



Epithelial Proliferative Lesions

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Epithelial Proliferative Lesions

Epithelial proliferative lesions of the breast are a heterogeneous group of intraepithelial lesions that includes ductal hyperplasia without atypia, atypical ductal hyperplasia (ADH), low-grade ductal carcinoma in situ (DCIS), glandular adenosis, intraductal papillomas, lobular intraepithelial neoplasia (LIN), and radial scar (RS)/complex sclerosing lesion (CSL). These can be extremely difficult to subclassify on cytological specimens [Sneige and Staerke, 1994; Frost et al., 1997; Silverman et al., 1993], but a strong effort must be made by cytopathologists to make a distinction between the major categories, especially those requiring different management and treatment. Beyond the direct consequences of a “benign” or a “malignant” diagnosis, the correct identification of proliferative breast lesions is fundamental in predicting the possible subsequent development of invasive carcinoma [Abendroth et al., 1991].

Note that a definite diagnosis of proliferative breast lesions may be difficult also on core needle biopsy and even on a surgical specimen due to the marked interobserver variability and the heterogeneity of the lesions themselves, which may show a mix of coexisting different features [Schnitt et al., 1992]. In this chapter, we give some hints regarding the interpretation

of aspirates taken from epithelial proliferative lesions, trying to underline the differences between the main categories in order to guide the patients to the best management.

Ductal Epithelial Hyperplasia

Introduction/Epidemiology

Ductal epithelial hyperplasia without atypia or usual hyperplasia lies at one end of the spectrum of breast proliferative lesions, opposite to high-grade DCIS. It is a common breast alteration, as it is found in approximately 30% of breast biopsies with a benign diagnosis [Lakhani et al., 2012]. It is a nonpalpable lesion and might be detected in the presence of calcifications or be a part of a complex lesion.

Histological Features

Usually, hyperplasia consists of an increase in the number of epithelial cell layers lining the ducts, which may form cellular bridges across the duct lumen. The nuclei have a haphazard orientation and do not show significant irregularities in size, shape, and chromatin pattern (Fig. 1). The histolog-

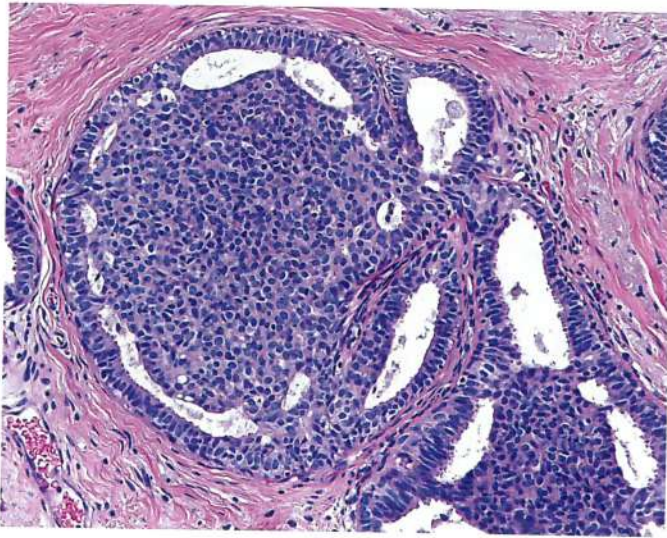


Fig. 1. Histology of usual epithelial hyperplasia. The proliferating ductal epithelial cells form cellular bridges across the lumen. The nuclei have a haphazard orientation and do not show significant irregularities in size, shape, and chromatin pattern. H&E. Low power.

ical definition of this lesion includes the terms *mild* ductal hyperplasia when there are 2 or 4 ductal cell layers, *moderate* hyperplasia when there are more layers, and *florid* hyperplasia when the layers are so numerous to fill the ductal lumen completely. This might determine the formation of secondary, slit-like lumina at the periphery of the duct.

Cytology

Aspirates from areas of ductal hyperplasia without atypia usually display wide monolayer sheets of ductal cells with round to oval nuclei, a discrete amount of cytoplasm, and visible intercellular spaces in a honeycomb structure (Fig. 2). Myoepithelial cells are evident above ductal cells. Some single epithelial cells with intact cytoplasm may be present, mimicking low-grade carcinoma, but these cells do not show significant nuclear atypia: nuclear borders are neat and regular, chromatin is finely dispersed, and nucleoli are small. Epithelial layers may seldom show digit-form projections similar to those seen in aspirates from fibroadenomas (Fig. 3) [see Chapter 7, this vol., pp. 58–67].

Aspirates should be considered benign (C2) if they are mainly composed of cohesive epithelial monolayer sheets with evident myoepithelial cells and without significant atypia, a concept that will be explained in detail in the following paragraphs.

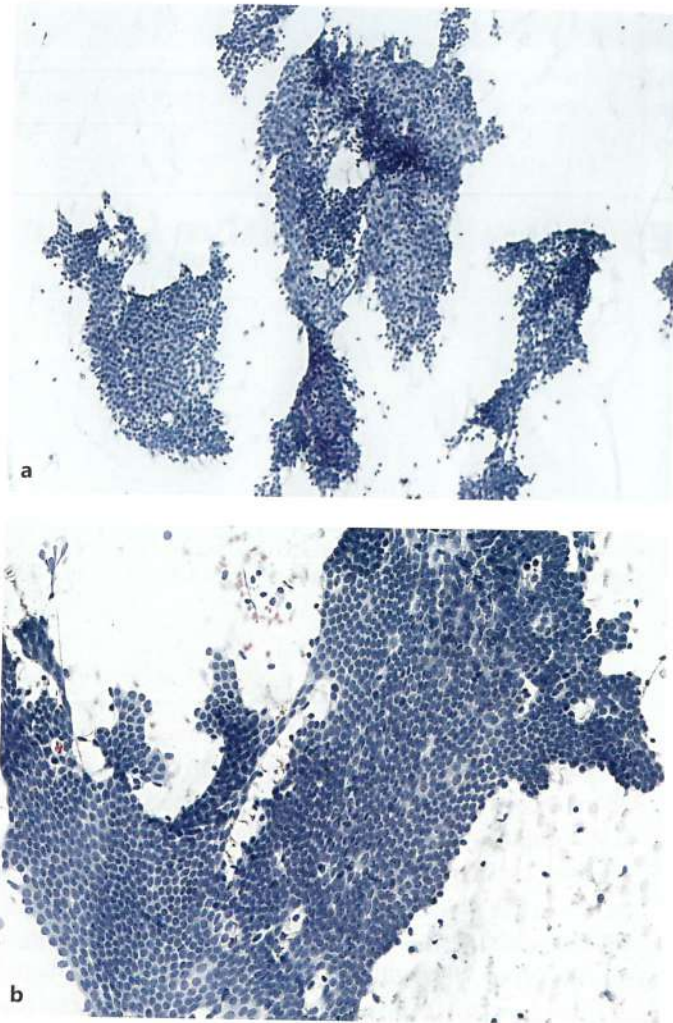


Fig. 2. Cytology of usual epithelial hyperplasia. This smear is highly cellular and is composed mainly of wide monolayer sheets of uniform ductal cells with honeycomb structure and myoepithelial cells. These epithelial layers show focally a cribriform configuration (b). Scattered bare nuclei are evident in the background. Papanicolaou. **a** Low power. **b** Intermediate power.

Summary

Key Cytological Features of Ductal Epithelial Hyperplasia

- Moderate to marked cellularity
- Monolayer sheets of ductal cells with myoepithelial cells
- Low to moderate number of isolated epithelial cells
- No cytological atypia

Common Pitfalls of FNA: Ductal Epithelial Hyperplasia

- High number of isolated cells
- Slight nuclear atypia

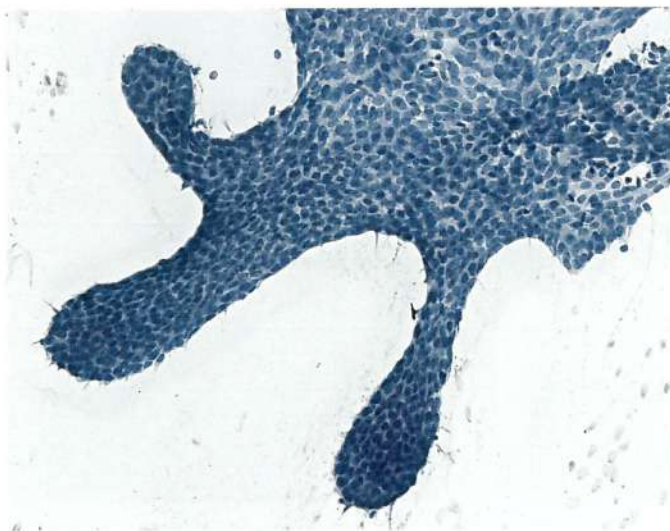


Fig. 3. Usual epithelial hyperplasia. Epithelial cell clusters may form digit-form projections resembling those of fibroadenomas. Note the neat and curved edges of the cluster, presence of myoepithelial cells, and homogeneity of nuclei. Papanicolaou. Intermediate power.

