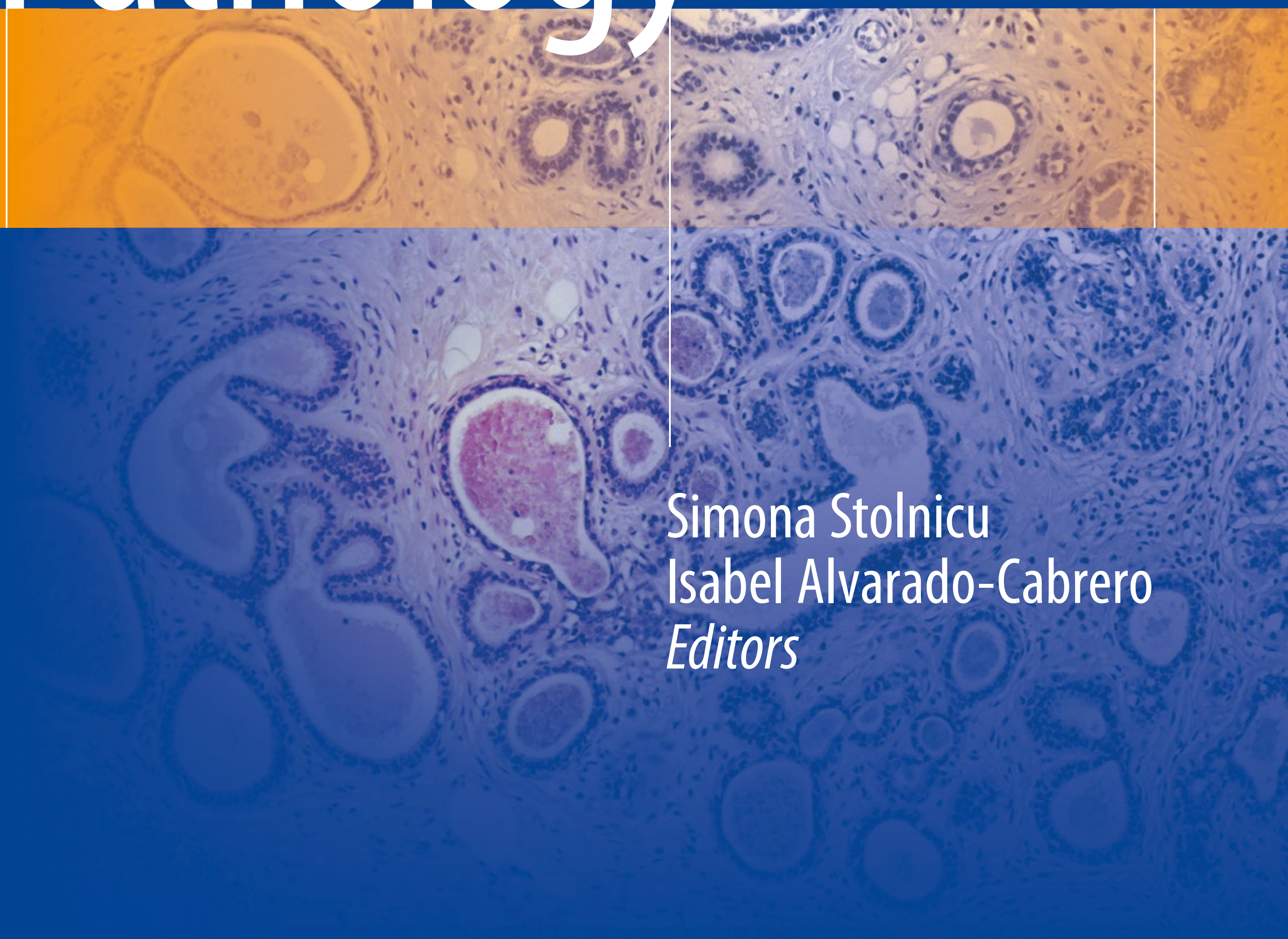
Practical Atlas of Breast Pathology



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Editors

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ISBN 978-3-319-93256-9 ISBN 978-3-319-93257-6 (eBook)
https://doi.org/10.1007/978-3-319-93257-6

Library of Congress Control Number: 2018949947

This Springer imprint is published by Springer Nature, under the registered company Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my family, for their endless love and support to achieve an academic career.

Simona Stolnicu

To my mother, who taught me the love for reading.
To my siblings for the shared adventures.
To you.... the wind beneath my wings.

Isabel Alvarado-Cabrero

Foreword

As the title indicates, this breast pathology atlas is focused on providing the reader with a practical approach to breast pathology. The editors have assembled an international group of breast pathology experts who present up-to-date criteria for diagnosis and differential diagnosis of breast lesions. Succinct text is accompanied by numerous illustrations. The focus of the atlas is, as it should be, on diagnosis of breast lesions using hematoxylin- and eosin-stained sections, but the role of adjunctive studies to aid in diagnosis is emphasized and illustrated where appropriate. Important contemporary issues such as core needle biopsy (with an emphasis on the importance of radiologic–pathologic correlation), sentinel lymph node biopsy, and treatment-related changes are each addressed in their own chapters, as are the role of immunohistochemistry in breast pathology, prognostic and predictive factors, and molecular pathology basics. This atlas should serve as a useful, easy-to-use resource for pathology trainees and practicing pathologists alike.

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Preface

In recent decades, there has been remarkable progress due to many changes and discoveries that have been published in the breast pathology field. Diagnosis of breast lesions has become challenging for pathologists, but also very important concerning the impact on the patient's treatment and, consequently, on survival.

There are many breast pathology textbooks available on the market that often present exhaustive information. Our book is an atlas, designed as a practical approach for understanding and practicing breast pathology through pictures.

This atlas is mainly dedicated to trainees and practicing pathologists in surgical pathology with an interest in breast pathology and tackling the daily sign-out. This easy-to-use practical guidebook explains how to tackle the diagnosis, emphasizing diagnostic clues for each entity as well as pitfalls and mimickers. This is the reason why each chapter includes short and concise text mostly illustrated with numerous high-quality pictures with explanatory legends highlighting the pearls and pitfalls in the diagnosis of breast lesions. This manner of presentation will help readers quickly assimilate the essential information about all breast lesions.

We have included the most important and frequent benign and malignant lesions of the breast. We have also included a separate chapter dedicated to normal breast anatomy and histology, which is very important for understanding breast pathology, and a separate chapter for breast radiology–pathology correlations, which is essential in understanding and diagnosing the breast lesions especially in a multidisciplinary team. We dedicated a special chapter to the core needle biopsy with radiological–pathological correlations since breast lesions are diagnosed using this method in most medical centers all over the world. Additionally, because cytology is still used in many breast units to diagnose breast lesions, we have added a chapter dedicated to this technique, which is easy to apply and cheaper compared to others, although sometimes it has its limitations. Sampling is essential in breast pathology and for this reason we have demonstrated the grossing method in a separate chapter. The molecular classification and its surrogate immunohistochemical evaluation have completely changed the diagnosis and treatment for breast carcinoma, which is why we have dedicated special chapters to these topics.

We hope that both pathologists and clinicians with a particular interest in this area will find this book interesting.

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Mexico City, Mexico — Isabel Alvarado-Cabrero, MD, PhD

Acknowledgments

We would like to thank Adrian Naznean from the Foreign Language Department, University of Medicine and Pharmacy of Tirgu Mures, for translating and correcting several chapters of this book. We would also like to thank Dr. Susan DeWyngaert for providing the radiologic images and Dr. Esteban Gnass for his help with the images in Chapter 9. We thank our colleagues who provided interesting and challenging cases in consultation over the years. Also, we would like to thank our residents who helped us in our daily practice but also for raising interesting questions that helped us to better understand breast pathology.

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1 Histology of the Normal Breast, Normal Changes, and Abnormalities of Breast Development

Simona Stolnicu

The breast, a modified sweat gland and target for different hormones, lies on the anterior chest wall over the pectoralis major muscle and has the specialized function of feeding the newborn infant. The breast displays various morphologic alteration throughout the reproductive life cycle (menarche, pregnancy, lactation, and menopause, in addition to maternal hormonal effects in utero). By understanding its normal morphology, normal changes, and immunohistochemical profile, breast pathologists are better able to identify and diagnose breast lesions, also by using ancillary examinations. A variety of abnormalities can occur during the development of the breast, most of which can be easily corrected with the help of cosmetic surgery.

1.1 Histology of the Normal Breast and Normal Changes

The mammary gland is a modified sweat gland, influenced by the hormones prolactin, estrogen, and progesterone, which have active or passive roles in its physiology. This gland is located on the anterior thoracic wall, corresponding to the space between ribs 2 and 6 in the vertical axis and between the sternal edge and the midaxillary line in the horizontal axis, wrapped by the superficial pectoral major muscle fascia, which is the posterior/deep margin, and the underlying deep pectoral fascia (which covers the pectoralis major muscle). The two fasciae are connected by fibrous strips (Cooper's ligament attachment), which is a natural support for the breast tissue.

