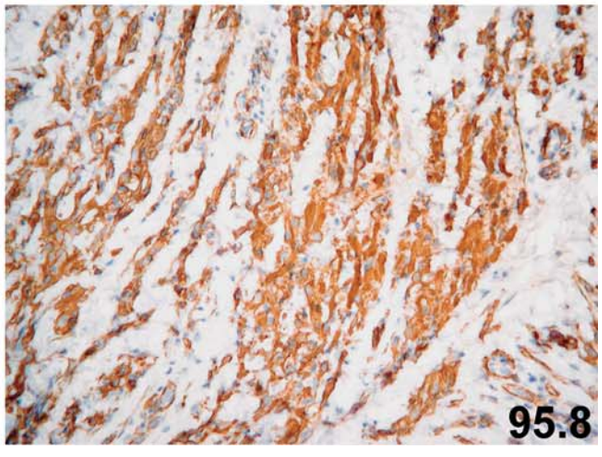
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Fig. 96: Osteogenic sarcoma.

Case history: A 70-year-old woman presented with a 4-cm hard tumor in the upper, outer quadrant of her left breast. Excisional biopsy was performed and showed a sharply defined and lobulated soft gelatinous to hard greyish-white tumor (4×2.5×1.5 cm).The tumor was grossly described as gritty under the knife.

Figs. 96.1 and **96.2:** The tumor is composed of spindle to oval tumor cells with variable amounts of osteoid or osseous tissue.

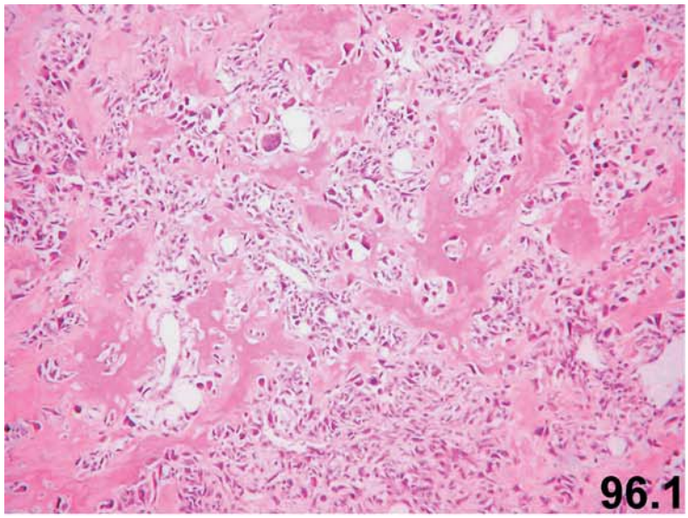
Fig. 96.3: Mononuclear and multinuclear tumor cells proliferating among branching trabeculae of bone and osteoid.

Fig. 96.4: Osteoclastic tumor cells admixed with atypical plump stromal cells.

Figs. 96.5 and **96.6:** While some areas of the tumor appear benign with layers of osseous tissue alternating with uniform spindle cells, several other areas reveal atypical cells with hyperchromatic and large nuclei. The tumor also showed an infiltrating growth pattern focally (not shown).

Fig. 96: Final remarks

- Primary osteogenic sarcoma (osteosarcoma) of the breast is extremely rare. One should always exclude the possibility of a metaplastic (sarcomatoid) carcinoma and a phylloides tumor before calling a tumor a primary (osteo) sarcoma. Extensive sampling of the tumor in this case did not reveal a phylloides tumor. Immunohistochemistry for several cytokeratins was also negative in the tumor cells.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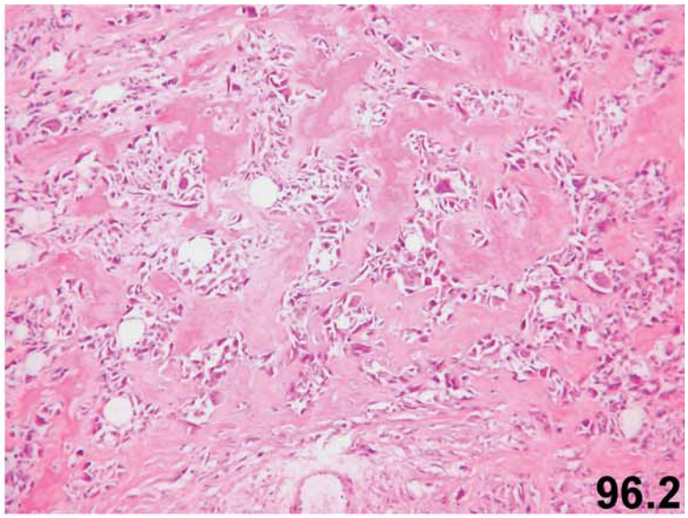
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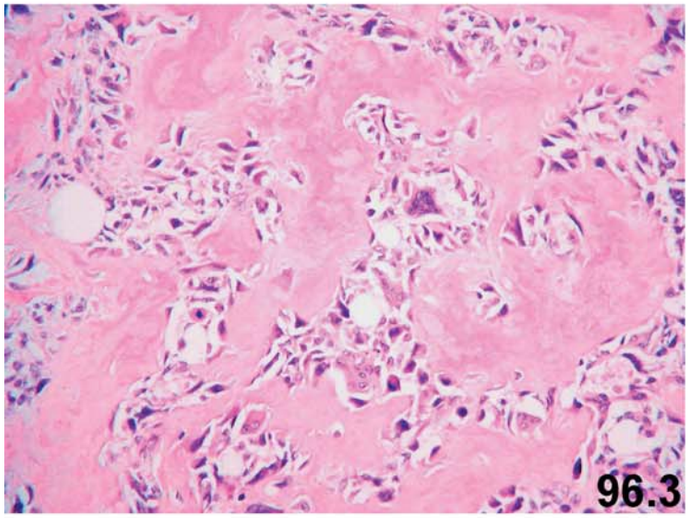
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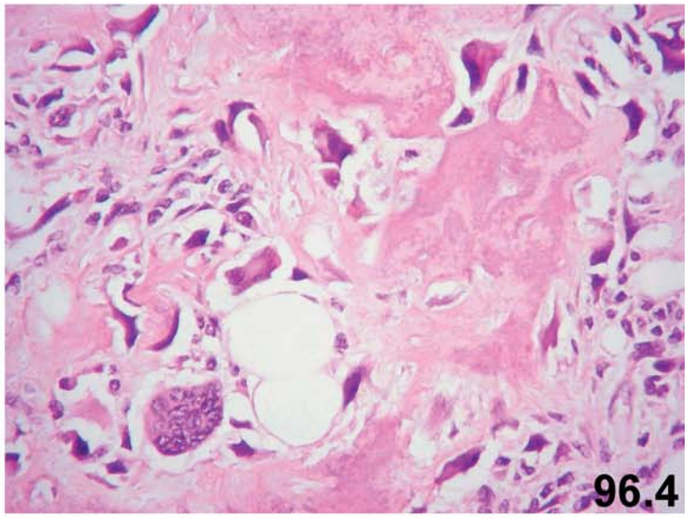
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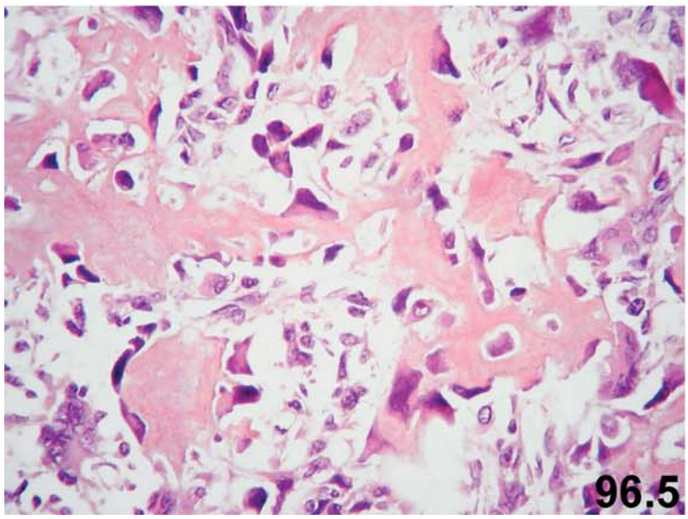
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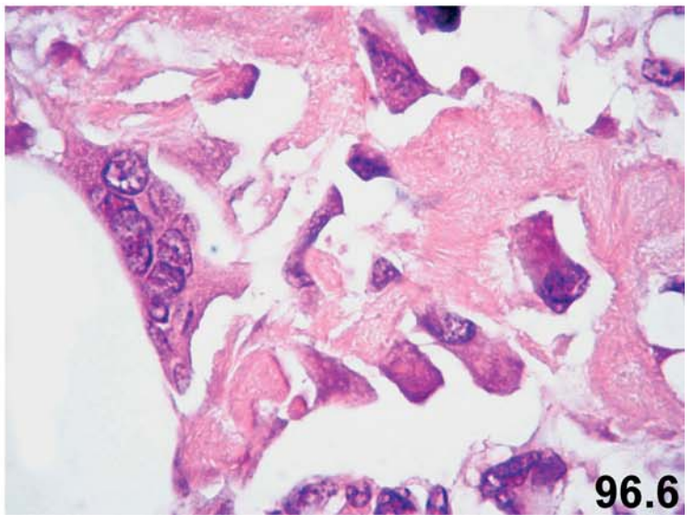
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Fig. 97: High-grade sarcoma, not otherwise specified (sarcoma, NOS-type).

Case history: A 46-year-old woman presented with a rapidly growing firm tumor of her right breast. A needle core biopsy of the tumor revealed a high-grade malignant tumor (metaplastic carcinoma? sarcoma?). A modified radical mastectomy was performed.

Fig. 97.1: Massive enlargement of the right breast due to a rapidly growing tumor

Fig. 97.2: Mastectomy specimen showing a large (13 cm) tumor. The cut surface of the tumor is partly greyish-white and shows several areas of hemorrhage and necrosis. The tumor also infiltrates into the pectoralis muscles. (Courtesy of Drs. A. Roessner and P. Buhtz, Magdeburg, Germany).

Figs. 97.3 and **97.4:** The tumor has a sarcomatoid appearance showing spindle cells with no recognizable mesenchymal differentiation. In some areas of the malignant tumor, interlacing spindle cell fascicles are present.

Fig. 97.5: Significant nuclear atypia and numerous mitoses are present.

Fig. 97.6: Higher magnification reveals moderate to severe nuclear atypia. Even after extensive search, there was no biphasic or phylloides tumor. There was no association with recognizable malignant epithelial tumor cells.

Fig. 97.7: Immunohistochemically, the tumor cells are positive for p63, which is a myoepithelial (or basal cell) marker. The tumor cells were, however, completely negative for several cytokeratins such as pancytokeratin, CK34BE12, CK5/6, and CK14 (not shown).

Fig. 97.8: Immunohistochemistry for CD10 reveals a diffuse and intense positive reaction in the tumor cells. The tumor cells also focally showed a positive reaction for smooth muscle actin (not shown).

Fig. 97: Final remarks

- This case demonstrates an example of high-grade sarcoma of the breast with no recognizable specific differentiation. The most appropriate designation for this very rare variant of malignant breast tumor is NOS sarcoma.
- The major differential diagnoses in this case are fibromatosis, metaplastic (sarcomatoid) carcinoma, and sarcomatous overgrowth in a high-grade phylloides tumor. Spindle cell sarcoma, NOS type should not be diagnosed without extensive sampling and performance of immunohistochemistry. Note that like sarcomatoid (metaplastic) carcinoma that often shows myoepithelial differentiation, NOS-type sarcoma of the breast also exhibits some myoepithelial cell differentiation based on immunohistochemical markers such as CD10, p63, and smooth muscle actin. In contrast to sarcomatoid (metaplastic) carcinoma, the tumor cells in NOS-type sarcoma are completely negative for cytokeratins such as pancytokeratin, CK34BE12, CK5/6, CK14, and CK17.


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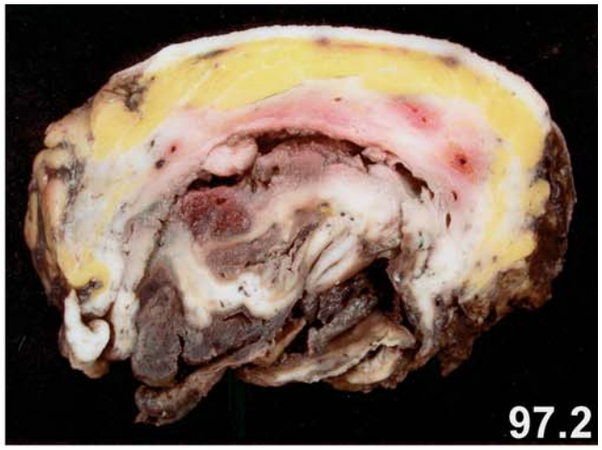
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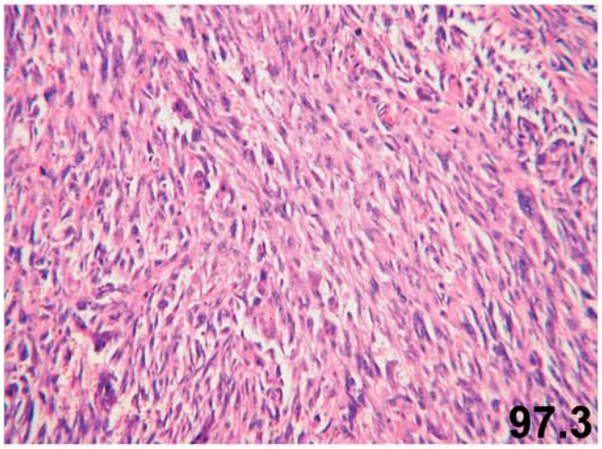
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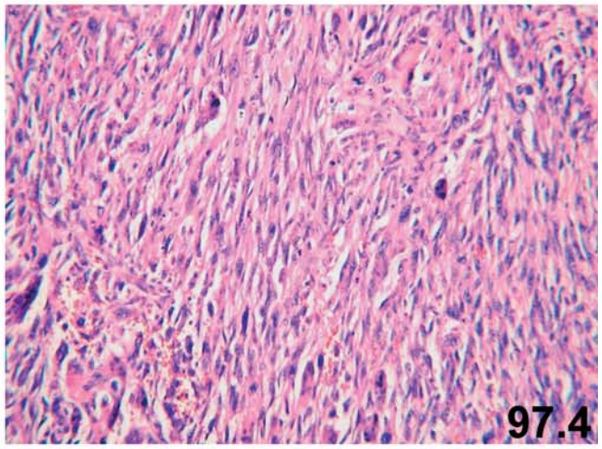
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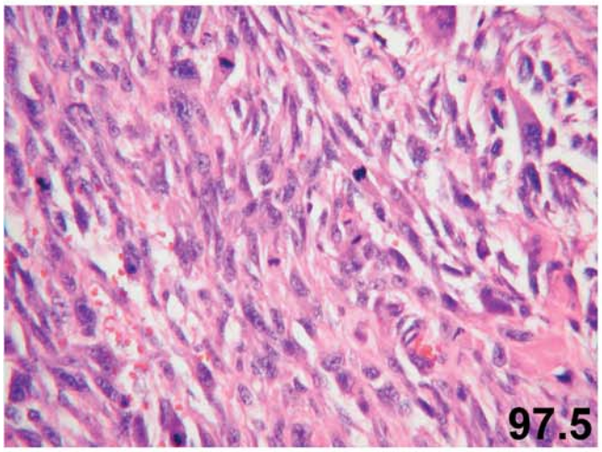
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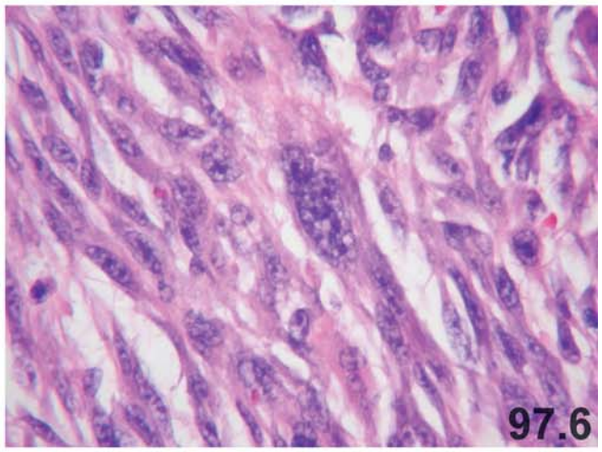
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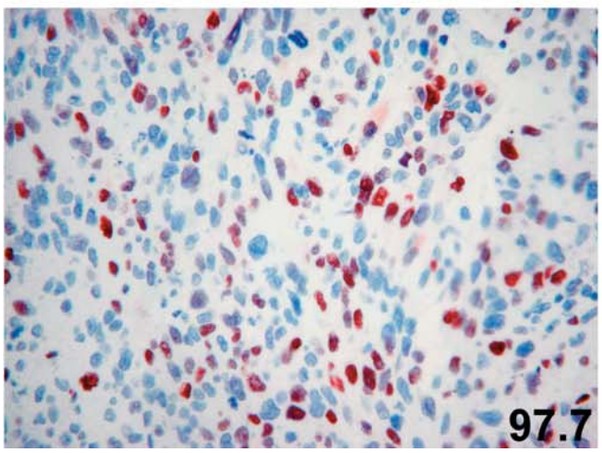
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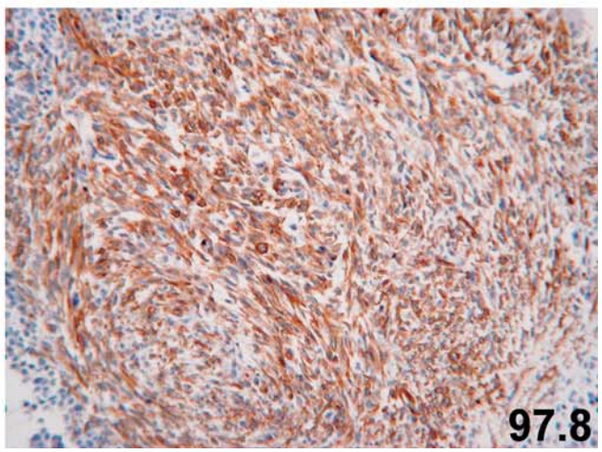
97.8

Myoepithelial Lesions/Neoplasms

Contents

CHAPTER 15 Myoepithelial Lesions/Neoplasms

15.1 Background

The appearance of myoepithelial cells varies significantly from a bipolar "naked" nuclei with very scant cytoplasm to cells with rounded nuclei with abundant eosinophilic or clear cytoplasm. Several benign and malignant neoplasms in the breast are mainly or partly related to myoepithelial cells. Myoepithelial lesions such as hypertrophy or hyperplasia, adenomyoepithelioma, carcinoma arising in the background of adenomyoepithelioma, and carcinoma with MEC differentiation (myoepithelial carcinoma) are the subjects of this chapter. Adenoid cystic carcinoma, which is also related to myoepithelial cells, is discussed elsewhere (breast carcinomas, special types).

15.2 Immunoprofile

It is important to keep in mind that myoepithelial cells can be positive for some of the "myoepithelial markers" but completely negative for others. The immunoreactivity of myoepithelial cells is often a matter of differentiation and function of the cells and, therefore, can vary significantly, even within the same lesion.

Currently, no single specific myoepithelial marker is available. But a number of myoepithelial markers can be used reliably, particularly in combination and in association with the morphology.

Myoepithelial cells are commonly positive for smooth muscle (SM) actin, calponin, SM myosin (heavy chain), S100 protein, CD10, and p63. Recent markers include 14-3-3 sigma, CD29, and nerve growth factor receptor (NGFR/p75) [18, 20, 22, 24, 25].

Normal and neoplastic myoepithelial cells are very often positive for SM actin, S100 protein, CD10, and p63. In difficult cases, at least two of these markers should be used in combination. The immunoreaction for these markers can be diffuse and intense or focal. Basal-type cytokeratins such as CK5/6, CK14, and CK17 are usually positive in MEC, and they can also be positive in some luminal epithelial cells. These cytokeratins should not be used alone as reliable markers for myoepithelial cells. Estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) are characteristically negative in normal and neoplastic myoepithelial cells. Desmin is also negative.

15.3 Myoepithelial Cell Hypertrophy

15.3.1 Definition

Prominent presence of a myoepithelial cell layer characterized by enlargement of cells with abundant cytoplasm.

15.3.2 Microscopic Features (Fig. 98)

- Even at low magnification, a distinct cell population of basally located cells surrounding luminal epithelial cells of ducts and lobules is present.
- At higher magnification, one cell layer of enlarged myoepithelial cells with abundant clear or eosinophilic cytoplasm is evident.
- Sometimes a plasmacytoid appearance of myoepithelial cells with eccentric nuclear position can be observed. A hobnail pattern of myoepithelial cells can rarely be found.
- Myoepithelial cells may show a myoid look, with spindle-shaped cells with deep eosinophilic, fibrillar cytoplasm (also called as myoid differentiation).
- Association with adenosis, epithelial hyperplasia, and papilloma is not infrequent.

15.3.3 Additional Comments

By definition, hypertrophy should be distinguished from hyperplasia of myoepithelial cells; whereas in hypertrophy there is only one layer of enlarged myoepithelial cells, myoepithelial cell hyperplasia or myoepitheliosis is characterized by a numerical increase of myoepithelial cells with or without enlargement of such individual cells.

In rare cases, myoepithelial cell hypertrophy may be associated with some degree of nuclear atypia. The significance of atypia in that setting is not clear.

15.4 Myoepitheliosis (Myoepithelial Hyperplasia)

15.4.1 Definition

Hyperplasia of myoepithelial cells growing into and/or around small ducts and lobules. Often a microscopic, multifocal finding.

15.4.2 Macroscopy

Either normal or firm irregular area of the cut surface.

15.4.3 Microscopic Features

- Usually, there is a multifocal proliferation of myoepithelial cells in the peripheral duct system (terminal duct/lobular units).

- Spindle, round, or cuboidal myoepithelial cells are evident, with eosinophilic or clear cytoplasm.
- Rarely, a plasmacytoid appearance is seen.
- The cuboidal cells may show longitudinal nuclear grooves mimicking transitional cells.
- Mitotic activity and nuclear atypia may rarely be present.
- Association with (sclerosing) adenosis and peripheral intraductal papilloma can occur.

15.4.4 Additional Comments

The presence of significant nuclear atypia in myoepitheliosis warrants a designation of atypical myoepitheliosis. The clinical significance of atypia in that setting is, however, not investigated.

In some cases of adenosis, prominent myoepithelial hypertrophy and hyperplasia may occur; these cases have been designated adenomyoepithelial adenosis. The distinction between adenomyoepithelial adenosis and small adenomyoepithelioma, however, is subjective and not well defined.

15.5 Adenomyoepithelioma

15.5.1 Definition

A solitary and often centrally located tumor composed of proliferating myoepithelial cells around small epithelial-lined spaces.

15.5.2 Macroscopy

Sharply delineated, round to multilobulated tumor with firm to rubbery consistency and greyish-white, yellow, or pink cut surface. Some cases may show irregular and infiltrating margins. In large tumors, cystic areas and necrosis may occur.

15.5.3 Microscopic Features (Fig. 99)

- Most adenomyoepitheliomas are circumscribed, showing aggregates of nodules.
- Layers or aggregates of myoepithelial cells around epithelial lined spaces are evident.
- The tumor often shows a lobulated growth pattern. Prominent spindle cells or a tubular pattern may also be present.
- The lobulated type (variant) of adenomyoepithelioma displays solid nests of myoepithelial cells with eosinophilic or clear cytoplasm proliferating around compressed epithelial cells.
- Rounded aggregates of tumor cells may infiltrate into the surrounding normal breast tissue.
- Focal or multifocal necrosis may be seen.
- Neoplastic myoepithelial cells with a plasmacytoid appearance showing abundant eosinophilic cytoplasm and eccentrally located nuclei may be present.
- The tubular variant often has ill-defined margins and displays rounded tubules lined by easily identifiable luminal epithelial and basally located myoepithelial cells.
- Sometimes spindle cells are the predominant cell component, with few epithelial-lined spaces.
- Many tumors have one or more nodules in which there is a focal papillary growth pattern.
- Up to three mitotic figures per 10 hpf may be seen in myoepithelial cells.
- Apocrine and mucinous metaplasia can be present. Apocrine metaplastic cells may show some degree of nuclear variation and atypia.
- Central hyalinization, particularly in the lobulated variant, is a common finding.
- Satellite nodules adjacent to the lobulated variant can be seen in some cases.
- Intraductal papillary configurations extending into ducts outside the gross tumorous lesion may be observed.
- Rarely, areas of squamous metaplasia or sebaceous differentiation are present.
- Rarely, chondroid metaplasia and a pattern closely similar to salivary gland pleomorphic adenoma may occur.

Caution

- An adenomyoepithelioma with combined atypical features including high-grade nuclear atypia, increased mitotic activity (more than three mitosis per 10 hpf), and focally infiltrative margins should be interpreted very cautiously; these features would strongly favor a carcinoma arising in the background of adenomyoepithelioma. If there is no clear-cut invasive carcinoma, wide local excision of the atypical adenomyoepithelioma with close clinical follow-up is recommended.

15.5.4 Additional Comments

Some investigators regard most adenomyoepitheliomas as a variant of intraductal papillomas that are associated with prominent myoepithelial hyperplasia. On the other hand, it has been suggested that some adenomyoepitheliomas may represent a variant of nodular adenosis (adenosis tumor) with significant myoepithelial hypertrophy and hyperplasia (adenomyoepithelial adenosis) [11, 12].

The group of tumors sometimes referred to as mixed tumors or pleomorphic adenomas of the breast are mostly variants of adenomyoepithelioma.

The majority of adenomyoepitheliomas are benign. Tumors with infiltrating margins or those with high mitotic activity have a potential for recurrence and/or distant (lung) metastases [2, 4, 8, 15, 17, 25, 26].

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15.6 Sarcomatoid Carcinoma with Myoepithelial Differentiation (Myoepithelial Carcinoma, Malignant Myoepithelioma)

15.6.1 Definition

A malignant epithelial spindle cell tumor with immunoprofile of myoepithelial cells (myoepithelial differentiation).

15.6.2 Macroscopy

A solitary firm to rubbery greyish-white tumor, often with irregular and infiltrating margins.

15.6.3 Microscopic Features (Figs. 69–73)

- The tumor is composed almost entirely of interlacing spindled cells without a glandular component. The hallmark of the tumor is a sarcomatoid appearance.
- A storiform pattern is often present.
- Significant nuclear atypia and numerous mitotic figures are often readily present .
- Rarely, the tumor cells appear very bland (low-grade carcinoma).
- Giant tumor cells with bizarre hyperchromatic nuclei may be present.
- Infiltration of the surrounding normal breast tissue is common.
- Aggregates of collagen and prominent central hyalinization may be present.
- Refer also to the section on metaplastic carcinoma.

Caution

- The differential diagnosis includes sarcomatous overgrowth in a phylloides tumor; mammary sarcoma, NOS type; spindle cell variant of squamous cell (metaplastic) carcinoma; fibromatosis; and myofibroblastic neoplasms.
- Carcinoma with myoepithelial differentiation can easily be mistaken for sarcoma. Primary mammary sarcoma without association with high-grade phylloides tumors are, however, extremely rare and should be diagnosed very cautiously; immunohistochemistry for a variety of cytokeratins and myoepithelial markers is often necessary to identify or exclude a carcinoma with myoepithelial differentiation.
- Occasionally, spindle cell carcinomas with myoepithelial cell differentiation reveal very bland-looking nuclei and no increased mitotic activity. These features can easily be misinterpreted as reactive stromal changes.
- Carcinoma with myoepithelial differentiation (myoepithelial carcinoma) usually show at least a focal positive immunoreactivity for basal-type cytokeratins such as CK5/6, CK34BE12, CK14, or CK17 (carcinoma with basal-like differentiation). A myoepithelial differentiation can be recognized after performance of immunohistochemistry for SM actin, p63, CD10, or CD29. Two more recently introduced myoepithelial markers include 14-3-3 sigma and p75 neurotrophin receptor (nerve growth factor receptor, NGFR/p75), which are frequently positive in tumors with myoepithelial differentiation.

15.6.4 Additional Comments

Sarcomatoid carcinoma of the breast with myoepithelial differentiation has also been designated myoepithelial carcinoma or malignant myoepithelioma. Based on the morphology, immunohistochemistry, and ultrastructural features, a myoepithelial origin of the tumorous spindle cells has been suggested. While a myoepithelial differentiation can be observed in the vast majority of such cases, a myoepithelial origin of tumor cells cannot be proved in most cases and currently remains a matter of speculation [6]. The designation of sarcomatoid carcinoma with myoepithelial differentiation therefore seems -more appropriate.

Spindle cell squamous (metaplastic) breast carcinoma typically shows a positive immunoreaction for basal-type cytokeratins and p63 but is negative for actin and CD10 [1, 2, 5, 6, 7a, 8–10].

Like other myoepithelial markers, 14-3-3 sigma protein is not specific for myoepithelial cells [7b]. In normal human tissues, the strongest immunoreactivity for 14-3-3 sigma protein is observed in squamous epithelial cells at various sites, followed by basal and myoepithelial cells of various glands.

15.6.5 Further Reading

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Fig. 98: Myoepithelial cell alterations including hypertrophy, myoid hypertrophy, and atypia

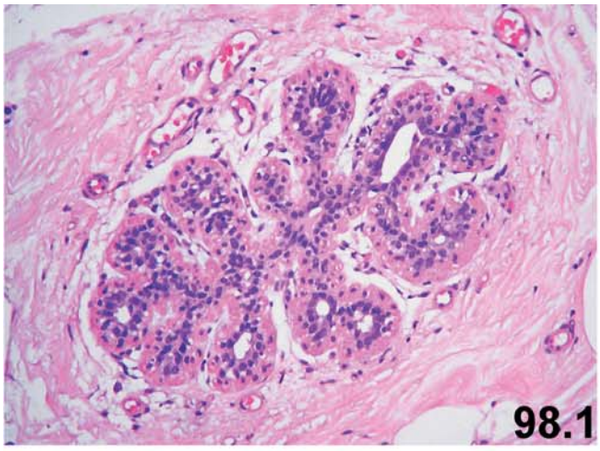
Figs. 98.1, 98.2, and **98.3:** Lobules with myoepithelial cell hypertrophy showing a prominent myoepithelial cell layer characterized by enlargement of cells with abundant cytoplasm. Even at low magnification, a distinct cell population of basally located cells is present surrounding luminal epithelial cells.

Figs. 98.4, and **98.5:** Sometimes myoepithelial cells may show a myoid look; spindle shaped cells with deep eosinophilic, fibrillar cytoplasm (myoid differentiation).

Figs. 98.6, 98.7, and **98.8:** In rare cases, myoepithelial cell hypertrophy may be associated with significant cytologic atypia characterized by enlarged hyperchromatic nuclei, irregular nuclear membrane, and prominent nucleoli. However, the significance of myoepithelial cell atypia is unclear.

Fig. 98: Final remarks

- By definition, hypertrophy should be distinguished from hyperplasia of myoepithelial cells. In hypertrophy, there is only one layer of enlarged myoepithelial cells with abundant cytoplasm. Myoepithelial hyperplasia or myoepitheliosis is characterized by a numerical increase of myoepithelial cells with or without enlargement of such individual cells.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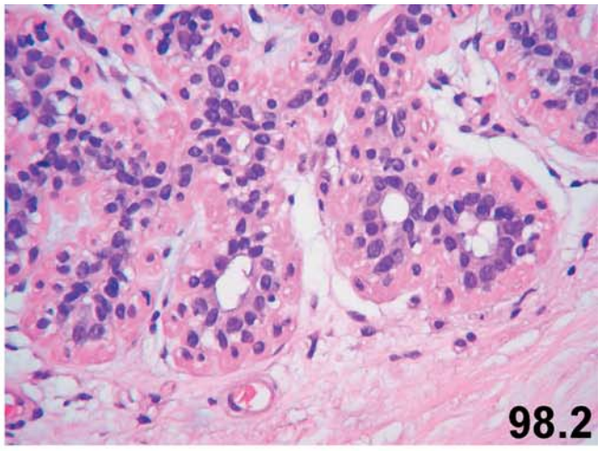
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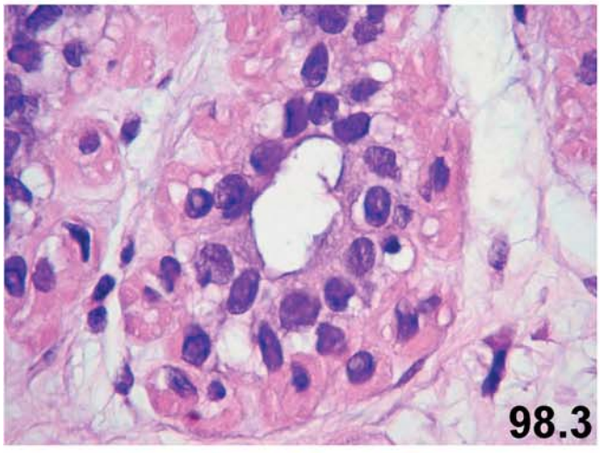
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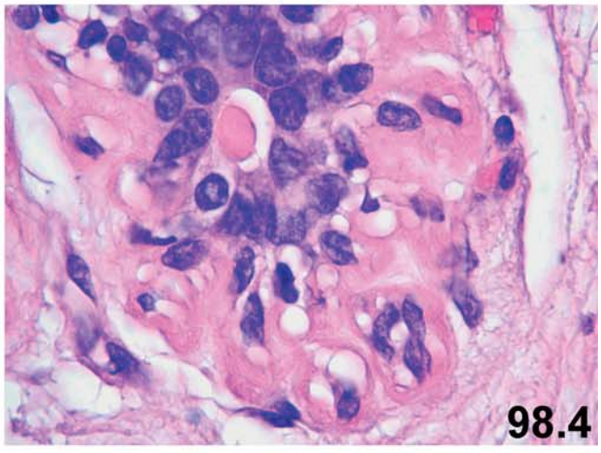
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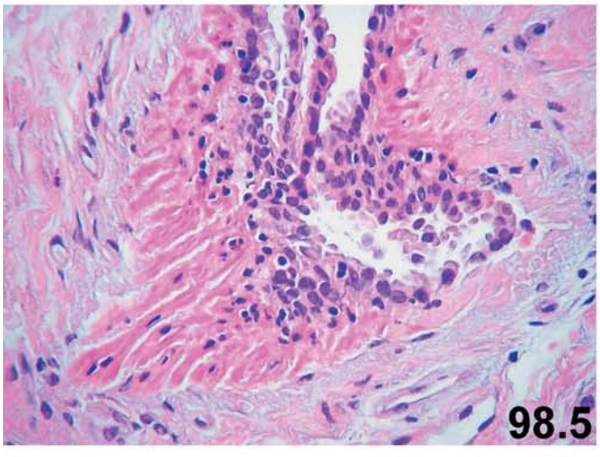
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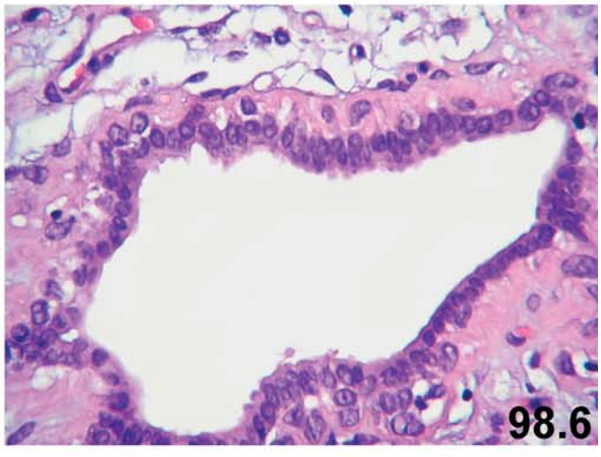
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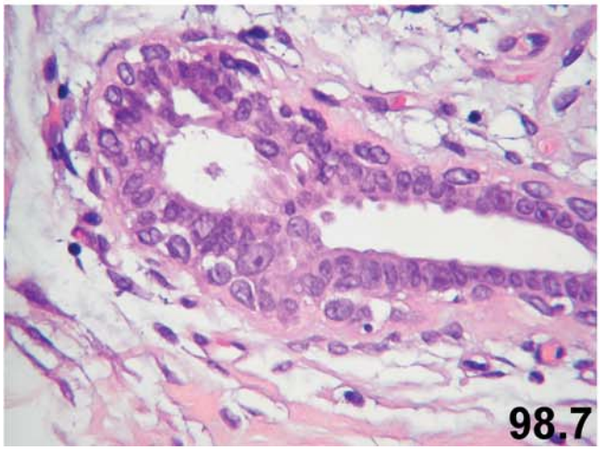
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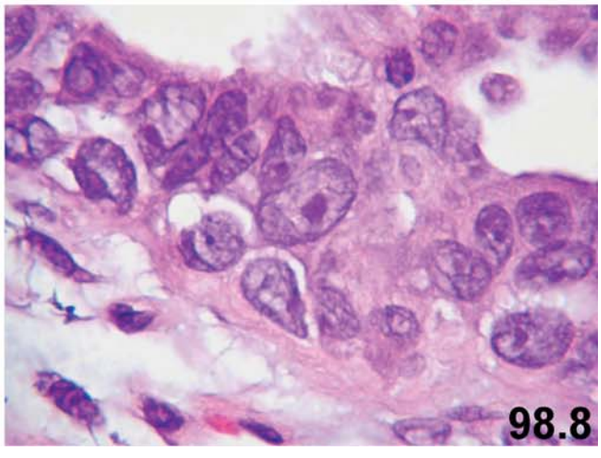
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Fig. 99: Adenomyoepithelioma.