Atypical Epithelial Hyperplasia and Low-Grade Ductal Carcinoma in situ

Introduction/Epidemiology

ADH and low-grade DCIS represent both close steps in the spectrum of breast epithelial proliferative lesions. They are usually asymptomatic and detected through mammography in the presence of calcifications, which are typically assessed as “indeterminate” by the radiologists, and contrary to the coarse, pleomorphic, and branched ones seen in high-grade DCIS with comedo necrosis. Some low-grade DCIS might be mass forming and present as palpable masses.

DCIS is a heterogeneous disease that can be divided into several subgroups (namely *solid*, *papillary*, *cribriform*, and *comedo*) based on its architectural features and into low and high grade based on the degree of nuclear alterations and the presence or absence of necrosis. Low- and high-grade DCISs represent 2 genetically distinct entities, which may lead to the development of different types of invasive breast carcinoma. High-grade lesions have a greater tendency to evolve into invasive cancer (usually high-grade histotypes), they are easy to recognize as malignant lesions on aspirates as well as core biopsies, and the main differential diagnosis includes invasive cancer. Conversely, low-grade DCIS is an indolent and slowly progressing lesion that may evolve

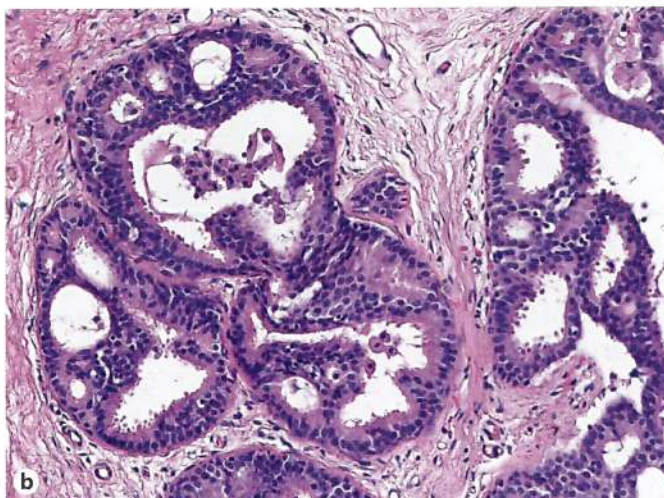
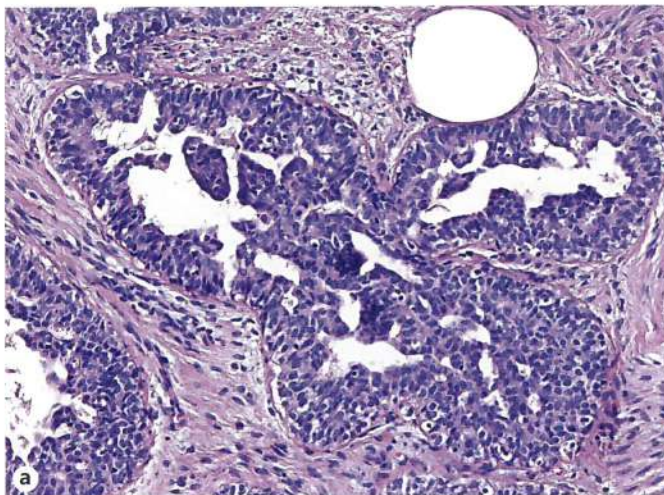


Fig. 4. Histological features of atypical ductal hyperplasia/low-grade ductal carcinoma in situ. Ductal spaces are partially filled with hyperplastic epithelium showing mild nuclear atypia and a micropapillary (a) or cribriform (b) configuration. The distinction between atypical ductal hyperplasia and low-grade ductal carcinoma in situ is mainly based on dimensions. H&E. Intermediate power.

into well-differentiated invasive carcinomas [Simpson et al., 2005].

We defer the discussion on high-grade DCIS to Chapter 8 [this vol., pp. 68–93]; its cytological findings are very similar to those of invasive breast carcinoma.

Histological Features

ADH and low-grade DCIS present histologically as monotonous epithelial ductal proliferations with a solid, micro-

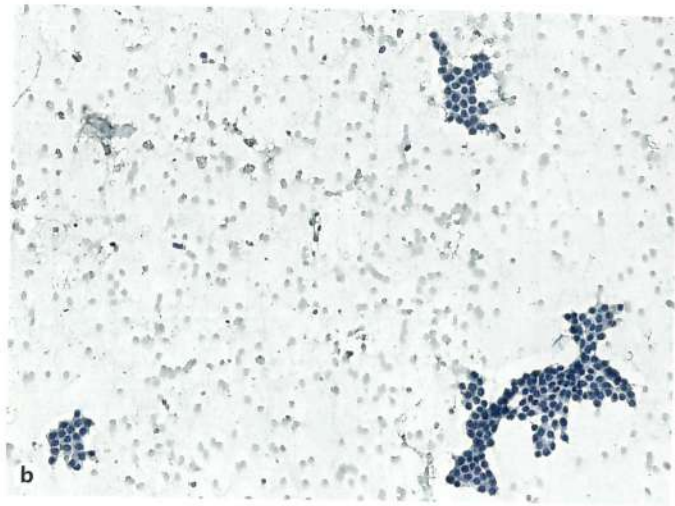
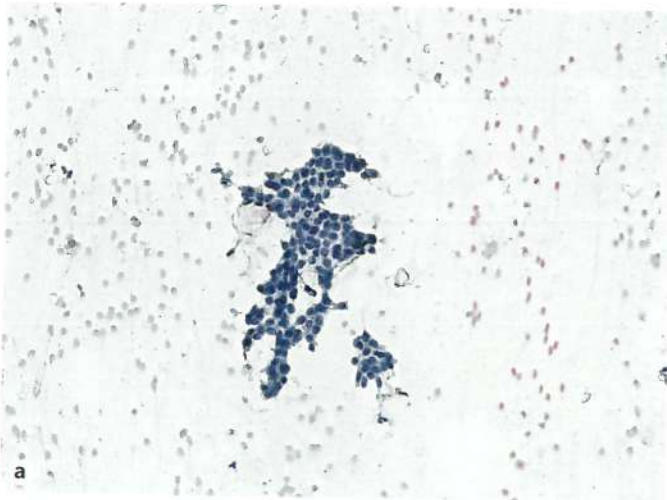


Fig. 5. Epithelial hyperplasia with mild atypia. Cellularity in this smear is composed of monolayer or slightly hyperplastic clusters of rather uniform epithelial cells. These are not the broad sheets with honeycomb structure of a completely benign-looking proliferation and show slight architectural complexity (**a, b**). Some clusters lack myoepithelial cells. This lesion was prudently assessed as “undetermined, probably benign” (C3) and close follow-up was recommended. Papanicolaou. **a, b** Intermediate power.

papillary, or cribriform architecture lacking necrosis or with only small foci of necrosis and without severe nuclear atypia (Fig. 4). The distinction between ADH and low-grade DCIS is mainly based on their dimensions or quantitative characteristics [Lakhani et al., 2012] and thus cannot be assessed on cytological specimens.

Cytology

The diagnosis of atypia in breast FNAC is a source of controversy between cytopathologists [Lim et al., 2004]. It includes nuclear atypia and/or architectural atypia (poor cellular cohesiveness and complexity and branching of tissue fragments) [Dawson et al., 1995; Sneige and Staerkel, 1994].

Aspirates taken from ADH or low-grade DCIS show moderately to highly cellular epithelial layers, which may show a cribriform or papillary architecture, solid 3-dimensional aggregates, and a discrete number of isolated intact epithelial cells. Epithelial cell nuclei are usually 1.5–2 times the size of a red blood cell and may show some slight irregularity in size, shape, or chromatin pattern but are generally monotonous. The smears typically display an admixture of normal benign epithelial fragments and atypical clusters (Fig. 5–7) [Shin and Sneige, 1998].

The presence of such characteristics is usually sufficient to enter the case in the category of undetermined (C3) or suspicious lesions (C4), which need further diagnostic investigation through a tissue biopsy.

The presence of many dispersed cells with high-grade nuclear abnormalities and an inflammatory background raises the possibility of a high-grade comedo DCIS or a high-grade invasive carcinoma. Cytology is unable to make an accurate distinction between in situ and invasive carcinoma, also because they are frequently found in association to each other. Thus, the finding of high-grade malignant cells must lead the pathologist to consider the lesion as malignant and immediately address the patient to the adequate treatment.