The shape, weight, size, density, and spread of breast tissue into the adjacent tissue (for example, within pectoralis muscle fibers) differ from one person to another and are influenced by the individual's body habitus. This has a very practical impact on cosmetic surgery, but also results in the fact that even a total mastectomy does not achieve the removal of all breast glandular tissue, meaning that prophylactic mastectomy substantially, but not entirely, reduces the risk of developing breast cancer [1].

Primitive mammary crests (or milk lines) develop in the human embryo in the fifth week of gestation and consist of two epidermal thickenings, which stretch from the armpit to the groin. Immediately after their formation, the greatest part regresses, except for a small portion of the pectoral region. In weeks 12–16 of gestation, the nipple and areola develop. Sequentially, the underlying epithelial buds appear. All these changes are independent of hormonal influences. The first differences between the sexes occur at the end of the first

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S. Stolnicu, I. Alvarado-Cabrero (eds.), *Practical Atlas of Breast Pathology*, https://doi.org/10.1007/978-3-319-93257-6_1

trimester of pregnancy, under the action of estrogen and testosterone. Throughout the third trimester (weeks 20–32), under the influence of placental hormones, a channeling system develops from the epithelial buds, initially in the form of full cords in which ducts form in time, which will give rise to lactiferous ducts. The myoepithelial cells are differentiated in weeks 24–28 of intrauterine life, and will undergo subsequent quantitative or morphological changes only in pathological lesions. Between weeks 32 and 40, nipple and areola pigmentation occur.

Immediately after birth, a transient breast hyperplasia may occur, due to the transplacental action of maternal hormones. Breast tissue appears as dilated ducts filled with secretory material, which is also observed as a liquid in the nipple in both sexes. This typically continues until weeks 3–4 postpartum, but can sometimes extend to several months or even up to puberty. This type of breast hyperplasia should not be confused with a pathological process because its surgical excision leads to amastia.

Until puberty, the primary duct system branches, but remains at a rudimentary stage in both sexes (Figs. 1.1 and 1.2).

At puberty, the mammary gland in females develops under the action of hormones secreted by the pituitary gland and ovaries. This occurs by the continuous branching of the ducts simultaneously with the proliferation of periductal stroma (under the effect of ovarian estrogen) and by the development of lobules (under the effect of estrogen and progesterone). Regarding the lobules, at the end of elongated and branched ducts, an initial thickening of the channeling epithelium will occur, forming the so-called “waiting buds.” They consist of small spheroid masses composed of polygonal epithelial cells, which do not define a lumen. These spherules, along with intralobular channels, will form Type 1 lobules, features of nulliparous women (Fig. 1.3). In younger patients (during puberty), as compared to adults, the intralobular stroma is dense and appears to have a similar appearance to the extralobular one (Fig. 1.4). This increase in the amount of connective tissue at this age can produce pseudo-nodular areas on palpation (by the clinicians) but also on macroscopic and microscopic examination (especially by inexperienced pathologists), and should not be confused with the pathologic process of fibrosis because it may lead to unnecessary surgery.

Sometimes, before puberty, an increase in the size of the mammary gland may occur under the action of endogen hormones. This anomaly is called premature thelarche and, on microscopy, it is characterized by a proliferation of the ducts and acini, arranged in a denser collagenous stroma. Simultaneously, an increase in the volume of adipose tissue occurs. These patients may be at early puberty, but studies have also shown frequent association of this condition with the subsequently development of breast carcinoma.

The mammary gland presents complete pigmentation of the areola and nipple in adults. The nipple is located in the central area of the breast and is surrounded by areola. It consists of bundles of smooth muscle fibers and elastic tissue, passed through by lactiferous ducts (14–24 ducts may be seen within each nipple), which end in an opening. Smooth muscle fibers are arranged radially and longitudinally (Figs. 1.5, 1.6, and 1.7). In some cases, in the region of the nipple the smooth muscle bundles show hyperplasia, which may lead to the increase of the nipple volume (Fig. 1.8). This process must be differentiated from leiomyoma (a benign nodule with well-defined margins) or leiomyosarcoma (a malignant tumor with infiltrative margins, atypia, presence of atypical mitoses and areas of necrosis) of the nipple. In up to 20% of cases, careful examination of the nipple will also reveal mammary lobules (this is the reason that some special subtypes of breast carcinoma also occur initially within the nipple and not only in the terminal duct-acini unit) (Figs. 1.9 and 1.10) [2, 3]. The epidermis covering the nipple and areola is composed of stratified squamous epithelium in the thickness of which clear cells can be identified in some patients (considered Paget precursor cells, also known as Toker cells) (Figs. 1.10 and 1.11). These cells are larger than the adjacent keratinocytes, with a round or oval nucleus and pale cytoplasm, but no intracytoplasmic mucin is present, and they are negative for carcinoembryonic antigen (CEA). Some authors have highlighted pre-Paget dysplastic changes within these cells. As such, they should not be confused with Paget cells. The dermis may present sebaceous and eccrine sweat glands, and hair follicles may sometimes appear on the margin of the areola (Fig. 1.12). Some large sebaceous glands open to the surface through a duct, corresponding to 10–15 small rounded uniform formations called Montgomery tubercles (present in both women and men) (Fig. 1.13). These structures can proliferate after puberty and become prominent during pregnancy, but they undergo atrophy with age and have little importance in the routine practice because pathological lesions develop very rarely at this site. However, sebaceous gland hyperplasia was described for the first time in the areolar area in an adult patient, as a bilateral lesion developed after the patient gave birth [4]. Few other communications of this lesion have been published in either women or men; most of those that have been reported were of a bilateral presentation, whereas in others the presentation was unilateral [5]. Macroscopically, nipple sebaceous gland hyperplasia consists of multiple, soft, normal-colored or yellowish papules or nodules, with central umbilication (Fig. 1.14). When the lesions involve large areas of the nipple and areola, and when they develop in postmenopausal patients, Paget’s nipple disease associated with malignant breast lesions should be ruled out from a clinical point of view. Microscopically, the lesion is represented by hyperplastic and hypertrophic mature sebaceous glands aggregated in the dermis, sometimes extending into the epidermis (Fig. 1.15).

The area of the areola increases in size during pregnancy and becomes more pigmented, changes that do not disappear subsequently. Inverted nipple is a congenital anomaly that can sometimes occur, predisposing the female to the development of mammary duct ectasia (Figs. 1.16 and 1.17). It should not be confused with an invasive malignancy on macroscopic or microscopic examination (Fig. 1.18).

The adult mammary gland is composed of 15–20 independent glandular units called mammary lobes, arranged radially around the nipple. Each lobe drains through a single channel, called the lactiferous canal, which opens in the nipple. A lobe is in turn constituted by a ductal-acini structure, surrounded by fibrous connective septa. The septa separate one breast lobe from another and divide each lobe into a variable number of lobules. Highlighting the septa is difficult in terms of both surgical and anatomical pathology. For this reason it is almost impossible to define the boundaries between lobes from a surgical point of view and to perform a "segmentectomy" in some of the breast lesions. The connective tissue, which forms the septa, is not hormone-dependent. Histologically, the ductal (canalicular) system is divided into several segments. The deep segment of the ductal system is called terminal duct and comprises an intralobular portion and an extra-lobular one. Several terminal ducts unite and constitute subsegmental ducts, which in turn drain into segmental ducts. Segmental ducts unite and form lactiferous ducts, which open in the nipple (Fig. 1.19).

The superficial portion of the duct orifice is covered by squamous epithelium, which may extend for a short distance into the most distal portion of the duct (Fig. 1.20). The squamous-columnar junction, where the squamous epithelium joins the columnar epithelium, is normally distal to a dilated segment of the duct called the lactiferous sinus. The extension of the squamous epithelium beyond the lactiferous sinus is called squamous metaplasia, a condition that may lead to the obstruction of the lactiferous duct and the development of a subareolar abscess.