Case history: A 66-year-old woman presented with a solitary and centrally located firm tumor in her right breast. The excisional biopsy showed a well-delineated, multilobulated, greyish-white tumor with firm to rubbery consistency. The tumor measured 2.9 cm in greatest diameter.

Figs. 99.1 and **99.2:** The tumor is predominantly sharply delineated, revealing a lobulated growth pattern.

Figs. 99.3 and **99.4:** Focally, the tumor shows an infiltrative growth pattern with irregular nests of tumor cells with clear cytoplasm.

Fig. 99.5: In addition to solid nests of tumor cells, several areas of the tumor display a tubular growth pattern with easily identifiable luminal epithelial and basally located myoepithelial cells. Note the clear cell change of the myoepithelial cells.

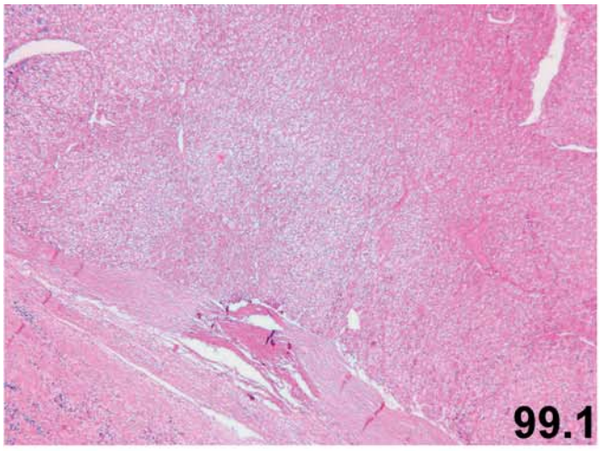
Fig. 99.6: Areas of the tumor showing elongated tubules and aggregates of myoepithelial cells with abundant clear cytoplasm. There is no cytologic atypia or increased mitotic activity.

Fig. 99.7: Immunohistochemistry for smooth muscle actin demonstrates a prominent myoepithelial cell component of this tumor. Note the lobulated growth pattern of the tumor.

Fig. 99.8: Higher magnification of immunoreaction for smooth muscle actin shows positive myoepithelial cells and negative luminal epithelial cells. Several other myoepithelial markers such as smooth muscle myosin (heavy-chain), calponin, p63, and CD10 were also positive in this tumor (not shown).

Fig. 99: Final remarks

- The focal presence of infiltrative growth pattern in an adenomyoepithelioma in the absence of significant cytologic atypia and/or increased mitotic activity (more than three mitoses per 10 hpf) can be ignored and should not lead to the diagnosis of atypical adenomyoepithelioma or adenomyoepithelial carcinoma.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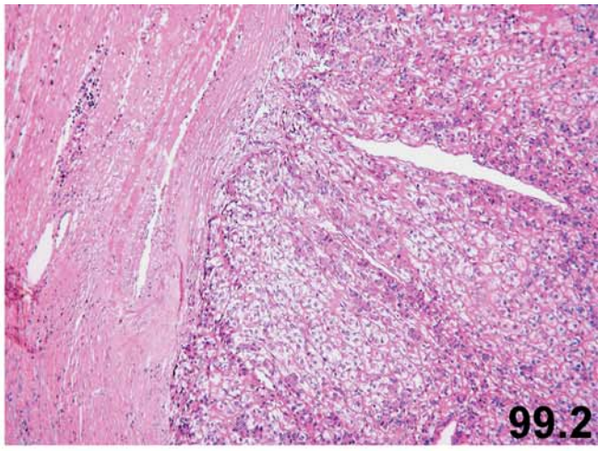
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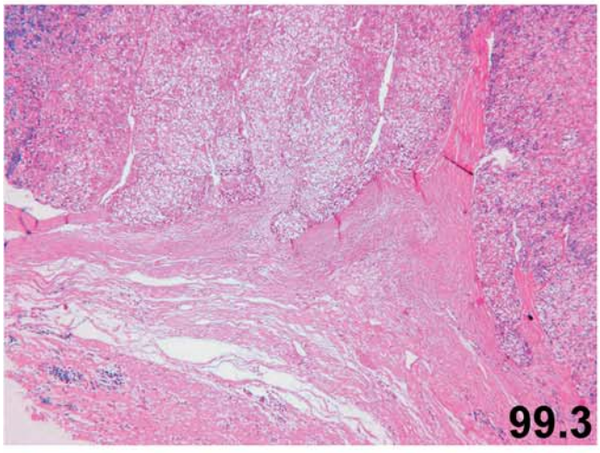
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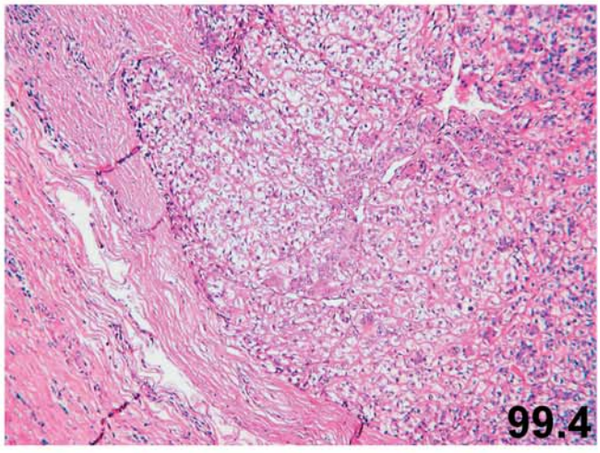
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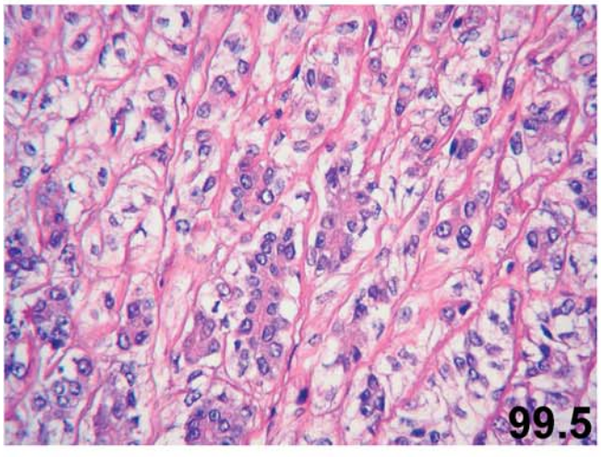
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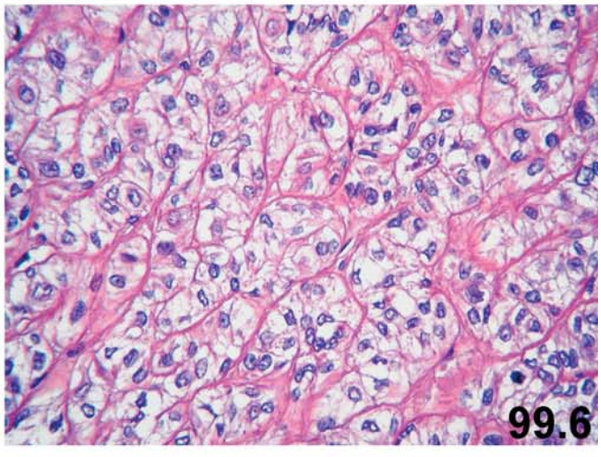
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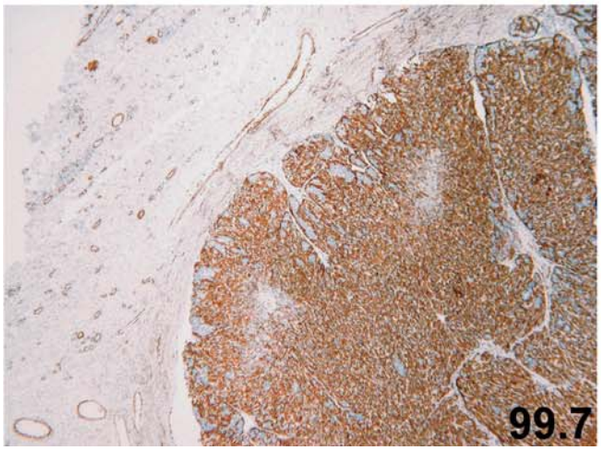
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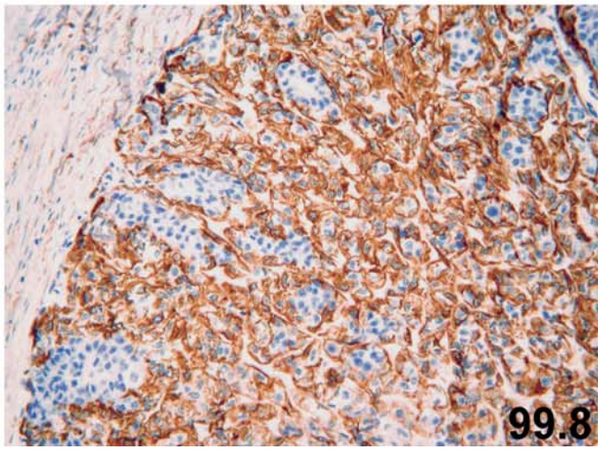
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Miscellaneous Lesions

Contents

CHAPTER 16 Miscellaneous Lesions

16.1 Acute Mastitis (Puerperal Mastitis)

16.1.1 Definition
Acute inflammation of the breast, predominantly composed of neutrophilic granulocytes, seen mostly in lactating women.

16.1.2 Microscopic Features (Fig. 100)
- Massive aggregates of neutrophilic granulocytes around the ducts and lobules.
- Intraepithelial infiltration of leukocytes with some reactive and/or degenerative epithelial changes.
- Focal necrosis may be present.
- In the later stage, granulation tissue with activated fibroblasts/myofibroblasts is present.
- Without antibiotic treatment, the condition usually progresses to form an abscess. At a chronic stage, fistulas may develop.

Caution

- Acute inflammation may be associated with severe reactive epithelial changes showing significant enlargement of nuclei, a high nuclear-cytoplasmic (N/C) ratio, and prominent nucleoli. These changes may occur in areas with usual ductal hyperplasia causing diagnostic difficulties. As a rule, the interpretation of proliferative epithelial lesions in association with acute (puerperal) mastitis should be conservative.

16.1.3 Additional Comments
Puerperal mastitis typically occurs within 2–3 weeks of the start of lactation. The most common organism is *Staphylococcus aureus* transmitted from the infant through the skin (nipple). The overlying skin becomes edematous and red, an appearance that may be confused with inflammatory breast carcinoma [4, 15].

16.2 Subareolar Abscess

16.2.1 Definition
A chronic/acute inflammatory condition located in the subareolar or periareolar region that can develop in both lactating and nonlactating women.

16.2.2 Microscopic Features
- A localized and relatively well-circumscribed inflammatory infiltrate predominantly composed of neutrophilic granulocytes in the center of the lesion.
- Macrophages, lymphocytes, and plasma cells are present, particularly at the periphery of the lesion.
- A fibrous capsule may be present.

16.2.3 Additional Comments
About 20% of the cases are bilateral, and recurrences develop in almost 90% of patients. Nipple inversion or retraction can be found in more than 50% of the cases. Commonly, there is a complete replacement of the native glandular epithelium of the lactiferous duct(s) by extensive squamous metaplasia and obstruction by keratinous and cellular debris [13].

16.3 Plasma Cell Mastitis

16.3.1 Definition
A rare and extreme variant of periductal mastitis (duct ectasia) with an intense plasmacytic reaction to secretion of the involved ducts.

16.3.2 Macroscopy
Ill-defined area with dilated ducts containing thick, creamy, white to yellow secretions, often simulating comedo necrosis.

16.3.3 Microscopic Features
- Severe, diffuse, plasma cell infiltrate surrounding the ducts and lobules.
- Often, a histiocytic reaction with giant cells with or without granulomas.
- Lipid-rich and thick intraluminal secretory material associated with desquamated epithelium.
- Often, hyperplasia of ductal epithelium.
- Variable presence of neutrophils and lymphocytes.
- Rarely, periductal fibrosis and obliteration of the ducts.

Caution

- Plasma cell mastitis can easily be mistaken for carcinoma clinically and mammographically. Its gross appearance (thick creamy material) can be misinterpreted as comedo carcinoma. The frozen section can be very worrisome; hyperplastic epithelial cells with reactive and/or degenerative changes may appear very atypical, even in paraffin sections. It is important to note that the distinction between plasma cell mastitis and comedo carcinoma requires careful analysis of paraffin sections. In diagnostically difficult cases, immunohistochemistry for high molecular weight cytokeratins such as CK5/6 or CK34BE12 can be very helpful; in contrast to ductal intraepithelial neoplasia (DIN; DCIS), hyperplasia associated with mastitis is always intensely positive for HMW-CK.

16.3.4 Additional Comments

The vast majority of patients with this condition have a history of relatively recent pregnancy. Nipple discharge of thick secretion, nipple retraction, and edematous skin changes usually associated with an ill-defined firm to hard mass are usually present and closely resemble (inflammatory) breast cancer. Ulceration of the skin and fistulas may occur. Wide excisional biopsy is the recommended treatment for this condition [1, 4].

16.4 Idiopathic Granulomatous Mastitis

16.4.1 Definition

A granulomatous inflammation of the breast in the absence of specific infections, trauma, foreign material, or sarcoidosis.

16.4.2 Synonym

Granulomatous lobular mastitis

16.4.3 Macroscopy

A palpable mass with firm-to-hard consistency and a greyish-white to tan cut surface with a faintly nodular appearance.

16.4.4 Microscopic Features (Fig. 101)

- Numerous granulomas involving and often distorting the lobules.
- Granulomas extend to the surrounding stroma and adjacent ducts.
- Granulomas are composed of epithelioid histiocytes, Langhans giant cells, lymphocytes, and plasma cells.
- Occasional eosinophils may be found within and around the involved lobules.
- Rarely, squamous metaplasia and foreign body giant cells are identified.
- Fat necrosis and microabscess formation are not uncommon.
- Focal lactational changes may be seen in lobules.
- Duct ectasia with or without periductal fibrosis may be present.
- There is no vasculitis. Stains and cultures for bacteria, acid-fast organisms, and fungi are all negative.

16.4.5 Differential Diagnosis

Tuberculosis, sarcoidosis, cat scratch disease, and reaction to foreign material need to be excluded. A granulomatous reaction to DIN (DCIS) or invasive carcinoma should be taken into consideration.

16.4.6 Additional Comments

The diagnosis of idiopathic granulomatous mastitis should be made after excluding a specific infection or other disease process in granulomatous mastitis, including systemic autoimmune diseases. The exact pathogenesis of this disease is unknown. The changes may reflect a localized autoimmune reaction to the retained and extravasated fat and protein-rich secretions.

Hyperprolactinemia has been rarely reported in patients with granulomatous mastitis.

The lesion can simulate malignancy, both clinically and mammographically [3, 5, 17, 20, 21, 23].

16.5 Lymphocytic Mastitis (Diabetic Mastopathy)

16.5.1 Definition

A chronic inflammation of the breast composed of mature lymphocytes, occurring mostly in association with extramammary autoimmune diseases such as type I diabetes mellitus or Hashimoto's thyroiditis.

16.5.2 Macroscopy

Mostly ill-defined fibrous stroma without a visible tumor but with firm or hard lesions up to 6 cm. Homogeneous greyish-white cut surface.

16.5.3 Microscopic Features (Fig. 102)

- A predominantly lobulocentric lymphocytic infiltration composing of mature (polyclonal B) lymphocytes.
- A periductal or perivascular pattern of infiltration may occur.
- Collagenous stroma, sometimes with keloidal features, is present.
- The affected lobules may show extensive sclerosis and changes similar to involution.
- Migration of lymphocytes in the epithelial cell layer of the affected lobules and ducts is a common finding.
- There is increased presence of stromal spindle cells, often with activated nuclei (fibroblasts/myofibroblasts).
- Polygonal epithelioid stromal cells are present within the collagenous stroma.
- Follicles with germinal centers are rarely formed.
- Fat necrosis, duct ectasia, and multinucleated stromal giant cells are usually absent.

Caution

- The presence of large epithelioid stromal cells either as isolated cells or in clusters within the densely collagenous stroma may be prominent, raising the possibility of carcinoma. The epithelioid stromal cells, however, are negative for cytokeratin but positive for vimentin and actin.

16.5.4 Additional Comments

Lymphocytic mastitis is commonly associated with type I (insulin-dependent) but not type II diabetes mellitus [24]. Several reports have also documented an association of the lesion with thyroiditis and arthropathy, raising the possibility of an autoimmune disease with mammary manifestation [19]. Lymphoepithelial lesions, a finding commonly associated with extranodal marginal zone B-cell/mucosa-associated lymphoid tissue (MALT) lymphomas, are often present in lymphocytic mastitis. Although an association with malignant lymphoma of the breast has been speculated by a few studies, a recent study found no increased risk for breast lymphoma [24].

16.6 Eosinophilic Mastitis

16.6.1 Definition

A rare type of mammary inflammation characterized by an extensive eosinophilic infiltrate around ducts and lobules.

16.6.2 Microscopic Features

- Massive infiltration of eosinophilic granulocytes around ducts and lobules.
- Lymphocytes and plasma cells are often admixed with eosinophilic infiltrate.
- A granulomatous reaction may rarely be observed.
- The involved ducts and lobules may display reactive epithelial changes with enlarged nuclei, high N/C ratio, and prominent nucleoli.
- There is no morphological evidence for a parasitic infestation.

Caution

- An intense eosinophilic mastitis can be associated with severe reactive epithelial changes of the affected ducts and lobules. These changes could easily be mistaken for DIN (DCIS). As in other types of mastitis with severe inflammation, a conservative approach in interpreting such lesions is recommended. In a difficult case, immunostaining with HMW-CK (CK5/6) is advised.

16.6.3 Additional Comments

Eosinophilic mastitis is extremely rare and is not associated with peripheral eosinophilia or an allergic condition. It may reflect a localized inflammatory reaction to intraluminal secretory material [4, 16].

16.7 Silicone Mastitis and Diseases Associated with Cosmetic Augmentation

16.7.1 Definition

Inflammatory reaction in the breast after either injection of liquid silicone (not performed any more!) or silicone implantation for breast augmentation.

16.7.2 Macroscopy

Greyish-white to tan firm fibromembranous structure adherent to the implant. In rare cases, marked calcification of the capsule with a hard, gritty consistency.

16.7.3 Microscopic Features (Fig. 103)

- The capsule shows dense collagenous connective tissue with (myo)fibroblasts admixed with histiocytes, lymphocytes, plasma cells, and giant cells of foreign body type.
- The foreign body giant cells in the capsule contain birefringent material.
- Numerous microcysts (or clusters of small vacuoles) alternate with coalescent, round empty spaces of various size closely simulating fat necrosis.
- Numerous histiocytes, foreign body giant cells , and crystals of varying shapes are located adjacent to the microcysts.
- Synovial metaplasia (either as flat or papillary type) can be observed in 30–50% of the implant surface of the capsule. The fibrohistiocytic or metaplastic cells are polarized perpendicular to the surface.
- There is a distinct zone of capillaries in a region composed of loosely organized polygonal histiocytic cells incompletely invested by reticulin fibers beneath the synovial-like membrane.
- Calcification with or without bone formation can be found.
- Squamous metaplasia can rarely be observed in the capsule.

Caution

- A prominent papillary synovial metaplasia in the capsule of the implant may cause diagnostic problems and may be mistaken for papillary carcinoma. Empty microcysts or irregular clusters of vacuoles should not be misinterpreted as liposarcoma!

16.7.4 Additional Comments

The lining cells in synovial-like membrane (synovial metaplasia) display immunohistochemical properties similar to those of synovial cells; they are positive for vimentin, CD68, alpha1-antichymotrypsin, and lysozyme. Immunostains for cytokeratins and factor VIII are negative. Electron microscopic examinations have confirmed synovial-like cells in the capsule of the implants [10, 11, 14, 18].

Complications of silicone implants include infection, marked capsule formation with chest wall pain, rupture, and hemorrhage.

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16.9 Pathologic Effects of Adjuvant Radiotherapy

16.9.1 Microscopic Features (Fig. 104)

- The major changes in normal breast tissue occur in terminal duct-lobular units and include epithelial atrophy, intralobular sclerosis, thickening of periacinar and periductular basement membranes, and mild to marked cytologic atypia of epithelial cells. In some cases, atypical (myo)fibroblasts with enlarged and hyperchromatic nuclei in the intralobular or interlobular stroma may be present.
- The effects on the larger normal ducts are usually less pronounced.
- Radiation-induced vascular changes include endothelial atypia, degenerative changes and fragmentation of elastica, and intimal proliferation. These changes may lead to vascular sclerosis. Marked cytological atypia in the endothelial cells of capillaries can also be observed.
- Marked cytologic atypia in apocrine metaplasia often occurs.
- Ductal and lobular intraepithelial neoplasia (DIN, LIN) usually do not show prominent alterations; in particular, low-grade lesions remain largely intact. The neoplastic cells of DIN (DCIS), however, may show isolated bizarre nuclei with a degenerative chromatin pattern (smudge chromatin structure) or cells with large cytoplasmic vacuoles.

Caution

- Radiation-induced cytologic atypia may occur in epithelial, endothelial, or stromal cells, thus causing diagnostic problems. The atypical cells display enlarged, hyperchromatic nuclei with an increased N/C ratio. While the nuclei are hyperchromatic, the chromatin pattern is blurred (smudge chromatin pattern), which is a characteristic feature of degenerative nuclear changes. As a rule, interpretation of cytological atypia after radiation or chemotherapy should be conservative.

16.9.2 Further Reading

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16.10 Pathologic Effects of (Neo)adjuvant Chemotherapy

16.10.1 Microscopic Features

- The changes in non-neoplastic breast tissue include focal or diffuse glandular atrophy and cytologic atypia in ductal and lobular epithelial cells.
- There is a varying degree of stromal fibrosis and elastosis in areas close to infiltrating carcinoma.

- A decrease in tumor cellularity and seemingly multifocality of invasive areas is a common finding.
- In cases with complete response to neoadjuvant (preoperative) chemotherapy, no residual carcinoma can be identified. These cases may reveal extensive degenerated or necrotic (infarcted) tissue components with decreased architectural detail.
- Stromal alterations include edema and granulation tissue with increased capillaries.
- In cases with partial response, carcinoma cells may show large, hyperchromatic, and sometimes bizarre or pleomorphic nuclei.
- Numerous lymphatic emboli may be observed even after significant response to the chemotherapy.
- Areas of DIN (DCIS) are frequently present, either unaltered or with marked degenerative-type atypia showing bizarre nuclei and a smudge chromatin pattern. The neoplastic cells of DIN (DCIS) may show cytoplasmic vacuolization.
- Axillary lymph nodes may contain unaltered metastatic foci even by a complete response of primary tumor. The lymph nodes may also show extensive fibrosis and atrophy of lymphatic tissue with no or very small metastatic foci.

Caution

- In cases with complete response to neoadjuvant chemotherapy, careful pathologic examination of the entire nonfatty tissues with extensive search for small areas of invasive carcinoma is necessary. Immunostaining for cytokeratin is helpful to identify very small areas of invasion or isolated tumor cells.
- Because of partial response of invasive carcinoma and therapy-related fibrosis, a discontinuous pattern of invasion or multiple foci of invasive carcinoma can be present, simulating a multifocal carcinoma.
- Use of cytokeratin immunostaining is recommended in axillary lymph nodes that seem to be free of metastatic breast carcinoma but that show extensive areas of stromal fibrosis and other chemotherapy-related alterations.

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16.11 Malignant Lymphoma

16.11.1 Definition

A malignant lymphatic neoplasm of the breast either as primary or secondary tumor. There are no morphological criteria to separate primary from secondary malignant lymphomas.

16.11.2 Macroscopy

Solitary well-circumscribed, lobulated, soft or firm tumor with a fish-fleshy greyish-white to pink cut surface.

16.12 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of primary lymphoma of the breast and is characterized by a diffuse infiltrative pattern showing large tumor cells.

16.12.1 Microscopic Features

- Variation in tumor cell morphology with uniform to pleomorphic lymphatic tumor cells.
- Mostly, the tumor cells resemble immunoblasts or centroblasts.
- Often oval nuclei with prominent single or multiple nucleoli.
- Numerous mitotic and apoptotic figures are seen.
- Numerous macrophages may be present (starry-sky appearance).
- There is often admixture with smaller, reactive lymphocytes.
- Infiltration of breast lobules may simulate lymphocytic lobulitis (mastitis).
- Broad or fine bands of sclerosis may be observed.
- Rarely, a T-cell/histiocyte-rich variant with a major component of non-neoplastic T-cells with or without histiocytes and fewer than 10% larger neoplastic B-cells may be present. An anaplastic variant is rarely observed; it shows very large round, oval, or polygonal cells with bizarre pleomorphic nuclei resembling Reed–Sternberg cells.

16.12.2 Immunoprofile

DLBCLs express various pan-B markers such as CD19, CD20, CD22, and CD79a, but they may lack one or more of these. DC30 is positive in the anaplastic variant. Nuclear expression of BCL6 is found in a very high proportion of cases. BCL2 is positive in approximately 30–50% of cases. Surface and/or cytoplasmic immunoglobulin (IgM, IgG, IgA) can be demonstrated in 50–70% of cases. The proliferative fraction as detected by Ki-67 immunostaining is usually high (more than 40%) [9].

16.13 Burkitt's Lymphoma

16.13.1 Microscopic Features

- Morphologic features identical to those seen in extramammary Burkit lymphoma.
- Diffuse infiltration of uniform, primitive-looking lymphocytic cells with round and multiple nucleoli and coarse chromatin.
- Cohesive clusters of tumor cells.
- Fine lipid-containing cytoplasmic vacuoles.
- After fixation, the cells sometimes exhibit squared-off borders of retracted cytoplasm.
- Mitotic and apoptotic figures are numerous.
- Numerous tingible-body macrophages are evenly dispersed among the neoplastic cells, producing a characteristic, but not pathognomonic, starry-sky appearance.
- A variant of Burkitt's lymphoma with plasmacytoid differentiation may rarely be observed; the tumor cells show eccentric basophilic cytoplasm with often a single central nucleolus.

16.13.2 Immunoprofile

Tumor cells express membrane IgM with light chain restriction and B-cell-associated antigens such as CD19, CD20, and CD22. CD10 and BCL6 are positive. The cells are negative for CD5, CD23, and TdT. BCL2 is not expressed. Nearly 100% of the cells are positive for Ki-67. EBV is commonly found in endemic but not in sporadic cases [9].

16.13.3 Additional Comments

Patients with mammary Burkitt's lymphoma are usually pregnant or lactating women. Massive bilateral breast swelling is a typical presentation of mammary Burkitt's lymphoma.

16.14 Extranodal Marginal-Zone B-Cell Lymphoma of MALT Type

16.14.1 Microscopic Features

- Small lymphocytes, centrocyte-like, and/or monocytoid B-cells, often interspersed with larger blastic cells.
- The lymphoma cells infiltrate around reactive B-cell follicles external to a preserved follicle mantle in a marginal zone distribution, spreading out to form larger confluent areas.
- Plasmacytic differentiation may be present.
- A lymphoepithelial lesion, defined as an infiltration of glandular epithelium by clusters of neoplastic lymphatic cells and commonly seen in MALT lymphoma of the gastrointestinal tract, is rarely observed.
- Large tumor cells resembling centroblasts or immunoblasts are usually present but are in the minority.

16.14.2 Immunoprofile

Tumor cells typically express IgM and less frequently IgA or IgG, and display light chain restriction. There is positive reaction for CD20, CD79a, and CD43, and negative reaction for CD5, CD10, and CD23 [9].

16.15 Follicular Lymphoma

16.15.1 Microscopic Features

- Most cases have a predominantly follicular pattern.
- Neoplastic follicles are often poorly defined and usually lack mantle zones; they are closely packed.
- There is no prominent starry-sky pattern.
- Diffuse areas may be present, often with sclerosis.
- The pattern is reported as follicular (more than 75% follicular), follicular and diffuse (25–75% follicular), or minimally follicular (less than 25% follicular).
- Two types of tumor cells are characteristically present: (1) small to midsize centrocytes with angulated, elongated, twisted, or cleaved nuclei, inconspicuous nucleoli, and scant pale cytoplasm, and (2) centroblasts with round or oval vesicular nuclei, one to three peripheral nucleoli, and a narrow rim of cytoplasm.

16.15.2 Immunoprofile

The tumor cells are usually positive for B-cell-associated antigens such as CD19, CD20, CD22, and CD79a. They express CD10, BCL2, and BCL6. Positive reactions for CD21 and CD23 are present in follicular areas.

16.15.3 Additional Comments

Follicular lymphoma is graded by the proportion of centroblasts. According to the WHO recommendations [9], a three-grade system should be used, based on counting the absolute number of centroblasts in 10 neoplastic follicles, expressed per 40× high-power fields (hpf). Grade 1 has 0–5 centroblasts/hpf, grade 2 has 6–15 centroblasts/hpf, and grade 3 has more than 15 centroblasts/hpf. Ten high-power fields within different follicles are counted.

Caution

- The diagnosis of primary mammary malignant lymphoma should be made only after exclusion of lymphoma involving other organs, recognition of breast tissue in or adjacent to the lymphoma infiltrate, and exclusion of concurrent nodal disease (except for the ipsilateral axillary lymph nodes).
- Mammary malignant lymphoma may be misdiagnosed as poorly differentiated carcinoma, invasive lobular, or medullary carcinoma. On the other hand, poorly differentiated carcinoma and invasive lobular carcinoma with prominent lymphocytic stromal infiltration may be misinterpreted as malignant lymphoma.
- Mammary malignant lymphoma is often solitary, but patients with multiple tumors and diffuse infiltration have been reported. Skin fixation, sometimes associated with inflammatory changes, may occur; these changes can clinically resemble inflammatory carcinoma of the breast.

- Unusual inflammatory conditions with prominent lymphocytic infiltration or pseudolymphoma (synonym: atypical lymphocytic infiltrate) should always be considered in the differential diagnosis of mammary malignant lymphoma; clonal analyses such as gene rearrangement studies and immunohistochemistry for the presence of kappa and lambda light chains are helpful in difficult cases. Pseudolymphoma (atypical lymphocytic infiltrate) is polyclonal and often shows a massive cellular infiltrate composed of T- and B-lymphocytes and plasma cells migrating into the epithelial lining of the acinar and ductal structures, sometimes completely distorting them (lymphoepithelial lesions). While pseudolymphoma is mostly considered to be a reactive and self-limiting inflammatory condition, it has not been well established whether it may progress to lymphoma locally or systemically. Close follow-up of patients with pseudolymphoma is therefore prudent.

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Fig. 100: Mastitis puerperalis.

Case history: A 25-year-old woman with a history of recent pregnancy developed severe inflammatory changes of her right breast within 3 weeks of starting lactation.

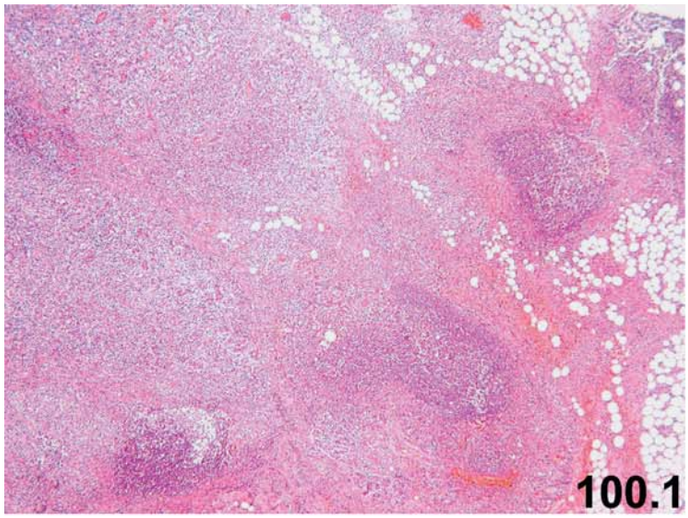
Figs. 100.1 and **100.2:** The sections show numerous aggregates of neutrophilic granulocytes around the ducts and lobules.

Figs. 100.3 and **100.4:** Several areas reveal formation of abscess.

Figs. 100.5 and **100.6:** Marked intraepithelial infiltration of neutrophilic granulocytes with reactive and/or degenerative epithelial changes.

Fig. 100: Final remarks

- Mastitis puerperalis or any type of acute mastitis may be associated with severe epithelial alterations, including nuclear enlargement, vesicular or hyperchromatic nuclei, high nuclear-cytoplasmic ratio, and prominent nucleoli. As a rule, the interpretation of epithelial cell changes in association with acute (puerperal) mastitis should be very conservative.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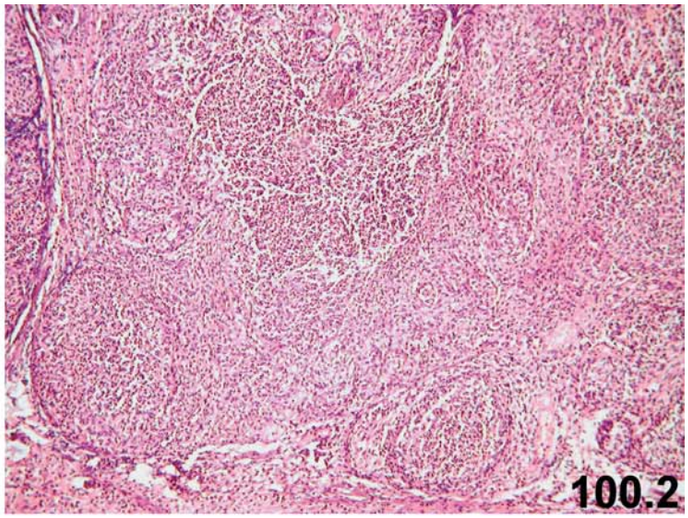
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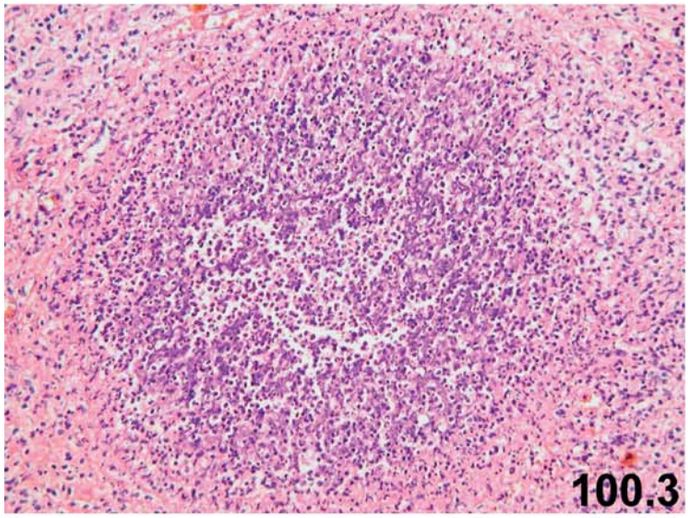
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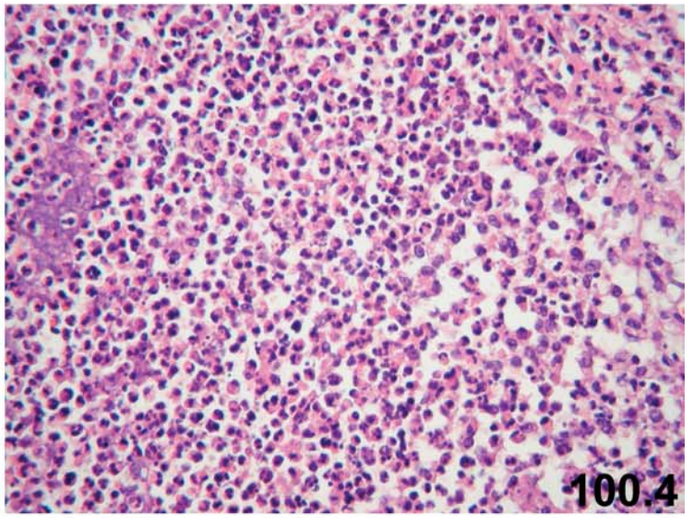
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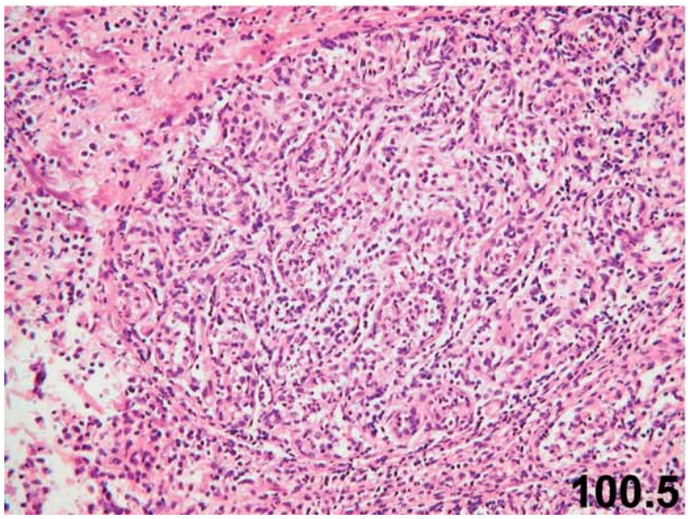
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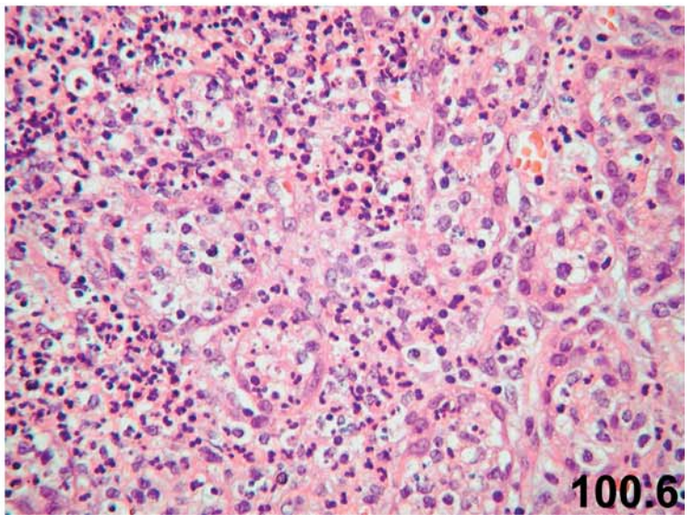
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Fig. 101: (Idiopathic) granulomatous mastitis.