Summary

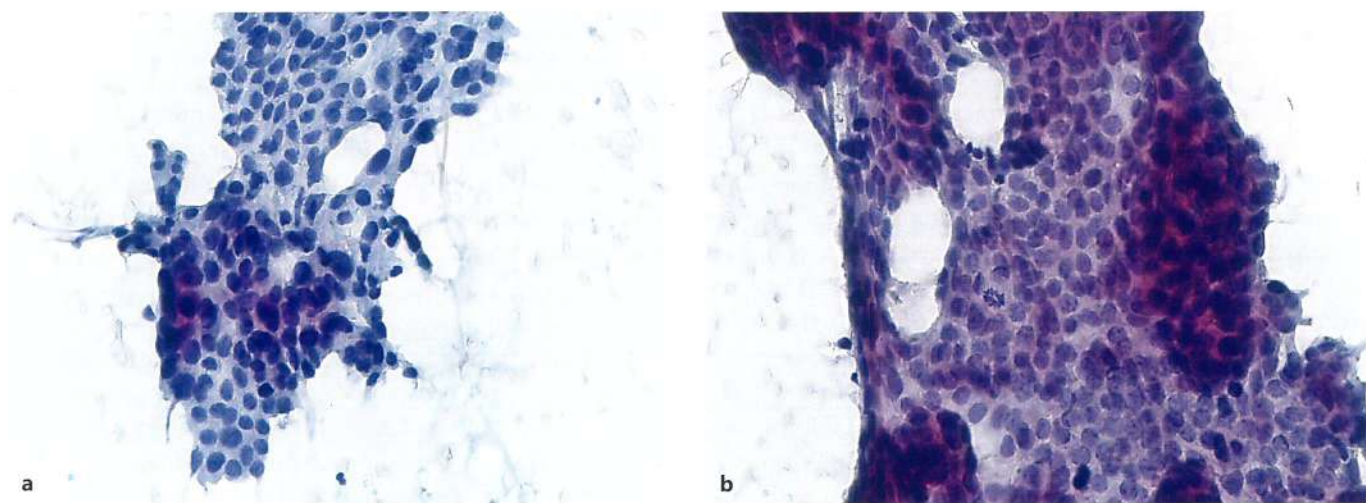
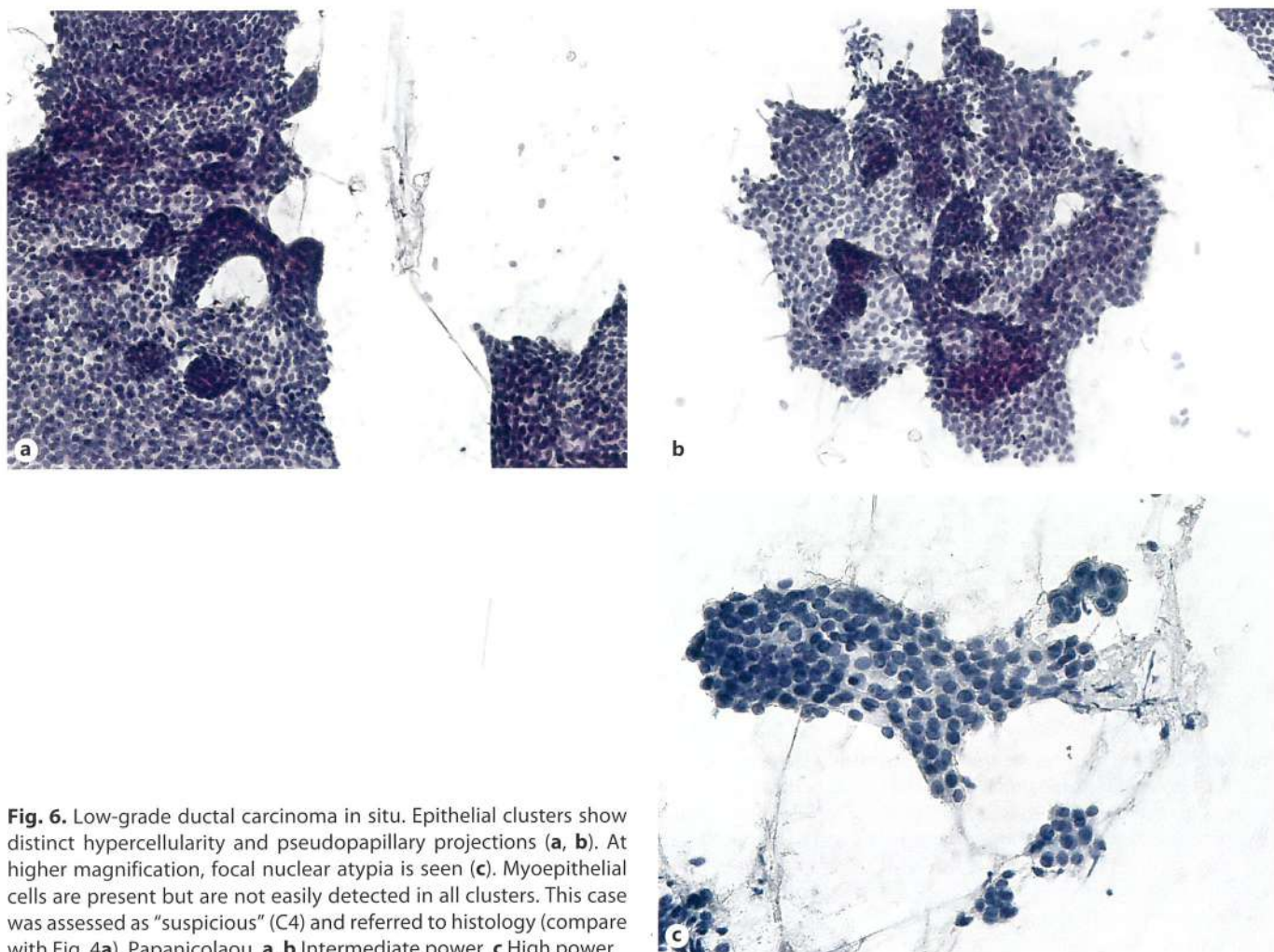
Key Cytological Features of Atypical Ductal Hyperplasia/Low-Grade Ductal Carcinoma in situ

- Moderate to marked cellularity
- Variable number of single dissociated cells
- Some 3-dimensional clusters and epithelial layers with pseudopapillary and/or cribriform arrangement
- Slight nuclear abnormalities (shape, size, and chromatin distribution)
- Admixture of benign and atypical cell layers

Lobular Intraepithelial Neoplasia

Introduction/Epidemiology

The term lobular intraepithelial neoplasia includes lesions defined as atypical lobular neoplasia and lobular carcinoma



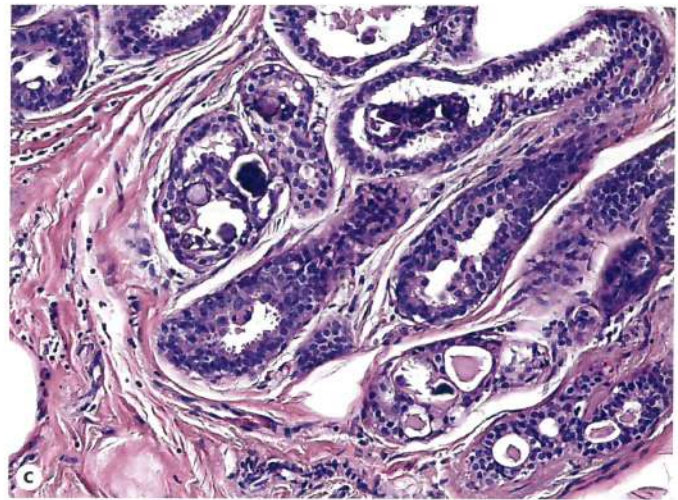
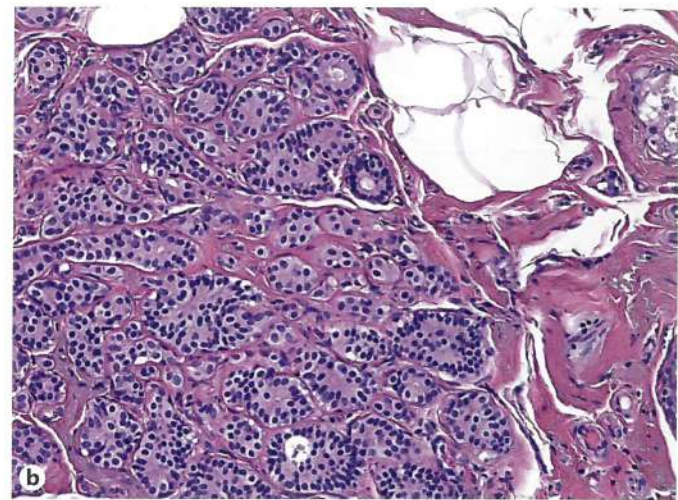
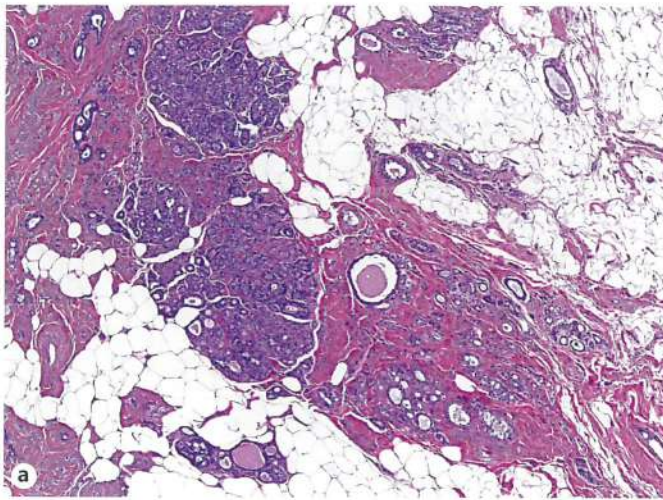