Except for a small portion adjacent to the nipple, in which the system of ducts is covered by squamous epithelium, the whole ductal system is lined by two layers of cells: the inner continuous layer formed by epithelial cells (which can be flattened, cuboidal, or columnar, and have pale eosinophilic cytoplasm and uniform oval nuclei), and the outer layer consisting of myoepithelial cells (often showing a bipolar elongated dense nuclei and small cytoplasm; however, the cytoplasm contains glycogen, which gives a cleared appearance in the Hematoxylin-Eosin stained slides) (Fig. 1.21). Sometimes, the myoepithelial cells have a myoid appearance with a spindle shape and dense eosinophilic cytoplasm (Fig. 1.22). Of interest, the myoepithelial layer may be discontinuous, or, in very rare instances, it may be absent, even in normal breast tissue (Fig. 1.23) [6]. At the periphery, the two layers are surrounded by a basement membrane and fibroblasts. Also, elastic tissue fibers are variably present around normal ducts while they are absent at the lobular level. Terminal ducts deepen into mammary acini, called by some authors "terminal ductules." The intralobular segment of the terminal duct, along with the acini, will constitute mammary lobules, also called terminal ductal-lobular units (TDLU) (Figs. 1.24 and 1.25). This is the level where most benign or malignant breast lesions occur. Breast lesions will be further divided and called *ductal* or *lobular* depending on the morphological and immunohistochemical appearance of proliferation, but also because they are, from a clinical and developmental point of view, totally different from one another. The terms "ductal" and "lobular" do not relate to the origin of the lesion within ducts or acini (lobule). Acini are also lined by the two cell layers, and are surrounded by a basement membrane and fibroblasts. Some authors have suggested the presence of a third layer of intermediate cells called basal cells or clear cells in both the acini and in the ducts. Also, some authors describe the existence of stem cells (also called progenitor cells) spread throughout the system of mammary ducts and acini, more numerous in the acini. These cells proliferate during pregnancy, and some studies suggest that they are the origin of the capability of different breast tumor lesions to differentiate into both glandular epithelial cells and myoepithelial cells.

Around the acini and the ducts, the stroma is hormone-dependent and is more cellular (intralobular stroma), while interlobular stroma is less cellular and is not hormone-dependent (Fig. 1.26). Hormone-dependent stroma consists of collagenous connective bundles, abundant fundamental substance, and fibroblast cells. The laxity of intralobular stroma facilitates the distension of acini during pregnancy and lactation. Also, the intralobular stroma often displays a mucoid character (positive for Alcian blue) (Fig. 1.27). Of interest, the intralobular stroma of mammary glands free of pathological changes usually presents a varying number of lymphocytic and/or plasma cells (Fig. 1.28). Additionally, these cells do not normally occur in the epithelium of the ducts or acini. Also, mast cells, histiocytes, and ochrocytes (periductal histiocytes with lipofuscin pigment) are sometimes present around ducts [7]. The interlobular stroma is composed of a dense connective tissue, consisting of thick connective tissue bundles, with a low level of fundamental substance and reduced number of cells. Adipose tissue can be found only between mammary lobes, and it never appears intralobularly (Fig. 1.29). The adipose tissue varies quantitatively according to the age of the patient and among individuals. The interlobular stroma may also present multinucleated giant cells or bizarre cells (Fig. 1.30). Their significance is unknown, and they should not be misinterpreted as malignant cells. This interlobular tissue may also host encapsulated lymph nodes, usually with less than 5 mm, which may appear as densities on mammography and can be detected when grossing a surgical specimen (Fig. 1.31). The presence of these nodes (most often incidentally identified in surgical specimens) is important because they may play a fundamental role in the metastasis of breast carcinoma. If present, the metastases of a breast carcinoma must be recorded in the histopathological report along with axillary lymph nodes metastases, and must be taken into account when staging the breast carcinoma.

During the early follicular phase, the acini show poorly defined lumina surrounded by epithelial cells with dark, centrally located nuclei and very rare mitoses and eosinophilic cytoplasm. During the luteal phase, it shows vacuolization and swallowing of the myoepithelial cells due to the increase in the amount of glycogen cytoplasmic contents, while the epithelial cells have prominent apical snouting (Figs. 1.32 and 1.33). Also, during the luteal phase, the lumen of the acini is enlarged and contains eosinophilic secretory material, while the intralobular stroma is loose edematous with congested blood vessels (Fig. 1.34). In contrast, the intralobular stroma is dense cellular with plump fibroblasts in the follicular phase. Sometimes, the epithelial cells in the TDLU show prominent clear cell changes in the cytoplasm at any age, and unrelated to pregnancy or exogenous hormonal administration (Fig. 1.35). A potential pitfall is mistaking benign clear cell change for involvement of lobules by clear cell variants of *in situ* carcinoma. Very rarely, it may represent metastatic clear cell carcinoma from other sites.

In contrast with females, the breast of adult males is primarily composed of ductal structures within collagenized stroma, with lobular elements absent or rare as compared to the female breast. The lobular elements in males develop under hormonal stimulation (Fig. 1.36). The nipple, however, has a similar appearance to that of females (Fig. 1.37).

Epithelial and myoepithelial cells present distinct immunohistochemical features and this information is of great importance for the breast pathologist when dealing with differential diagnosis of a breast lesion. Epithelial cells are strongly positive for low molecular weight cytokeratin (CK) such as CK 7, 8, 18, and 19. Also, epithelial cells express a heterogeneous reaction for high molecular weight cytokeratin such as CK34betaE12, and CK 5/6, and are variably positive for S-100 protein and negative for Cytokeratin 20 [8]. The epithelial cells are also sporadically positive for estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) (Fig. 1.38). This positivity is variable with age, location (ducts versus acini or within different lobules), and menstrual phase. The epithelial cells also express E-cadherin, Mammaglobin, GCDFP-15, and GATA 3. In contrast, the myoepithelial cells are positive for Actin (smooth muscle actin or muscle-specific actin), smooth muscle myosin heavy chain, calponin, p63, CD10, 14-3-3 sigma, and sometimes for S-100 protein. For a practical perspective, the markers highlighting the myoepithelial cells vary in both specificity and sensitivity. Myoepithelial cells are almost always negative for ER, PR, and AR [8, 9]. The vast majority of myoepithelial cells are negative for low molecular weight CK or may show focally and have weak positivity. Also, the myoepithelial cells may show a heterogeneous positivity for high molecular weight CK such as CK34betaE12, and CK 5/6 [8]. It has been shown that there is an endocrine cell population in a normal mammary gland positive for Chromogranin, discontinuously located between the epithelial cells. Intralobular stroma is negative for RE, RP, and AR. Basement membrane is positive for Laminin, and Collagen IV.

During pregnancy, significant hormonal changes occur. The placenta and the pregnancy corpus luteum produce large amounts of estrogen and progesterone, leading to higher levels of prolactin. Increased hormone secretion causes mammary gland secretion. The most significant changes occur in the lobules. As the pregnancy progresses, the number of acini increases, along with progressive accumulation of secretory material and, consequently, the lobules become bigger. The waiting buds turn into glandular acini and thus type 2 lobule develops (Figs. 1.39 and 1.40). Myoepithelial cells become obscured by the epithelial cells, but are still present (the positivity for myoepithelial markers confirms this, using ancillary examinations). Proliferative activity, reflected in the number of mitoses, is greatest in the 20th week of pregnancy and declines afterwards. The appearance of epithelial cells is different in the acini as opposed to the ones that line the ducts, due to the fact that the secretory material accumulates particularly in the cytoplasm of the epithelial cells of the acini, which becomes vacuolated.

During pregnancy, especially during the third semester, localized adenomatous lactational hyperplasia may lead to the development of one or more nodules, called lactational adenomas (Figs. 1.41 and 1.42). Also, pronounced areolar pigmentation and dilation of superficial cutaneous veins become apparent.

During lactation, the amount of estrogen and progesterone decreases, whereas that of prolactin increases. Because of the secretory activity, their lumen accumulates lactation and the acini expand, developing mammary alveoli (type 3 lobules). Myoepithelial cells continue to have a weakened appearance.

The act of sucking stimulates the nipple and leads to the release of oxytocin, which stimulates the myoepithelial cells to contract and release milk from the mammary alveoli. The process of lactation ceases 7–10 days after the cessation of nipple stimulation. The process of breast tissue involution, called post-gestational involution, lasts 3–4 months and is not uniform. In its first stage, the lobules regress, and become irregular in shape due to the uneven distribution of acini and ducts and due to their angular shape of these structures, especially of the ducts. The epithelium is flattened and the basement membrane is castellated, while the intralobular stroma shows an inflammatory lymphoplasmacytic infiltrate. In time, the lobules become fibrotic and hyalinized, decrease in size and number, and the amount of fibrous tissue and fat around them increases (Figs. 1.43 and 1.44). In some mammary alveoli, in which milk secretion persists, the expansion of the lumen (called galactocele) and the rupture of the wall can occur (Figs. 1.45 and 1.46). The involution process is controlled by hormonal changes and reduction in the level of prolactin, but other vascular or cellular factors (the presence of macrophages with phagocytic action) are also involved.

In general, the florid changes and areas of infarction seen during pregnancy and lactation can be alarming for an inexperienced pathologist. However, pseudolactational changes may occur in patients under treatment with medication. These patients can present with changes that are usually incidentally diagnosed; in some cases, however, they can produce a nodule. Microscopic examination reveals partial involvement of some of the terminal ductal-lobular units, which are composed of dilated acini lined by vacuolated epithelial cells, while the myoepithelial cells are attenuated. Some of the cases may also show hobnail cells (hobnail type of pseudolactational changes) (Figs. 1.47 and 1.48).