Case history: A 29-year-old woman presented with a palpable mass in the upper inner quadrant of her left breast. The excisional biopsy showed a greyish-white to tan cut surface with faintly nodular appearance.

Figs. 101.1, 101.2, and **101.3:** Several lobules and ducts show marked inflammation. The inflammatory cells are composed of lymphocytes and neutrophilic granulocytes.

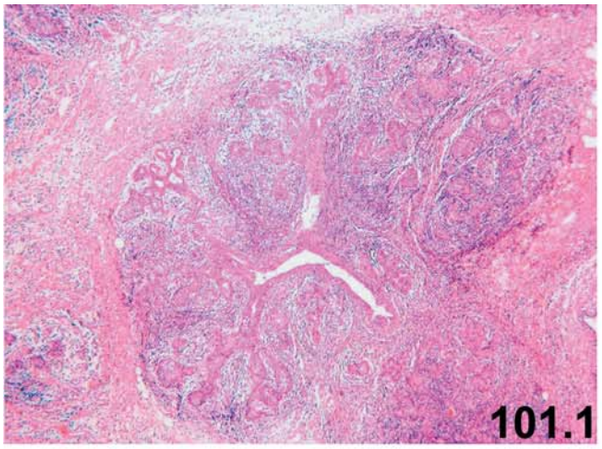
Fig. 101.4: In addition, some areas of the lesion show numerous eosinophilic granulocytes.

Figs. 101.5 and **101.6:** The lesion shows numerous granulomas involving the lobules. The granulomas are composed of epithelioid histiocytes, lymphocytes, and plasma cells.

Figs. 101.7 and **101.8:** Several involved lobules and ducts show epithelial cell alteration characterized by large vesicular nuclei, high nuclear-cytoplasmic ratio, and prominent nucleoli. Note, however, the regular chromatin distribution.

Fig. 101: Final remarks

- This is an example of granulomatous mastitis. Tuberculosis, sarcoidosis, cat scratch disease, and reaction to foreign material need to be excluded in this case. The diagnosis of idiopathic granulomatous mastitis should be made after excluding a specific infection or systemic autoimmune diseases.
- The epithelial cell alterations in association with severe inflammation are of reactive type and should not be misinterpreted as neoplastic.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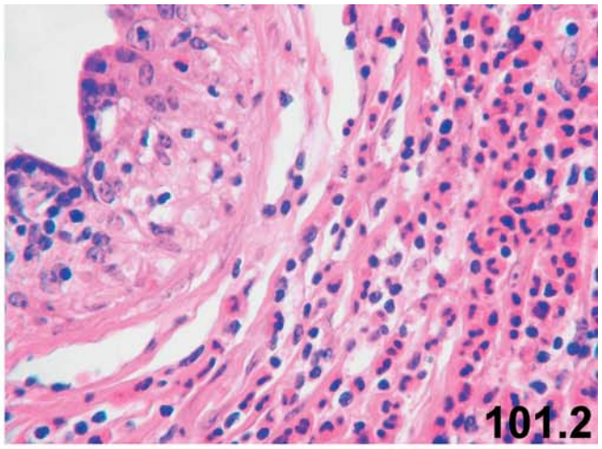
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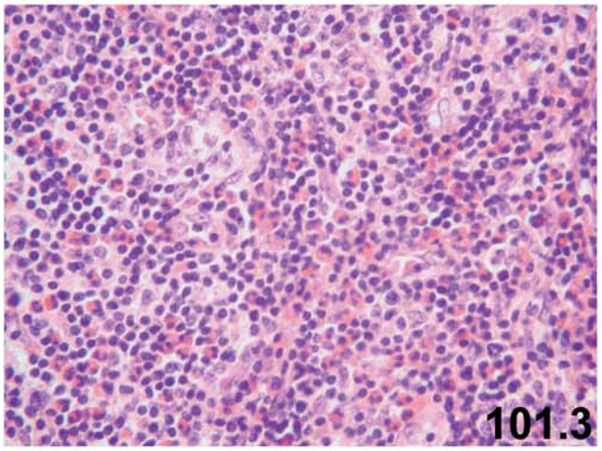
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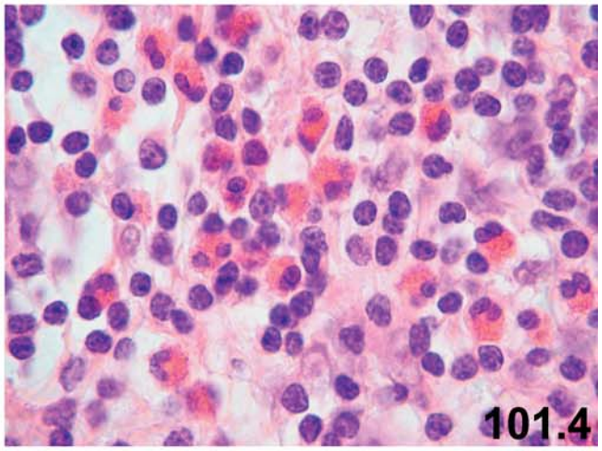
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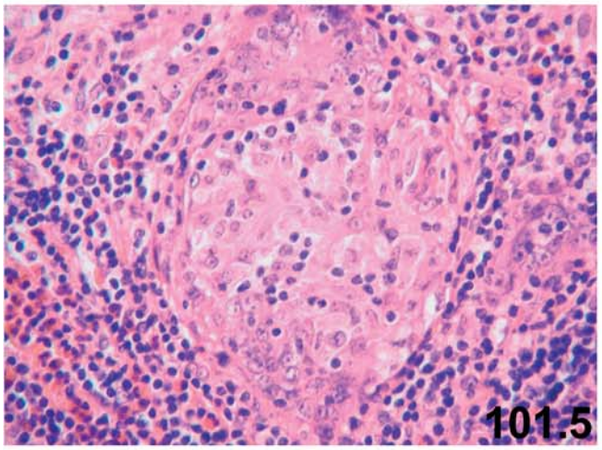
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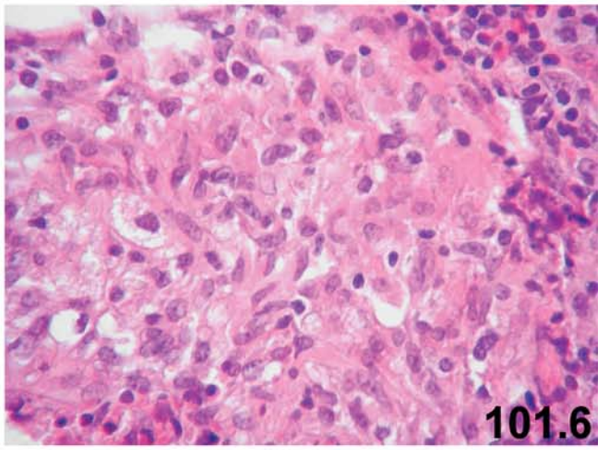
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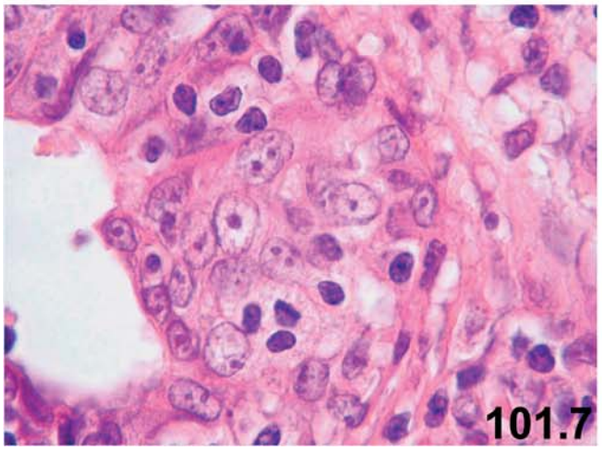
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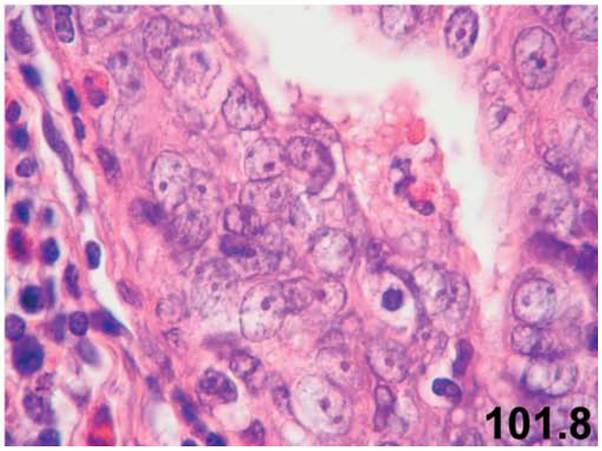
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Fig. 102: Lymphocytic mastitis.

Case history: A 38-year-old woman with type I (insulin-dependent) diabetes mellitus presented with an ill-defined hard lesion in the upper outer quadrant of her left breast. A needle core biopsy revealed breast tissue with prominent sclerotic stroma. Excisional biopsy was performed to exclude malignancy.

Fig. 102.1: Excisional biopsy showing a predominantly lobulocentric lymphocytic infiltration composed of small (mature) lymphocytes.

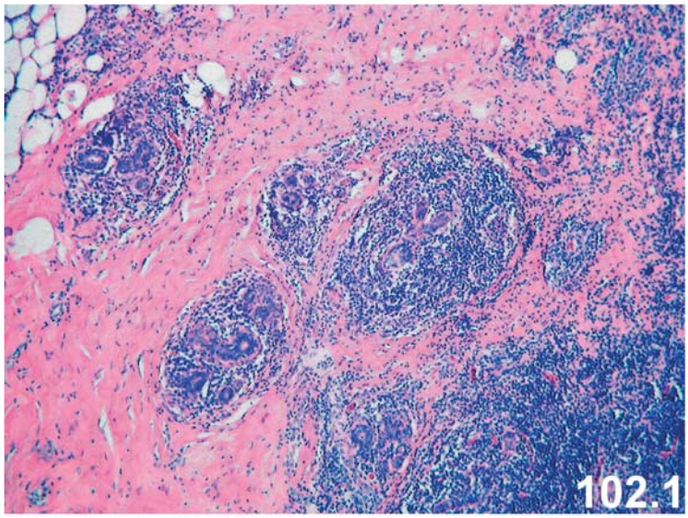
Fig. 102.2: Several areas of the lesion show lymphoid follicles with activated germinal centers. The affected lobules display sclerosis and migration of lymphocytes into the epithelial cell layer.

Fig. 102.3: In some areas, periductal lymphocytic infiltration is present as well.

Fig. 102.4: Several areas show a dense collagenous stroma (keloidal features).

Fig. 102: Final remarks

- This is an example of chronic or lymphocytic mastitis. This type of mastitis is commonly (but not always) associated with extramammary autoimmune diseases such as type I diabetes mellitus or Hashimoto's thyroiditis.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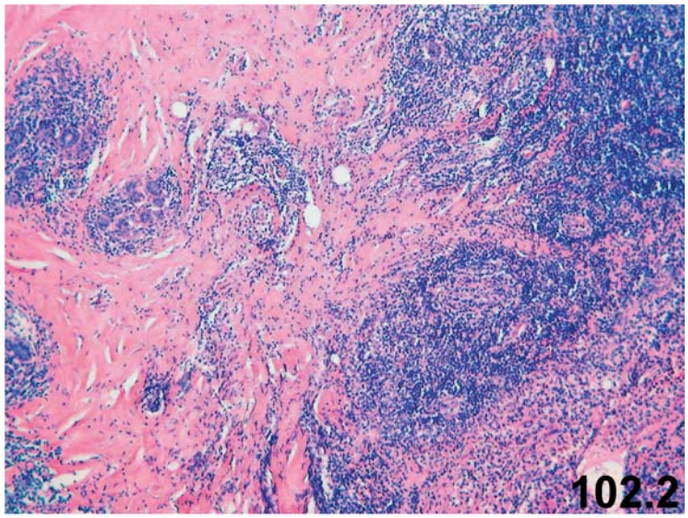
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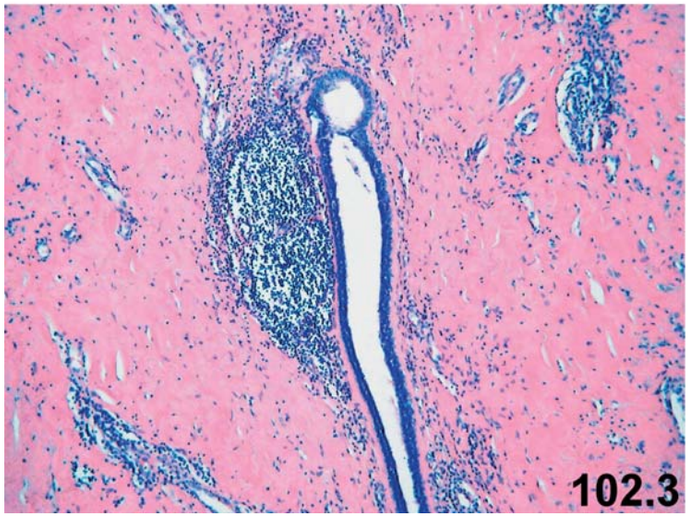
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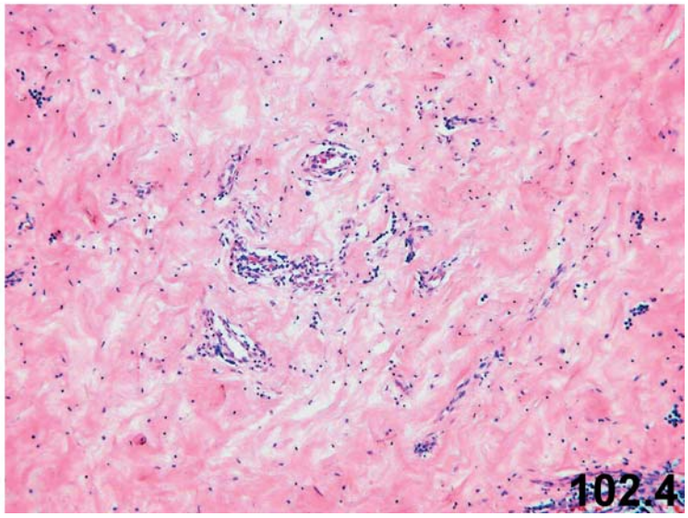
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Fig. 103: Silicone-associated changes.

Case history: With silicone implants, a 37-year-old woman presented with diffuse and painful inflammatory skin changes of the right breast.

Fig. 103.1: Surgical specimen showing fibromembranous structure of the capsule.

Fig. 103.2: Synovial metaplasia of the implant surface of the capsule is present. The fibrohistiocytic or metaplastic cells are polarized and perpendicular to the surface.

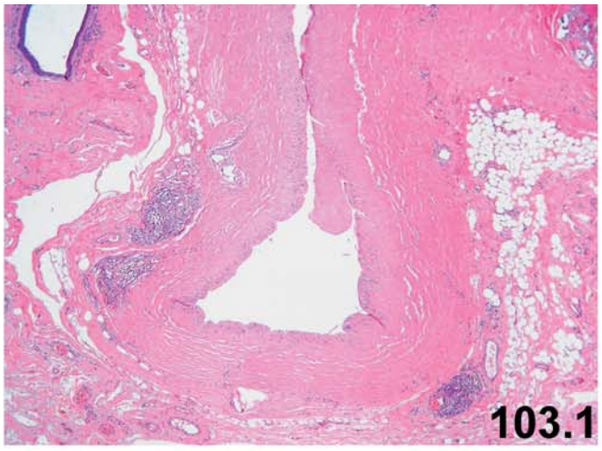
Fig. 103.3: Some areas of synovial metaplasia show multinucleated giant cells.

Fig. 103.4: Numerous microcysts or clusters of small vacuoles alternate with coalescent round or irregular empty spaces closely simulating fat necrosis.

Fig. 103.5: Numerous histiocytes and foreign body giant cells are located adjacent to the microcysts.

Fig. 103.6: The foreign body giant cells in the capsule contain birefringent material.

Figs. 103.7 and **103.8:** Other areas of the implantation capsule display papillary synovial metaplasia.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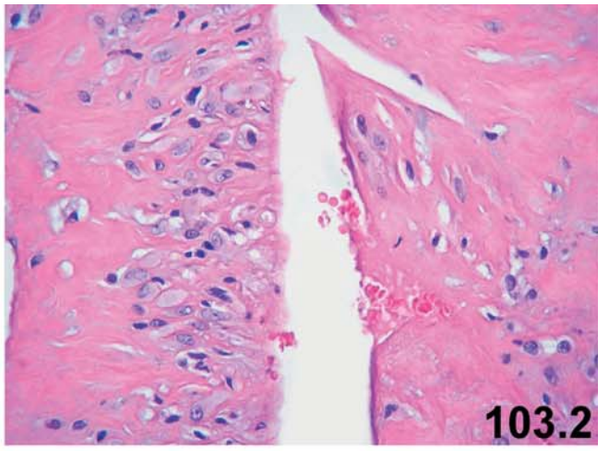
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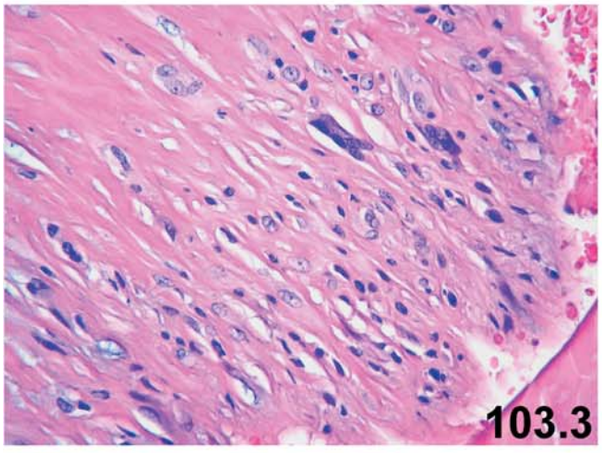
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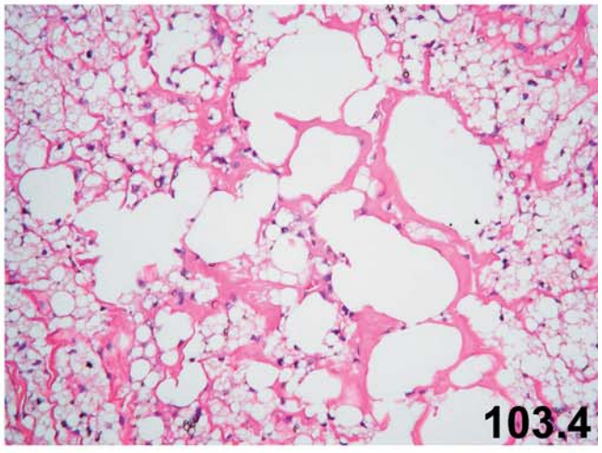
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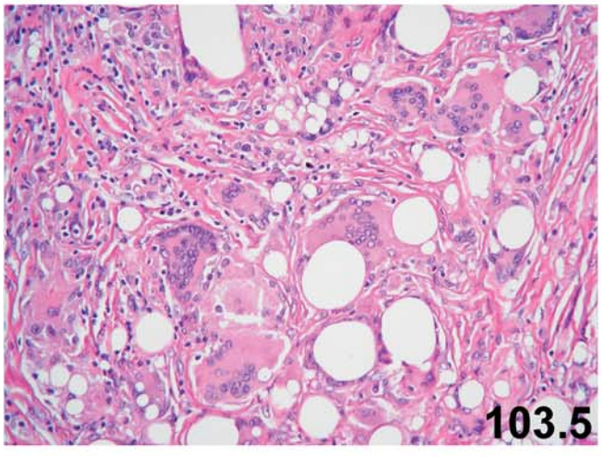
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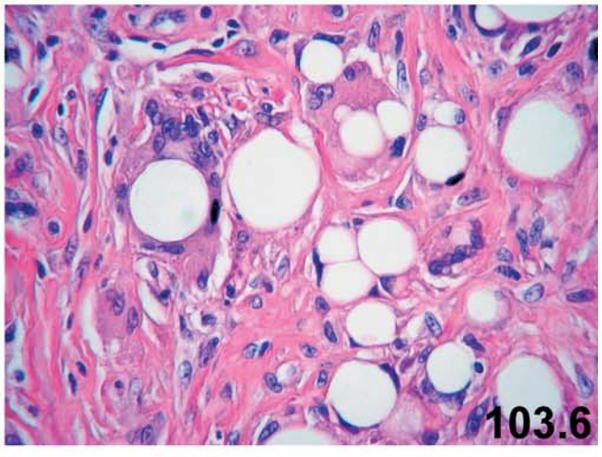
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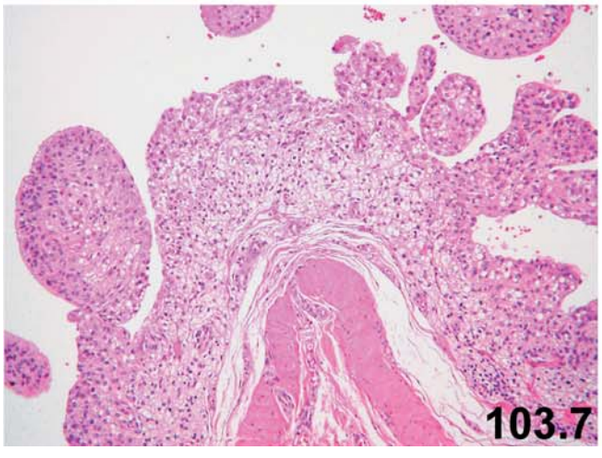
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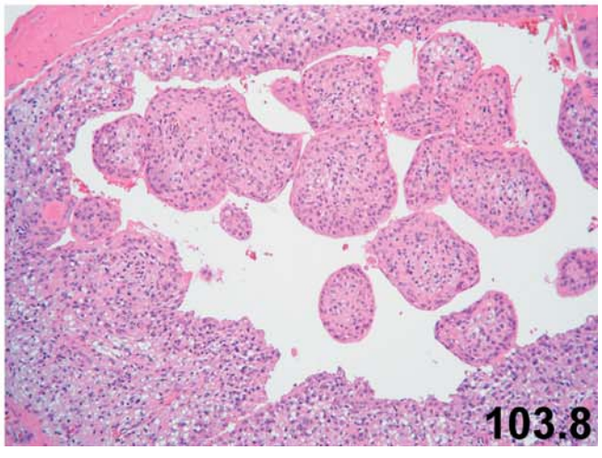
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Fig. 104: Pathologic effects of radiotherapy.

Case history: Mammography of a 69-year-old woman with a history of infiltrating ductal carcinoma (left breast) that had been treated by lumpectomy and radiation therapy revealed multiple areas of microcalcification in the left breast. These areas, found 3 years after the initial treatment, were suspicious for malignancy. Excisional biopsy was performed. (This case is courtesy of Dr. Fattaneh A. Tavassoli, Yale University School of Medicine, USA.)

Fig. 104.1: Low magnification of a lobule shows several acini (ductules) with hyperchromatic nuclei.

Fig. 104.2: Low magnification of another area displays thickening of periacinar basement membranes and epithelial cells with enlarged, hyperchromatic nuclei.

Fig. 104.3: Several terminal duct-lobular units show subtle luminal microcalcifications. The acini (ductules) are dilated.

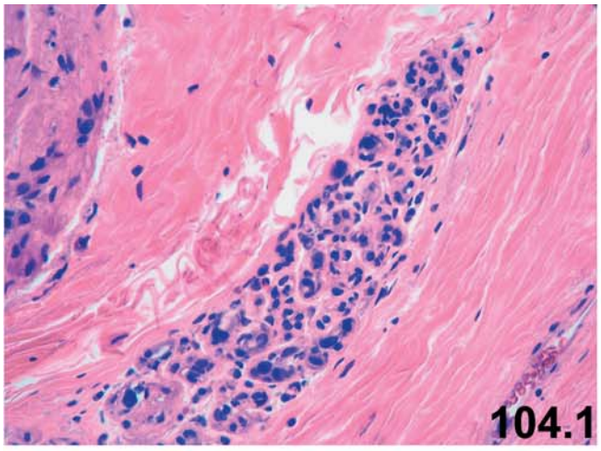
Fig. 104.4: Higher magnification displays a ductule with enlarged, hyperchromatic nuclei of luminal epithelial cells. Note the thickening of basement membrane and the presence of a few myoepithelial cells with enlarged nuclei. Luminal microcalcification is evident.

Figs. 104.5 and **104.6:** At higher magnification, several acinar structures (ductules) exhibit marked degenerative epithelial cell changes, including smudge chromatin pattern and large, vacuolated cytoplasm. Note the intralobular sclerosis and thickening of the basement membranes in Fig. 104.6.

Figs. 104.7 and **104.8:** High magnification of several blood vessels and capillaries shows radiation-induced changes characterized by atypical endothelial cells with enlarged and hyperchromatic nuclei. The chromatin patter is, however, blurred.

Fig. 104: Final remarks

- Radiation-induced cytologic atypia may occur in epithelial, myoepithelial, endothelial, or stromal cells and is characterized by enlarged, hyperchromatic nuclei with high nuclear-cytoplasmic ratio. While the nuclei are often hyperchromatic, the chromatin pattern is blurred, which is a typical feature of degenerative cell changes.
- Interpretation of cytologic atypia after radiation therapy or chemotherapy should be conservative.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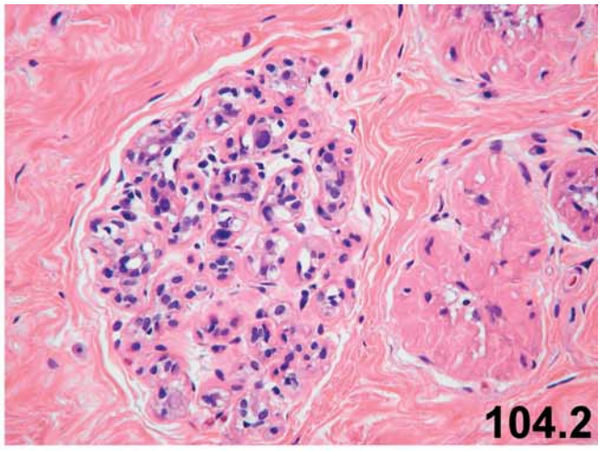
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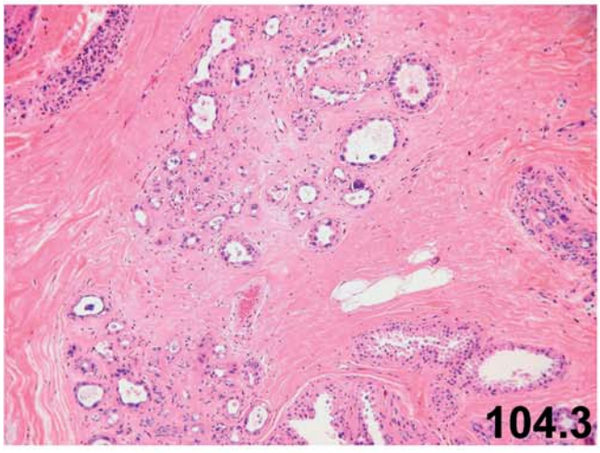
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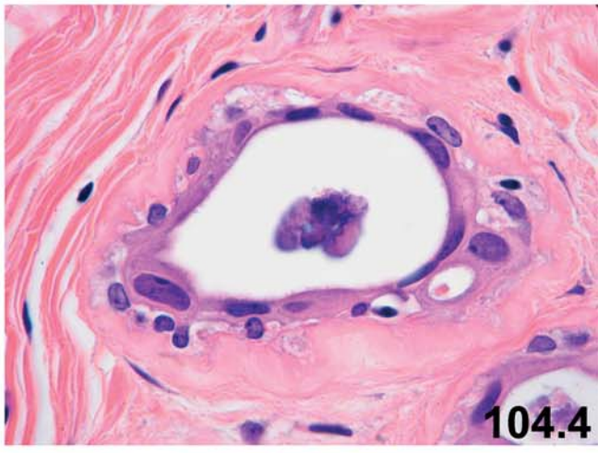
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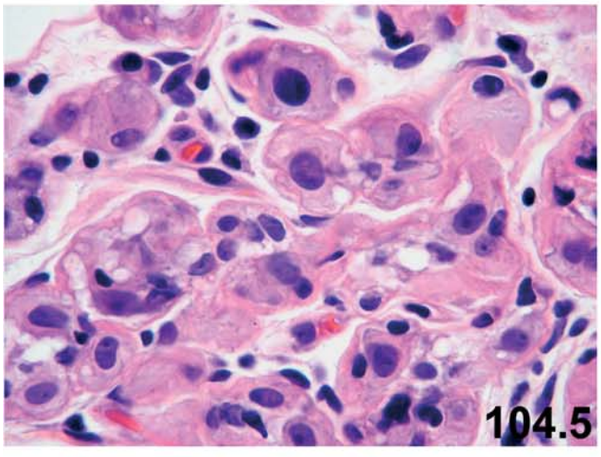
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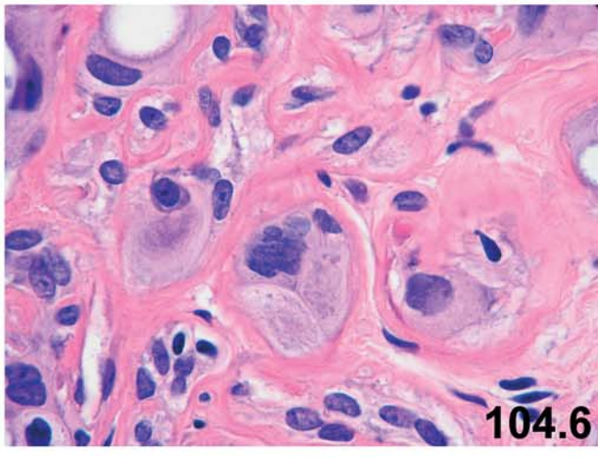
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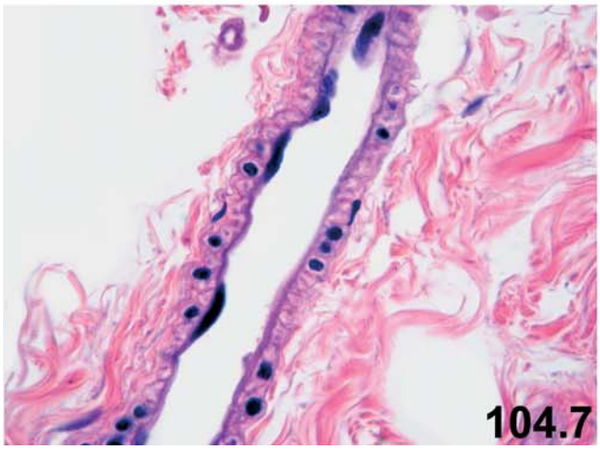
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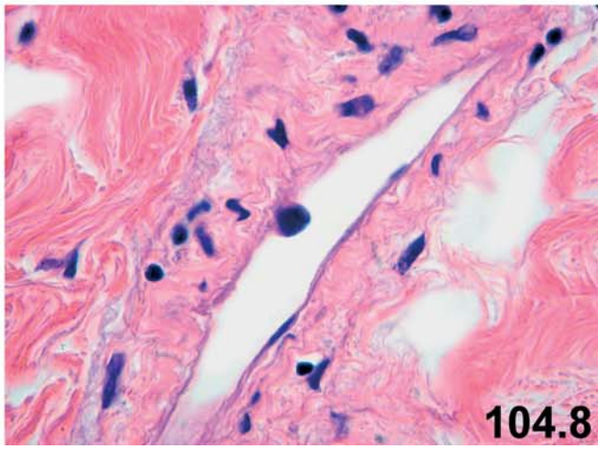
104.8

Cytopathology of Benign and Malignant Lesions (Selected Topics)

Contents

CHAPTER 17

Cytopathology of Benign and Malignant Lesions (Selected Topics)

17.1 Introduction

Fine needle aspiration (FNA) cytology of palpable breast lesions has several advantages: simplicity, low cost, low morbidity, and the ability to rapidly deliver an accurate diagnosis. In experienced hands, this method has a high sensitivity and specificity, particularly when used in combination with accurate physical examination and mammography (triple diagnosis). However, one of the major disadvantages of FNA is that it cannot reliably separate noninvasive or intraepithelial tumors from invasive carcinomas. In contrast, core needle biopsies of the breast are increasingly used for evaluating palpable and nonpalpable lesions because this method can reliably distinguish between invasive and noninvasive breast tumors.

Imprint cytology (touch preparation) of fresh breast specimens is another useful method that can be used as an adjunct to histological examination. In combination with macroscopic evaluation, it can be used as a rapid and reliable method for intraoperative consultation of breast specimens. Imprint cytology can reliably be used to evaluate sentinel lymph nodes and resection margins of excisional biopsies.

Caution

- *For educational purposes and as a valuable adjunctive method, imprint cytology of a variety of breast specimens is highly recommended.*

In this chapter, the cytological features of common benign and malignant breast lesions are briefly presented.

17.2 Fibrocystic Change

- Low cellularity with fragments of adipose tissue or stroma.
- Often, apocrine metaplastic cells and foam cells.
- Cohesive clusters or sheets of epithelial cells admixed with myoepithelial cells (dual cell population).

17.3 Proliferative Breast Diseases Without Atypia (Adenosis, Ductal Hyperplasia; Fig. 105)

- Moderate to high cellularity.
- Highly cohesive cell clusters showing a dual cell population of epithelial and myoepithelial cells (heterogeneous cell population).
- The epithelial clusters may show a streaming or swirling pattern.
- The epithelial clusters reveal variability in nuclear cell size, overlapped nuclei, and some loss of polarity.
- Nuclear enlargement and increased nuclear-cytoplasmic (N/C) ratio may be present. However, the chromatin distribution is regular.
- Nucleoli may be prominent.
- Apocrine cells, histiocytes, and calcified particles can be present.
- In the background, isolated myoepithelial cells and bipolar naked nuclei.
- Fragments of fibroconnective tissue and fat tissue.

Caution

- One of the most important diagnostic criteria for benign breast lesions is the presence of cell clusters with admixed cell population of epithelial and (modified)myoepithelial cells: dual or heterogeneous cell population.
- Epithelial cells of adenosis or florid ductal hyperplasia may show enlarged overlapped nuclei, a higher N/C ratio, and prominent nucleoli. In the presence of a heterogeneous cell population within the cohesive epithelial clusters, and with bipolar naked nuclei in the background, all of these seemingly atypical features should be interpreted conservatively.
- It is not possible to make a specific diagnosis of adenosis or ductal hyperplasia based on the cytologic features.

17.4 Proliferative Breast Lesions with Atypia

- High cellularity.
- Cohesive and loosely cohesive epithelial clusters showing epithelial cells with enlarged, hyperchromatic nuclei.
- While some of the clusters reveal a myoepithelial cell component, multiple clusters are composed of a homogeneous cell population without myoepithelial cells.
- Coarse and/or irregular chromatin distribution may be present.

Caution

- The distinction of ADH from low-grade DCIS is impossible in cytologic specimens. But both lesions belong to the category of low-grade ductal intraepithelial neoplasia (DIN).
- The presence of a homogeneous cell population of epithelial cells within the clusters is always highly suspicious for a neoplastic proliferation. Therefore, the possibility of atypical ductal hyperplasia (ADH)/ductal carcinoma in situ (DCIS) should be a serious consideration in that setting.
- The presence of anisonucleosis and loss of polarity by no means indicate an atypical proliferation.
- Whereas immunocytochemistry of benign proliferative lesions without atypia displays a positive reaction for high molecular weight cytokeratin (CK5/6), the cells in DIN (ADH/DCIS) are characteristically negative for CK5/6.

17.5 Lactating Adenoma and Lactating Changes

- High cellularity; numerous densely packed lobules with myoepithelial cells at the periphery.
- Loosely cohesive epithelial clusters.
- Smooth rounded borders of acini or monolayered sheets of epithelial cells.
- Epithelial cells with enlarged nuclei and prominent nucleoli but uniform chromatin distribution.
- Abundant vacuolated or granular cytoplasm.
- The epithelial cells are often fragile; large naked nuclei of epithelial cells in the background.
- Proteinaceous, bubbly vacuolated material in the background.

Caution

- The epithelial cells in lactating adenoma may show large and atypical-looking nuclei with prominent nucleoli, mimicking a carcinoma. But an important cytologic feature of lactating adenoma is the presence of abundant bubbly, vacuolated secretory material in the background and numerous isolated naked round nuclei of epithelial cells.

17.6 Fibroadenoma (Fig. 106)

- High cellularity.
- Numerous cohesive epithelial clusters admixed with myoepithelial cells (dual cell pattern).
- Monolayered clusters with a honeycomb pattern.
- Often, branching antler-horn or fingerlike pattern of epithelial clusters.
- Numerous bipolar naked nuclei (nuclei of intralobular stromal cells and/or myoepithelial cells) in the background.
- Fragments of hypocellular or acellular stromal tissue.