Fig. 8. Histological features of sclerosing adenosis. Sclerosing adenosis is a complex histologic lesion characterized by expansion of the terminal ductal lobular units and fibrosis of the intralobular stroma. The lesion might show a pseudo-infiltrative growth pattern that renders its sonographic findings suspicious. The stromal fibrosis and epithelial proliferation might obliterate the small duct lumina and produce microcalcifications (c). H&E. **a** Scanning magnification. **b, c** Intermediate power.

in situ, which are distinguished based on quantitative criteria [Lakhani et al., 2012]. LIN is typically asymptomatic; unlike DCIS, it does not produce calcifications, even remains undetected by high-resolution radiological techniques, and is most of the time an incidental finding in breast biopsies performed for other reasons. It is reported in approximately 0.5–4% of otherwise benign breast biopsies, but its true incidence is largely unknown. LIN is considered a risk factor for the development of invasive breast carcinoma of either ductal or lobular type in either breast [Ellis et al., 2003].

Because of the difficulty in identifying LIN through mammography and ultrasound, the frequent multicentricity and bilaterality of the lesion, and its unpredictable behavior, the management of patients diagnosed with LIN on biopsy is still a highly debated topic. Some authors recommend excisional biopsy when a focal lesion can be

identified, since on surgical excision LIN is associated with a more serious lesion in a significant number of cases [Elsheikh and Silverman, 2005; Purdie et al., 2010], while others advocate close follow-up and recommend excision only when radiology/pathology discordance is found [Nagi et al., 2008].

Histological Features

LIN is characterized by the presence of a uniform population of small, round-shaped, monomorphic cells filling the acini with obliteration of the acinar lumina and possible extension to the adjacent ductal epithelium with a *pagetoid* pattern. These small cells typically do not show significant atypia, with the exception of the pleomorphic variant, and lack the immunohistochemical expression of E-cadherin.

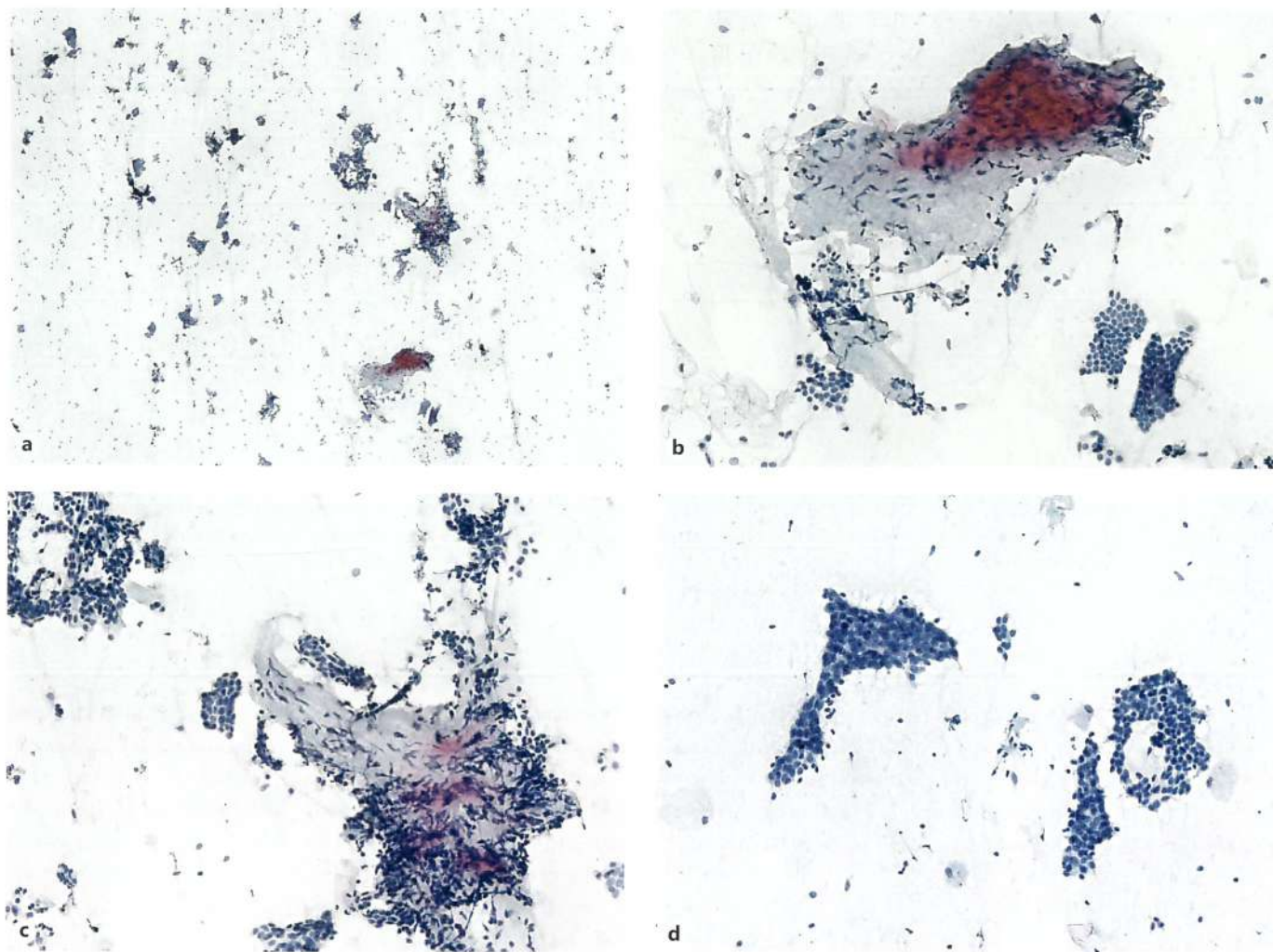


Fig. 9. Cytology of sclerosing adenosis. Cellularity of aspirates taken from sclerosing adenosis can vary widely and is moderate in this case, with many epithelial cell clusters of different shapes and sizes (a). At higher magnification, these clusters are slightly hypercellular and have tubular or acinar configuration, with evident myoepithelial cells on the surface (b, c). Additional findings include sclerotic stromal fragments (c), scattered bare nuclei, and foamy cells in the background (d). Papanicolaou. **a** Scanning magnification. **b–d** Intermediate power.

Cytology

LIN is rarely encountered in FNAC, since it is not palpable and not detected by ultrasound. Nevertheless, it might occur adjacent to or in the context of another lesion and present in the aspirate as an occasional finding. It displays a variable number of uniform, small cells with bland, eccentric nuclei and vacuolated cytoplasm, arranged singly or in tight clusters.

The main differential diagnosis to be considered is invasive lobular carcinoma, which is made up of the same cells, and, in such cases, the radiological features of the lesion are helpful. Since LIN is asymptomatic and neither visualized

by ultrasound nor by mammography, features of the original lesion that lead to a biopsy should be present in the aspirate.

Adenosis and Sclerosing Adenosis

Introduction/Epidemiology

“Adenosis” is a term used to define an increment in the number of acinar structures in breast lobules. Sclerosing adenosis is a distinct lesion characterized by the architectural disorganization of the terminal ductal-lobular unit with epithelial and myo-