After menopause, due to the decrease in estrogen and progesterone levels, breast tissue atrophy occurs by a reduction in the number of acini, epithelial and myoepithelial cells mitigation, luminal obliteration, and basement membrane thickening. The hormone-dependent stroma turns into a dense hyaline tissue. Over time, the ducts and acini atrophy and become completely hyalinized, forming hyaline nodules (Figs. 1.49, 1.50, 1.51, and 1.52). Sometimes, the acini expand and become cystic, a change termed cystic atrophy, which needs to be differentiated on microscopic examination from fibro-cystic changes (Fig. 1.53). Of interest, cystic atrophy is never associated with ductal or lobular hyperplasia (Fig. 1.54). Myoepithelial cells can sometimes become prominent due to hypertrophy or hyperplasia. This transformation was termed *myoepithelial atrophy*, a misnomer considering that myoepithelial cells become more prominent. The stroma undergoes involution changes, with alterations of elastic and collagen fibers and fat-tissue growth. The process of atrophy may occur in a heterogeneous way, in which some lobules are changed while others are not. The process of post-menopausal mammary involution is not uniform throughout the gland; on palpation, therefore, more consistent areas in the vicinity of flaccid ones are often detected. Occasionally, microcalcifications can occur in atrophic acini and ducts, being diagnosed on mammography and identified during microscopic examination (Fig. 1.55). Vascular calcifications become more prominent, especially in those with coronary artery disease and diabetes. Elastosis (excess elastic fibers) is found in 50% of women aged 50 years and older without breast disease, either diffusely in stroma, around vessels, or around ducts. Also, arteries in the breast undergo sclerotic changes comparable to those seen in other organs with increasing age. Arterial calcifications may be seen in the breast in postmenopausal women, which can be detected on mammography but are different from those associated with glandular parenchyma.

Blood circulation in the breast is ensured by the thoracic branches of the axillary artery, internal thoracic artery (internal mammary artery), and intercostal arteries. The venous vessels are the branches of the axillary vein and internal thorax.

The lymphatic vasculature is particularly important in breast pathology because it is the main route of metastasis of breast carcinoma. Most of the lymph drains into the axillary lymph nodes, a smaller quantity into the internal mammary lymph nodes, and a very small amount drains into the posterior intercostal lymph nodes. 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 (of interest, glandular tissue is most abundant in the upper outer quadrant of the breast and as a result, half of all breast cancers occur here). In general, tumors located in upper and external quadrants metastasize to the axillary lymph nodes, whereas tumors located in central or internal quadrants metastasize to the internal mammary lymph nodes. However, this is not a general rule. It is possible to encounter metastases with paradoxical localization due to anatomic variations or blockage of the lymphatic pathways. Sappey's subareolar plexus drains the lymph in subcutaneous channels.

Regional lymph nodes are divided into four categories: axillary, infraclavicular, internal mammary, and supraclavicular. Axillary lymph nodes are the primary lymph nodes likely to metastasize due to a breast carcinoma. They are divided into three levels according to their location along the axillary vein and its branches. Rotter interpectoral lymph node is also included in the category of axillary lymph nodes. With the introduction of the sentinel lymph node method, extensive studies regarding the mammary lymphatic drainage have been reported. The existence of more than one sentinel lymph node in some of the patients implies that a hierarchy exists in the anatomical and functional distribution of the lymph nodes in the axilla as they relate to the breast.

Mammary gland innervation is ensured by the anterior and lateral cutaneous branches of intercostal nerves II–IV.

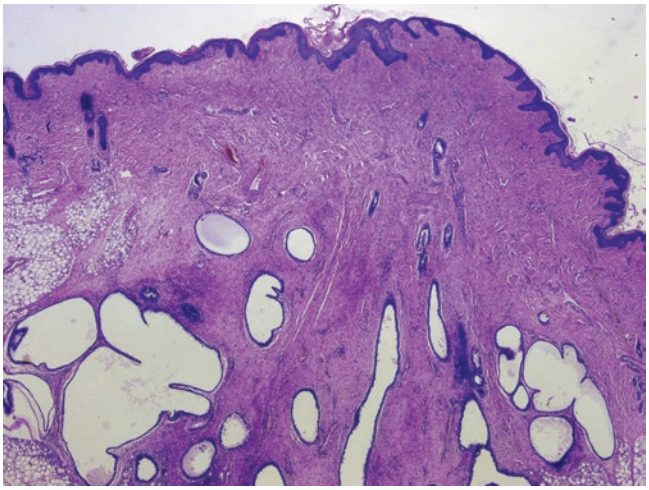

Fig. 1.1 Breast tissue in the newborn: primary duct system branches can be detected on microscopic examination (19 days old)

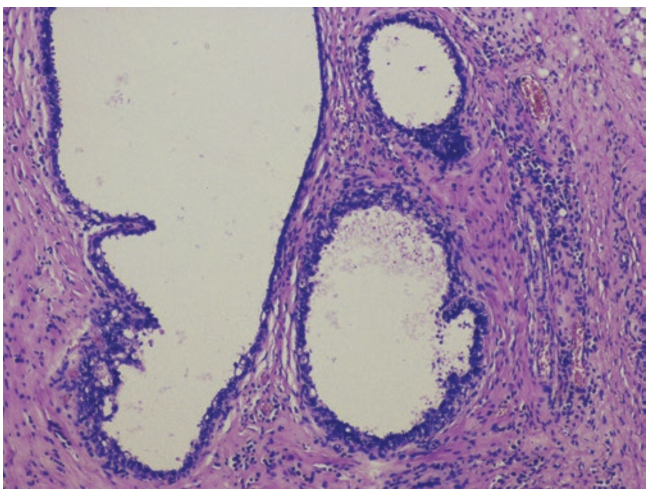

Fig. 1.2 Breast tissue in the newborn: primary ducts are lined by epithelial and myoepithelial cells and some of them are cystically dilated (19 days old)

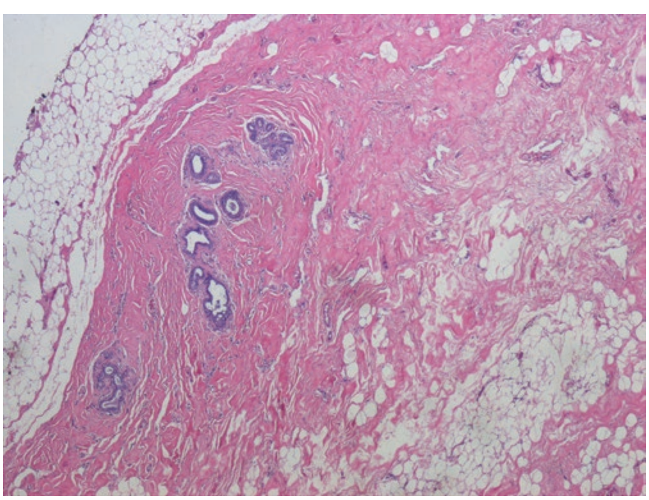

Fig. 1.3 At puberty in females, under the action of hormones, the lobules develop (12-year-old patient)

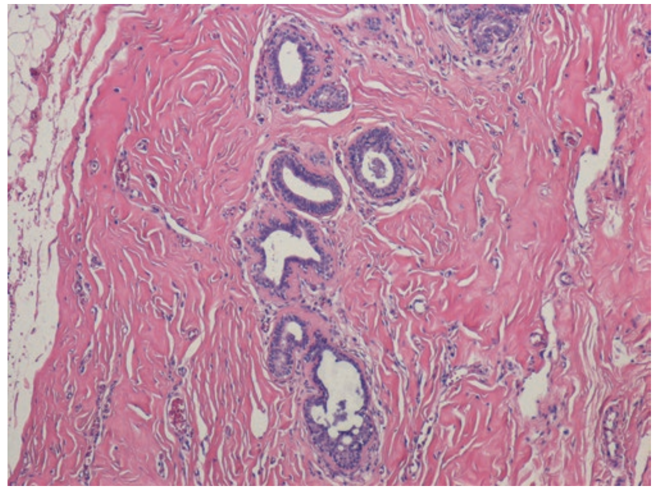

Fig. 1.4 During puberty, the intralobular stroma is dense and has a similar appearance to the extra-lobular stroma (12-year-old patient)

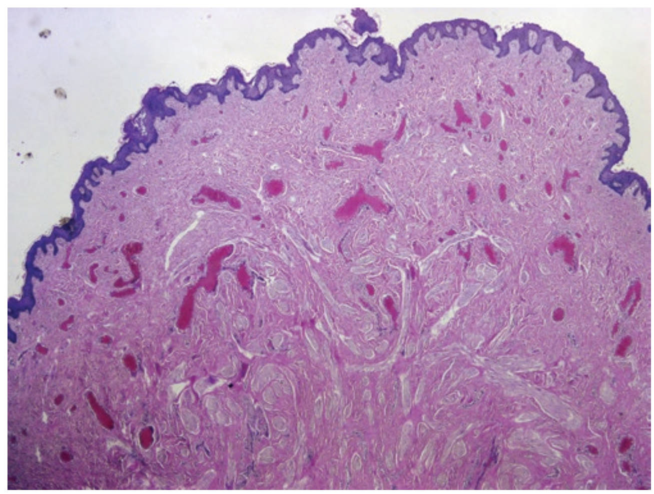

Fig. 1.5 The nipple of an adult female consists of bundles of smooth muscle fibers and elastic tissue