Caution

- Cellular (juvenile) fibroadenoma and fibroadenoma in pregnant women may cause serious diagnostic problems and could easily be misinterpreted as carcinoma. High cellularity, loss of polarity, anisonucleosis, hyperchromasia, and the presence of isolated atypical epithelial cells with enlarged nuclei may lead to a false-positive diagnosis. The heterogeneity of cell population (epithelial/myoepithelial cells) of fingerlike, branching cell clusters and the presence of abundant round or bipolar nuclei in the background are the most important cytologic clues for making the correct diagnosis.
- The distinction between cellular fibroadenoma and low-grade phylloides tumor is almost impossible based on the cytologic features.

17.7 Intraductal Papilloma

- High cellularity with numerous three-dimensional, papillary (with fibrovascular cores), or pseudopapillary (without fibrovascular component) clusters.
- Bipolar myoepithelial cells at the periphery of clusters (heterogeneous cell population).
- Proteinaceous or bloody background.
- Foamy or hemosiderin-containing vacuoles.

Caution

- The cytologic distinction of papilloma from a papillary intraductal carcinoma can be very difficult. It must be emphasized that *the presence of three-dimensional papillary or pseudopapillary clusters without a myoepithelial component is highly suspicious for a papillary carcinoma.*

17.8 Ductal Intraepithelial Neoplasia (Ductal Carcinoma In Situ) (Figs. 107 and 108)

- Mostly high cellularity.
- Numerous cohesive and loosely cohesive epithelial cells without a myoepithelial cell component (homogeneous cell population).
- In low-grade DIN (DCIS), monomorphic epithelial cells (monotonous cell population) with only mild nuclear atypia. In high-grade lesions, polymorphic epithelial cells with severe nuclear atypia.
- Often, no bipolar naked nuclei in the background.
- In high-grade DIN (DCIS), often dirty or necrotic background (comedo type necrosis) associated with apoptotic bodies and degenerative polymorphic tumor cells.

Caution

- A reliable separation between DIN (DCIS) and infiltrating carcinoma cannot be made based on the cytologic features. A homogeneous cell population with uniform or monotonous epithelial cells that is not associated with myoepithelial cells is always highly suspicious for carcinoma or DIN (DCIS).

17.9 Lobular Intraepithelial Neoplasia (Fig. 109)

- Moderate cellularity.
- Loosely cohesive groups of medium to small uniform epithelial cells.
- Small cells with eccentric nuclei, sometimes with irregular nuclear membrane.
- Intracytoplasmic vacuoles (lumina) containing eosinophilic secretory material (targetoid cells).
- Sometimes a signet-ring cell differentiation.

Caution

- The distinction between lobular intraepithelial neoplasia (LIN; atypical lobular hyperplasia [ALH]/lobular carcinoma in situ [LCIS]) and infiltrating lobular carcinoma is not possible on cytologic specimens.
- The cellularity can be low. Isolated small uniform epithelial cells with eccentric nuclei and vacuolated cytoplasms are suspicious for tumor cells with lobular differentiation.
- The cytological distinction between lobular and ductal neoplasia is not reliable. The distinction should be made after histological evaluation of surgical biopsy specimens.

17.10 Intraductal Papillary Carcinoma

- Three-dimensional papillary or pseudopapillary clusters containing atypical epithelial cells.
- The cohesive clusters are composed of a homogeneous cell population (no myoepithelial cell component).
- Hemosiderin-containing macrophages and occasional necrotic debris.

Caution

- The cytologic distinction between intraductal papilloma, atypical papilloma, and intraductal papillary carcinoma can be very difficult or even impossible. Therefore, histological evaluation of surgical biopsy specimen is required for a definitive diagnosis of all papillary breast tumors.

17.11 Infiltrating Ductal Carcinoma

- Usually highly cellular specimen.
- Loosely cohesive aggregates of atypical epithelial cells.
- Three-dimensional epithelial clusters.
- Gland-like arrangements.
- Numerous individual tumor cells. The isolated tumor cells often show eccentric nuclei or plasmacytoid appearance. Isolated tumor cells may display triangular cytoplasm.
- The epithelial clusters lack a myoepithelial cell component.
- Bipolar naked nuclei are absent or very rare.
- Necrotic background may be present.

Caution

- The tumor cells of a low-grade IDC are uniform with mild nuclear atypia. The lack of significant nuclear atypia may lead to a false-negative diagnosis. One should always keep in mind that a homogeneous cell population of epithelial cells (lack of a myoepithelial cell component within the clusters) is highly suspicious for carcinoma.
- It is not possible to make a reliable distinction between DIN (DCIS) and infiltrating ductal carcinoma (IDC) based on the cytologic findings.
- Potential pitfalls leading to a false-positive diagnosis of carcinoma include a cellular (juvenile) fibroadenoma, inflammatory lesions with reactive epithelial alteration (atypia), and lactational adenoma, as well as radiation changes.

17.12 Infiltrating Lobular Carcinoma (Fig. 109)

- Low-to-moderate cellularity.
- Small tumor cells forming small clusters and short chains (single-cell file).
- Single cells with eccentric round or oval nuclei, often with a plasmacytoid appearance.
- Cytoplasmic vacuoles (targetoid cells).
- Signet-ring cells may be present.
- Lack of myoepithelial cells, lack of bipolar naked nuclei.
- The tumor cells may sometimes be quite polymorphic or show abundant eosinophilic cytoplasm (pleomorphic variant, apocrine-like differentiation).

Caution

- Infiltrating lobular carcinoma (ILC) is an entity in which no hypercellularity occurs on the cytologic specimen. Because of scant cellularity, lack of significant cellular atypia, and small size of the tumor cells, ILC can easily be missed on FNA or imprint cytology.

17.13 Tubular Carcinoma

- Moderate cellularity.
- Cohesive epithelial clusters, glandular structures, and monolayer sheets.
- Angulated glandular-tubular arrangements.
- Uniform cells with only mild atypia (angular nuclear membranes, nuclear grooves).
- Lack of myoepithelial cells within the epithelial clusters.
- Usually, lack of bipolar naked nuclei in the background.

Caution

- Tubular carcinoma shows some resemblance to fibroadenoma in that it features branching epithelial clusters. The lack of significant cellular atypia in tubular carcinoma can easily lead to a false-negative diagnosis. In contrast to fibroadenoma, the epithelial clusters of tubular carcinoma display a homogeneous cell population of epithelial cells and lack a myoepithelial cell component.
- While the presence of numerous bipolar naked nuclei is typical for fibroadenoma, this is not a feature of tubular carcinoma in the vast majority of cases. The presence of bipolar naked nuclei in the background, however, does not exclude the possibility of a tubular carcinoma.

17.14 Mucinous Carcinoma (Figs. 110)

- Three-dimensional clusters, monolayered sheets, or dissociated groups floating in the mucinous material.
- Abundant mucin in the background (metachromatic on Diff-Quik stain, and pale blue in Papanicolaou-stained material).
- Homogeneous cell population of uniform epithelial cells without significant atypia.

Caution

- Fibroadenoma with prominent myxoid stromal change and mucocele-like lesion of the breast should be included in the differential diagnosis. In contrast to fibroadenoma with myxoid changes, cells in mucinous carcinoma lack a myoepithelial component and do not show numerous bipolar nuked nuclei in the background. Mucocele-like lesions of the breast usually lack numerous epithelial clusters, which are commonly identifiable in mucinous carcinoma.

17.15 Medullary Carcinoma

- High cellularity.
- Numerous cohesive epithelial cell clusters in a syncytial arrangement.
- Homogeneous cell population of severely atypical cells, often with macronucleoli.
- Numerous lymphocytes and plasma cells.
- Necrosis.

Caution

- The distinction between poorly differentiated ductal carcinoma with prominent lymphocytic infiltration and medullary carcinoma cannot be made based on the cytologic features.

17.16 Apocrine Carcinoma

- High cellularity.
- Large atypical cells with abundant eosinophilic cytoplasm.
- Often, granular cytoplasm.
- Large round nuclei with irregular chromatin pattern and prominent nucleoli. Multiple macronucleoli may be present.
- Inflammatory background.

17.17 Adenoid Cystic Carcinoma

- Highly cellular material with numerous clusters of small cells with scant cytoplasm and round, hyperchromatic nuclei.
- Typical arrangement of cells around cores of acellular (hypocellular) homogeneous material.
- The acellular round cores or hyaline bodies are translucent with Papanicolaou stain and pink with Diff-Quik (or May-Grünwald-Giemsa) stain.
- A basaloid population of tumor cells and a smaller population of cells with eosinophilic cytoplasm surrounding amorphous material.
- Numerous bipolar naked nuclei in the background.
- Commonly, numerous thick basement-membrane-like structures with abnormal configuration.

Caution

- The cytology of adenoid cystic carcinoma may be misinterpreted as fibroadenoma or other benign tumors (lesions). The heterogeneity of the cell population (admixture of epithelial and myoepithelial cells), the presence of numerous bipolar naked nuclei in the background, and a lack of significant nuclear atypia are the main reasons for such misinterpretation. The presence of hyaline bodies and abnormal thick basement-membrane-like material are helpful diagnostic features of adenoid cystic carcinoma. One should keep in mind that the cell population of adenoid cystic carcinoma is quite heterogeneous because the tumor represents a neoplastic proliferation of epithelial and myoepithelial cells.

17.18 Metaplastic (Sarcomatoid) Carcinoma (Fig. 112)

- Variable cellularity depending on the lesion itself.
- Often, highly atypical tumor cells, with admixed epithelial or mesenchymal-like appearance.
- Spindle (sarcomatoid) tumor cells with elongated, hyperchromatic nuclei.
- Squamous cancer cells, often with deep eosinophilic cytoplasms.
- Pleomorphic and very large tumor cells with multinucleation.
- A background of granular or fibrillar metachromatic myxoid material.
- High mitotic rates.

Caution

- The cytological distinction between sarcomatoid carcinoma and sarcoma of the breast without the performance of immunocytochemistry is very difficult, if not impossible.

17.19 Phylloides (Phyllodes) Tumor

- Variable cellularity.
- Biphasic pattern (cohesive clusters of epithelial/myoepithelial cells with a background of numerous stromal cells).
- Cellular stromal component with large spindle cells.
- Variable cytologic atypia of stromal cells.

Caution

- Based on the cytologic features, a low-grade phylloides tumor cannot be reliably distinguished from a (cellular) fibroadenoma. A high-grade (malignant) phylloides tumor, can, however, be suspected cytologically when numerous highly atypical stromal cells are present in association with a pattern otherwise typical for fibroadenoma.

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Fig. 105: Usual ductal hyperplasia.

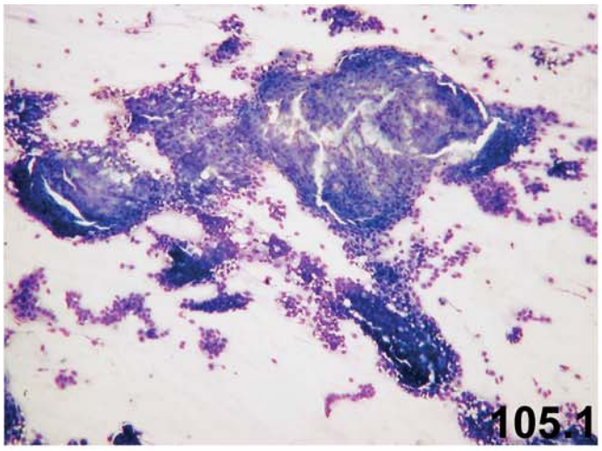
Case history: A 30-year-old woman presented with a small nodular firm lesion in her left breast. A needle core biopsy was performed. In addition (for educational purposes), touch imprint cytology from the fresh core needle biopsy was done.

Figs. 105.1 and **105.2:** Imprint cytology showing numerous cohesive epithelial clusters (Diff-Quik stain).

Figs. 105.3 and **105.4:** Numerous cohesive epithelial clusters with significant size variation. In the background are bipolar naked nuclei.

Figs. 105.5 and **105.6:** The clusters display a heterogeneous cell population composed of epithelial cells and myoepithelial cells. The myoepithelial cells show elongated or bipolar nuclei.

Figs. 105.7 and **105.8:** A needle core biopsy showing usual ductal hyperplasia characterized by irregular secondary lumens and a heterogeneous cell population of proliferating cells (epithelial/myoepithelial cells).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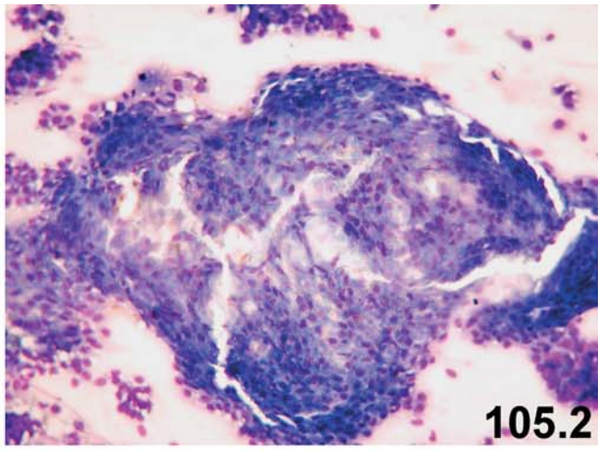
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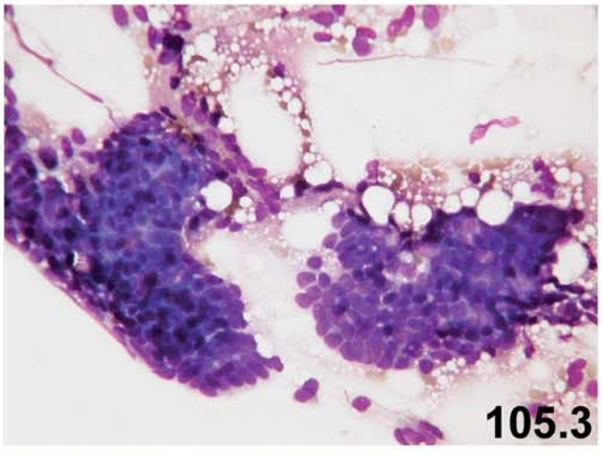
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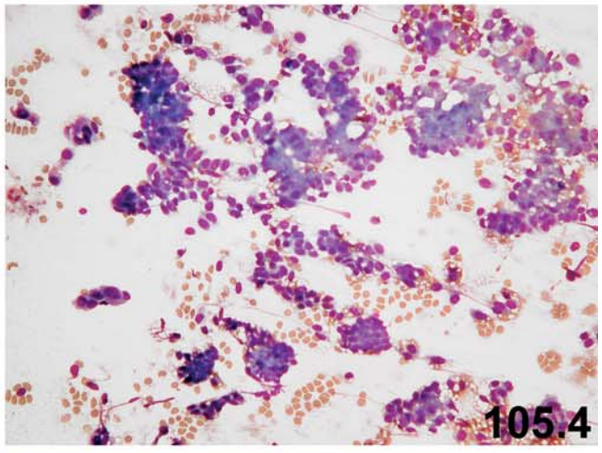
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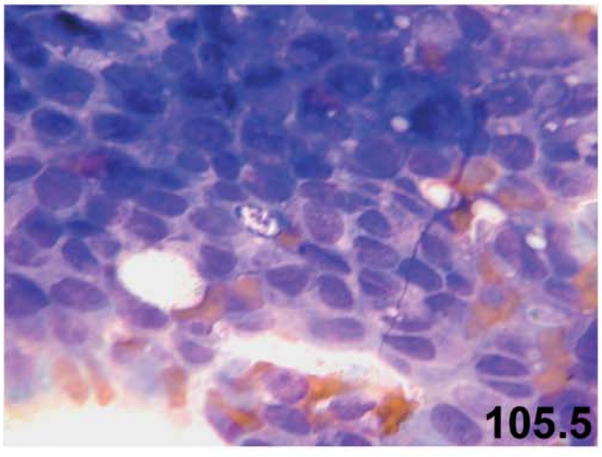
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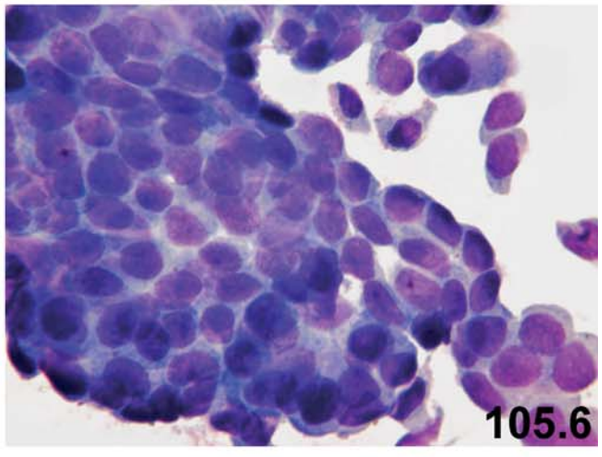
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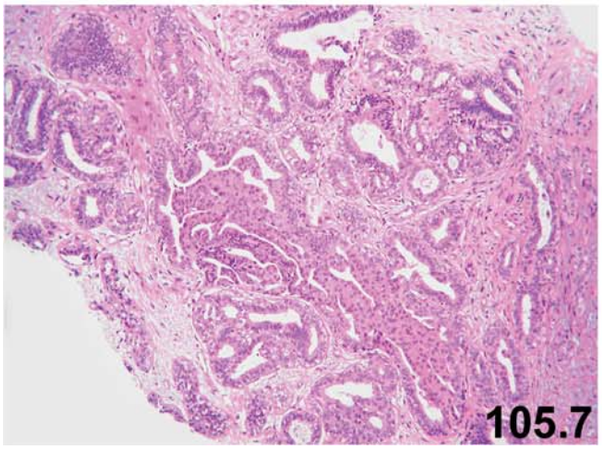
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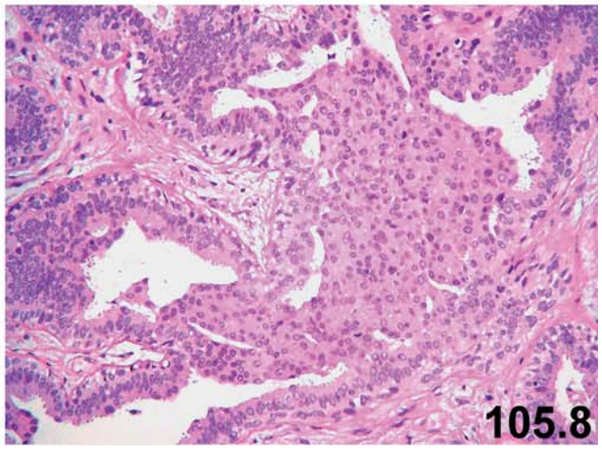
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Fig. 106: Fibroadenoma.

Case history: A 23-year-old woman presented with a mobile, well-circumscribed nodule in her right breast. Ultrasonography showed a 2-cm sharply-defined solid mass (consistent with fibroadenoma). Fine needle aspiration was performed.

Fig. 106.1: Fine needle aspiration reveals a very cellular material with numerous cohesive and branching epithelial clusters (Papanicolaou stain).

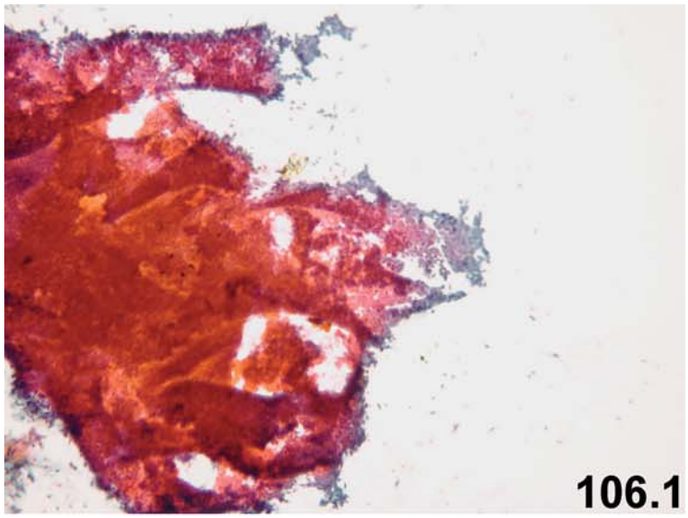
Fig. 106.2: There are several flat or two-dimensional clusters showing a heterogeneous cell population of epithelial and myoepithelial cells. The myoepithelial cells within the clusters show elongated (bipolar), dark nuclei (Papanicolaou stain).

Fig. 106.3: Branching epithelial clusters associated with isolated bipolar naked nuclei in the background.

Fig. 106.4: A cohesive cluster showing two distinct cell types: epithelial cells with vesicular, round to oval nuclei and uniform chromatin distribution, and myoepithelial cells with elongated or spindle-shaped dark nuclei. The heterogeneity of cell population within the clusters is characteristic for benign proliferative breast lesions.

Fig. 106.5: Numerous bipolar naked nuclei are present in the background (Diff-Quik stain). These cells represent proliferating intralobular stromal (and/or myoepithelial) cells. The combination of numerous bipolar naked nuclei and branching epithelial/myoepithelial cell clusters is characteristic for fibroadenoma.

Fig. 106.6: Histology of the same case (excisional biopsy of the nodule after 1 year) showing a typical fibroadenoma with intracanalicular growth pattern.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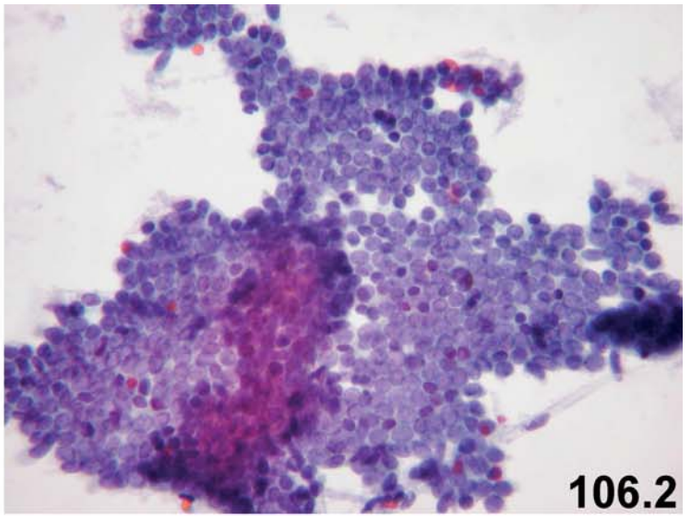
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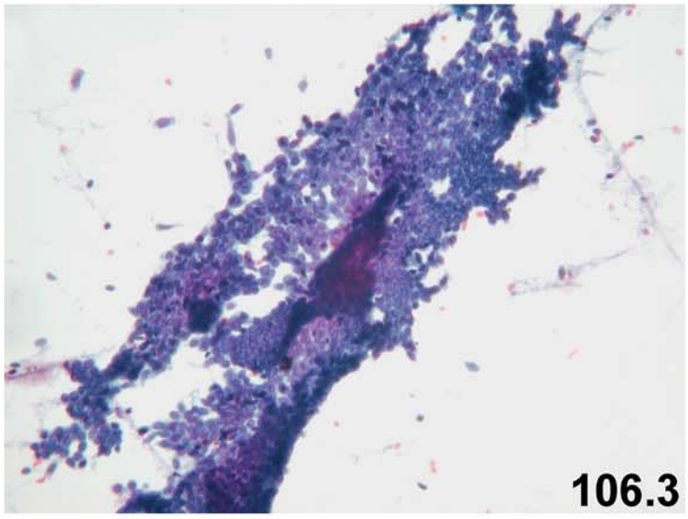
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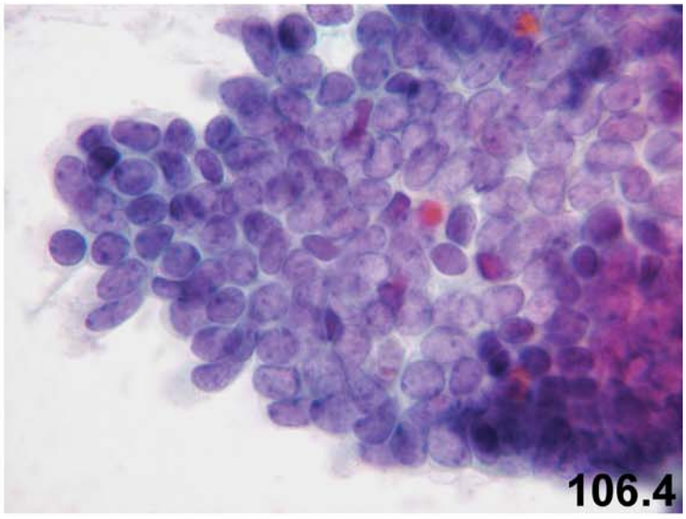
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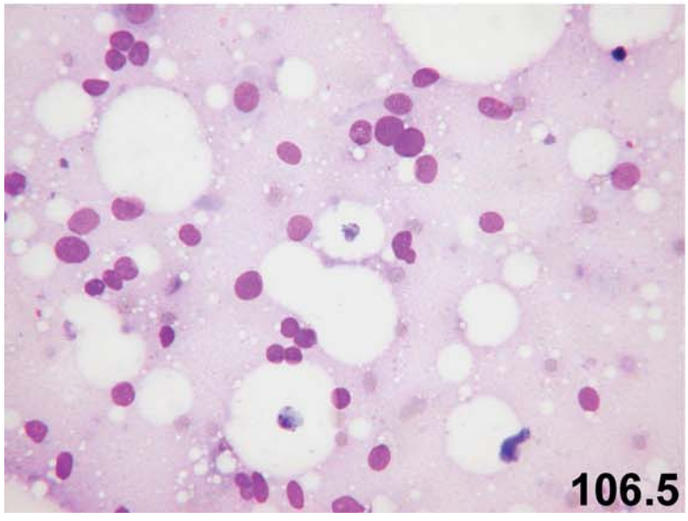
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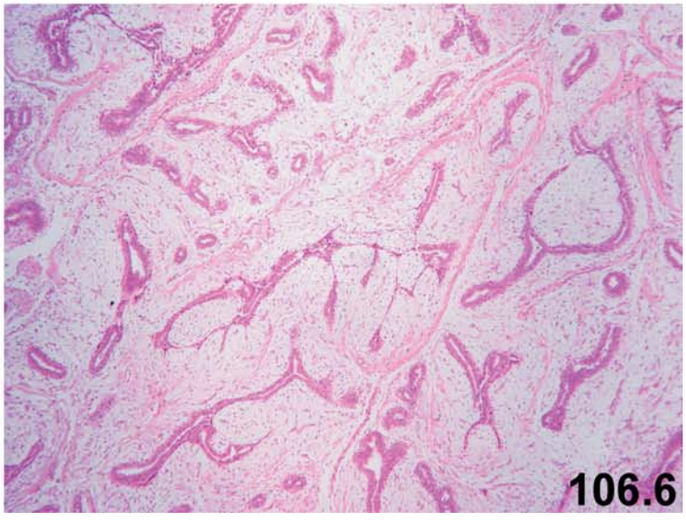
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Fig. 107: Low-grade DIN (DCIS)/low-grade carcinoma.

Case history: A 54-year-old woman presented with an abnormal mammogram showing suspicious microcalcifications and an ill-defined right lesion in the upper outer quadrant of her right breast. Excisional biopsy was performed. In addition, imprint cytology from the cut surface of the fresh surgical specimen was done.

Fig. 107.1: Imprint cytology revealing loosely cohesive epithelial cells and isolated cells (Papanicolaou stain).

Fig. 107.2: Several cohesive epithelial cells with a monotonous appearance without significant nuclear atypia. Note the absence of myoepithelial cells within the cluster. This epithelial cluster, even in the absence of significant nuclear atypia, is highly suggestive of malignancy because it is composed of a homogeneous cell population (Papanicolaou stain).

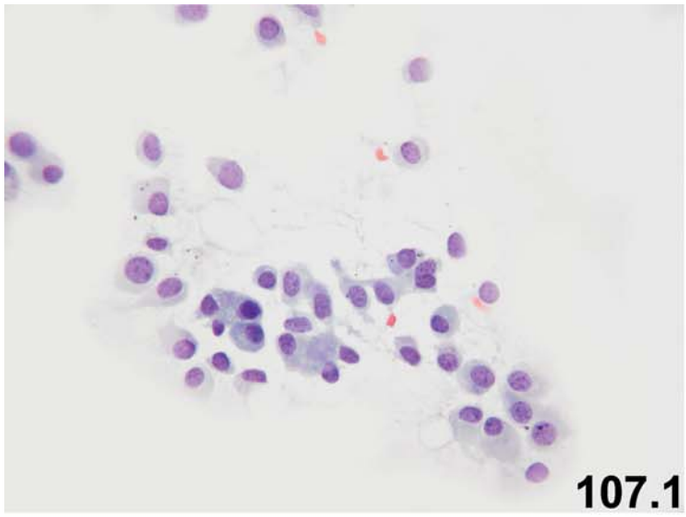
Fig. 107.3: A homogeneous epithelial cell population with no myoepithelial cells or bipolar naked nuclei. The epithelial cells show regular chromatin distribution and only minimal nuclear atypia (Papanicolaou stain).

Fig. 107.4: Numerous epithelial cells (Diff-Quik stain) composed of a homogeneous cell population. Note the lack of bipolar naked nuclei in the background. These features are highly suggestive of malignancy (low-grade neoplastic lesion).

Figs. 107.5 and **107.6:** Higher magnification reveals epithelial cells with a monotonous appearance. Note the regular arrangement of the nuclei and distinct cytoplasmic borders of the homogeneous epithelial cells.

Fig. 107: Final remarks

- The homogeneity of epithelial cell population, minimal nuclear atypia, and lack of bipolar naked nuclei should raise the possibility of a low-grade neoplastic lesion. The main differential diagnosis in this case is low-grade DIN (ADH/DCIS) and low-grade invasive carcinoma. The histology in this case showed a low-grade DIN (DCIS). No invasive carcinoma could be identified histologically.
- One must keep in mind that cytology of low-grade DIN (DCIS) and low-grade invasive ductal carcinoma is very similar. A reliable distinction between DIN (DCIS) and invasive carcinoma cannot be made based on the cytologic evaluation. The presence of numerous isolated atypical cells or necrosis in cytologic specimens is by no means indicative of invasion.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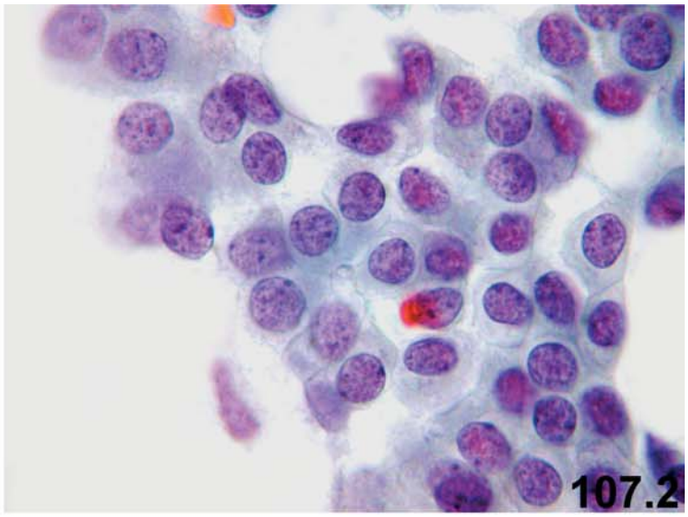
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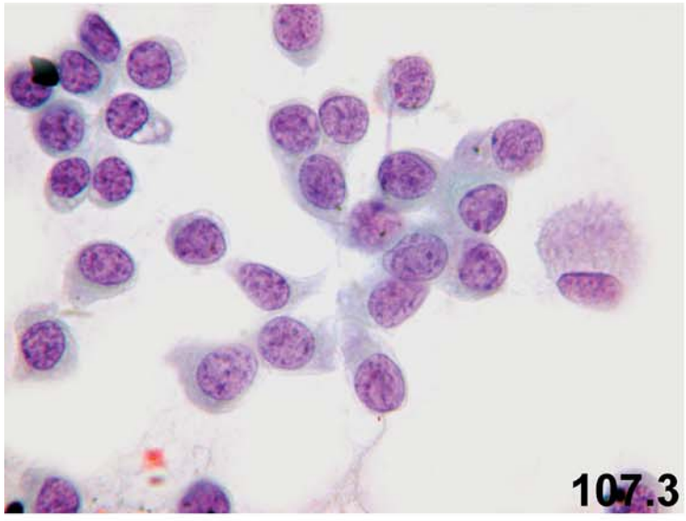
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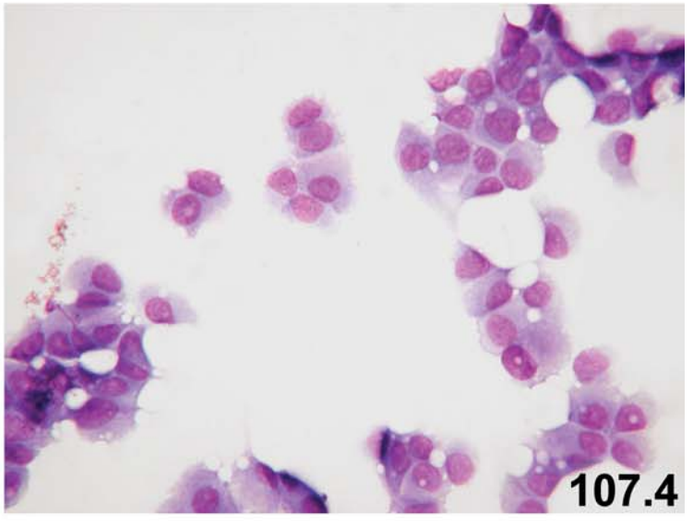
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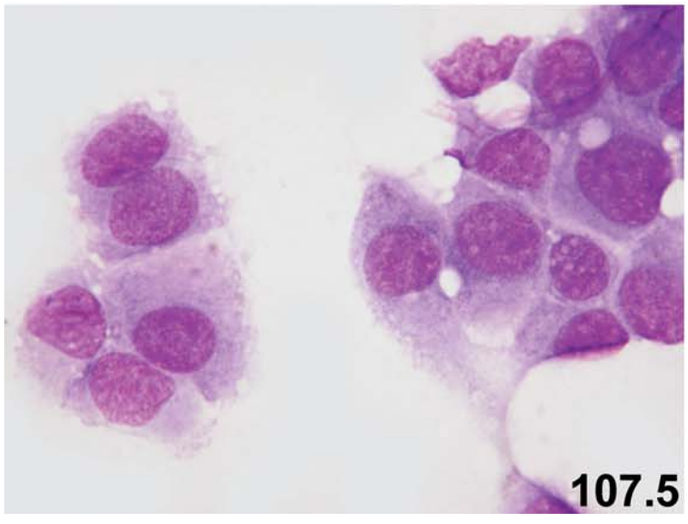
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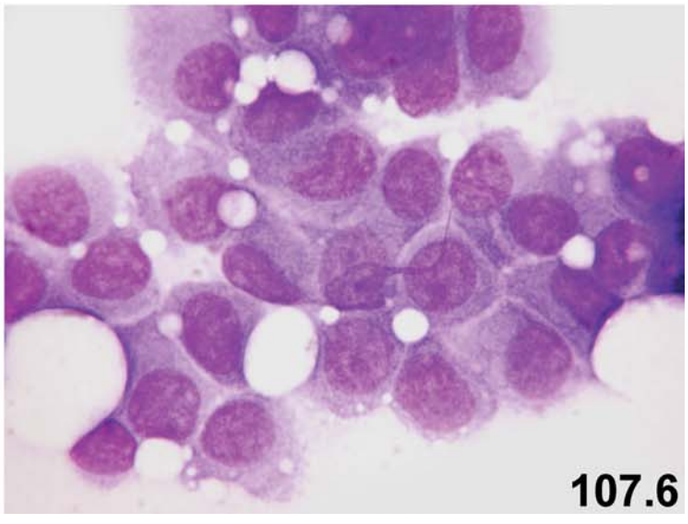
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Fig. 108: Bloody nipple discharge with highly atypical epithelial cells.

Case history: A 38-year-old woman presented with hemorrhagic nipple discharge of her right breast. There was no palpable tumor. Mammography showed neither a tumor nor microcalcifications.

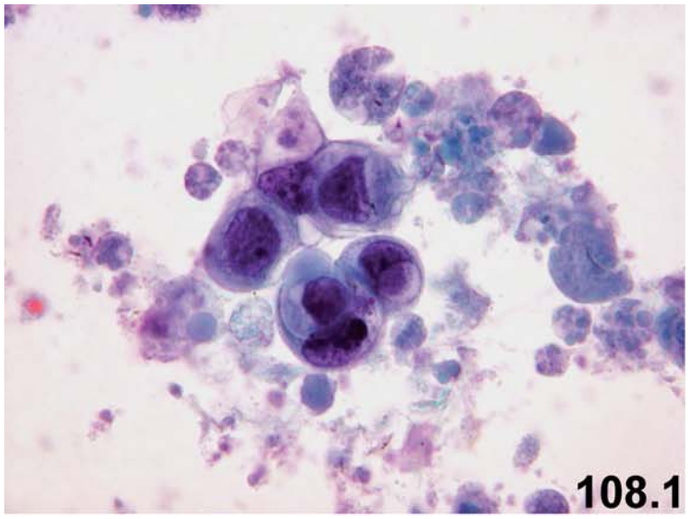
Fig. 108.1: Cytology shows a group of atypical cells displaying enlarged hyperchromatic nuclei (Papanicolaou stain).