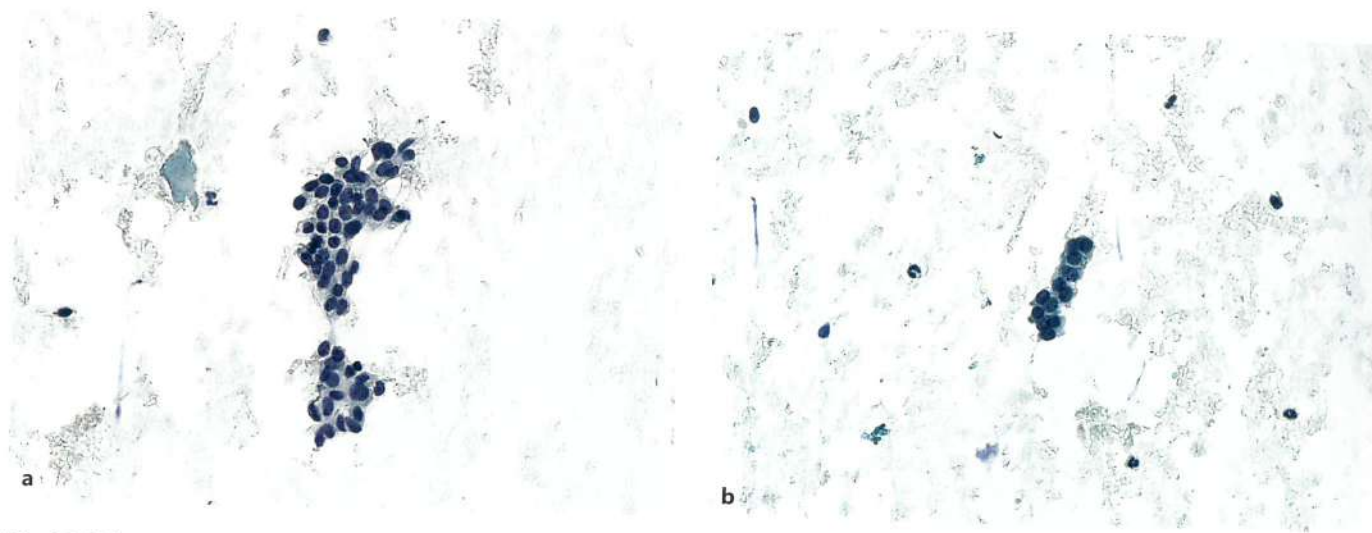


Fig. 10. Sclerosing adenosis. This smear is loosely cellular and has scattered, small epithelial cell clusters without significant cytological atypia (a). Myoepithelial cells are rare or even absent in some clusters, and this finding, together with the poor cell-to-cell cohesion and the occasional single cells (b), was sufficient to put this case in the suspicious category (C4). On histological evaluation, it turned out to be an area of sclerosing adenosis. Papanicolaou. a, b High power.

epithelial proliferation and stromal fibrosis [Jensen et al., 1989], a well-known source of diagnostic errors [Cho and Oh, 2001; Sreedharanunni et al., 2013]. It is a common finding, which occurs in 27.8% of all benign biopsies, and it is associated with an increased risk of invasive breast cancer [Visscher et al., 2014].

Histological Features

The histological examination of sclerosing adenosis shows expansion of the terminal ductal-lobular unit with increased numbers of small-sized acini and dense fibrosis of the intralobular stroma. Stromal fibrosis may compress the glands and obliterate ductal lumina, generating calcifications and giving the lesion a pseudo-invasive appearance (Fig. 8). The presence of myoepithelial cells is the most important clue to recognize this lesion and distinguish it from invasive carcinoma.

Cytology

The presence of irregular calcifications and architectural distortion in sclerosing adenosis may lead to diagnostic biopsies of masses suspicious of an invasive carcinoma. FNAC samples taken from areas of sclerosing adenosis are usually moderately cellular and display many small groups or acinar sheets of uniform ductal cells with myoepithelial cells and bare bipolar nuclei and some hyalinized stromal fragments in the background (Fig. 9). Focal apocrine metaplasia, foamy cells, and scattered individual epithelial cells might be present [Cho and Oh, 2001; Silverman et al., 1989]. The cellular-

ity of the smear and the presence of 3-dimensional clusters, as well as the presence of slight to moderate nuclear pleomorphism, can be misleading and result in false-positive results (Fig. 10). For this reason, much attention should be given to the myoepithelial cells above the epithelial cells and to the presence of bare nuclei.

Possible differential diagnoses include fibroadenoma, which typically shows high cellularity and an admixture of epithelial and stromal fragments. The key elements for this differential diagnosis are the acinar epithelial sheets typical of adenosis rather than in digit form or staghorn clusters of fibroadenoma, the presence of single epithelial cells, and the hyalinized stroma of sclerosing adenosis, which is different from the fibromyxoid one of fibroadenoma (Fig. 11) [Sreedharanunni et al., 2013].

Summary

Key Cytological Features of Sclerosing Adenosis

- Moderate to marked cellularity
- Small acinar and tubular clusters
- Myoepithelial cells and scattered bare nuclei
- Hyalinized stromal fragments

Common Pitfalls of FNA: Sclerosing Adenosis

- Three-dimensional clusters
- Epithelial dissociated cells
- Slight to moderate nuclear pleomorphism

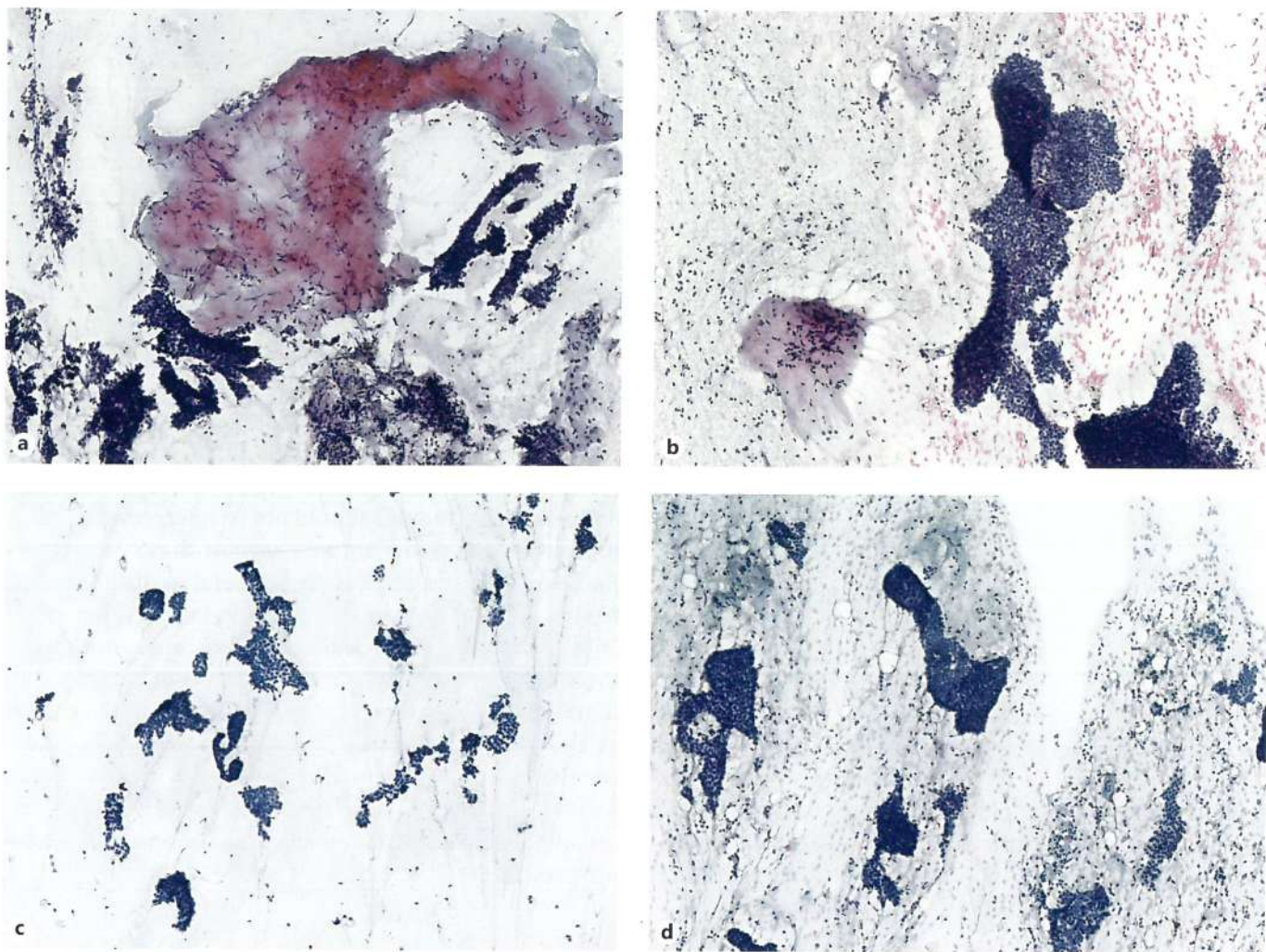


Fig. 11. Comparison between sclerosing adenosis and fibroadenoma. Sclerosing adenosis and fibroadenoma may look very similar to each other on the cytological smear, but a distinction can be made in most cases relying mainly on their different pattern at low magnification. Epithelial clusters of sclerosing adenosis (**a, c**) vary widely in size within the same lesion but are usually rather small, and typically they have a distinct tubular or acinar configuration. Conversely, epithelial clusters of fibroadenomas (**b, d**) tend to be larger, broader, and show neat round (digit-form) edges. Bare bipolar nuclei are extremely numerous in many fibroadenomas. Furthermore, stromal fragments are sclerotic and hyalinized in sclerosing adenosis, while they are typically myxoid or densely cellular in fibroadenomas. Papanicolaou. Low power.

Intraductal Papilloma (Benign Papillary Lesions of the Breast)

Introduction/Epidemiology

Intraductal papillary lesions of the breast form a wide spectrum of pathological changes, with benign intraductal papilloma on one end of the spectrum and papillary carcinoma at the other end. Papillary lesions may be solitary or multiple, central or peripheral; clinically, they may present as palpable masses or cause nipple discharge (sometimes hemat-

ic). Mammography may show well-circumscribed, single, or multiple lesions of varying size with or without calcification. Ultrasound of these lesions may show a complex intracystic lesion or a homogenous solid lesion, often accompanied by duct dilatation [Ganosan et al., 2006].