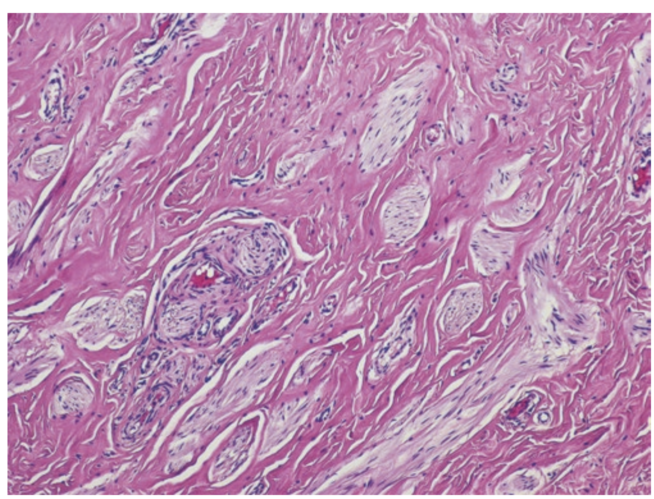

Fig. 1.6 The nipple of an adult female: smooth muscle fibers are arranged radially and longitudinally

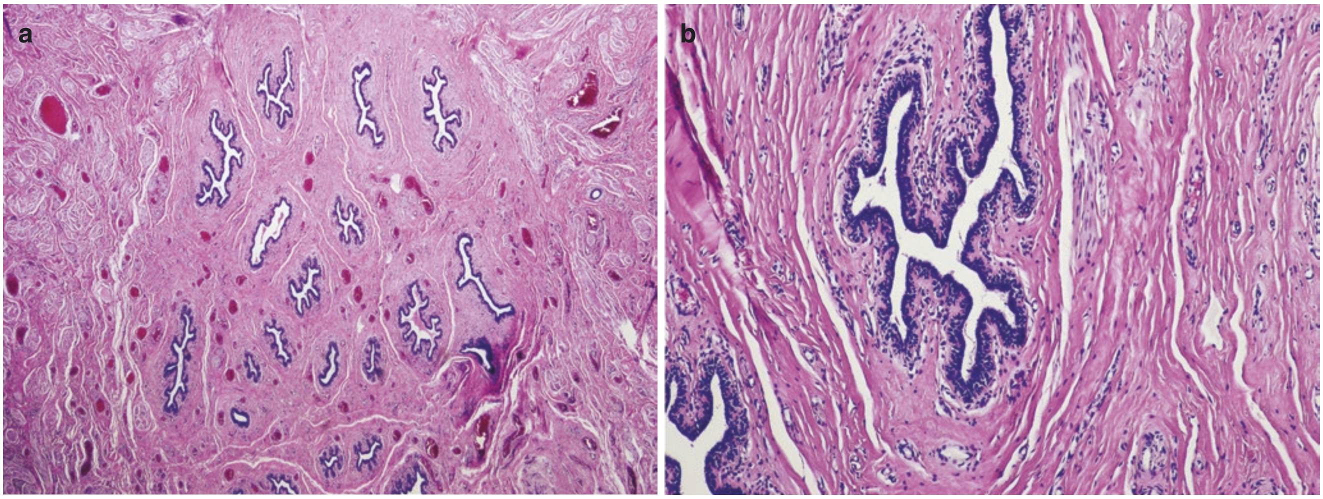

Fig. 1.7 (**a**) Nipple with lactiferous ducts. (**b**) Cross-section reveals that the duct is lined by two layers of cells

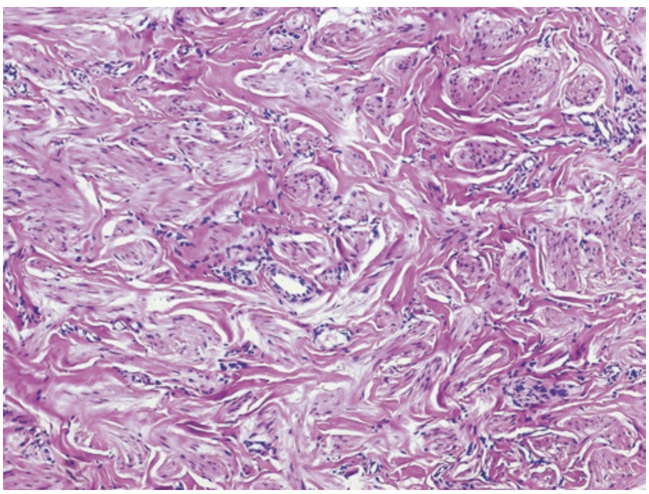

Fig. 1.8 In some cases, in the region of the nipple, smooth muscle bundles may show hyperplasia, which may lead to the increase of the nipple volume

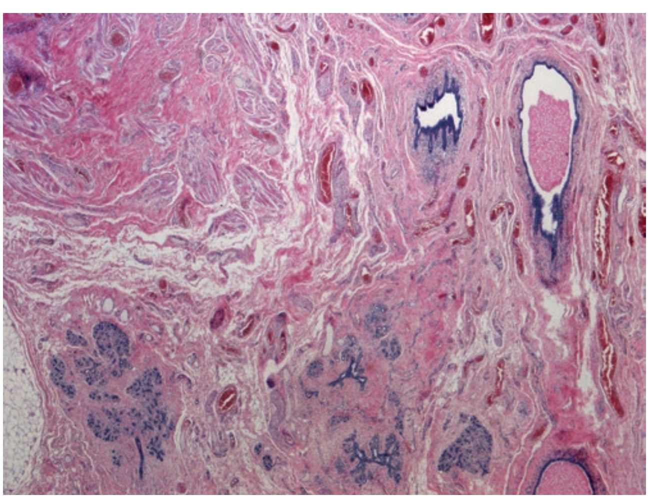

Fig. 1.9 Careful examination of the nipple may also reveal mammary lobules in some cases

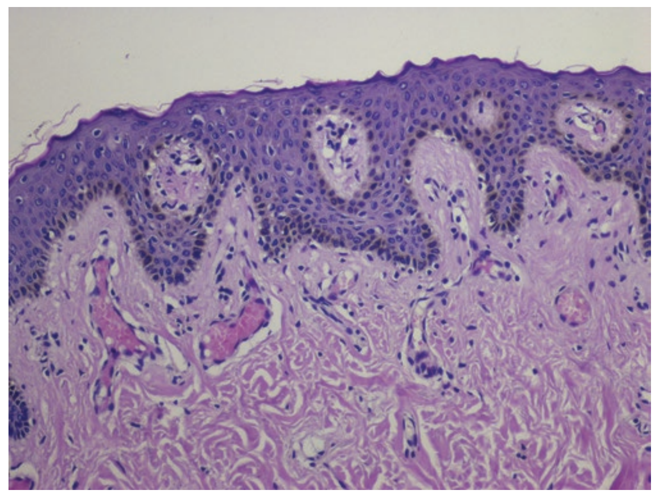

Fig. 1.10 The epidermis covering the nipple and areola is composed of stratified squamous epithelium