Fig. 108.2: Necrotic background (cell debris) showing apoptotic bodies and secretory-like material.

Figs. 108.3 and **108.4:** Two cohesive epithelial clusters with glandular arrangement displaying highly atypical cells. Note the absence of a myoepithelial cell component. The presence of homogeneous atypical cells associated with a necrotic background is highly suggestive of malignancy.

Figs. 108.5 and **108.6:** Excisional biopsy of the lesion was performed after recognition of highly atypical cells. At low magnification, the surgical specimen shows a large duct (lactiferous duct) with minimal epithelial proliferation.

Fig. 108.6: At higher magnification, epithelial cells with high-grade nuclear atypia are present.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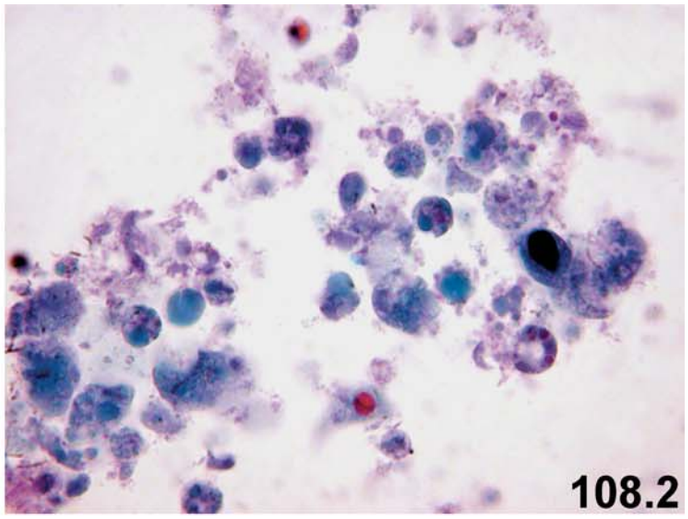
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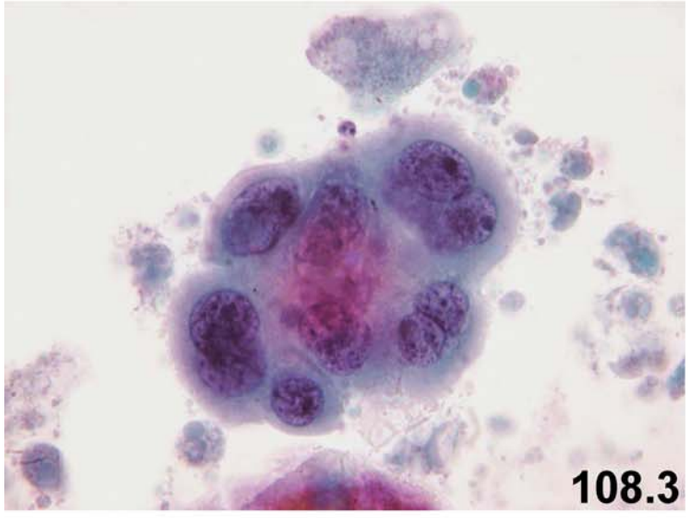
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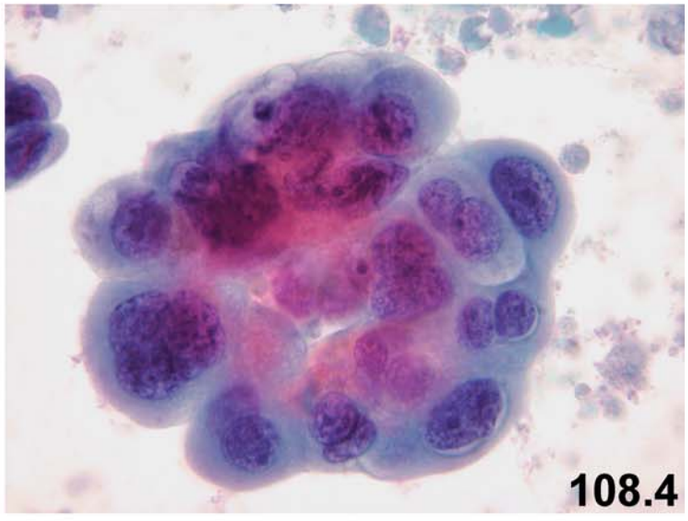
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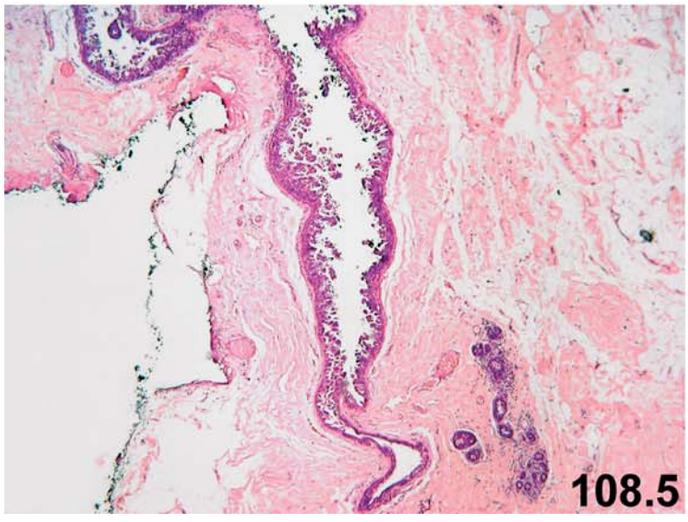
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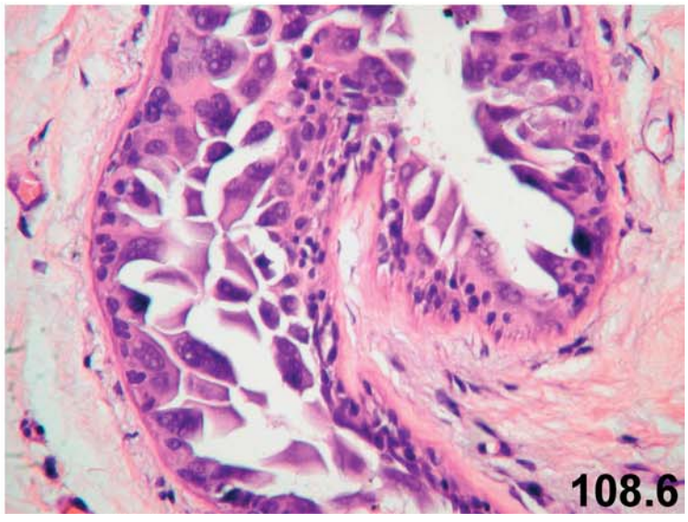
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Figs. 108.7 and **108.8:** At very high magnification (×1,000), the cytological details of highly atypical or anaplastic cells are clearly recognizable.

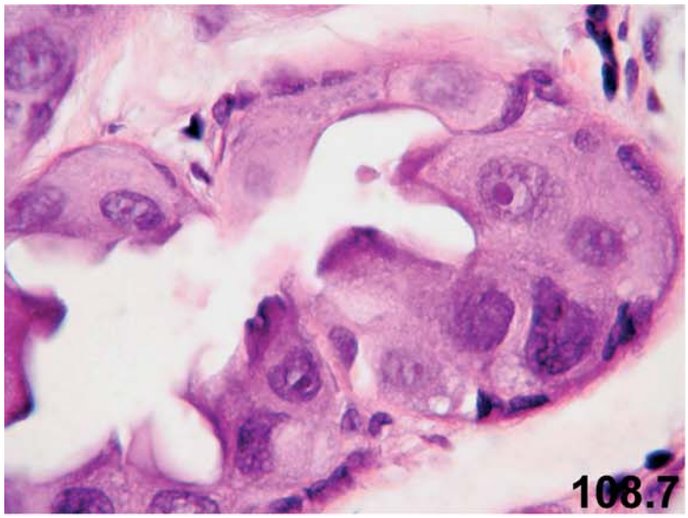
Fig. 108.9: One cell layer of highly atypical cells. Note the fragmented luminal secretory-like material, which indeed represents necrotic cell debris.

Fig. 108.10: Luminal necrotic cell debris (secretory-like material) showing several apoptotic bodies.

Figs. 108.11 and **108.12:** Other areas of the involved large ducts displaying one or very few cell layers of anaplastic tumor cells with abundant eosinophilic cytoplasm and central necrosis.

Fig. 108: Final remarks

- Although cytology in this case shows highly atypical cells associated with necrosis, it cannot reliably distinguish between high-grade DIN (DCIS) and a poorly differentiated invasive carcinoma.
- The fragmented and not uniform eosinophilic material is a worrisome finding and requires further histological evaluation of epithelial cells at higher magnification.
- This case represents an example of high-grade DIN (DCIS), predominantly of flat type (clinging carcinoma in situ, pleomorphic variant).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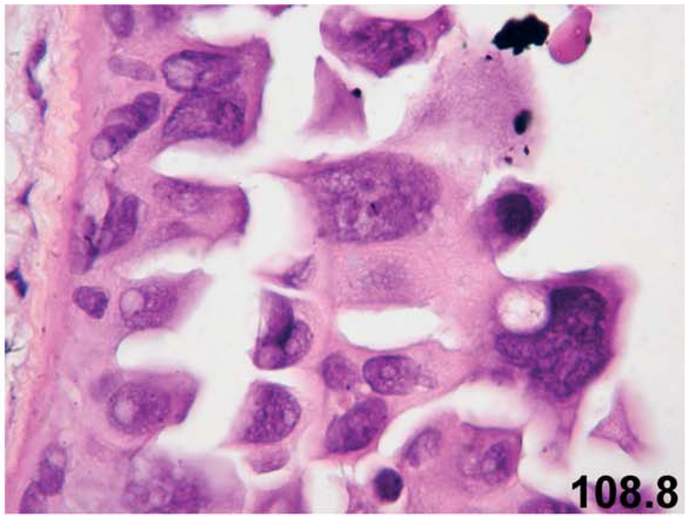
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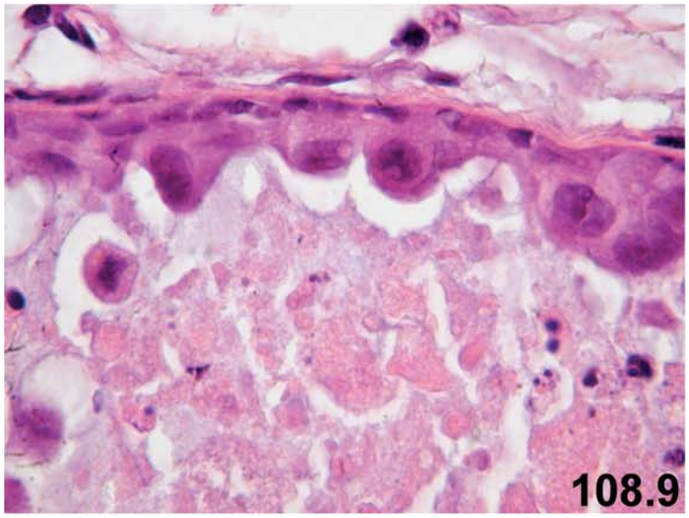
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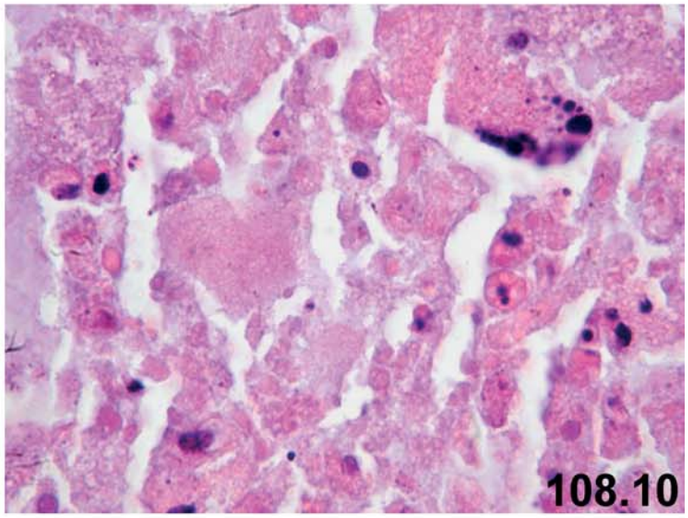
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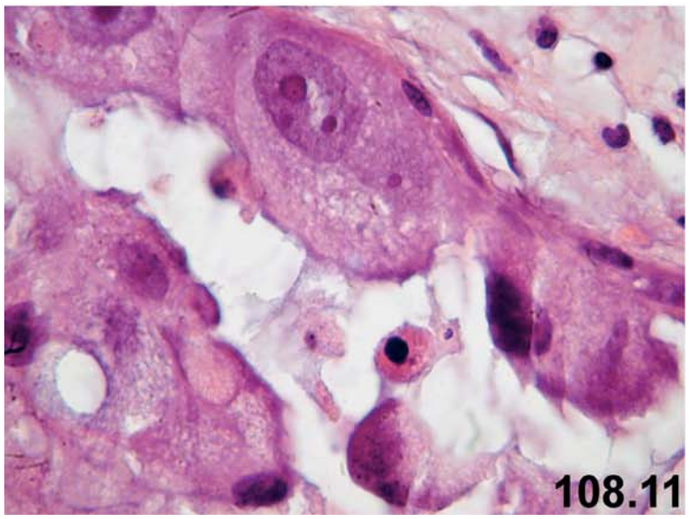
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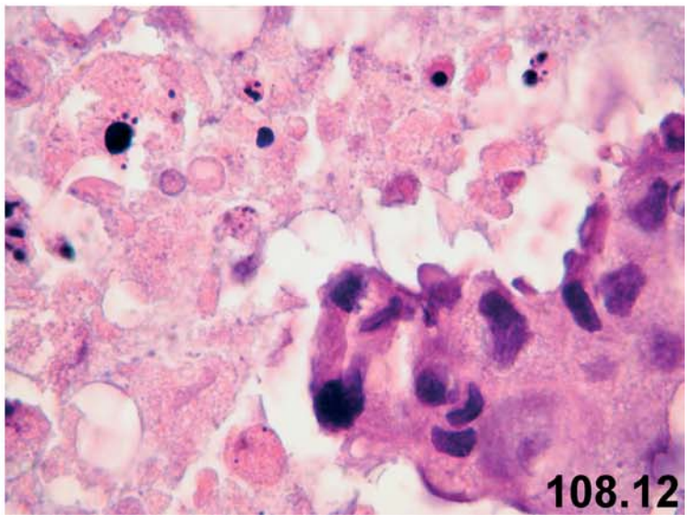

108.12

Fig. 109: (Lobular) carcinoma with targetoid cells.

Case history: A 69-year-old woman with an abnormal mammogram presented with a right breast tumor with infiltrating and irregular margins. Core needle biopsy of the tumor was performed. For educational purposes, imprint cytology from fresh core needle material was prepared.

Fig. 109.1: Loosely cohesive epithelial cells consisting of only one cell type. The epithelial cells show enlarged hyperchromatic nuclei. Some of the tumor cells show intracytoplasmic lumens. There are no bipolar naked nuclei in the background (Papanicolaou stain).

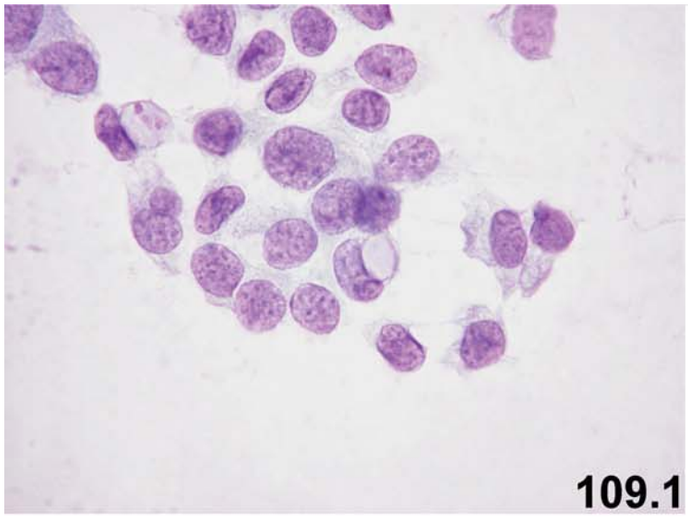
Fig. 109.2: Isolated epithelial cells without a myoepithelial cell component. The atypical cells are small and monotonous in appearance (Papanicolaou stain).

Figs. 109.3 and **109.4:** Homogeneous epithelial clusters without myoepithelial cell component. The cells reveal intracytoplasmic vacuoles (lumina) containing central secretory inclusions (targetoid cells).

Figs. 109.5 and **109.6:** Atypical epithelial cells with targetoid appearance. Note the absence of bipolar naked nuclei and the homogeneity of atypical cells (Diff-Quik stain).

Fig. 109: Final remarks

- The imprint cytology in this case is highly suggestive of malignancy. The differential diagnosis includes intraepithelial neoplasia and invasive carcinoma. The presence of small, atypical cells with targetoid appearance is in favor of neoplasia with lobular differentiation. The core needle biopsy in this case revealed infiltrating lobular carcinoma.
- The targetoid cells should not be mistaken for signet-ring carcinoma.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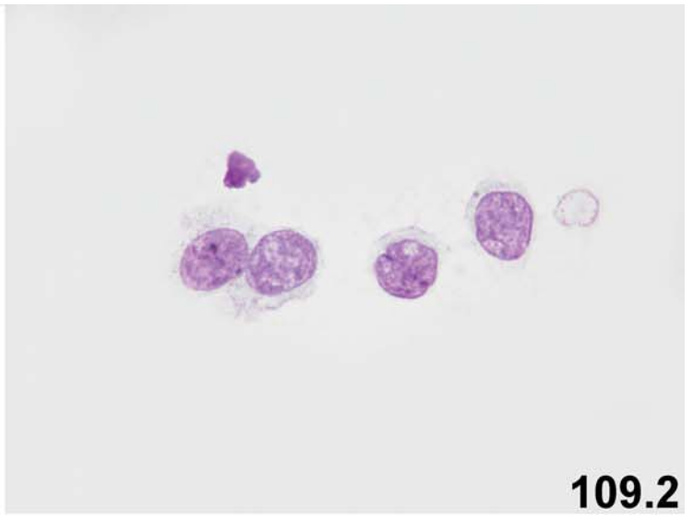
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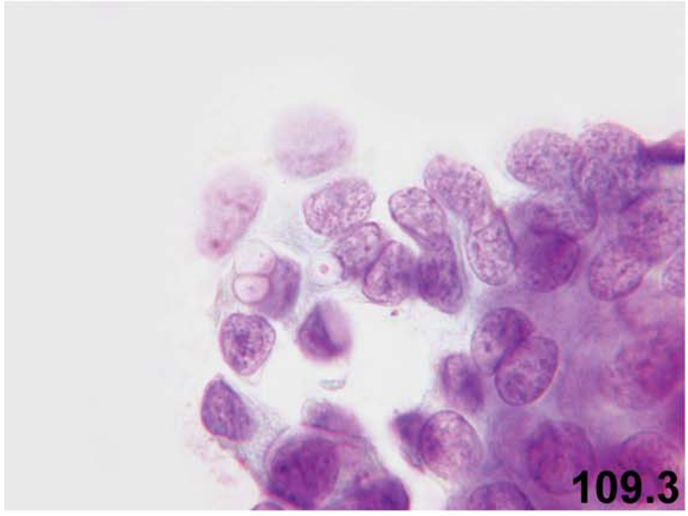
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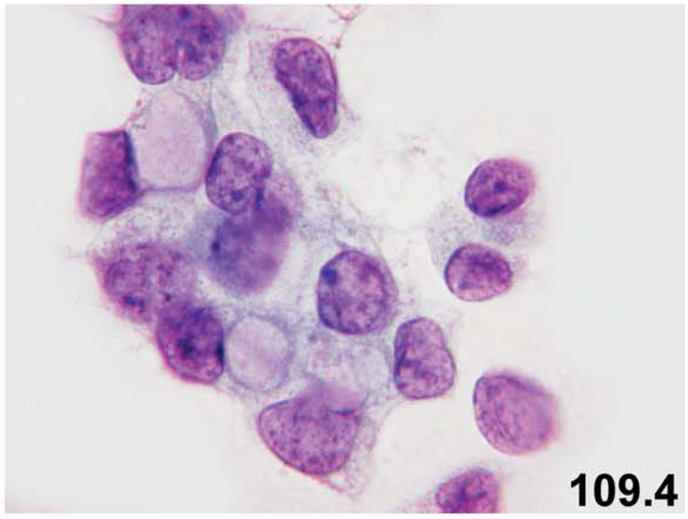
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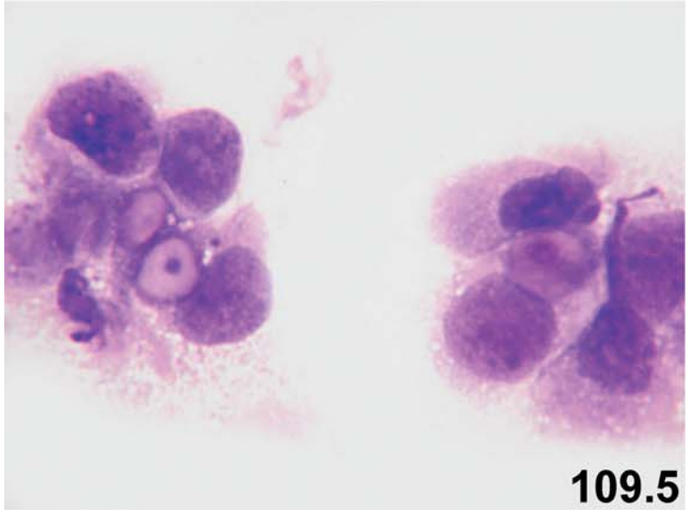
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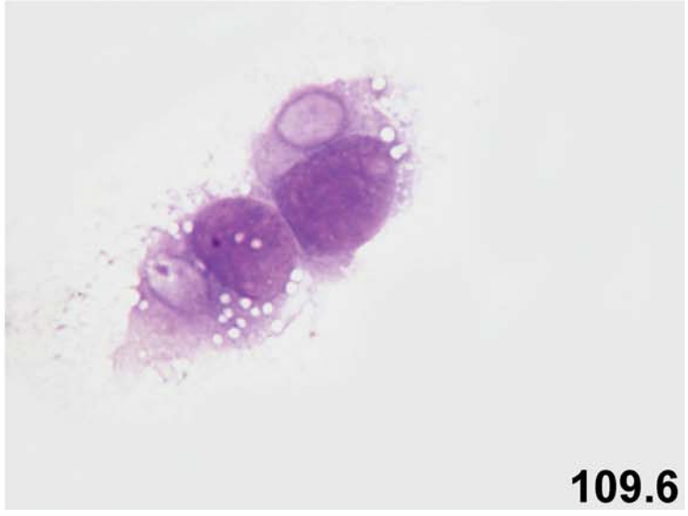
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Fig. 110: Mucinous carcinoma.

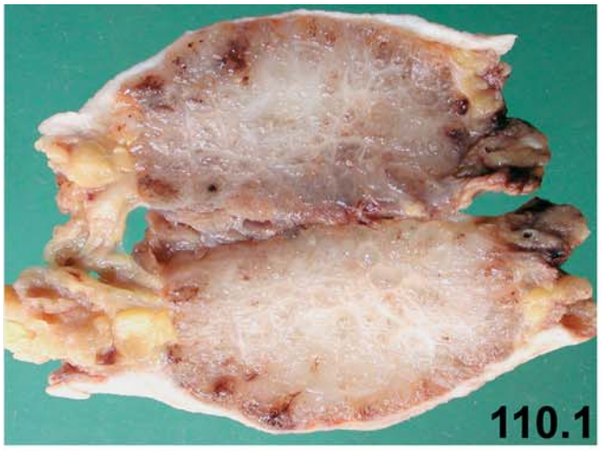
Case history: A 66-year-old woman presented with a 10-cm tumor in her right breast. A needle core biopsy of the tumor showed infiltrating ductal carcinoma with extracellular mucinous component (mucinous carcinoma?). Because of the tumor's large size, a modified radical mastectomy was done. Imprint cytology of the cut surface of the tumor was performed.

Fig. 110.1: Mastectomy specimen displaying a greyish-white tumor with colloid or mucinous appearance.

Figs. 110.2, 110.3, and **110.4:** Imprint cytology is highly cellular, showing numerous cohesive epithelial clusters (Papanicolaou stain).

Figs. 110.5 and **110.6:** Numerous three-dimensional cohesive epithelial clusters in a background of abundant mucinous material (Papanicolaou stain).

Figs. 110.7 and **110.8:** Higher magnification of epithelial clusters showing only one cell type or a homogeneous cell population with mild nuclear atypia. Note the lack of bipolar naked nuclei and the presence of extracellular mucinous material (Papanicolaou stain).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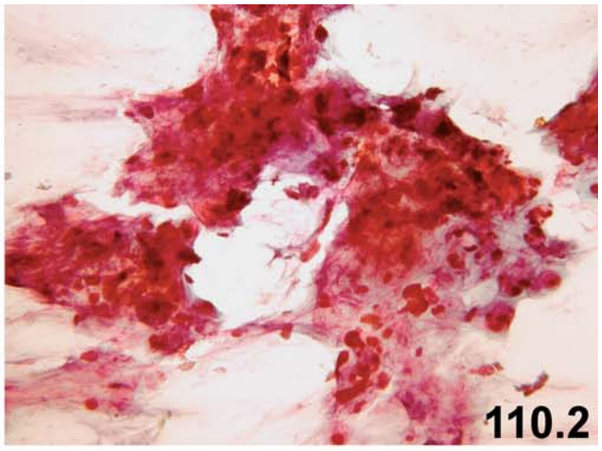
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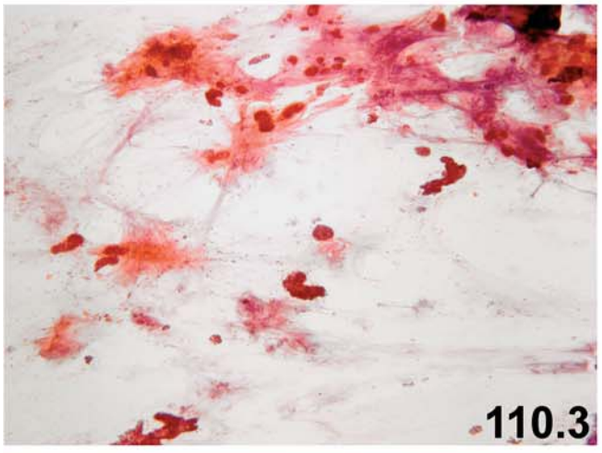
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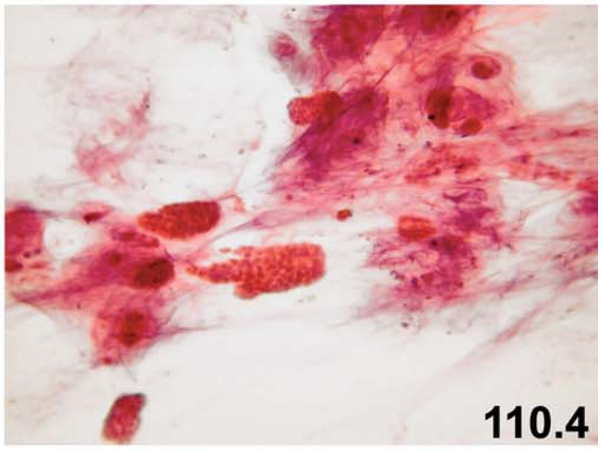
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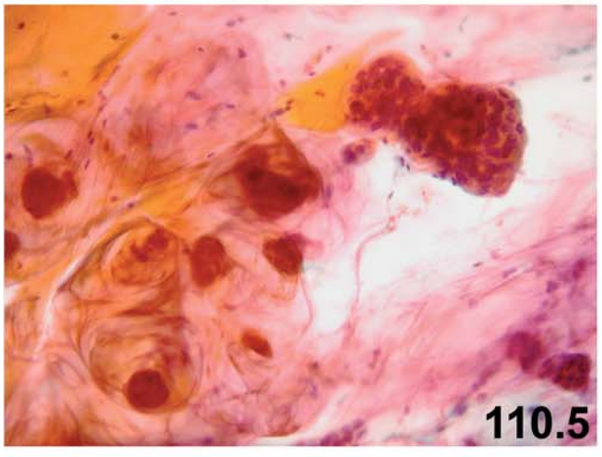
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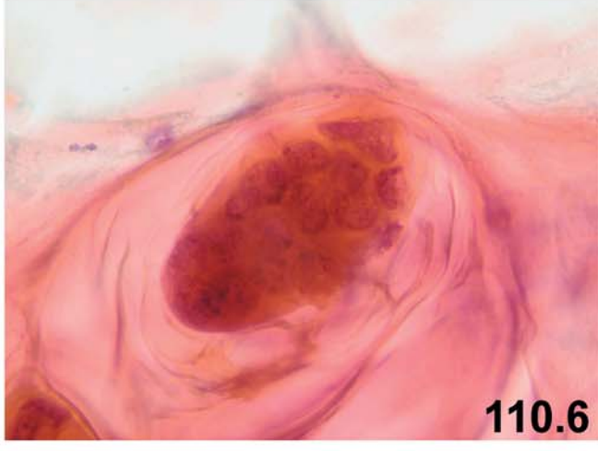
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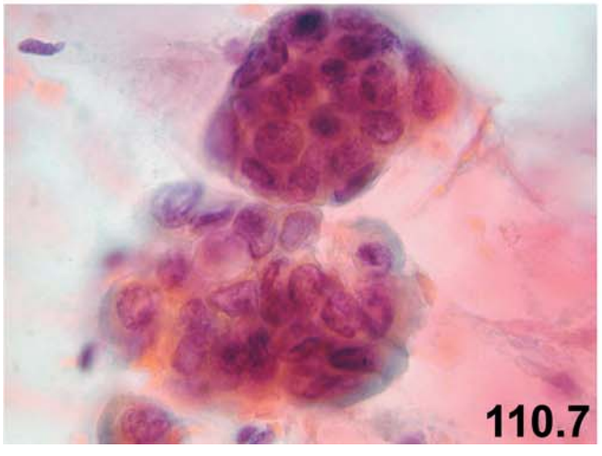
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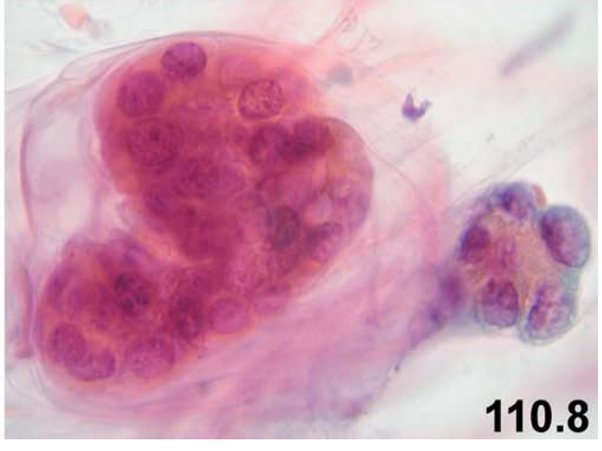
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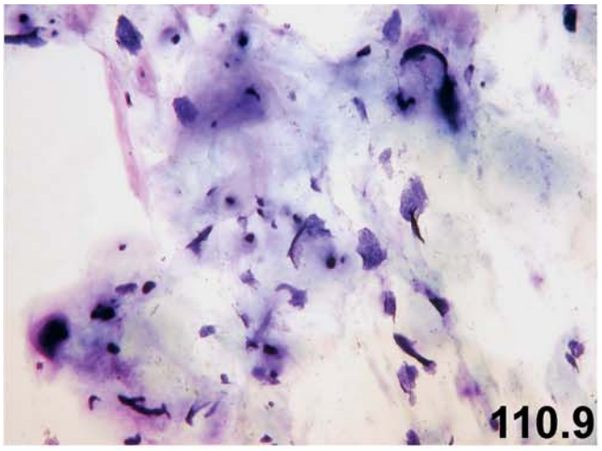
Figs. 110.9 and **110.10:** Abundant extracellular mucin and numerous cohesive epithelial clusters as shown by Diff-Quik stain.

Figs. 110.11 and **110.12:** Histology of the tumor removed by mastectomy exhibits a classic mucinous carcinoma of the breast.

Figs. 110.13 and **110.14:** Histology showing abundant extracellular mucinous material and small aggregates of epithelial tumor cells without significant nuclear atypia.

Figs. 110.15 and **110.16:** Comparison between imprint cytology (Fig. 110.15) and histology (Fig. 110.16) showing aggregates of epithelial cells with mild atypia. The tumor cells lack a myoepithelial cell layer.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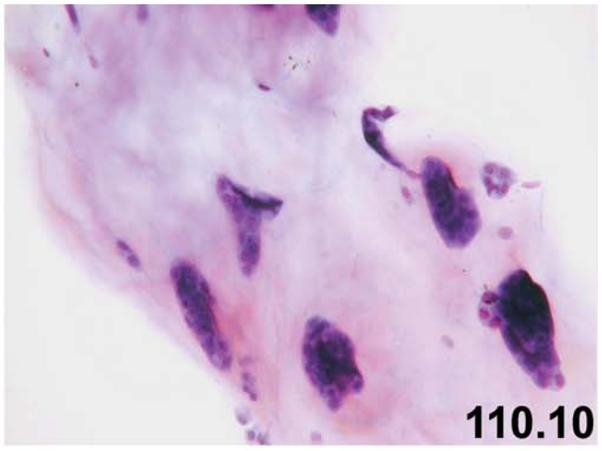
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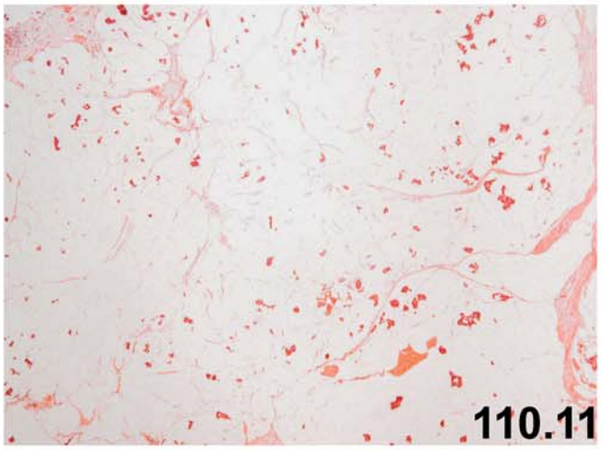
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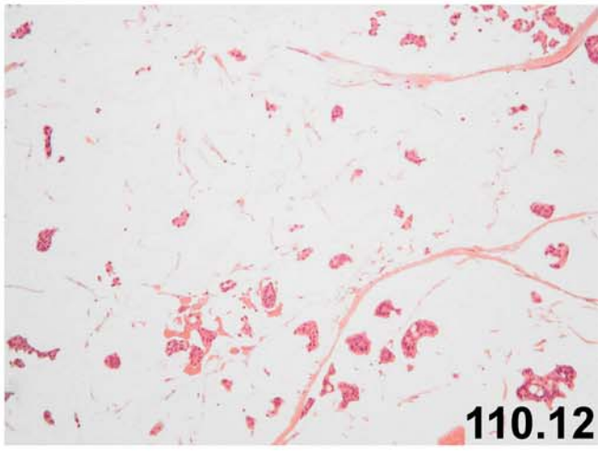
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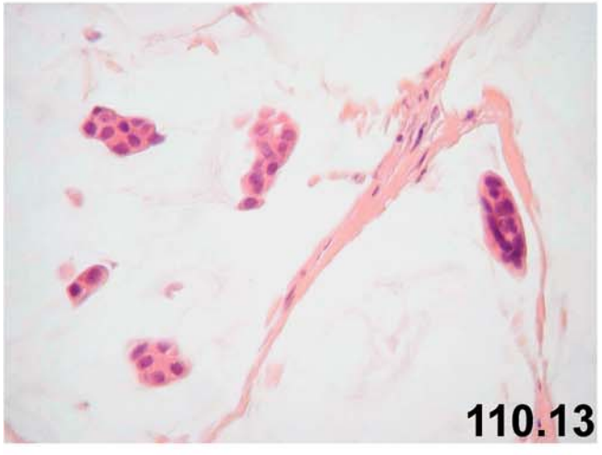
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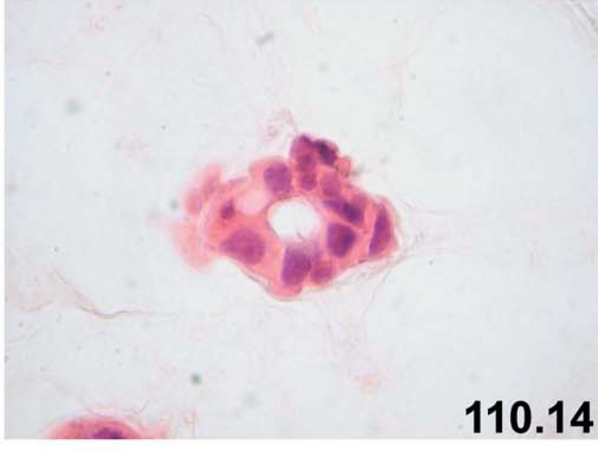
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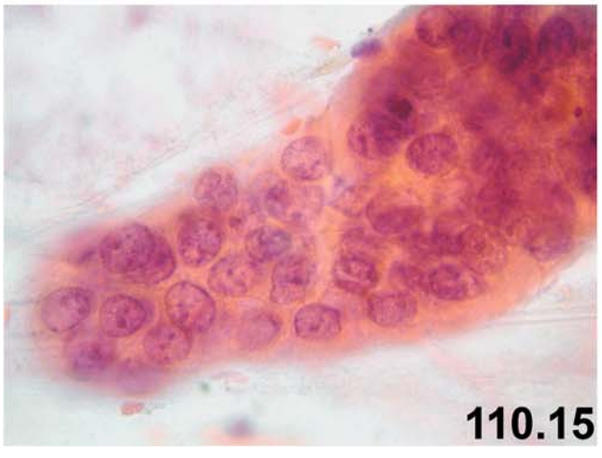
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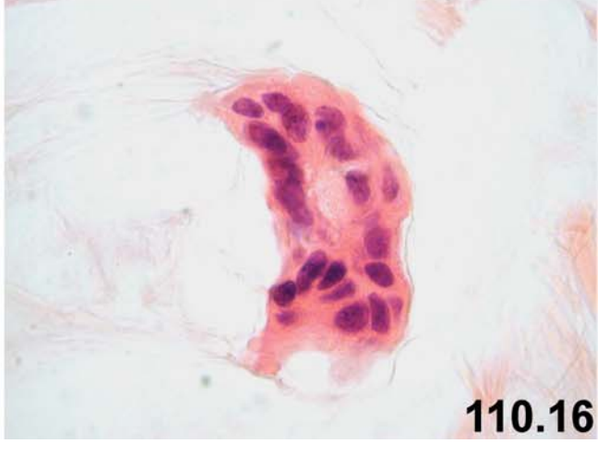

110.16

Fig. 111: Poorly differentiated ductal carcinoma.