Histological Features

Intraductal papillary lesions, whether benign or malignant, are characterized by the presence of fibrovascular cores lined by epithelial proliferation with varying degrees of

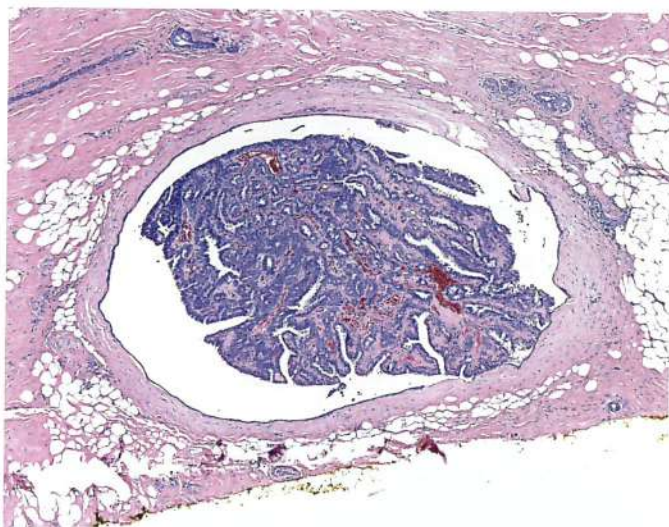


Fig. 12. Intraductal papilloma. This cystically dilated milk duct hosts a papillary lesion composed of a branching fibrovascular stalk lined by uniform columnar epithelial cells without atypia. H&E. Low power.

atypia (Fig. 12). Papillomas may vary in size from less than 1 mm to several centimeters; larger lesions may contain necrotic or hemorrhagic areas and microcalcifications and usually develop inside a dilated duct or a cyst. Ductal epithelial hyperplasia as well as apocrine metaplasia and even cytological atypia may coexist.

Cytology

Many different breast lesions may show “papillary” features on cytological preparations. These include true papillomas and other entities with papillary component, such as RS, fibrocystic change, fibroadenomas, and ductal carcinoma, both in situ and invasive. Though a definite diagnosis of the nature of papillary lesions is possible on an excision biopsy, the distinction is not easy on aspiration cytology. This is due to the overlapping cytological features between benign and malignant as well as other entities containing a papillary component [Simsir et al., 2003].

Cytological smears from intraductal papillomas show moderate to marked cellularity, with abundant isolated columnar cells and 3-dimensional, branched epithelial cell sheets. Tissue fragments are predominantly large, with some scattered smaller fragments (Fig. 13, 14, 16) [Field and Mak, 2006]. Fibrovascular cores are often (but not always) recognizable, as well as dispersed bare nuclei and cyst macrophages [Jeffrey and Ljung, 1994]. Field and Mak [2006] em-

phasized the importance of a clear terminology while describing the so-called “papillary clusters” or “papillary features” in aspirates from breast lesions. They described “stellate” and “meshwork” tissue fragments as highly sensitive and specific morphological features for the diagnosis of intraductal papillomas (Fig. 14).

Papillary lesions might display some features of suspicion in the form of complex papillae and single atypical cells, making the distinction from carcinoma difficult [Reid-Nicholson et al., 2006]. Infarcted papillomas may show moderate atypia, usually associated to hemosiderin-laden macrophages (Fig. 15). Apocrine metaplastic cells with large, granular cytoplasm and round nuclei with small nucleoli are a common finding in papillary lesions. Note that apocrine cell sheets typically do not show myoepithelial cells, and this should not be interpreted as a malignant feature. Some authors suggest that stromal bare nuclei and nuclear atypia may be useful in distinguishing benign from malignant papillary lesions [Nayar et al., 2001]. However, the lack of specificity and sensitivity of these features makes a definite diagnosis of benign papilloma impossible on aspiration cytology. The diagnostic category for such lesions should always be at least “indeterminate, probably benign” (C3), suggesting the need of a close follow-up or surgical excision when cytological-radiological discordance occurs or additional risk factors are present.

Summary

Key Cytological Features of Intraductal Papilloma

- Moderate to marked cellularity
- Predominance of large tissue fragments with scattered small tissue fragments
- Proteinaceous background with macrophages and/or siderophages
- Dissociated columnar cells
- Stellate tissue fragments
- Myoepithelial cells in epithelial cell layers
- Fibrovascular cores
- Apocrine cell sheets

Common Pitfalls of FNA: Intraductal Papilloma

- Cellular atypia
- Lack of myoepithelial cells
- Necrotic or hemorrhagic background

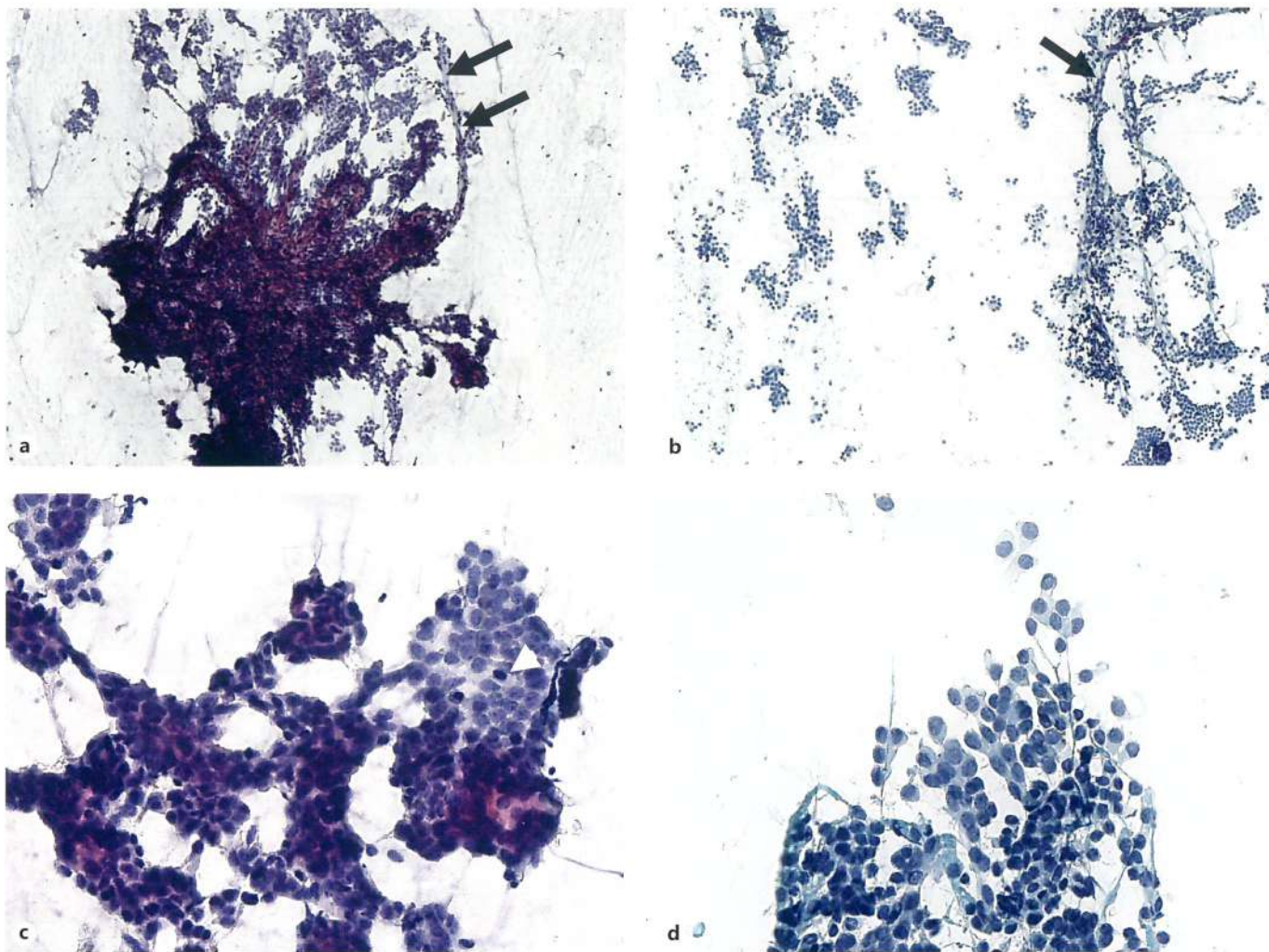


Fig. 13. Cytological features of benign papillary lesions. Aspirates from papillary breast lesions tend to be markedly cellular and show an admixture of large and small epithelial clusters with at least some tendency towards the loss of cell-to-cell cohesion. Larger tissue fragments are often 3-dimensional and branching, and a stromal fibrovascular core may be present (arrows) (**a**, **b**). At higher magnification, attention must be paid to nuclear features and the presence of myoepithelial cells (arrowhead) (**c**). Because of their unpredictable behavior, papillary lesions are never to be considered completely benign, and even those lesions without cytological atypia should be put in the undetermined category (C3). Papanicolaou. **a**, **b** Low power. **c**, **d** High power.