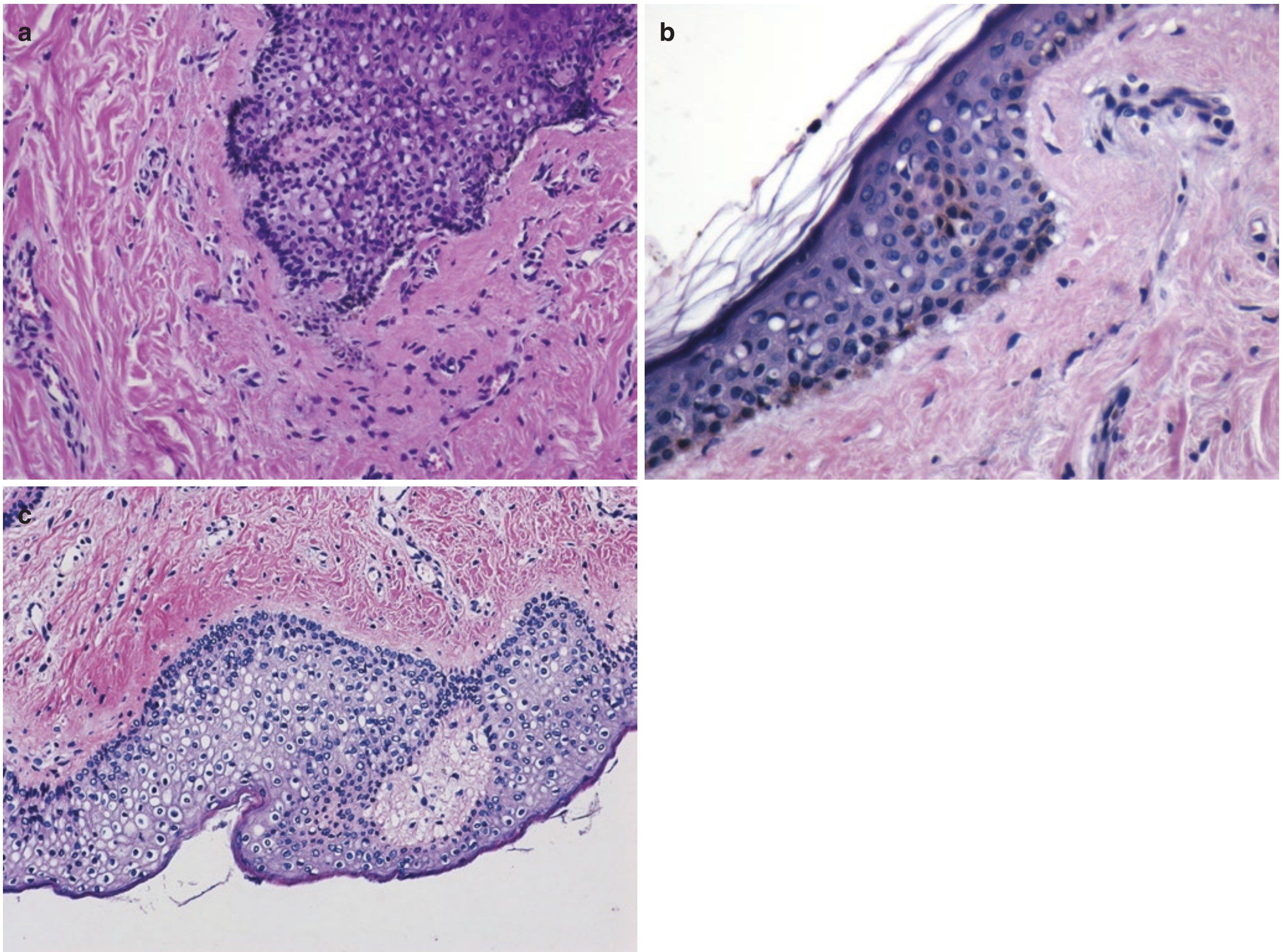

Fig. 1.11 (**a**) In the thickness of the epidermis covering the nipple, clear cells known as Toker cells can be identified in some patients. (**b**) These cells are larger than the adjacent keratinocytes, with a round or oval nucleus and pale cytoplasm, but no intracytoplasmic mucin can be detected using special stains. (**c**) Toker cells can also be appreciated in the epidermis covering the nipple of a newborn patient

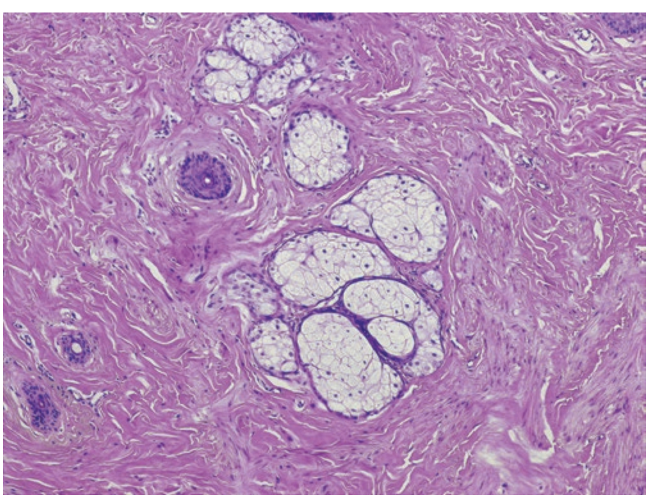

Fig. 1.12 In the nipple, the dermis may present sebaceous glands

Fig. 1.13 Nipple: some large sebaceous glands open to the surface through a duct, corresponding to small rounded uniform formations called Montgomery tubercles (Courtesy of Dr. Marius Florin Coros)

Fig. 1.14 Nipple sebaceous gland hyperplasia: multiple soft, yellowish papules or nodules, with central umbilication (Courtesy of Dr. Anca Chiriac)

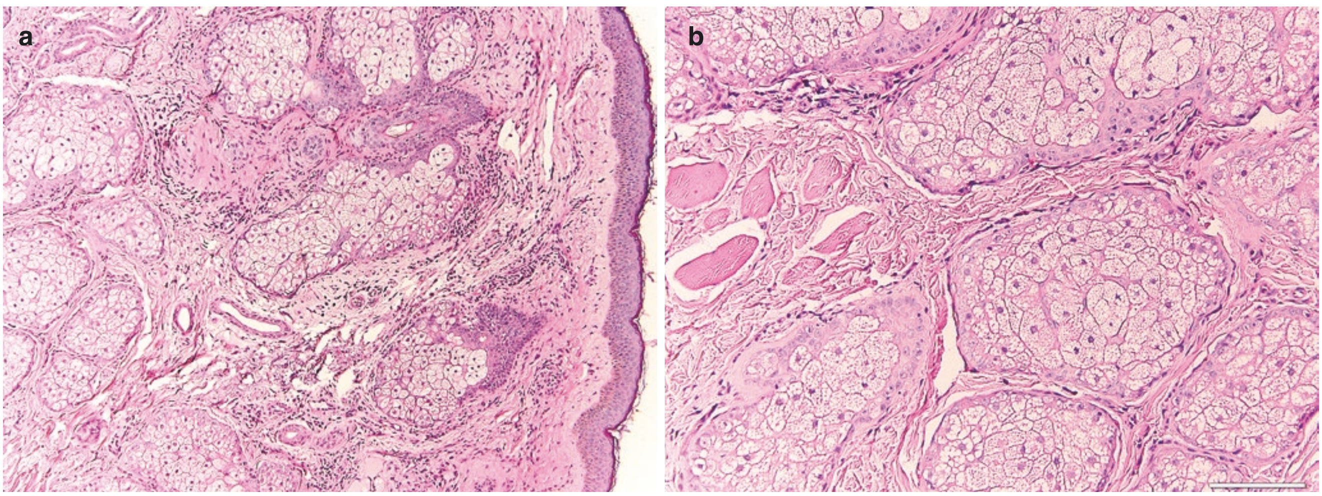

Fig. 1.15 (**a**) Nipple sebaceous gland hyperplasia: the lesion is microscopically represented by hyperplastic and hypertrophic mature sebaceous glands aggregates involving the dermis, (**b**) lacking atypical features (Courtesy of Dr. Sabina Zurac)

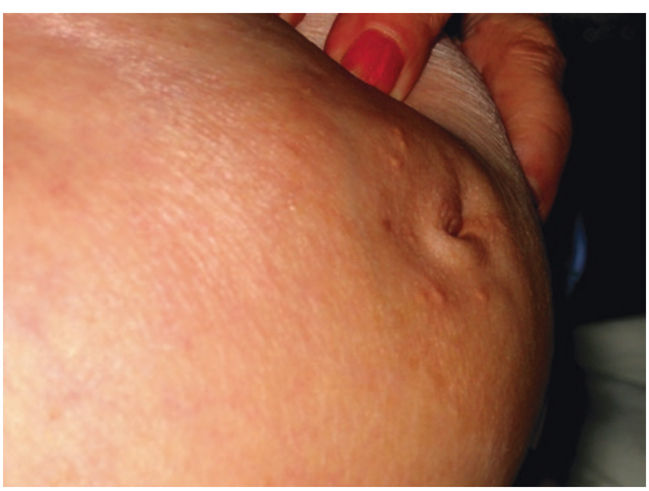

Fig. 1.16 Congenital inverted nipple: macroscopic appearance (Courtesy of Dr. Marius Florin Coros)