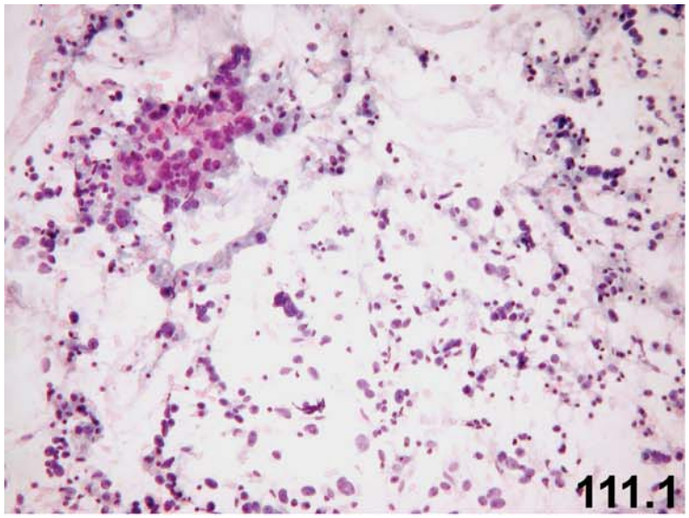
Case history: A 29-year-old woman presented with a firm, well-circumscribed nodule in her right breast. The nodule was 2 cm in greatest diameter and interpreted clinically and mammographically as a fibroadenoma. Fine needle aspiration of the tumor was done.

Fig. 111.1: Cytology is very cellular and shows numerous isolated cells and cell clusters (Papanicolaou stain).

Fig. 111.2: Numerous cohesive clusters and isolated tumor cells with highly atypical nuclei (Diff-Quik stain).

Figs. 111.3 and **111.4:** Highly atypical epithelial cells with prominent nucleoli. There are numerous atypical naked nuclei (Fig. 111.3, Diff-Quik stain) and tumor cells with prominent nucleoli (Figs. 111.3 and 111.4). Note the presence of only one cell type and the lack of myoepithelial cells. Cytology shows anaplastic tumor cells (pleomorphism of anaplasia).

Figs. 111.5 and **111.6:** Higher magnification (Diff-Quik stain) displays extremely atypical cells with macronucleoli. The cytology is consistent with poorly differentiated ductal carcinoma. Excisional biopsy of the tumor showed a poorly differentiated infiltrating ductal carcinoma.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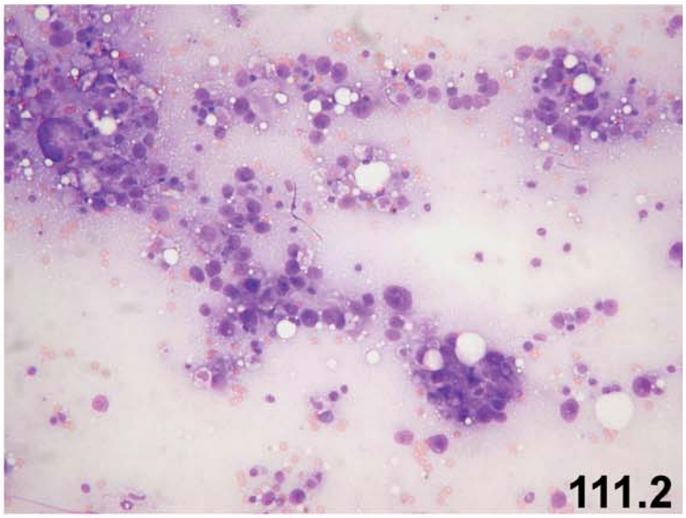
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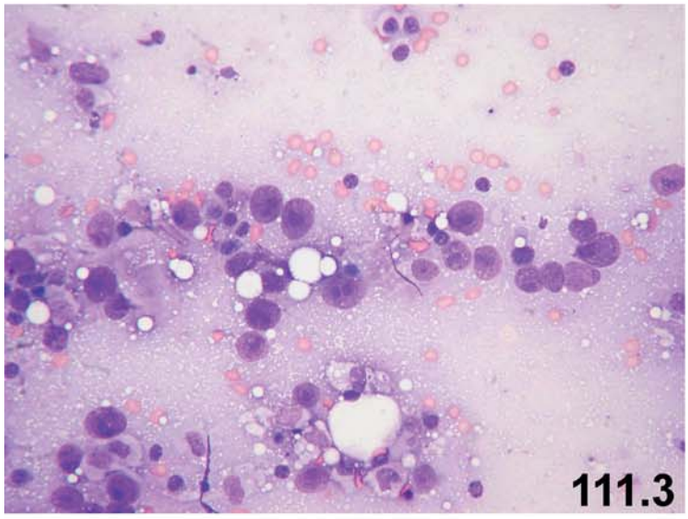
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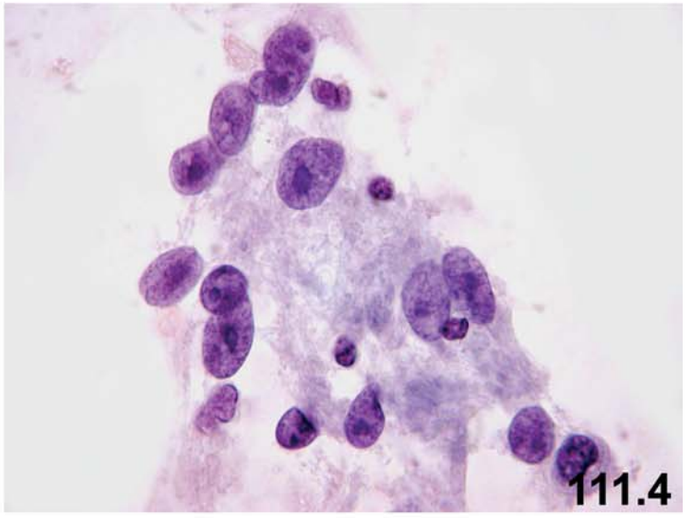
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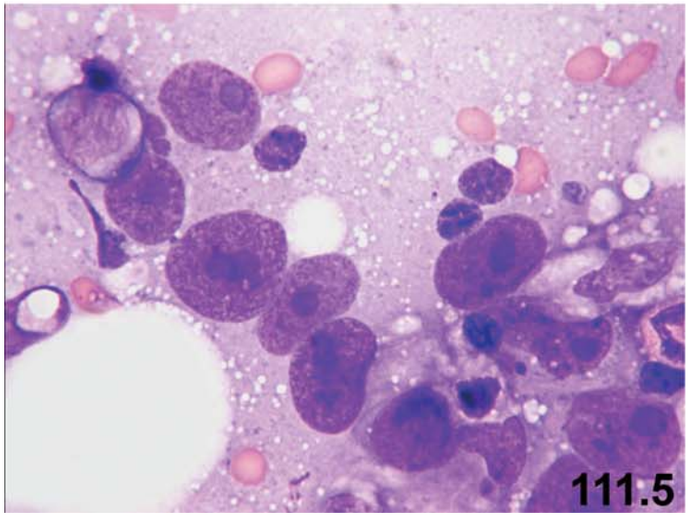
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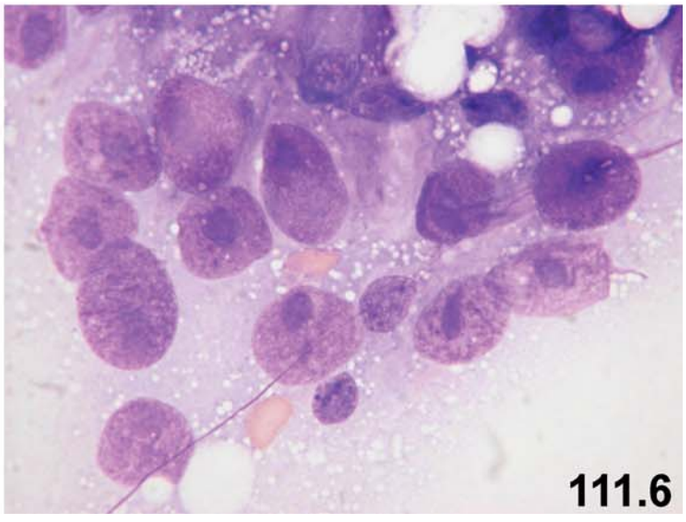
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Fig. 112: Sarcomatoid (metaplastic) carcinoma.

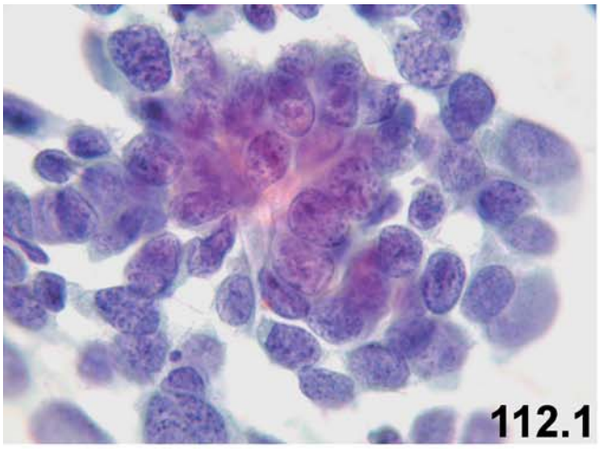
Case history: A 60-year-old woman presented with a 14-cm right breast tumor. A needle core biopsy revealed a poorly differentiated spindle cell tumor (carcinoma). Because of the tumor's large size, a mastectomy was done. For educational purposes, imprint cytology of the cut surface of mastectomy specimen (fresh surgical specimen) was prepared.

Fig. 112.1: Cytology (Papanicolaou stain) shows numerous cell clusters with round-oval nuclei and scant cytoplasm.

Figs. 112.2, 112.3, and **112.4:** In addition, there are numerous isolated, multinucleated tumor giant cells.

Figs. 112.5 and **112.6:** Comparison of cytology (Fig. 112.5) with histology (Fig. 112.6) shows tumor giant cells or anaplastic tumor cells with extremely large hyperchromatic nuclei and irregular chromatin distribution.

Figs. 112.7 and **112.8:** Highly atypical, spindle shaped tumor cells in cytologic (Fig. 112.7) and histologic (Fig. 112.8) preparations. Extensive sampling and additional immunohistochemical examination in this case revealed a metaplastic carcinoma (carcinosarcoma).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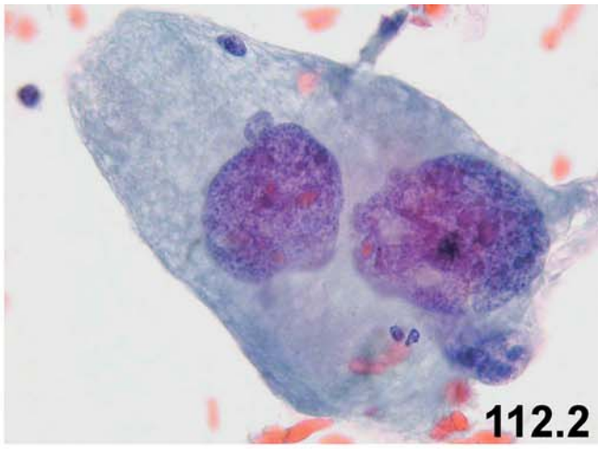
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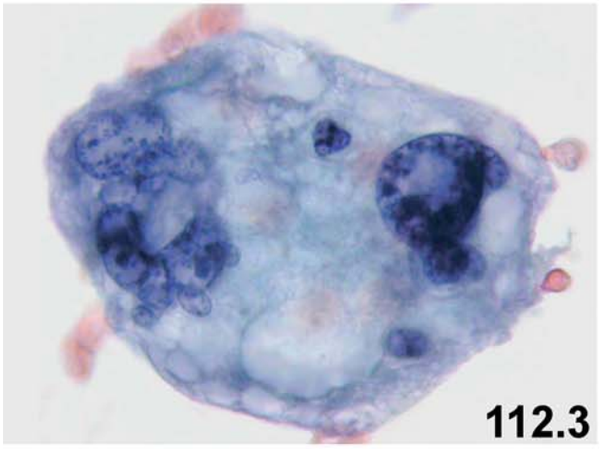
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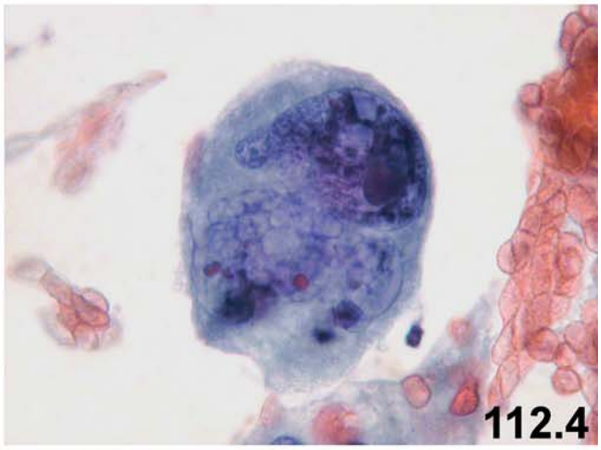
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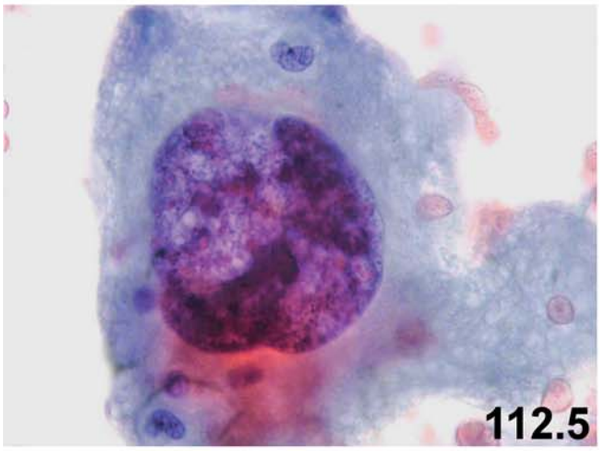
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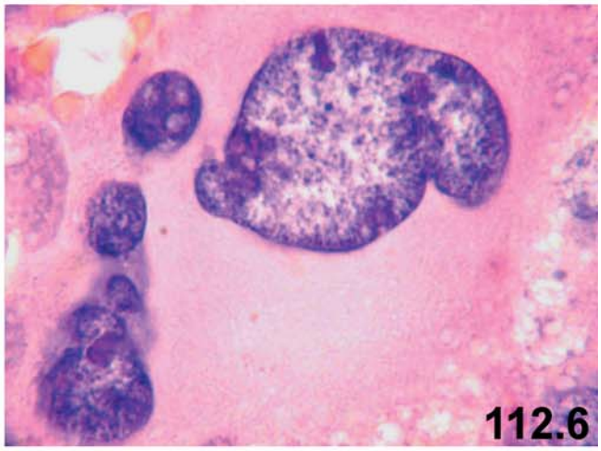
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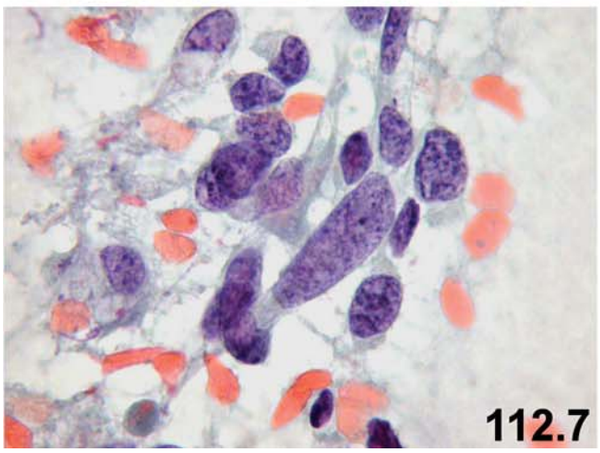
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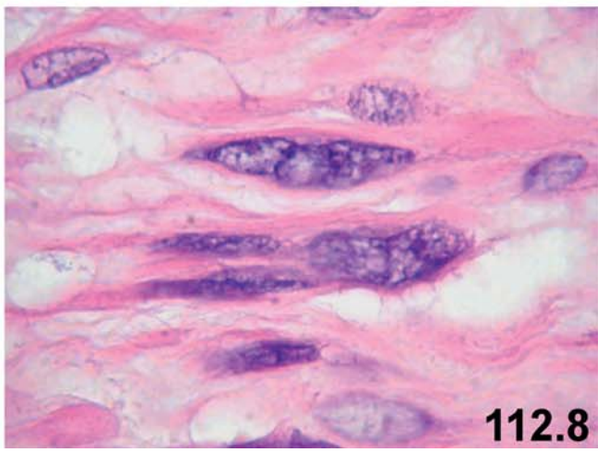
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Fig. 113: "Cold nodule" of the thyroid representing metastatic lobular carcinoma.

Case history: A 65-year-old woman with a history of invasive lobular carcinoma with signet-ring cell differentiation presented 5 years after the breast surgery with a firm, cold thyroid nodule. The thyroid nodule was 1.5 cm at its greatest diameter. Fine needle aspiration of the thyroid nodule was performed.

Fig. 113.1: Low magnification of the nodule shows loosely cohesive epithelial clusters and isolated cells.

Fig. 113.2: Isolated epithelial cells with round nuclei. Cells with eccentric nuclei are present.

Fig. 113.3: Higher magnification revealing relative uniform cells with scant cytoplasm. Note the large nuclei, which are four to five times larger than the erythrocytes in the background.

Fig. 113.4: Relatively uniform tumor cells with centrally or eccentrally located nuclei and regular chromatin distribution.

Fig. 113.5: Epithelial cells with linear (single file) arrangement showing occasional intracytoplasmic vacuoles or lumina.

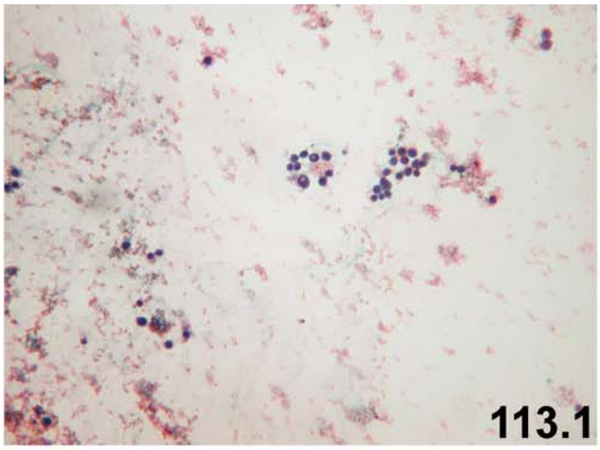
Fig. 113.6: Some of the tumor cells show intracytoplasmic vacuoles (lumina) containing eosinophilic inclusion (targetoid cells).

Fig. 113.7: Tumor cells with high nuclear-cytoplasmic ratio and centrally or eccentrally located nuclei. Some of the tumor cells show cytoplasmic pallor (mucin?).

Fig. 113.8: A careful search also reveals signet-ring tumor cells with hyperchromatic nuclei.

Fig. 113: Final remarks

- Fine needle aspiration cytology in this case is consistent with metastatic lobular carcinoma. Indeed, the breast carcinoma in this patient was of lobular type and showed a minimal component (less than 5%) with signet-ring cell differentiation (ILC with signet-ring cells). The histology of the thyroid nodule confirmed the above cytologic interpretation.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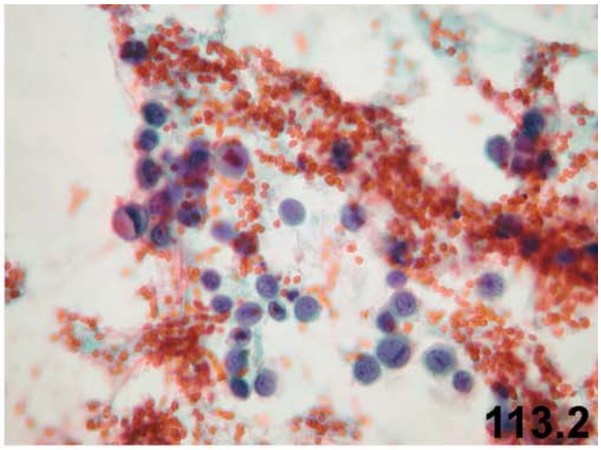
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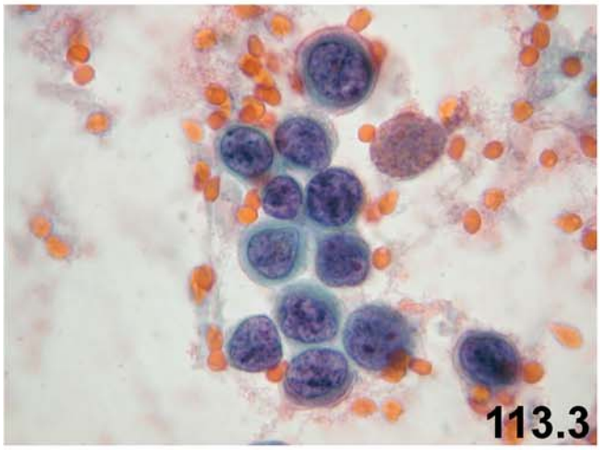
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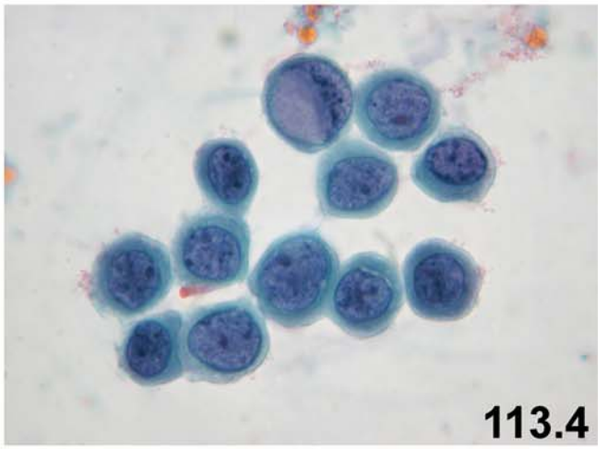
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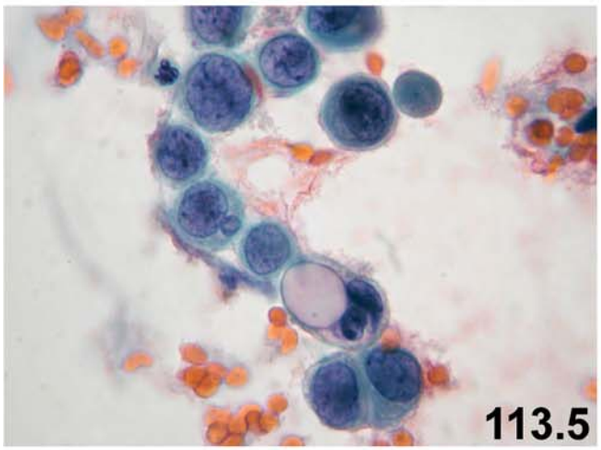
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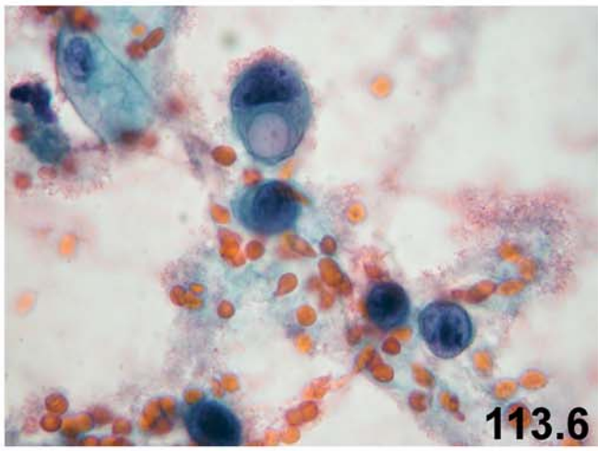
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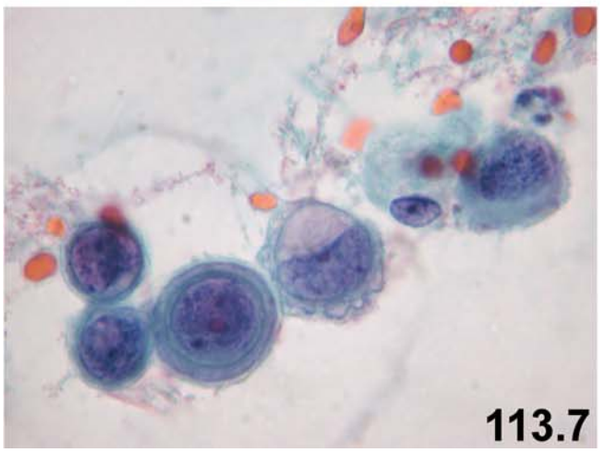
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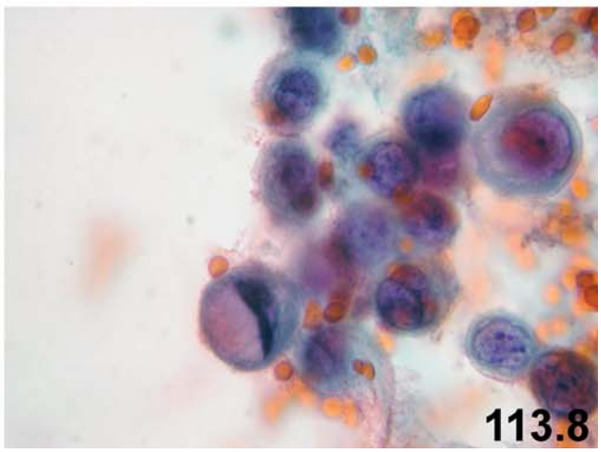

113.8

Fig. 114: Imprint cytology of sentinel lymph node showing metastatic carcinoma.

Case history: A 41-year-old woman presented with a moderately differentiated infiltrating ductal carcinoma diagnosed in needle core biopsy. Excisional biopsy revealed a 1.5-cm ductal carcinoma with infiltrating margins. Sentinel lymph node biopsy was performed and sent for frozen section examination. Touch imprint cytology of the cut surface of the sentinel node was also done. Imprint cytology was stained using the Diff-Quik method.

Fig. 114.1: Low magnification of sentinel node shows numerous normal lymphocytic cells.

Fig. 114.2: Low magnification shows numerous cohesive and isolated epithelial cells.

Fig. 114.3: Higher magnification reveals clusters of atypical epithelial cells. The atypical cells show eccentric nuclei. Note that epithelial cells have more cytoplasm compared with adjacent lymphocytic cells.

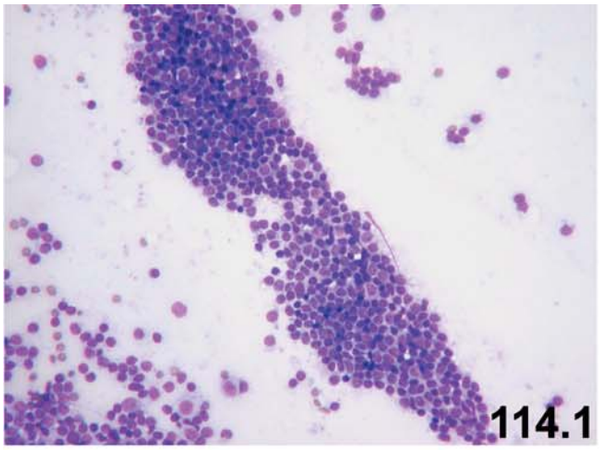
Fig. 114.4: A cluster of lymphocytic cells composed of small and medium-sized cells.

Figs. 114.5 and **114.6:** Epithelial cells with nuclear atypia showing enlarged, eccentric nuclei and abundant cytoplasm. Note the regular lymphocytic cells in the background.

Figs. 114.7 and **114.8:** Frozen section of the sentinel lymph node showing metastatic carcinoma (consistent with breast carcinoma).

Fig. 114: Final remarks

- Imprint cytology of sentinel lymph nodes is a rapid and reliable method with results comparable to those of frozen section examination. In cases of micrometastases, however, both methods may show false negativity. Note that recognition of small and uniform tumor cells can be very difficult in imprint cytology, particularly in metastatic lobular carcinoma.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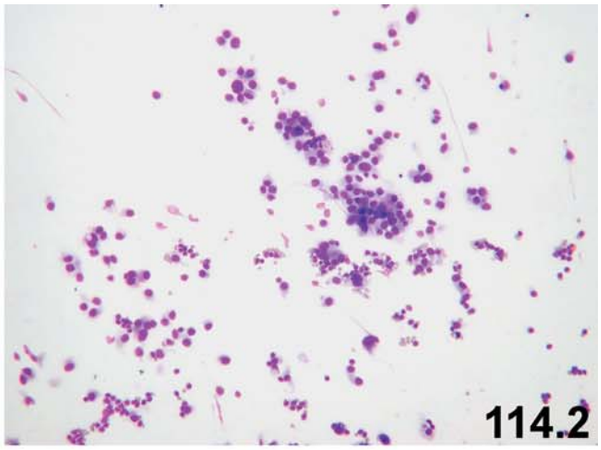
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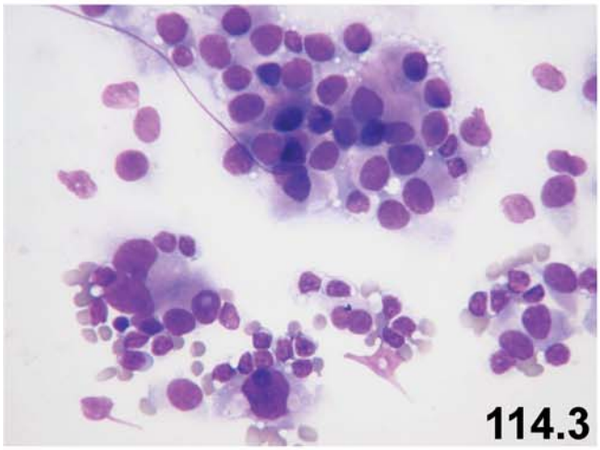
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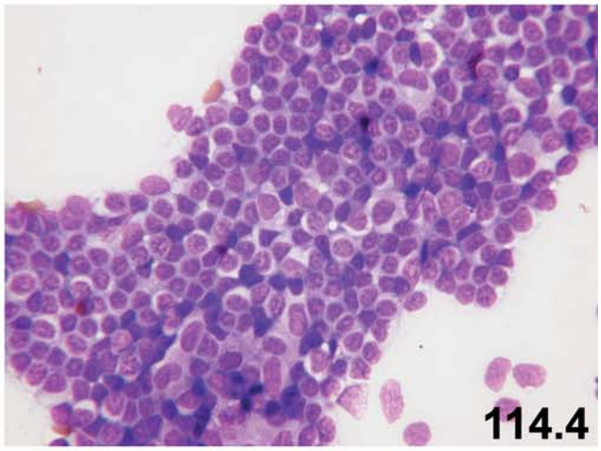
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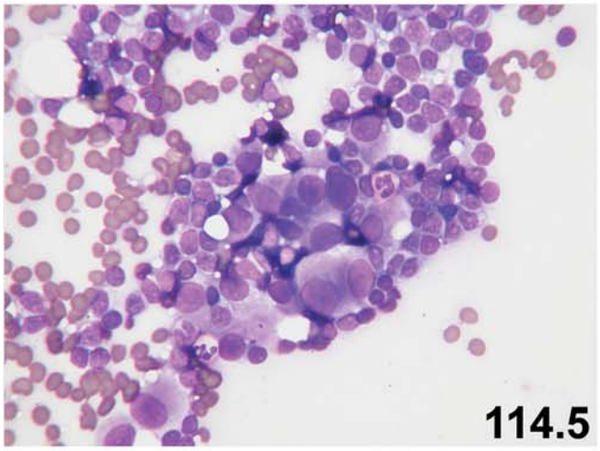
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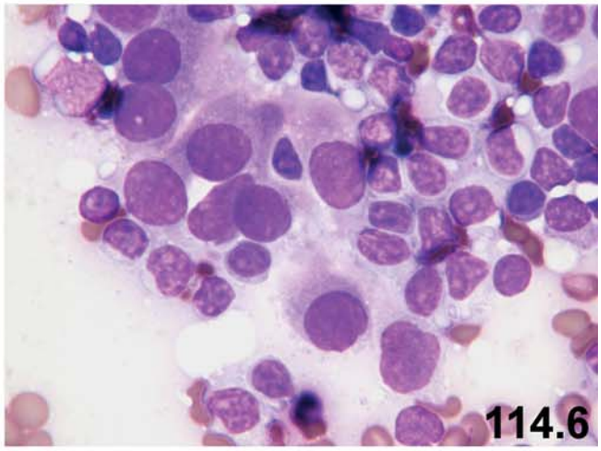
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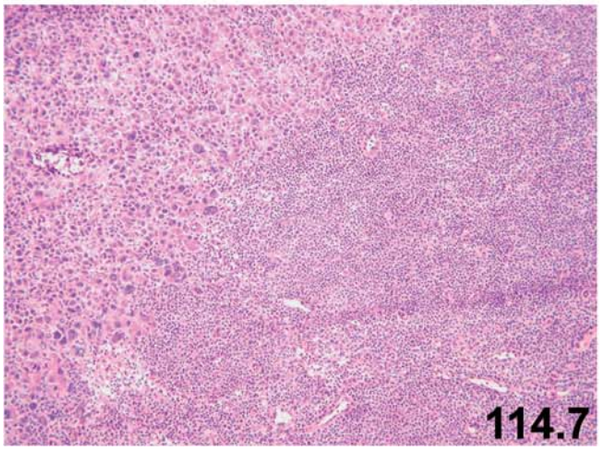
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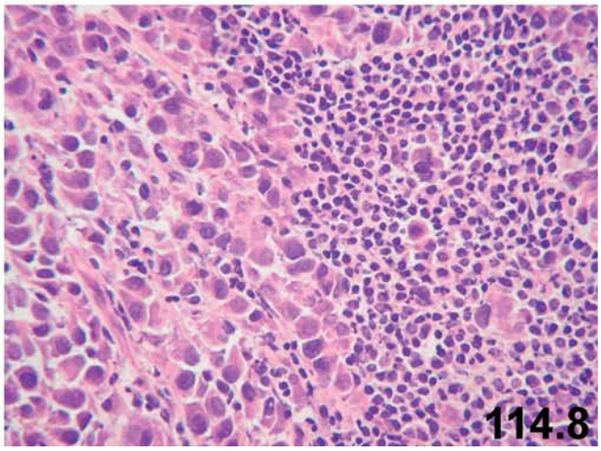
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Immunohistochemistry (Selected Topics)

Contents

CHAPTER 18 Immunohistochemistry (Selected Topics)

18.1 Role of Immunohistochemistry in Diagnostic Breast Pathology

As a general rule, immunohistochemistry cannot and should not replace the histopathology. It is, however, a valuable adjunct in diagnosing breast pathology (Fig. 115).

18.2 Immunohistochemistry in the Differential Diagnosis of Epithelial Lesions: Myoepithelial Cells

Recognition of myoepithelial cells in a variety of conditions is crucial for correct interpretation:

- Distinguishing benign non-neoplastic proliferative lesions such as the various forms of adenosis from carcinoma.
- Distinguishing intraepithelial neoplasia (ductal carcinoma in situ [DCIS], lobular carcinoma in situ [LCIS]) from invasive carcinoma.
- Distinguishing pseudoinvasive lesions from invasive carcinomas, such as intraepithelial neoplasia involving sclerosing adenosis and radial scar.
- Distinguishing intraductal papilloma from intraductal papillary carcinoma.
- Determining microinvasion in intraepithelial neoplasia such as ductal intraepithelial neoplasia (DIN; DCIS) and lobular intraepithelial neoplasia (LIN; LCIS).
- Identifying myoepithelial cell differentiation in metaplastic (sarcomatoid) breast carcinoma (metaplastic carcinoma with myoepithelial differentiation or myoepithelial carcinoma).

Caution

- In all of these conditions, it is the presence of a myoepithelial cell layer in close relationship with the epithelial cells that determines the differences between intraepithelial neoplasias (in situ carcinomas) and invasive tumors and between benign pseudoinvasive lesions and invasive carcinomas. Microglandular adenosis, a distinct infiltrative type of adenosis, is the only known benign breast lesion that lacks a myoepithelial cell layer.