Radial Scar/Complex Sclerosing Lesion

Introduction/Epidemiology

RS is a well-defined radiological and histopathological entity, characterized by a central fibroelastotic core and radiating bands of fibrous tissue containing varying degrees of epithelial proliferation, which can simulate cancer both macroscopically and on microscopic examination [Page and Anderson, 1987]. Lesions larger than 1 cm are defined

as CSL. They might be considered as an accentuation of fibrocystic changes associated with epithelial hyperplasia, adenosis, and papillomatosis. The lesion is by definition nonpalpable, and its detection is an incidental finding in 0.09% screening mammograms as a stellate opacity with thin and asymmetric spikes, radiolucent nucleus, and microcalcifications resembling a malignant lesion [Finlay et al., 1994; Loane, 2009].

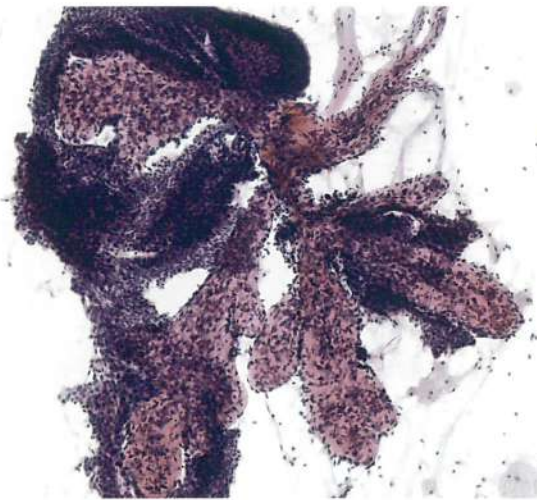


Fig. 14. Intraductal papilloma. The so-called “stellate” tissue fragments are regarded as a highly sensitive and specific morphological feature to correctly diagnose benign papillary lesions of the breast, since they are uncommon in other benign proliferative lesions as well as in papillary carcinomas. Papanicolaou. Low power.

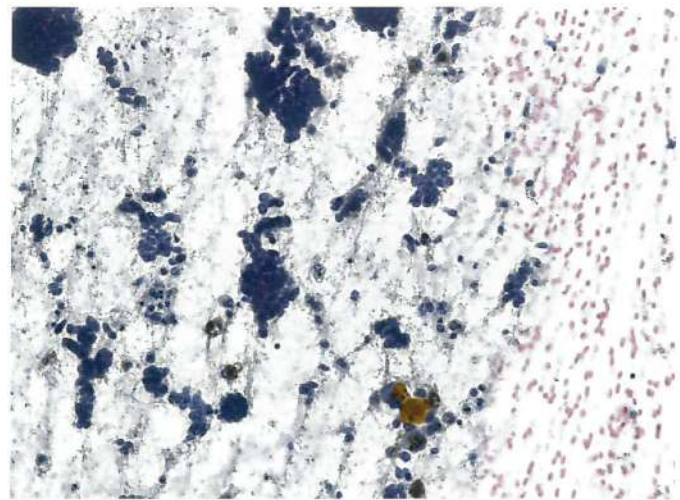


Fig. 15. Infarcted papilloma. The smear is highly cellular and some macrophages with hemosiderin granules in the cytoplasm lie between epithelial cell clusters. Many erythrocytes and granular proteinaceous material are present in the background. Papanicolaou. Intermediate power.

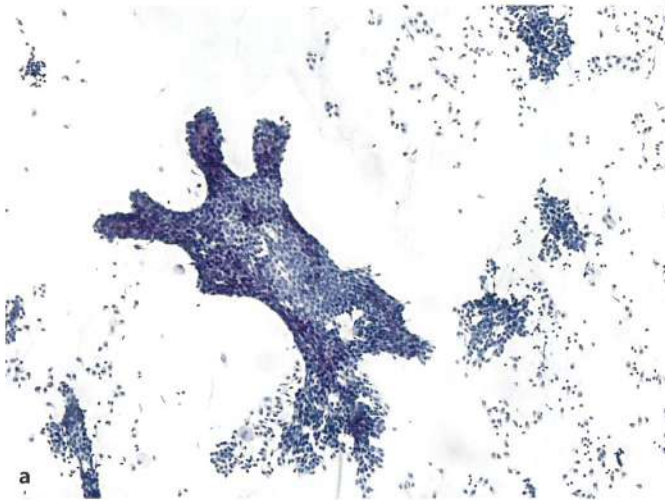


Fig. 16. Comparison between intraductal papilloma and fibroadenoma. Papillary projections of hypercellular epithelial layers in papillary lesions (a) may mimic the staghorn epithelial clusters of fibroadenomas (b). This resemblance is stronger when fibrovascular cores are not clearly visible in the papillary clusters, as it is in this case. Close examination of the papillary projections may reveal that cells tend to separate from each other, differently from those in the digit-form edges of cell clusters in fibroadenomas. Furthermore, papillary lesions tend to disperse single cells with columnar morphology and intact cytoplasm. Papanicolaou. Low power.

RS/CSL has been found in association with atypical epithelial hyperplasia and ductal carcinoma (both in situ and invasive) [Sloane and Mayers, 1993], and some authors consider it as an independent, increased risk marker for the development of subsequent breast cancer [King et al., 2000].

Histological Features

Histological examination of RS/CSL reveals a central fibroelastotic core with many entrapped small ducts displaying varying degrees of hyperplasia, papillomatosis, apocrine metaplasia, and calcification (Fig. 17). At the periphery of the lesion, normal-looking breast lobules are typically seen.

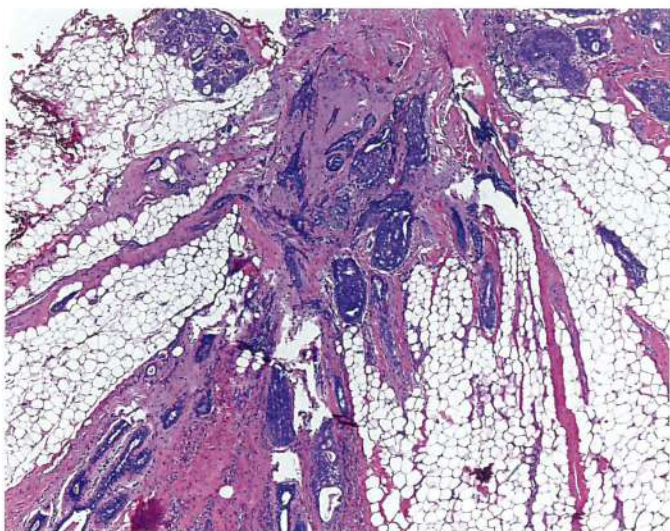


Fig. 17. Histology of radial scar/complex sclerosing lesion. This lesion is composed of a central fibroelastotic core from which many small ducts branch displaying varying degrees of epithelial hyperplasia. H&E. Scanning magnification.

CSL are typically heterogeneous, and, in a variable percentage of ADH cases, DCIS and invasive carcinoma may be present within or adjacent to the lesion. For this reason, some authors discourage the use of FNAC or core biopsy alone to make a definite diagnosis and stress the need of a complete excision, especially in lesions larger than 1 cm [King et al., 2000; Nassar et al., 2015].

Cytology

FNAC is generally able to distinguish RS/CSL from a malignant lesion, although the discordance with radiological findings, the various degrees of cytological atypia, and the awareness of having to deal with a heterogeneous and complex lesion should lead to consider a histological excisional approach.

The cytological smear is often moderately to highly cellular with an admixture of large monolayered epithelial sheets and small tubular or acinar clusters with myoepithelial cells and bare bipolar nuclei in the background (Fig. 18). Small papillary clusters, apocrine cells, microcalcifications, and foamy cells are variably present. Typical cytological findings are multiple fibrillary aggregates exhibiting a green tinge on Papanicolaou-stained preparations, representing elastotic material [Bonzanini et al., 1997]. Meshwork and stellate tissue fragments may be present, but are generally less prominent than in papillomas [Field and Mak, 2006].

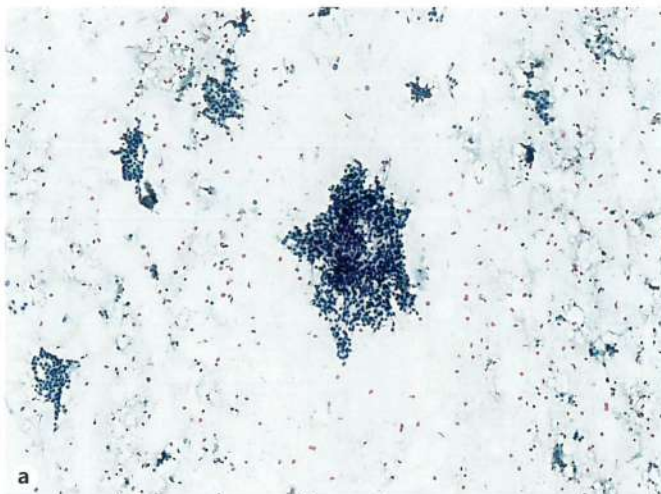


Fig. 18. Cytology of radial scar/complex sclerosing lesion. Aspirates from this kind of lesion usually show moderate to marked cellularity displaying many epithelial monolayer sheets which can have a tubular architecture (b). Bare nuclei and fibrillary stromal fragments are present in the background. These lesions are frequently the source of cytoradiological discrepancy. Papanicolaou. **a, b** Low power.