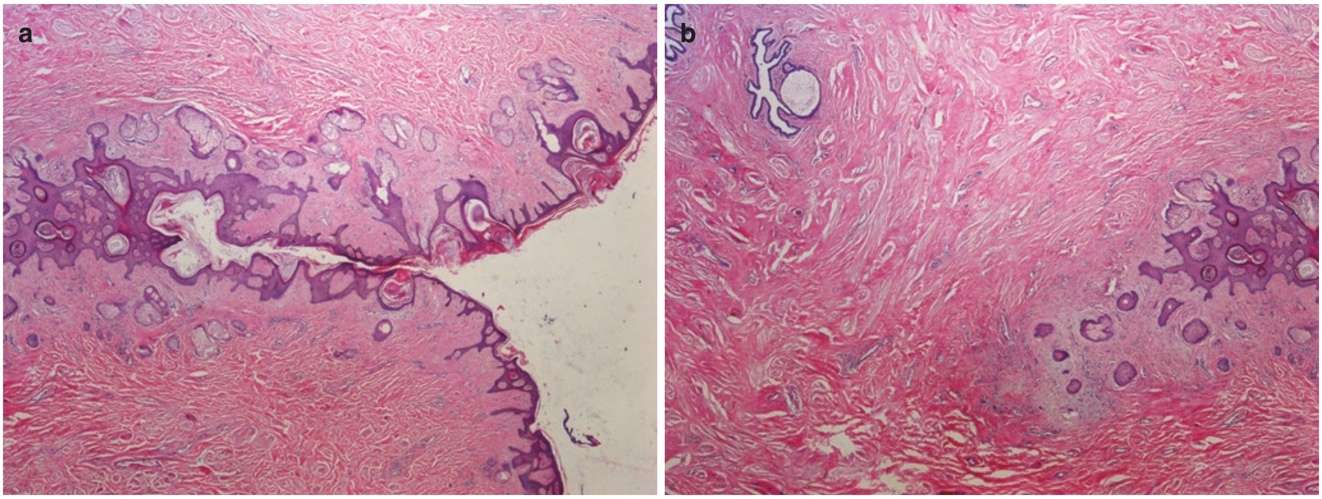

Fig. 1.17 Congenital inverted nipple: (**a**) microscopic examination revealed the squamous epithelium invaginated into the underlying stroma and (**b**) in the vicinity of lactiferous ducts, some of which can become dilated

Fig. 1.18 Acquired inverted nipple of the right breast in a patient with invasive carcinoma (Courtesy of Dr. Marius Florin Coros)

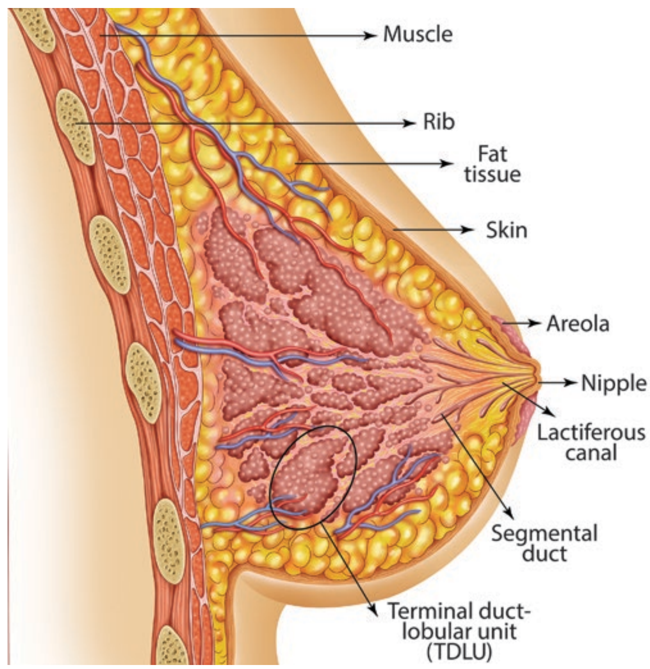

Fig. 1.19 The deep segment of the ductal system is called terminal duct; several terminal ducts unite and constitute subsegmental ducts that drain into segmental ducts; segmental ducts unite and form lactiferous ducts that open in the nipple (*From* Alexilusmedical/Shutterstock; *with permission*)

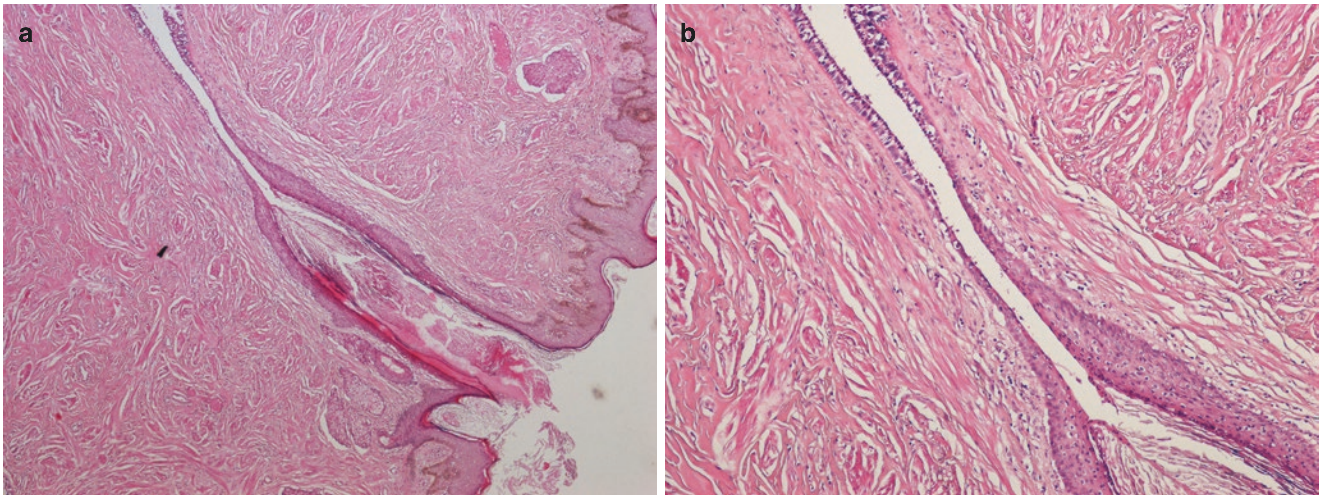

Fig. 1.20 (**a**) The superficial portion of the duct orifice is covered by squamous epithelium, and this epithelium may extend for a short distance into the most distant portion of the duct. (**b**) The area where the squamous epithelium joins the columnar epithelium is called the squamous-columnar junction

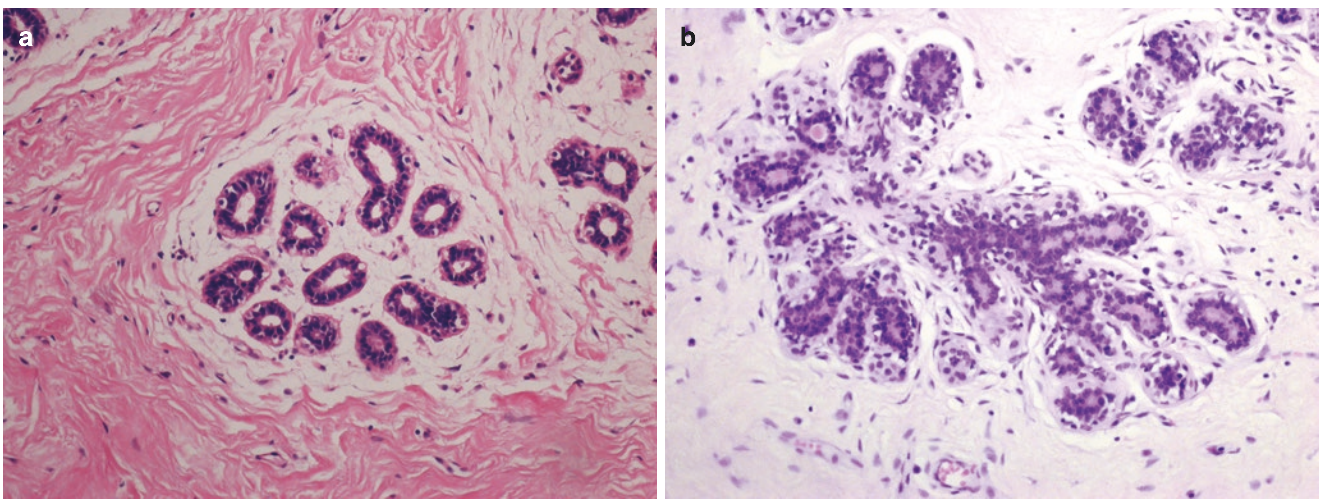

Fig. 1.21 (**a**) The whole ductal system as well as the acini are lined by two layers of cells: the inner layer of epithelial cells (flattened/cuboidal/columnar, with pale eosinophilic cytoplasm and uniform oval nuclei), and the outer layer of myoepithelial cells (the cytoplasm of which contains glycogen, which gives a cleared appearance in the Hematoxylin-Eosin stained slides). (**b**) At the periphery, the two layers are surrounded by a basement membrane and fibroblasts

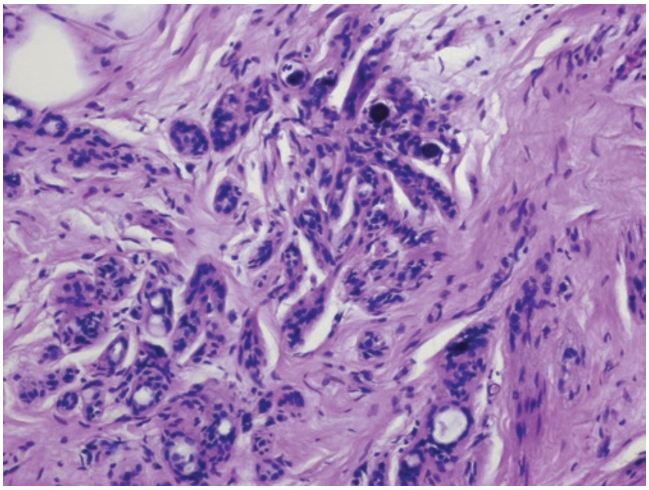

Fig. 1.22 The myoepithelial cells sometimes have a myoid appearance with a spindle shape and dense eosinophilic cytoplasm