- Myoepithelial cells can be easily identified in normal breast ductules and acini, but when these structures dilate and fill with intraluminal proliferating cells or are compressed, it can be difficult to recognize the attenuated myoepithelial cells. A careful search at higher magnification, however, reveals the presence or absence of myoepithelial cells in the vast majority of cases.
- Currently, several available markers reliably identify myoepithelial cells. These markers include smooth muscle actin (SM actin); muscle-specific actin (MS actin); calponin; smooth muscle myosin, heavy chain (SMMHC); CD10; and p63 [15, 20, 22, 24, 36, 39].
- It is important to note that antibodies to S100 protein often decorate myoepithelial cells, but they also react with some luminal epithelial cells. Antibodies to cytokeratins such as CK34BE12 (also known as K-903), CK5/6, CK14, and CK17 identify myoepithelial cells, but they also immunostain some of the luminal epithelial cells in the mammary ducts and acini. Anti-SM actin reacts with stromal myofibroblasts in addition to myoepithelial cells and thus is not specific for myoepithelial cells. The cross-reaction with myofibroblasts makes it difficult to identify myoepithelial cells, particularly in DIN (DCIS), in which there may be stromal desmoplasia around the involved ducts. MS actin (clone: HHF-35) often decorates myoepithelial cells, but there is substantial cross-reaction with stromal myofibroblasts.
- Calponin and SMMHC are two markers that very often (but not always) detect myoepithelial cells and, compared with SM actin or MS actin, rarely react with desmoplastic stromal myofibroblasts.
- The marker p63 is probably one of the most sensitive and specific myoepithelial cell markers in the breast. It belongs structurally, but not functionally, to the p53 family. A characteristic positive nuclear stain with antibody against p63 is evident in myoepithelial cells (breast, salivary glands), basal cells (prostate, skin), and transitional cells (urothelium) [24, 39, 45].
- CD10 (also known as CALLA) is also a highly sensitive and specific marker for myoepithelial cells in the breast. Maspin and CD29 also represent recent markers for myoepithelial cells [12, 21b, 25].
- 14-3-3 sigma and nerve growth factor receptor (NGFR/p75(NTR)) are two recently introduced myoepithelial markers [25, 39b].

Caution

- The immunohistochemical reaction of myoepithelial cells depends on the differentiation and functions of such cells. A negative immunoreaction (for example, with antibodies against SM actin or SM myosin) by no means excludes the presence of myoepithelial cells! One needs to rely on the microscopic impression and should try again with other markers such as p63 or CD10. If myoepithelial cells are present, one of these markers will decorate them.
- It is important to keep in mind that a continuous or discontinuous layer of myoepithelial cells is often present at the periphery of DIN (DCIS). Therefore, the peripheral location of myoepithelial cells does not exclude the diagnosis of DIN (DCIS)!
- Although the presence of a continuous layer of myoepithelial cells is characteristic of intraductal papilloma, the absence of myoepithelial cells is diagnostic for intraductal papillary carcinoma. On the other hand, the presence of myoepithelial cells does not exclude the possibility of a papillary intraductal carcinoma.

18.3 Carcinomas with Myoepithelial Differentiation Versus Primary Sarcoma

- Sarcomatoid (metaplastic) carcinomas of the breast often show a myoepithelial cell differentiation. The tumor cells are usually positive for high molecular weight cytokeratins (HMW-CKs) or basal-type CKs such as CK5/6, CK14, CK17, and CK34BE12. The tumor cells in sarcomatoid carcinomas often display positive immunoreactivity for at least some of the myoepithelial markers, including SMA, p63, CD10, 14-3-3 sigma, and NGFR/p75. The above-mentioned immunoreaction of tumor cells is usually heterogeneous and focal.
- In contrast, primary sarcomas of the breast (NOS-type) are negative for a variety of CKs (including pancytokeratin, CK5/6, CK14, and CK34BE12). But some of the myoepithelial markers such as CD10, p63, and SM actin can be positive in NOS-type sarcomas.

Caution

- A primary sarcoma of the breast is extremely rare and should not be diagnosed without immunohistochemical examination for a variety of cytokeratins (pancytokeratin, CK5/6, CK14, CK34BE12).

18.4 Microinvasive Carcinoma (Fig. 116)

Microinvasive carcinoma is defined as a tumor in which the dominant lesion is noninvasive but shows one or more clearly separate small microscopic foci of infiltration into the breast stroma. With regard to the size of microinvasion, there is no universally accepted definition.

The definition according to the TNM (UICC) classification [44b] is one or more areas of stromal infiltration not exceeding 1 mm in diameter. The recent WHO guidelines (2003) [47c] offer, in addition to the TNM definition, an alternative size limit for microinvasive breast carcinoma: "A single focus of invasion no larger than 2 mm in maximum dimension or two to three foci, none exceeding 1 mm in maximum dimension" [47c]

Caution

- The size definition of microinvasive carcinoma is arbitrary. It is not clear why the TNM defines the upper size limit of microinvasive breast carcinoma as 1 mm, while the upper size limit of micrometastasis of breast carcinoma in lymph nodes is defined as 2 mm in diameter.

Immunohistochemistry can be helpful for detecting microinvasion:

Antibody against collagen type IV: Lack of basal lamina in invasive carcinoma (a discontinuous layer can be present).

Antibodies to myoepithelial cells: Lack of positive reaction in small infiltrating epithelial cells. Isolated tumor cells or small clusters of microinvasive carcinoma are CK-positive!

Caution

- If there is doubt about the presence of microinvasion, the case should be classified as noninvasive (DIN; DCIS).
- A discontinuous layer of basal lamina (collagen type IV) around neoplastic glands does not automatically mean invasion because DIN (DCIS) can also show incomplete basal lamina.

18.5 Cell Population in Intraductal Proliferative Lesions: Homogeneous Versus Heterogeneous Cell Population (Neoplasia Versus Hyperplasia)

- The luminal epithelial cells (ducts, lobules) are characteristically positive for low molecular weight cytokeratins (LMW-CKs) such as CK8, CK18, and CK19. These cytokeratins are, however, rarely positive in myoepithelial cells.
- HMW-CKs show a heterogeneous positive reaction in some of the normal epithelial and myoepithelial cells. There are HMW-CKs such as CK34BE12, containing CKs 1, 5, 10, and 14, and monoclonal HMW-CKs such as CK5/6 or CK14. While in usual ductal hyperplasia an intense positive immunoreaction of HMW-CK (CK34BE12 or CK5/6) is always present, the vast majority of cases with DIN (DCIS) are either completely or predominantly negative for HMW-CK (almost 85–90% of cases are negative for HMW-CK). *Note that CK5/6 is more specific than CK34BE12* [12, 28, 35]

- LMW-CK is positive in hyperplasia and neoplasia! (Therefore, it is not useful for distinguishing different intraductal lesions).
- Atypical ductal hyperplasia shows the same type of immunoreactivity for HMW-CK as that of DCIS [12, 28].
- In a difficult case with florid intraductal proliferation, immunohistochemistry can identify whether the cell population in the proliferative zone is homogeneous (one cell type of epithelial cells without a modified myoepithelial cell component) or heterogeneous (mixed cell types of epithelial and modified myoepithelial cells). While an intense positive reaction for HMW-CK is characteristic for intraductal hyperplasia (due to a heterogeneous cell population), the absence of such an immunoreaction is highly suggestive of a neoplastic intraductal proliferation (atypical ductal hyperplasia/DCIS or DIN). The absence of HMW-CK reaction in the proliferative zone of DIN is due to the absence of modified myoepithelial cells among the proliferating luminal cells. One needs to keep in mind that a minority of DCIS lesions (10–15%) can be focally or diffusely positive for HMW-CK!
- While the lack of HMW-CK (CK5/6 or CK34BE12) is a characteristic feature of intraductal papillary carcinomas, intraductal papillomas with or without hyperplasia typically express HMW-CK.

18.6 Paget's Disease

- The highly atypical neoplastic epithelial cells are characteristically positive for LMW-CK (CK8, CK18, CK19) but completely negative for HMW-CK (CK34BE12 and CK5/6).
- The tumor cells are characteristically positive for CK7.
- Other markers such as GCDF-15 (BRST2) and CEA are usually positive. Paget cells are negative for S100 protein. The vast majority of cases of Paget's disease are negative for estrogen and progesterone receptors but positive for androgen receptors. The tumor cells overexpress HER2/neu in the vast majority of cases.
- MUC1 is another useful marker that is always positive in Paget's disease.

18.7 Distinction Between DIN (DCIS) and LIN (LCIS)

- DIN and LIN can often be separated based on their morphologic features. Occasionally however, the distinction can be difficult (intraepithelial neoplasia, not otherwise specified, or with combined features). In such situations, immunohistochemical examination for E-cadherin in combination with CK34BE12 can be helpful [8].

	E-cadherin:	CK34BE12 (HMW-CK):
DIN (ADH/DCIS)	positive	mostly negative
LIN (ALH/LCIS)	negative	mostly positive

Note that the tumor cells of both DIN (DCIS) and LIN are negative for CK5/6.

Mammary intraepithelial neoplasia, NOS type:
Both E-cadherin and CK34BE12 negative: negative hybrid lesion.
Both E-cadherin and CK34BE12 positive: positive hybrid lesion.

18.8 Systemic Metastasis of Breast Carcinoma

GCDFP is found in abundance in breast cystic fluid and any cell type that has apocrine features. Homologous-appearing carcinomas of the breast, skin adnexa (sweat glands, apocrine glands), and salivary glands demonstrate positive immunostaining for GCDFP-15 (BRST2). Aside from these immunoreactivities, most other carcinomas show no appreciable immunostaining [47b, 51].

Caution

- Estrogen and progesterone receptors can be positive in a variety of adenocarcinomas. Therefore, the positive immunoreaction for estrogen and progesterone receptors in a tumor cannot be used as evidence of a metastatic breast carcinoma.
- Primary signet-ring cell carcinomas of the breast are positive for CK7 but negative for CK20. In contrast, signet-ring cell carcinomas of the gastrointestinal tract are usually positive for CK20 but negative for CK7.
- Primary breast carcinoma in a male patient can be positive for prostate-specific antigen (PSA). Positivity for PSA should therefore not be used as evidence for metastatic prostate carcinoma.

18.9 Micrometastatic Disease in Axillary Lymph Nodes (Including Sentinel Nodes)

Micrometastatic disease in axillary lymph nodes is defined (TNM) [44b] as metastatic carcinoma larger than 0.2 mm but less than or equal to 2 mm. Isolated tumor cells or very small aggregates of metastatic tumor cells up to 0.2 mm in diameter are considered isolated tumor cells (pN0, i+) and, currently, should be separated from micrometastasis [44b].

Cytokeratin immunostaining (pancytokeratin, clone MNF116) of sentinel lymph nodes that are negative on sections stained with hematoxylin and eosin can be used to identify "hidden" micrometastasis or isolated tumor cells. However, it is currently not mandatory to perform immunohistochemistry (cytokeratin) on sentinel lymph nodes [17, 19].

Caution

- Dendritic cells in axillary lymph nodes often show a mild to moderate cytoplasmic reaction for pancytokeratin.
- The clinical significance of isolated tumor cells and submicrometastasis in sentinel nodes is uncertain. Currently, isolated tumor cells and very small aggregates of epithelial cells ⩽0.2 mm are classified as pN0 (i+).

18.10 Immunohistochemistry for Prognostic or Predictive Factors in Breast Carcinoma: Hormone Receptors

- Currently, several monoclonal antibodies against estrogen receptor (ER) and progesterone receptor (PR) can reliably be used in formalin-fixed, paraffin-embedded breast tissues. Quantification of results of immunohistochemistry for ER and PR is an issue of some controversy [2, 3, 17, 19, 21, 31, 33, 37, 41–43, 48]. While some authors set a positive ER or PR result at greater than or equal to 5% nuclear staining, many others define a positive result at a minimum of 10% nuclear staining [33, 37, 48]. Studies have shown that clinical response correlates with the value of 10% nuclear staining as a cutoff [33, 37]. *In contrast, some recent studies have reported that even patients with 1% positive staining for ER/PR benefit from antihormonal treatment* [2, 12, 13, 16, 19, 31].
- There are legitimate concerns worldwide that ER immunohistochemical testing methodologies are insufficiently standardized and that clinically significant false-negative rates exist.
- Some scoring systems have attempted to incorporate both tumor cell staining percentages and nuclear staining intensity into a single score. But no study has convincingly demonstrated the clinical importance of measuring (or attempting to quantify) ER staining intensity or heterogeneity.
- The American Society of Clinical Oncology has issued consensus panel statements supporting the use of a three-tiered categorization of ER staining percentages (using percentages as low as 1%) that acknowledges the existence of both "positive" and "low-positive" cases. Additionally, the National Institutes of Health Consensus Statement on Adjuvant Therapy for Breast Cancer also states that *any degree of ER nuclear staining detected by immunohistochemistry should be considered a positive result* [2, 19].

Caution

- If immunohistochemistry for ER and PR is negative in a core needle biopsy, it should be repeated on the excisional breast specimen.
- No internationally accepted definition currently exists regarding the cutoff level for immunohistochemistry positive ER and PR. However, several recent studies and reports consider any positive nuclear ER or PR immunostaining a positive result.
- Nuclear staining for PR by the immunohistochemistry method is usually more heterogeneous than ER and may be a cause of false-negative results.

18.11 HER2/neu Overexpression

- Several studies have shown that HER2/neu overexpression is an independent prognostic and predictor factor in breast carcinoma. Particularly, HER2/neu positive breast cancers with metastatic lymph nodes behave very aggressively. The prognostic role of HER2/neu in node-negative breast carcinoma, is, however, controversial. The current clinical use for the HER2/neu status in the treatment of breast cancer patients is twofold: (1) as a predictor of response to chemotherapy, especially for doxorubicin, and (2) to determine which patients would respond to monoclonal antibody therapy (Herceptin) [4, 7, 9, 29, 30, 34].
- While fluorescence in situ hybridization (FISH) detects gene amplification, immunohistochemistry detects gene product overexpression. Both methods can be performed on frozen and formalin-fixed tissues, as well as on cytologic preparations (FNA, touch imprint). There is a high concordance between FISH and immunohistochemistry [23].
- The scoring method follows from the Food and Drug Administration-approved Hercep Test Kit (Dako). Using immunohistochemistry with monoclonal antibody against HER2/neu receptor, a positive result is interpreted as 3+, which is characterized by strong, complete cell membrane ("chicken wire") staining. While an immunoscore of 2+ is defined as weak to moderate, mostly incomplete cell membrane reactivity, a score of 1+ represents a weak, cytoplasmic, and/or incomplete cell membrane reaction. *Using immunohistochemistry, at least 10% of tumor cells should reveal a score of 3+ in order to be reported as HER2/neu overexpression.*

Caution

- In breast carcinomas that are 2+ by immunohistochemical examination, or in the grey zone between 2+ and 3+, FISH for HER2/neu needs to be performed. Only cases with 3+ immunoreaction or 2+ cases that show amplification by FISH are considered positive for HER2/neu.
- Immunocytochemistry and FISH can easily and reliably be performed on touch imprint cytologic specimens of core needle or excisional breast biopsies.

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Fig. 115: Selected examples of immunohistochemistry in breast pathology.

Fig. 115.1: Immunohistochemistry of normal lobules with antibody against smooth muscle actin decorating a continuous layer of myoepithelial cells.

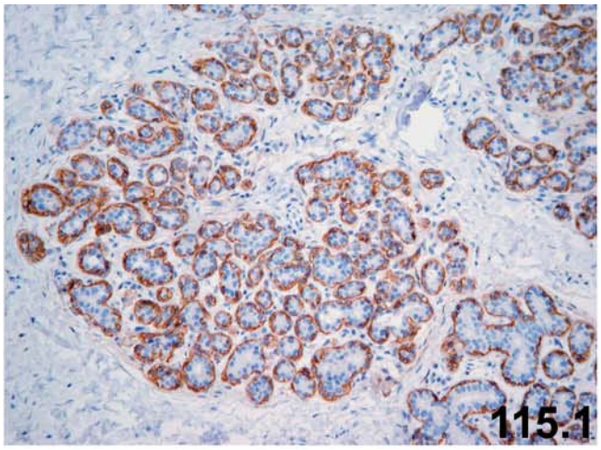
Fig. 115.2: Immunohistochemistry of myoepithelial cells with antibody against CD10.

Fig. 115.3: Myoepithelial cells within small ducts expressing p63.

Fig. 115.4: Positive immunoreaction of myoepithelial cells for calponin.

Figs. 115.5 and **115.6:** A case with a pseudoinvasive area closely mimicking invasive ductal carcinoma. Indeed, several pathologists were seriously concerned about (or made a definitive diagnosis of) carcinoma. The haphazardly arranged tubules, however, contain myoepithelial cells, as demonstrated by immunohistochemistry for p63 (Fig. 115.6). Several other markers including smooth muscle actin and CD10 were also positive in pseudoinvasive glands.

Figs. 115.7 and **115.8:** A case of intraductal papilloma with prominent myoepithelial hyperplasia (papillary type of adenomyoepithelioma) showing intense and almost diffuse reaction for smooth muscle actin (Fig. 115.7) and smooth muscle myosin, heavy chain (Fig. 115.8).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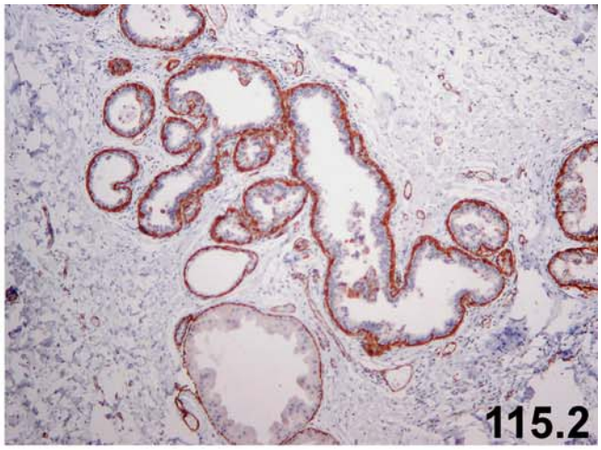
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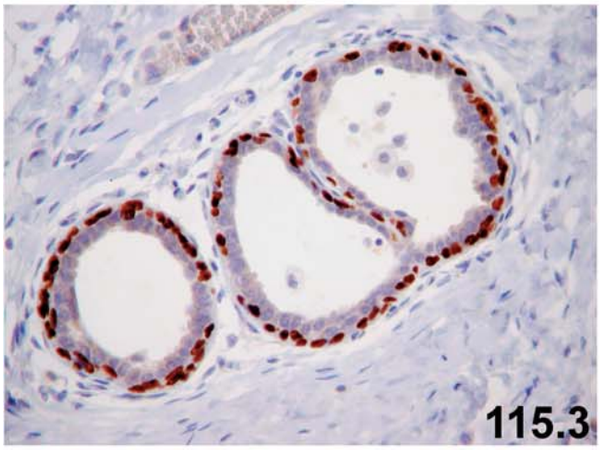
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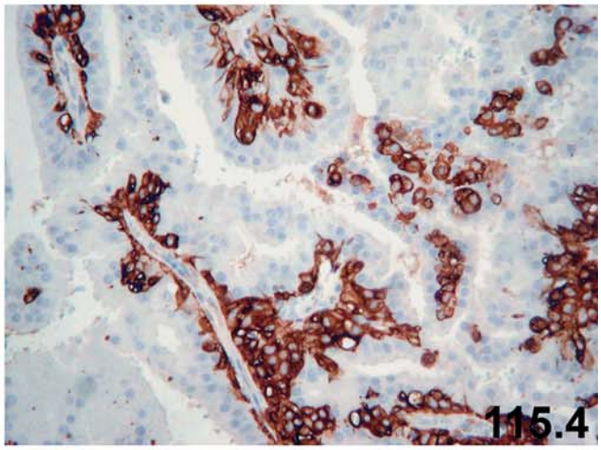
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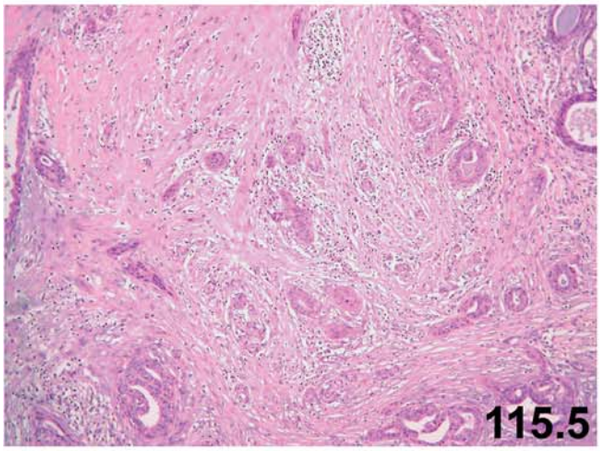
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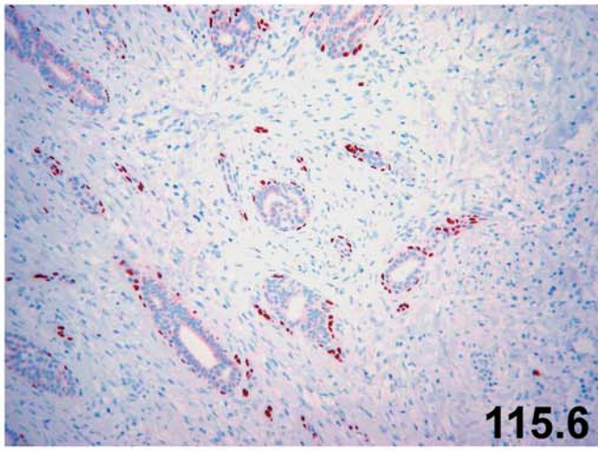
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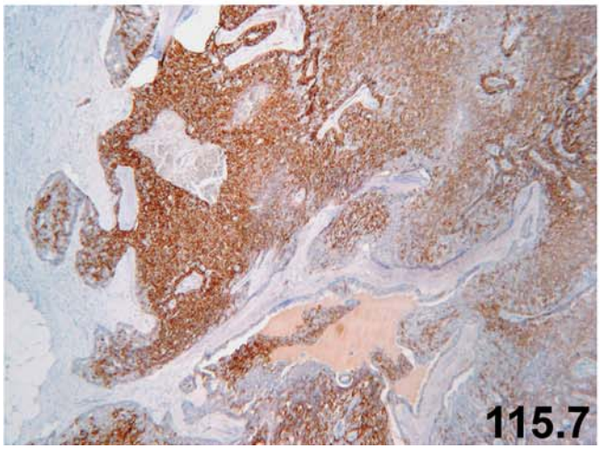
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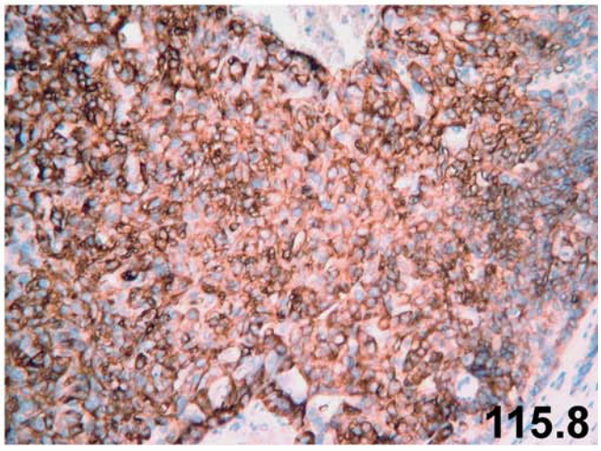
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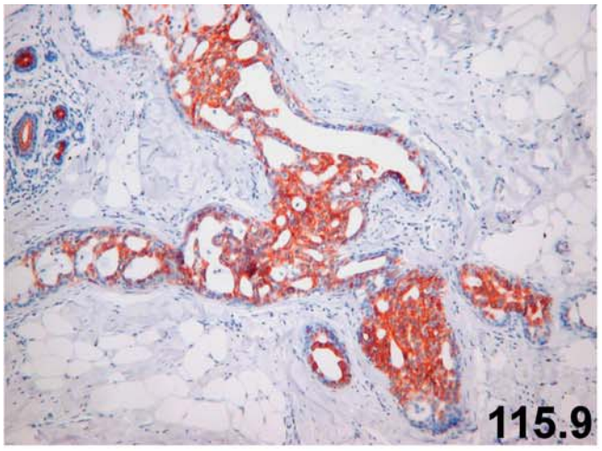
Figs. 115.9 and **115.10:** Immunohistochemistry of usual ductal hyperplasia (UDH) for high molecular weight cytokeratin (HMW-CK). The proliferating cells in UDH are characteristically positive for CK5/6. Other HMW-CKs such as CK14, CK17, and CK34BE12 are also typically positive in UDH. Note that the positive reaction in UDH can be diffuse or heterogeneous (mosaic pattern).

Figs. 115.11, 115.12, 115.13, and **115.14:** A difficult case of usual ductal hyperplasia (UDH) associated with prominent central necrosis. The presence of central necrosis and prominent intraductal proliferation in this complex case (which showed pseudoinvasion elsewhere) caused major diagnostic problems for several pathologists. Note the irregularity of secondary lumens and the heterogeneous cell population of proliferating cells characteristic for UDH. It must be kept in mind that luminal necrosis by no means excludes UDH. Immunohistochemistry for CK5/6 shows a diffuse positive reaction of intraductal proliferating cells (Figs. 115.13 and 115.14). The immunohistochemistry in this case is supportive of ductal hyperplasia associated with unusual prominent central necrosis.

Figs. 115.15 and **115.16:** A case with ductal intraepithelial neoplasia (DIN, DCIS) with micropapillary and cribriform growth patterns. Focally, there is an area with central necrosis (DIN2 or DCIS, G2; Fig. 115.15). CK5/6 is completely negative in intraductal neoplastic cells (Fig. 115.16). A negative immunoreaction for high molecular weight cytokeratins (CK5/6, CK14, CK17, CK34BE12) can be seen in the vast majority of cases with DIN (DCIS). In contrast, usual ductal hyperplasia is always positive for high molecular weight cytokeratins.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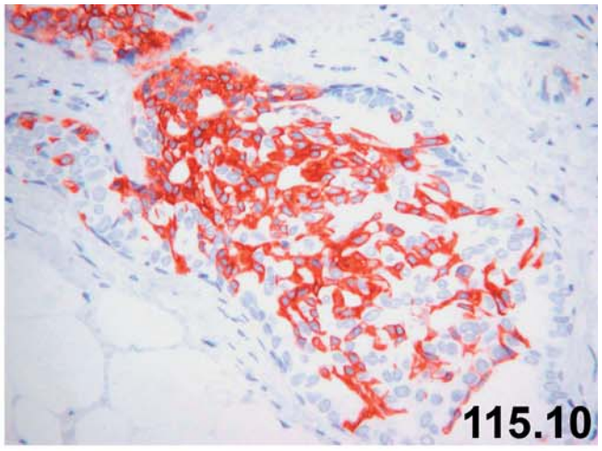
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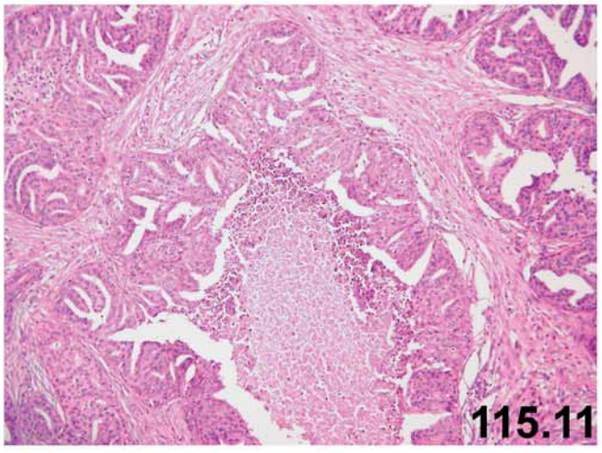
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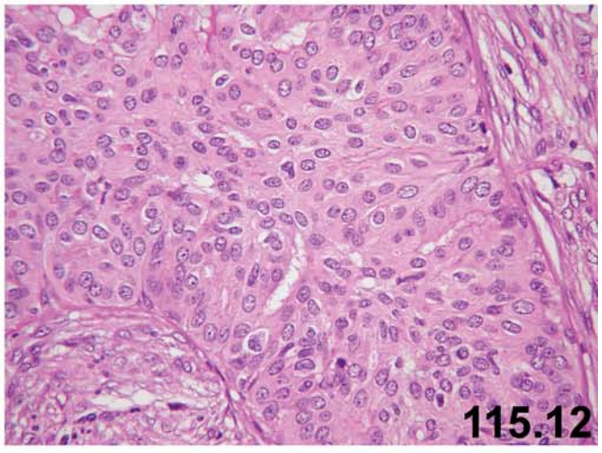
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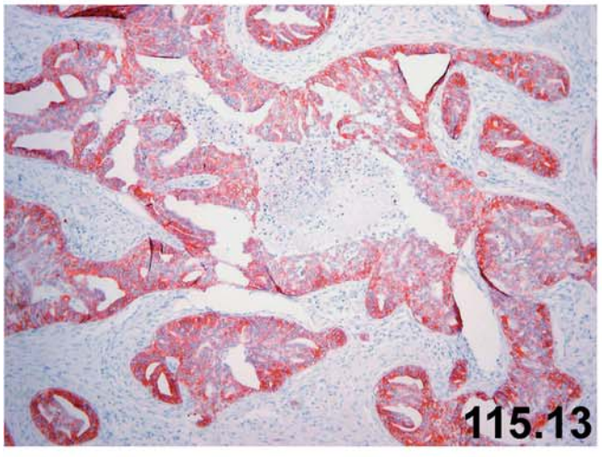
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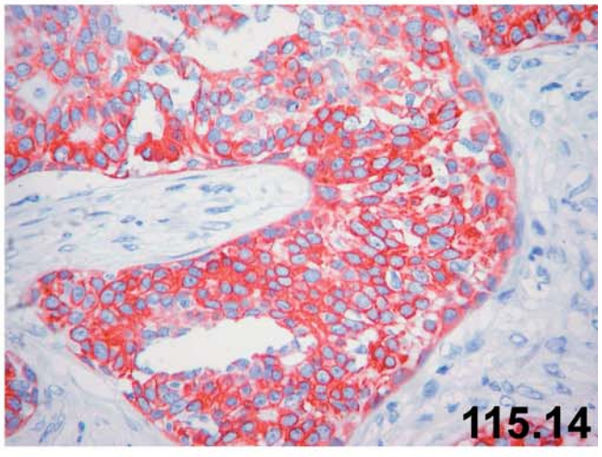
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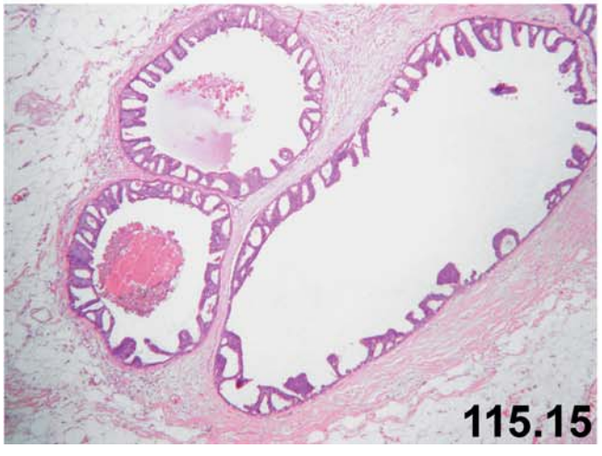
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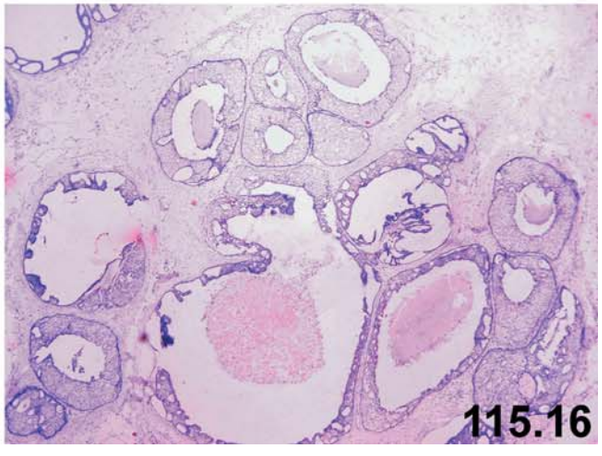
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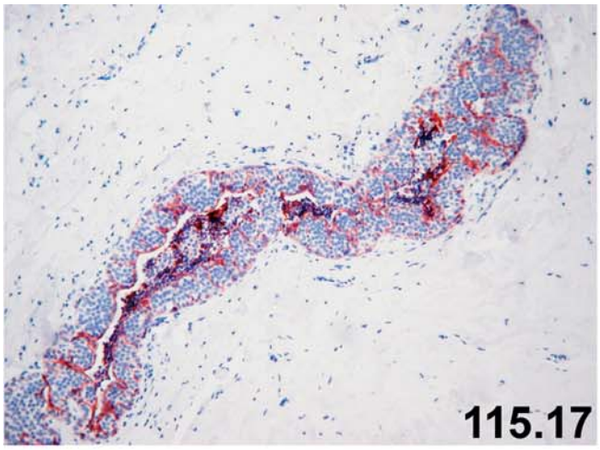
Figs. 115.17, 115.16, 115.17, and **115.18:** The neoplastic cells of lobular intraepithelial neoplasia (LIN) are typically negative for E-cadherin (Fig. 115.17), but they show a positive immunoreaction for CK34BE12 (Fig. 115.18). The immunohistochemistry of LIN is in contrast to that of DIN (DCIS), which is positive for E-cadherin but negative for CK34BE12. Note the perinuclear or cap-like positive reaction of neoplastic cells (Figs. 115.19 and 115.20). One must keep in mind that CK5/6 or CK14 is, however, negative in neoplastic cells of LIN. Therefore, CK5/6 or CK14 cannot be used for distinguishing between LIN and DIN (DCIS).