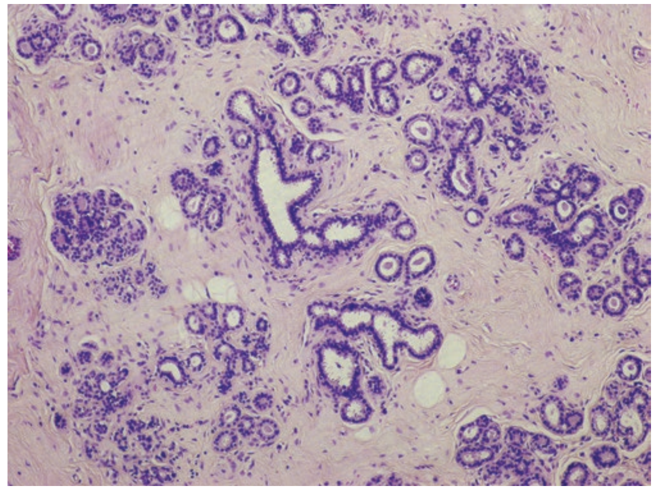

Fig. 1.24 The intralobular segment of the terminal duct along with the acini will constitute mammary lobules, also called terminal ductal-lobular units (TDLU)

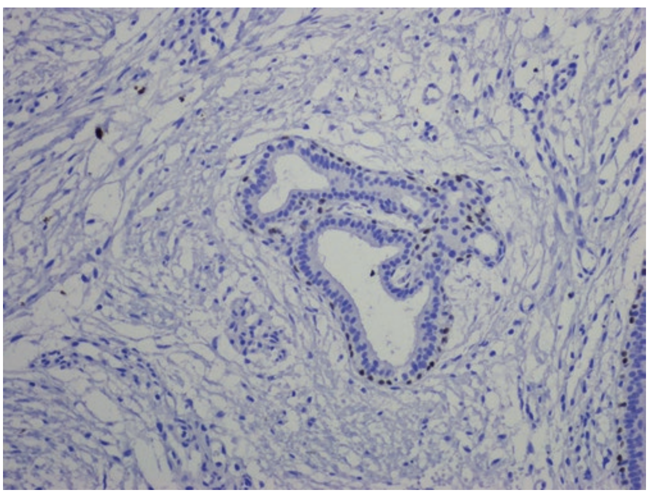

Fig. 1.23 p63 stain highlights the discontinuity of the myoepithelial layer in normal ducts

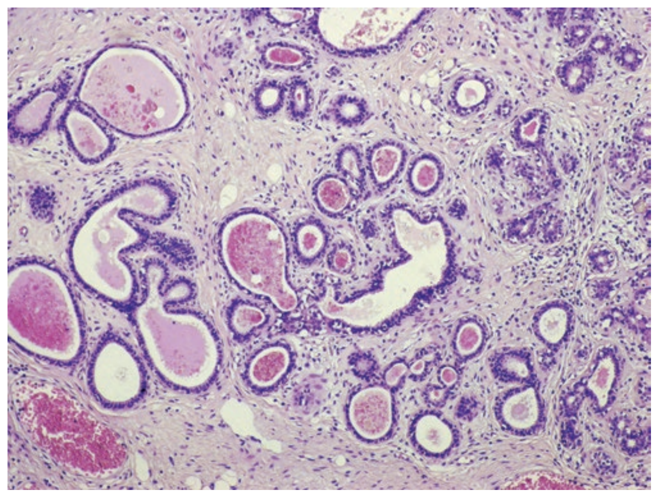

Fig. 1.25 In contrast with normal TDLU, the unfold lobule consists of acini and ducts that become larger and cystically dilated

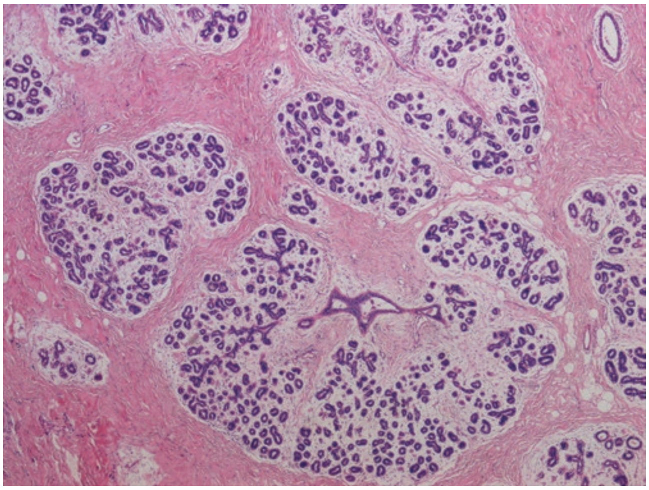

Fig. 1.26 Around the acini and the ducts, the stroma is hormone-dependent and is more cellular (intralobular stroma), while interlobular stroma is less cellular and is not hormone-dependent

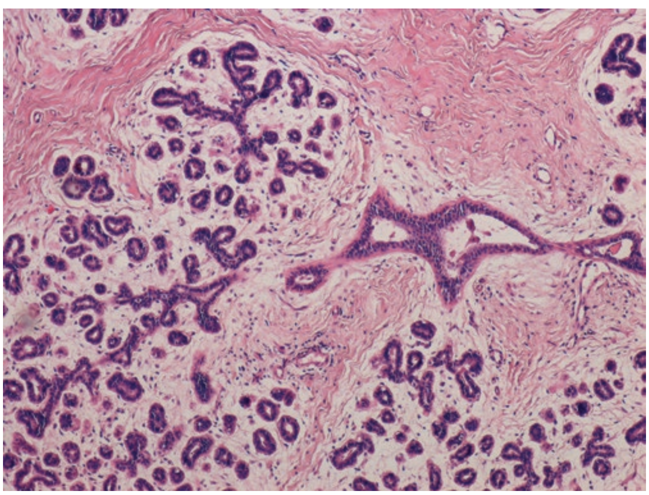

Fig. 1.27 Intralobular stroma consists of collagenous connective bundles, abundant fundamental substance, fibroblast cells, and often displays a mucoid character (positive for Alcian blue—not shown here)

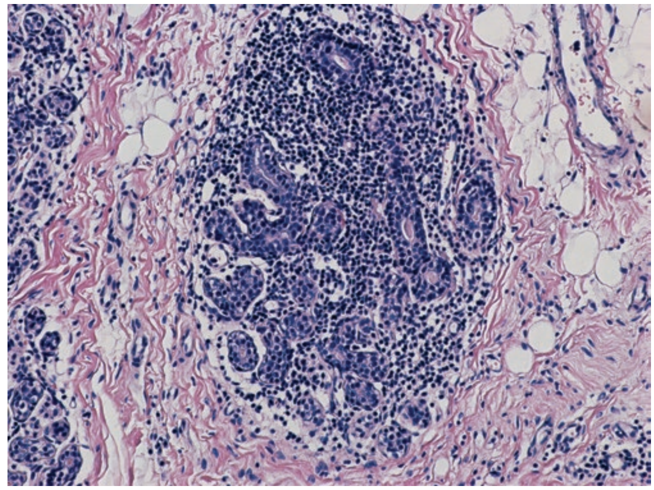

Fig. 1.28 The intralobular stroma of mammary glands free of pathological changes usually presents a varying number of lymphocytic and/or plasma cells

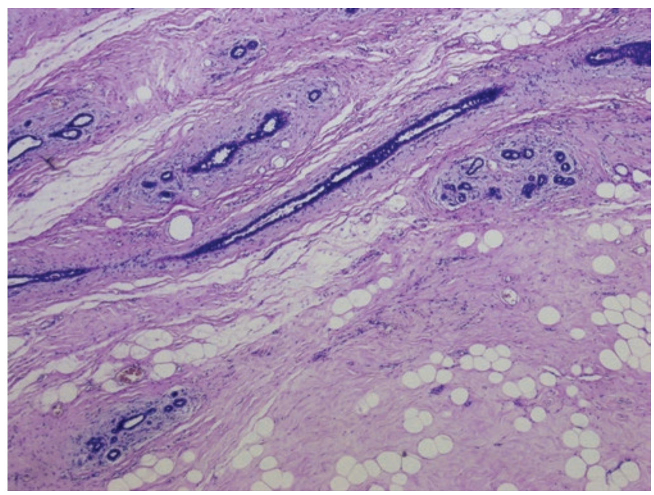

Fig. 1.29 Adipose tissue can be found only between mammary lobes and it never appears intralobularly