Figs. 115.21, 115.22, 115.23, and **115.24 (**see also **Figs. 115.25** and **115.26):** A difficult case of lobular intraepithelial neoplasia associated with central necrosis. The solid growth pattern of neoplastic cells and the presence of central necrosis closely mimic DIN (DCIS; Figs. 115.21, 115.22, and 115.23). Note that the neoplastic cells are positive for CK34BE12 (Fig. 115.24).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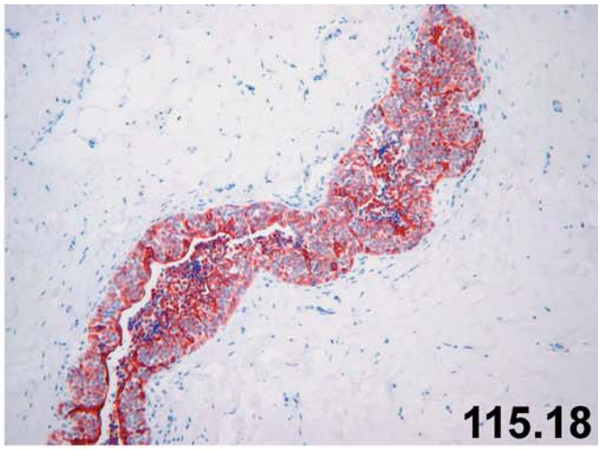
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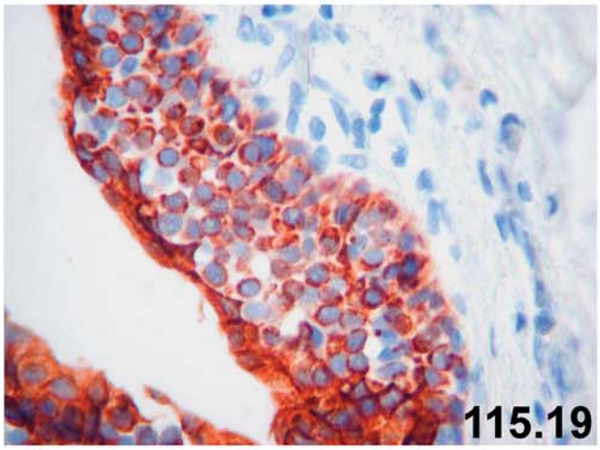
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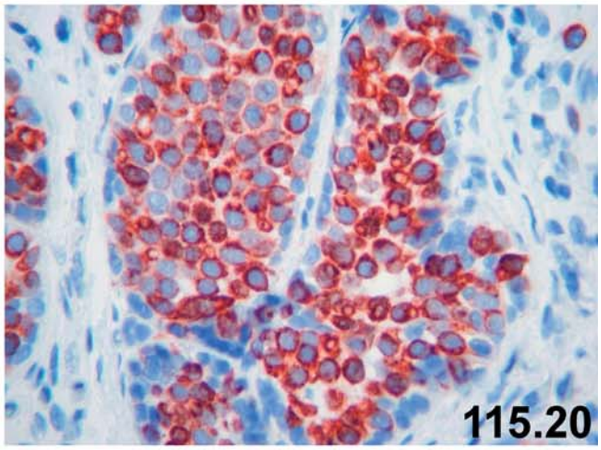
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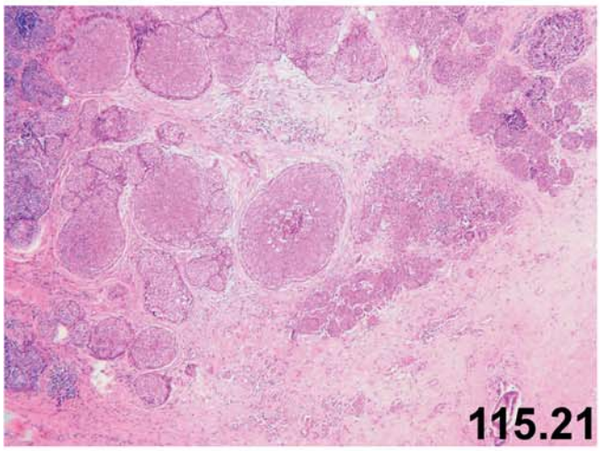
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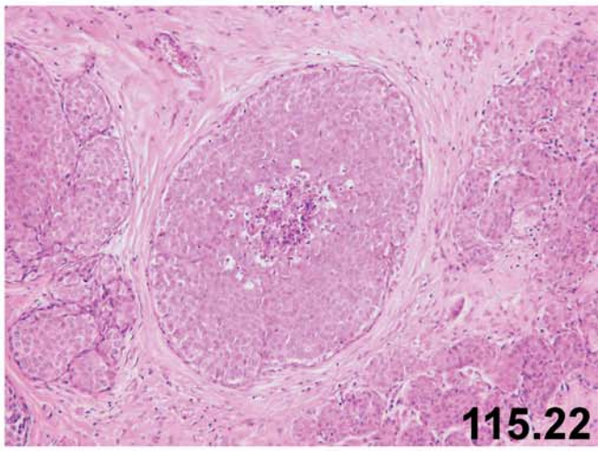
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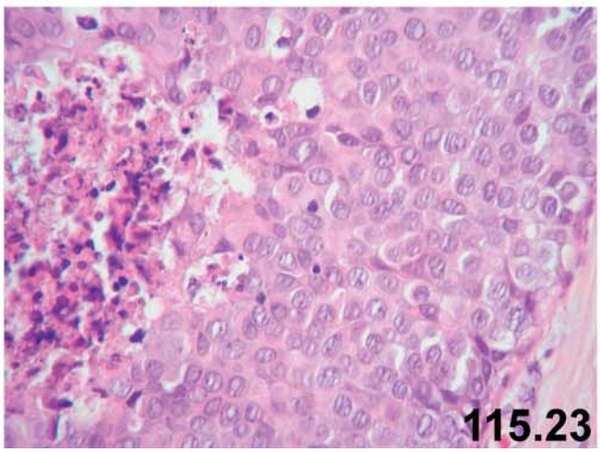
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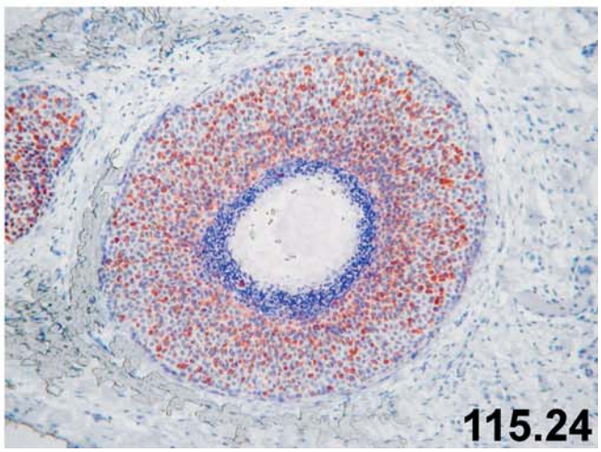
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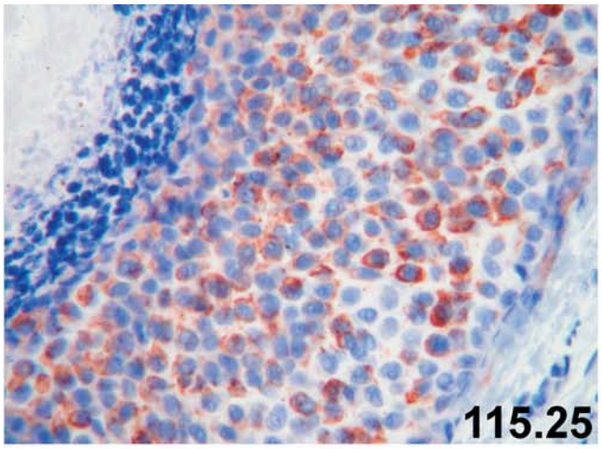
Figs. 115.25 and **115.26:** Higher magnification of immunohistochemistry for CK34BE12 reveals a typical perinuclear or cap-like positivity (Fig. 115.25). In contrast to DIN (DCIS), the neoplastic cells in this case are negative for E-cadherin (Fig. 115.26). The results of immunohistochemistry (negative immunoreaction for E-cadherin and positivity for CK34BE12) are in agreement with lobular intraepithelial neoplasia (LIN). Indeed, this case represents a rare example of LIN that is associated with central necrosis.

Figs. 115.27 and **115.28:** A case of sarcomatoid (metaplastic) carcinoma composed of spindle cells. The neoplastic spindle cells show a fibrosarcomatous growth pattern and can easily be confused with a sarcoma (Fig. 115.27). In such cases, immunohistochemistry for several cytokeratins and myoepithelial markers should be done. The neoplastic cells in this case show a positive reaction for CK5/6 (Fig. 115.28). Other high molecular weight cytokeratins or basal-type cytokeratins such as CK14, CK17, and CK34BE12 were also positive in this case (not shown). Based on the results of immunohistochemistry, this tumor would qualify as a „basal-like" carcinoma. The neoplastic spindle cells in this case, however, also showed positive immunoreaction for several myoepithelial markers such as CD10, smooth muscle actin, p63, S100 protein, and CD29. One should keep in mind that many cases of so-called basal-like carcinoma also express at least some myoepithelial markers. Indeed, the vast majority of sarcomatoid (metaplastic) carcinoma of the breast show myoepithelial differentiation when several myoepithelial markers are immunohistochemically examined. Furthermore, the positive reaction for basal-type cytokeratins is a common finding in sarcomatoid breast carcinoma.

Figs. 115.29, 115.30, 115.31, and **115.32 (**see also **Figs. 115.33** and **115.34):** Another case of metaplastic carcinoma that shows myoepithelial differentiation. The neoplastic cells display cordlike or fascicular arrangements (Figs. 115.29 and 115.30). The tumor cells are focally positive for smooth muscle actin (Fig. 115.31). The neoplastic cells are positive for CK5/6 (Fig. 115.32).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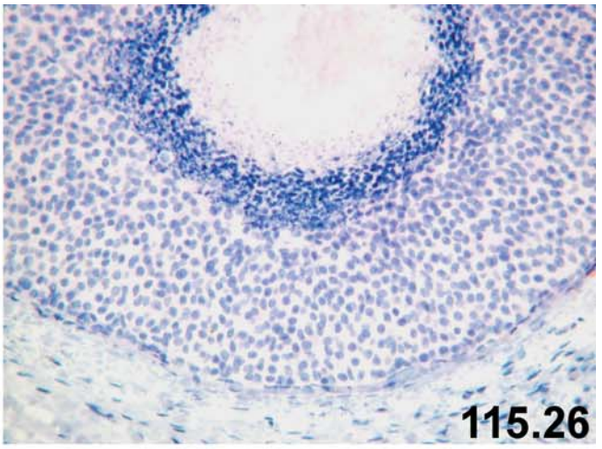
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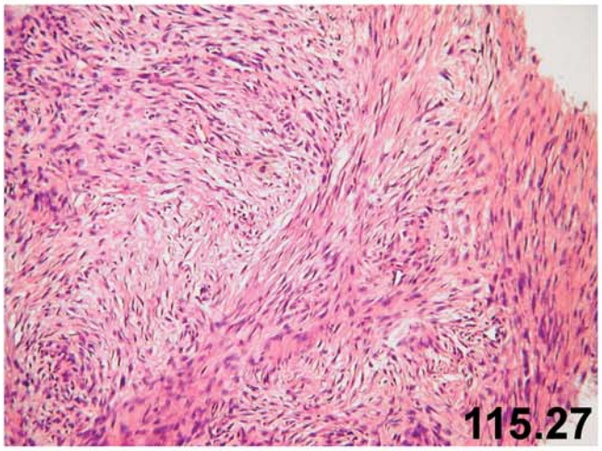
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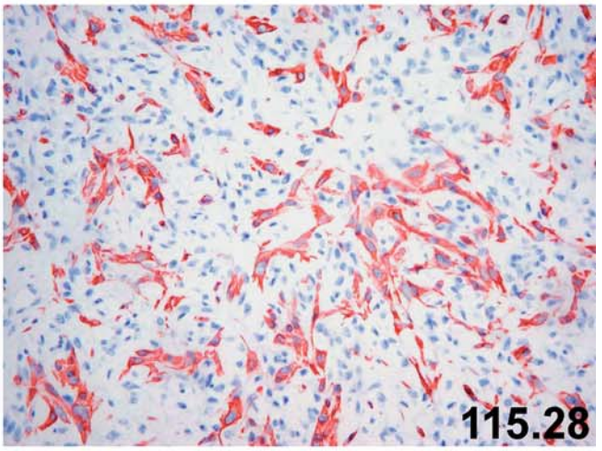
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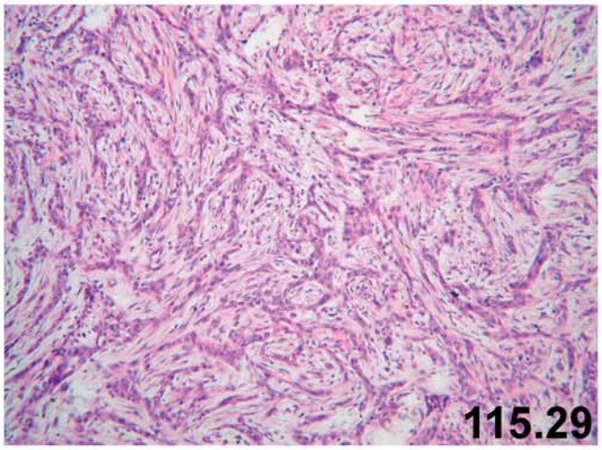
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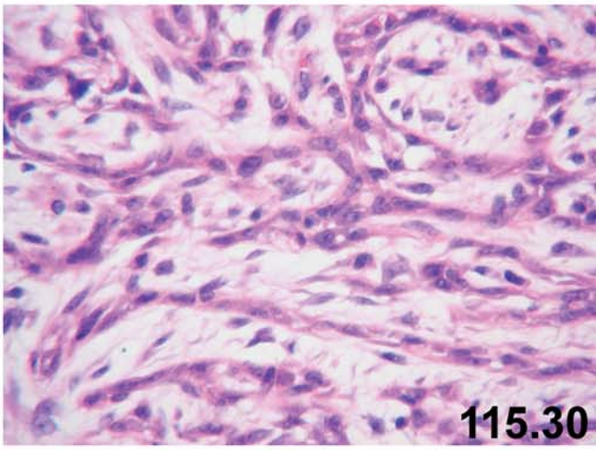
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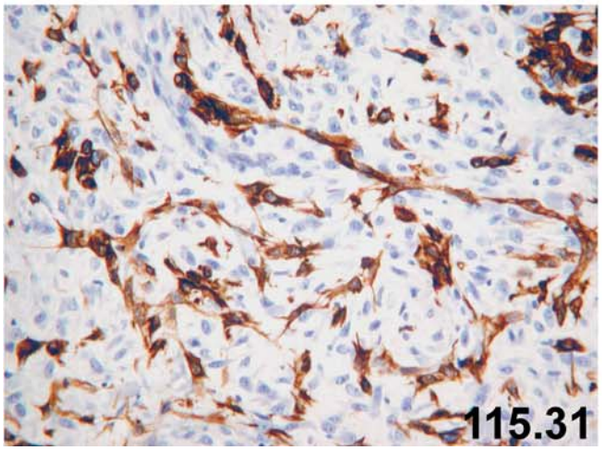
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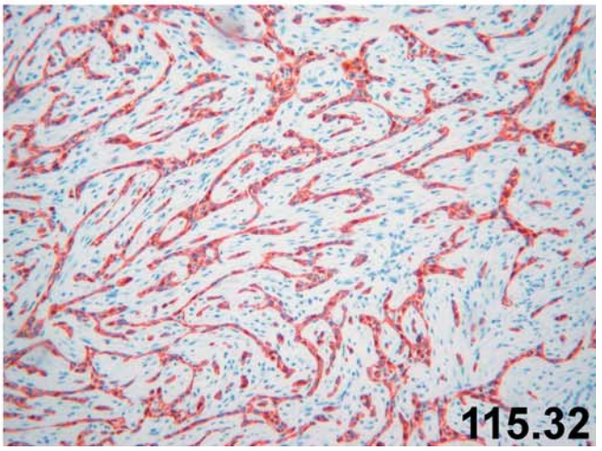
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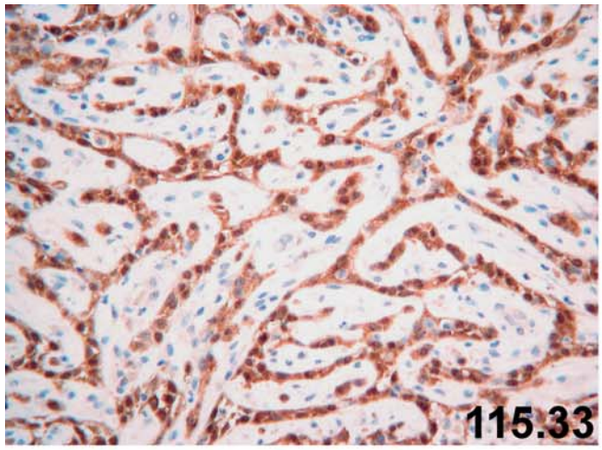
Figs. 115.33 and **115.34:** The tumor cells of metaplastic carcinoma with unusual cordlike growth pattern show a positive immunoreaction for 14-3-3 sigma (Fig. 115.33), another myoepithelial marker. The neoplastic cells are also positive for CD29 (Fig. 115.34), a new myoepithelial marker. This case demonstrates again that metaplastic or sarcomatoid carcinomas of the breast frequently show myoepithelial differentiation (myoepithelial origin?). Note that this rare type of breast carcinoma often expresses high molecular weight cytokeratins or basal-type cytokeratins.

Figs. 115.35, 115.36, and **115.37:** A case of DIN (DCIS) with apocrine differentiation with cribriform growth pattern (Fig. 115.35). While the apocrine neoplastic cells are negative for estrogen receptors (Fig. 115.36), they commonly express androgen receptors (Fig. 115.37).

Figs. 115.38 and **115.39:** Another case of high-grade DIN (DCIS) with negative immunoreaction for estrogen receptor (Fig. 115.38) and positive reaction for androgen receptor (Fig. 115.39). A positive cytoplasmic reaction without positive nuclear reactivity should not be regarded as positive for steroid receptors.

Fig. 115.40: Immunoexpression of estrogen receptors in invasive lobular carcinoma. The tumor cells in this case (ILC, G1) also showed positive nuclear reaction for progesterone receptors (not shown).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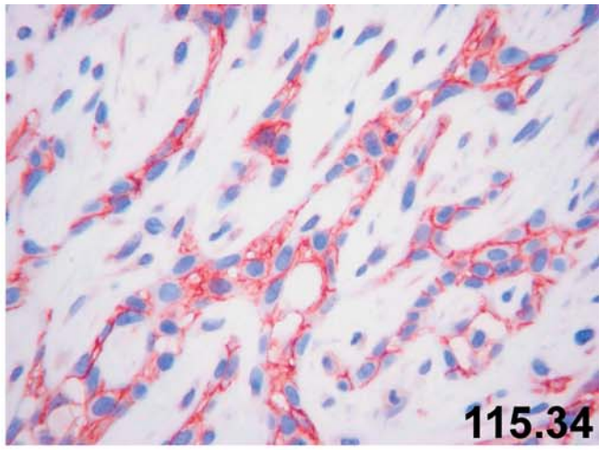
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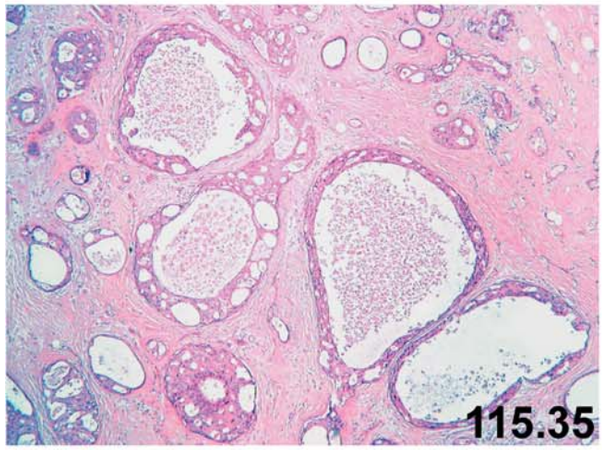
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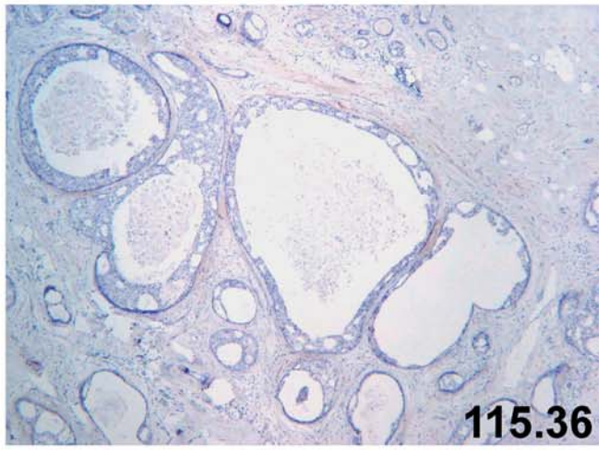
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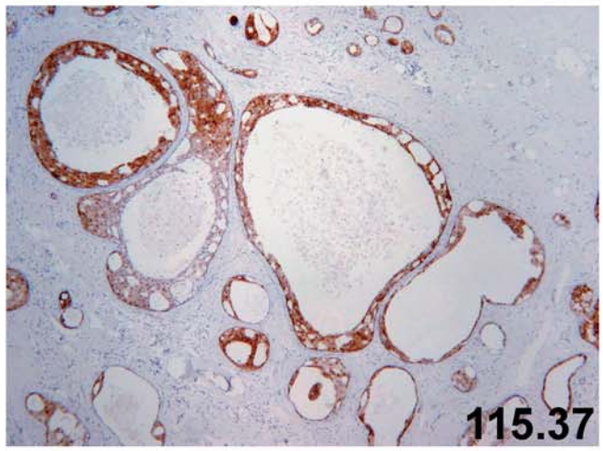
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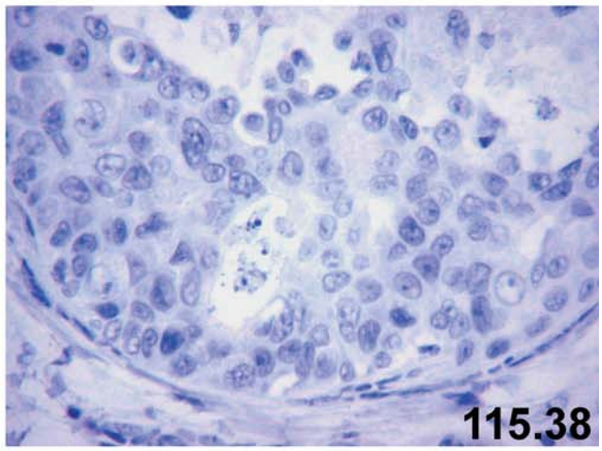
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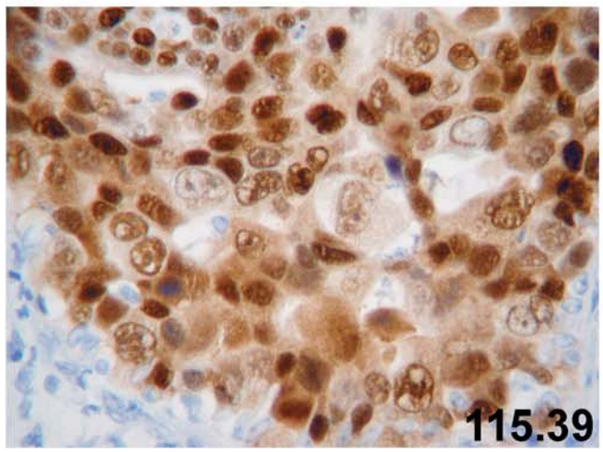
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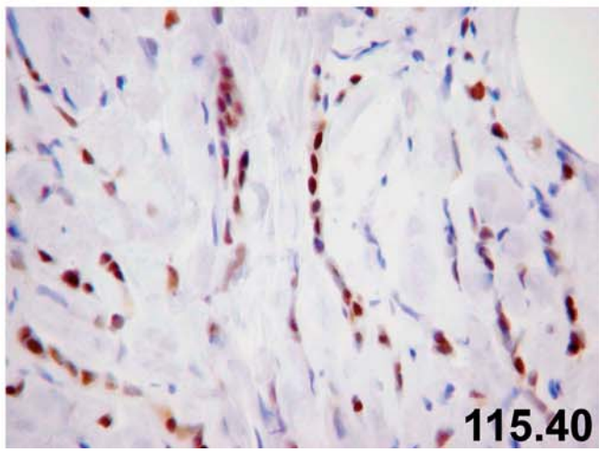
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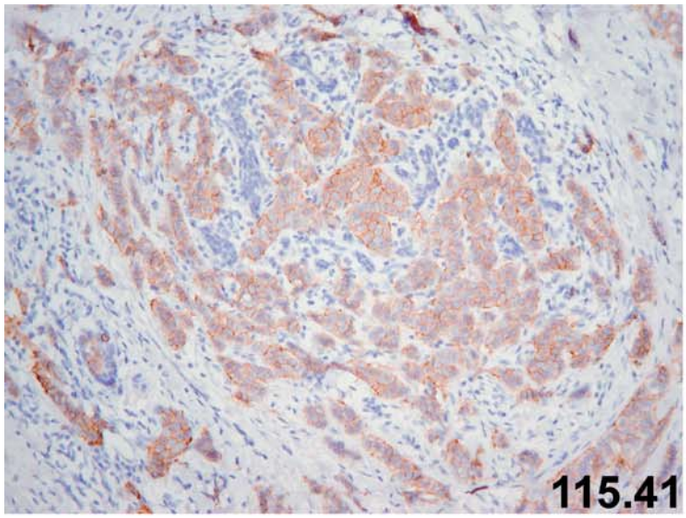
Figs. 115.41 and **115.42:** Immunohistochemistry of a case of infiltrating ductal carcinoma (G2) for HER2/neu. While the tumor cells show weak to moderate positive reaction, there is no circumferential or intense cell membrane reactivity for HER2/neu receptor (staining with HercepTest, DakoCytomation). The immunoreaction is to be scored as 2+ and needs to be followed by fluorescence in situ hybridization (FISH). The additional FISH analysis in this case did not reveal gene amplification.

Figs. 115.43 and **115.44:** The highly atypical neoplastic cells overexpress HER2/neu in high-grade DIN (DCIS, G3) (115.43) and in poorly differentiated invasive ductal carcinoma (115.44). Note the intense and circumferential cell membrane (3+) reaction for HER2/neu (staining with HercepTest, DakoCytomation). One should keep in mind that only a 3+ immunoreaction for HER2/neu or a 2+ reaction that shows gene amplification by fluorescence in situ hybridization should be reported as positive.

Fig. 115.45: FISH analysis of a poorly differentiated invasive ductal carcinoma (IDC, G3) showing amplification of the HER2/neu gene (chromosome 17) with multiple red spots per cell. Normal cells have only two copies of the HER2/neu gene (hybridization with the HER/neu FISH pharmDx Kit, Dako).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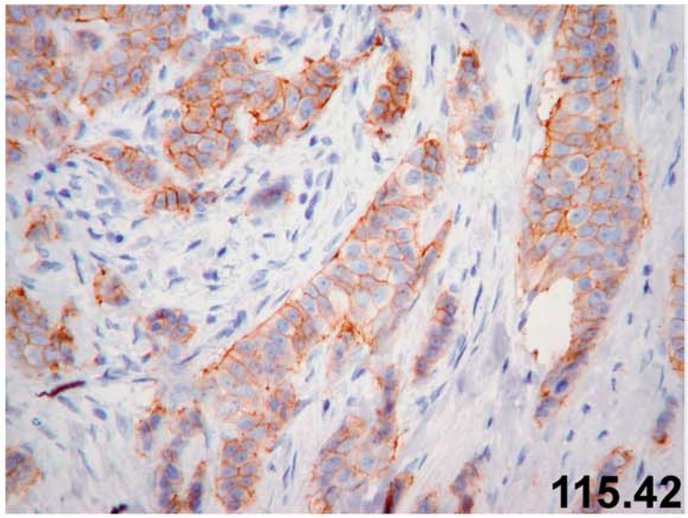
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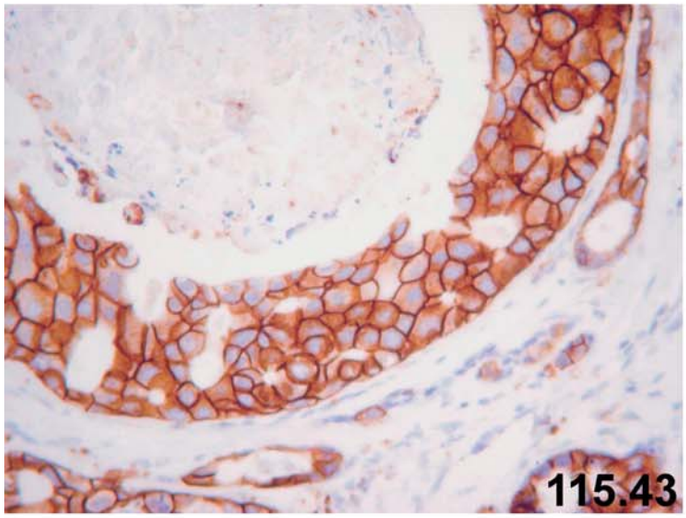
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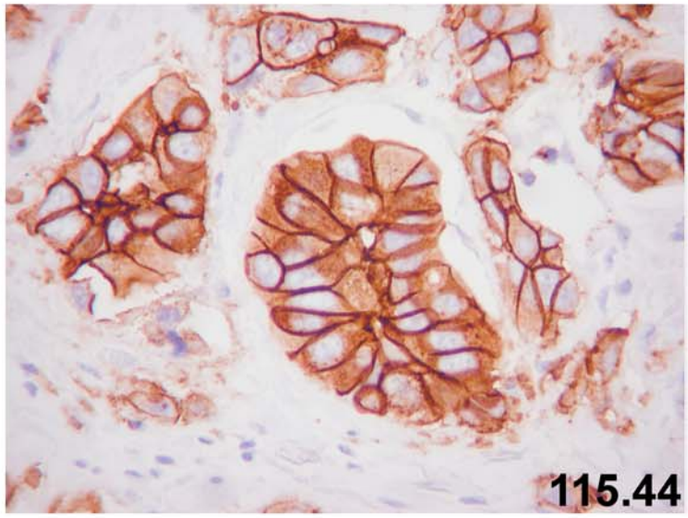
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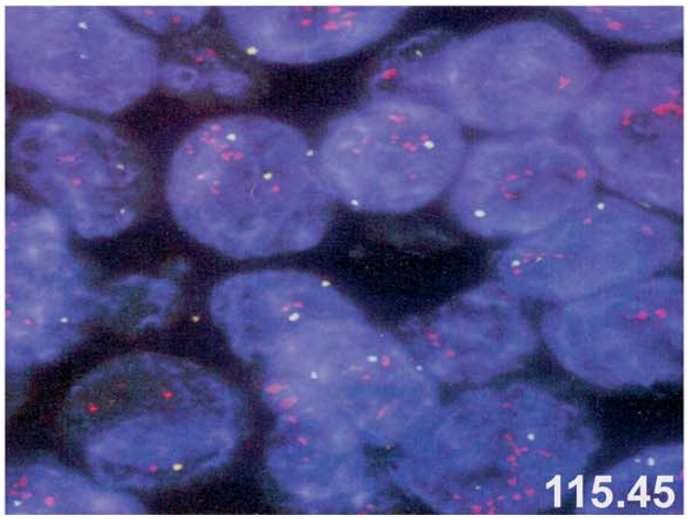
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Fig. 116: Microinvasive carcinoma of the breast with isolated tumor cells in a sentinel lymph node.

Case history: A 35-year-old woman had an abnormal mammogram of her left breast, showing several clusters of microcalcifications. There was no palpable tumor. Excisional biopsy was performed and revealed extensive areas of high-grade DIN (DIN3, DCIS, G3), partly with comedo-type central necrosis associated with luminal microcalcifications. The size (distribution) of DIN was about 5 cm. Because of the lesion's large size, sentinel lymph node biopsy was performed.

Figs. 116.1 and **116.2:** One hematoxylin and eosin section (one of 12 paraffin blocks) shows a focus of microinvasion (<1 mm in diameter) characterized by irregular small epithelial clusters and isolated tumor cells. While DIN (DCIS) shows a continuous layer of basement membrane, the microinvasive focus lacks basement membrane and a myoepithelial cell layer.

Figs. 116.3 and **116.4:** Very small clusters of microinvasive tumor cells accompanied by a lymphocytic stromal reaction. Note the absence of a myoepithelial cell layer.

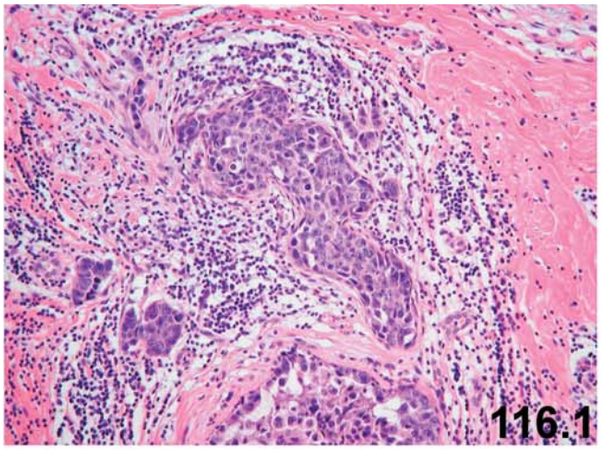
Fig. 116.5: Higher magnification of Fig. 116.4 reveals a single-file pattern of microinvasive tumor cells lacking a basement membrane and a myoepithelial cell layer.

Fig. 116.6: Higher magnification of Fig. 116.2 shows a very small cluster of epithelial tumor cells without a basement membrane.

Figs. 116.7 and **116.8:** Immunohistochemistry for pancytokeratin shows two very small clusters of epithelial tumor cells (<0.2 mm). According to the current TNM, this submicrometastasis should be classified as pN0 (i+). Note that i+ means isolated tumor cells or very small cell clusters that are ⩽0.2 mm in diameter.

Fig. 116: Final remarks

- This case was reviewed by several practicing pathologists. While some found no definitive area of microinvasion, others identified a focus of clear-cut microinvasion associated with high-grade DIN (DCIS).
- The clinical significance of isolated tumor cells in a sentinel lymph node or pN0 (i+) is unclear and needs to be investigated properly.
- A lymph node metastasis that is >0.2 mm but ⩽2 mm in diameter should be classified as pN1 (mi).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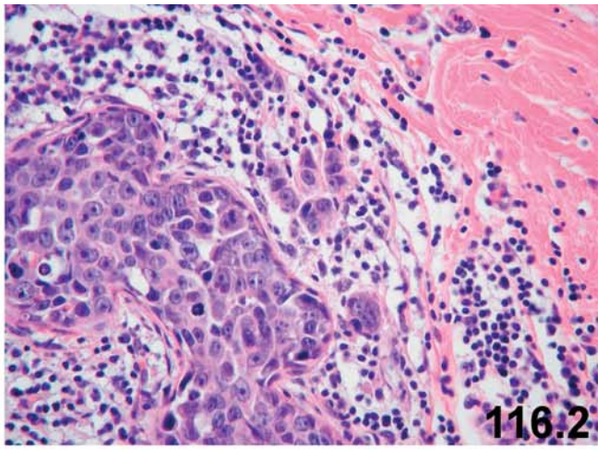
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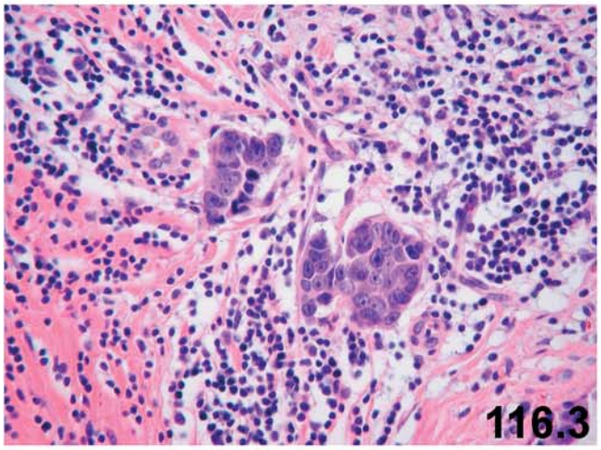
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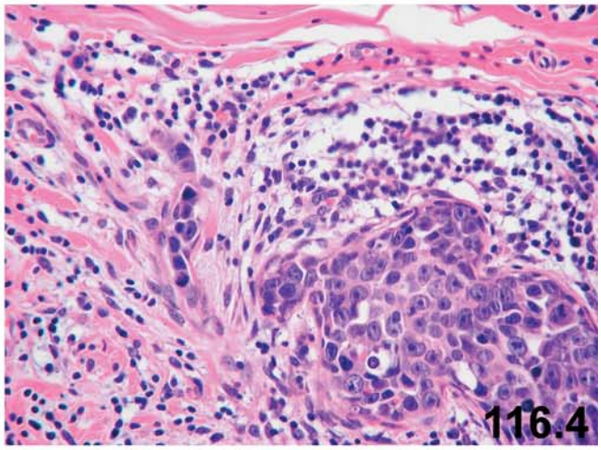
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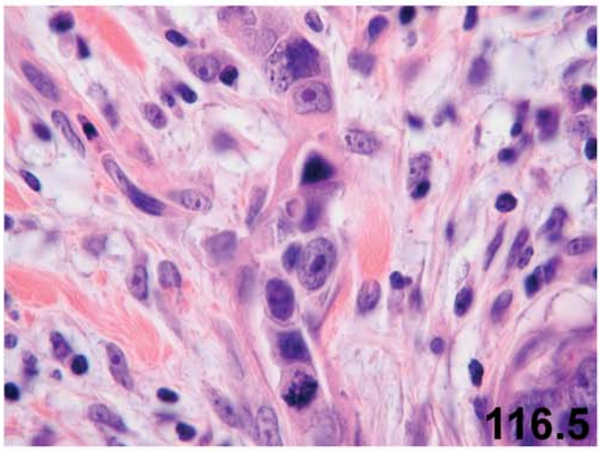
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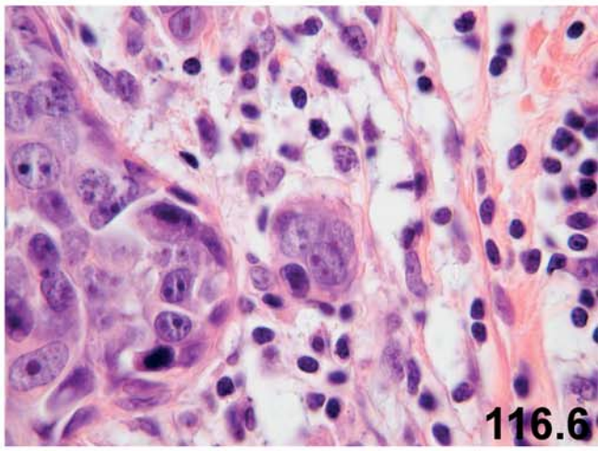
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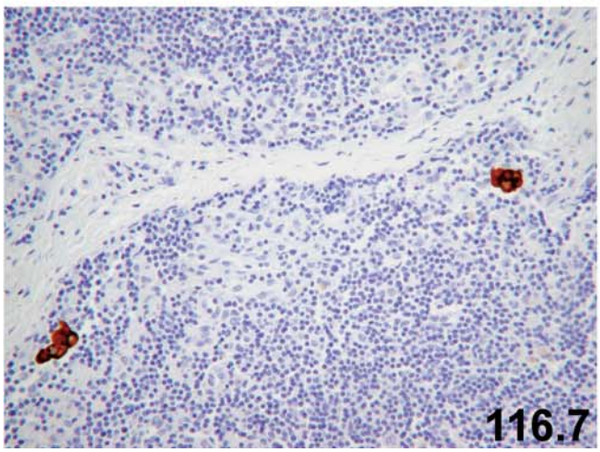
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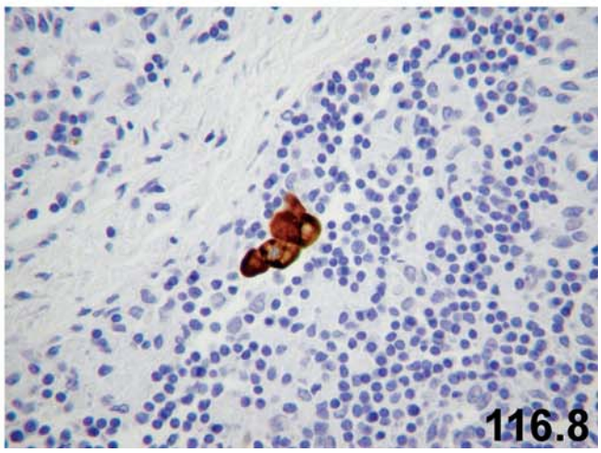
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