Prominent nucleoli, scarce cohesiveness, and lack of myoepithelial cells represent the major pitfalls that can pose the suspicion of a malignant lesion. In such cases, the lesion must be considered atypical (C3) or suspicious (C4), and should undergo biopsy for a histological confirmation. Conversely, in cases where cytological atypia is not found in the subsequent core biopsy, some authors suggest that radiological follow-up should be preferred to complete excision [Conlon et al., 2015].

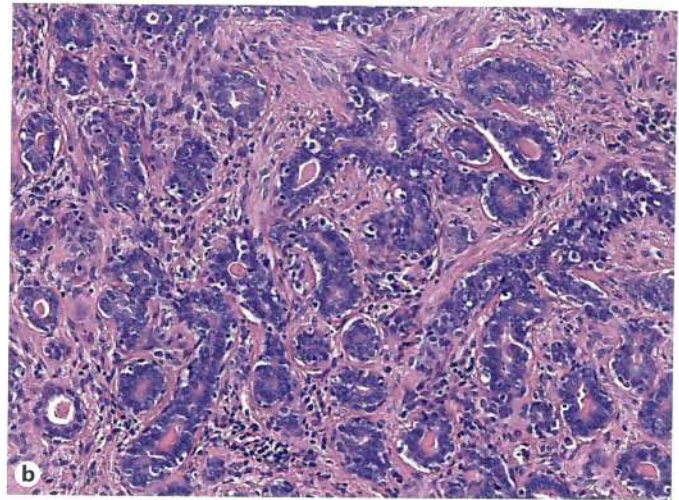
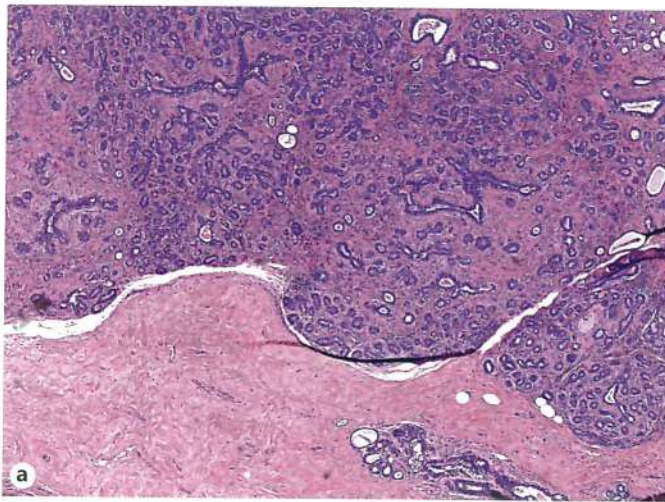


Fig. 19. Histology of tubular adenoma. Tubular adenoma is a nodular mass with neat borders composed of closely packed terminal ducts and acini immersed in a dense, fibrillary intralobular stroma, which, unlike that of fibroadenomas, is not prominent. Epithelial cells do not show significant atypia, and myoepithelial cells are easily detected. H&E. **a** Scanning magnification. **b** Intermediate power.

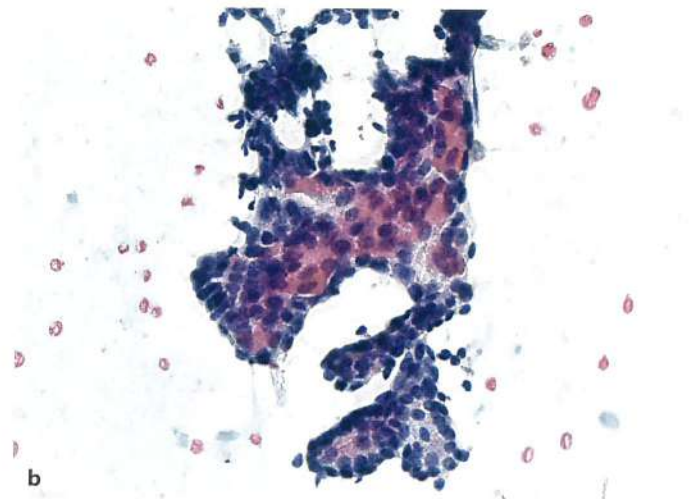
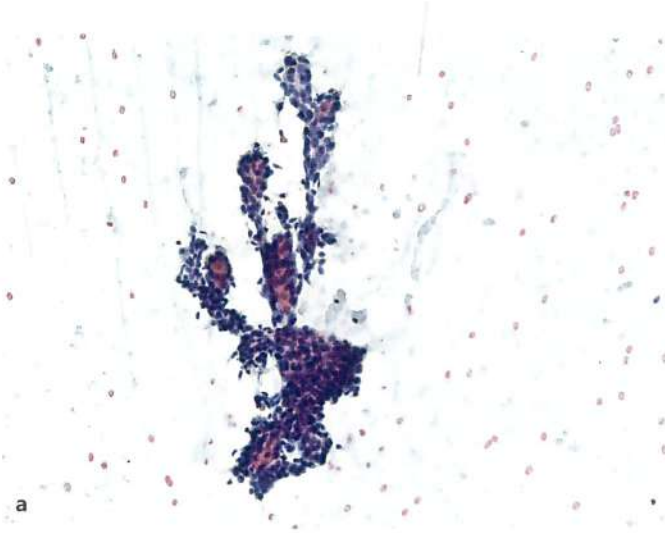


Fig. 20. Cytology of tubular adenoma. Small-sized, branching epithelial clusters with acinar configuration are present in this smear. Epithelial aggregates contain myoepithelial cells, but only occasionally scattered bipolar bare nuclei are present in the background. Papanicolaou. **a** Intermediate power. **b** High power.

Summary

Key Cytological Features of Radial Scar/Complex Sclerosing Lesion

- Moderate to marked cellularity
- Large epithelial honeycomb sheets
- Small tubular and acinar clusters
- Myoepithelial cells
- Papillary or stellate/meshwork tissue fragments
- Fibrillary aggregates

Common Pitfalls of FNA: Radial Scar/Complex Sclerosing Lesion

- Cytological atypia
- Loose cellular cohesiveness
- Lack of myoepithelial cells
- High radiological suspicion

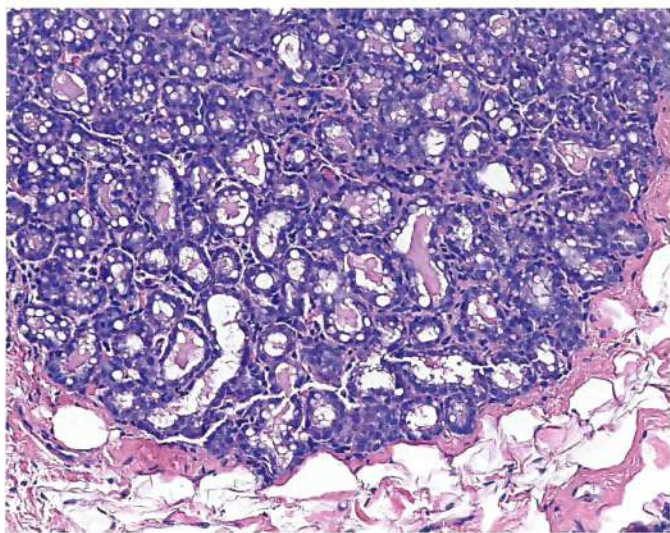


Fig. 21. Histology of lactation adenoma. This nodular lesion is composed of numerous packed small acini with dilated lumina and vacuoles within the epithelial cells. H&E. Intermediate power.

Tubular Adenoma

Introduction/Epidemiology

Tubular adenoma is a rare benign tumor of the breast morphologically related to fibroadenoma. It occurs prevalently in young nonpregnant women and presents as a single, well-defined mass that may be palpable. In these patients, the mammographic and ultrasonographical findings closely resemble those of fibroadenoma, although in older patients microcalcifications have been described, and the overall findings might be interpreted as suspicious for malignancy [Soo et al., 2000].

Histological Features

Tubular adenoma appears histologically as a single, sharply demarcated, 1- to 3-cm nodule without a true capsule and consists of closely packed, small, uniform tubular structures lined by a single layer of epithelial cells and an attenuated layer of myoepithelial cells [Kumar et al., 1998]. Unlike fibroadenoma, the intralobular stroma is not prominent (Fig. 19).

Cytology

The cytological findings of tubular adenoma include the presence of many benign ductal epithelial cells arranged in 3-dimensional cohesive ball-like clusters and tubular structures with myoepithelial cells and bare bipolar nuclei in the

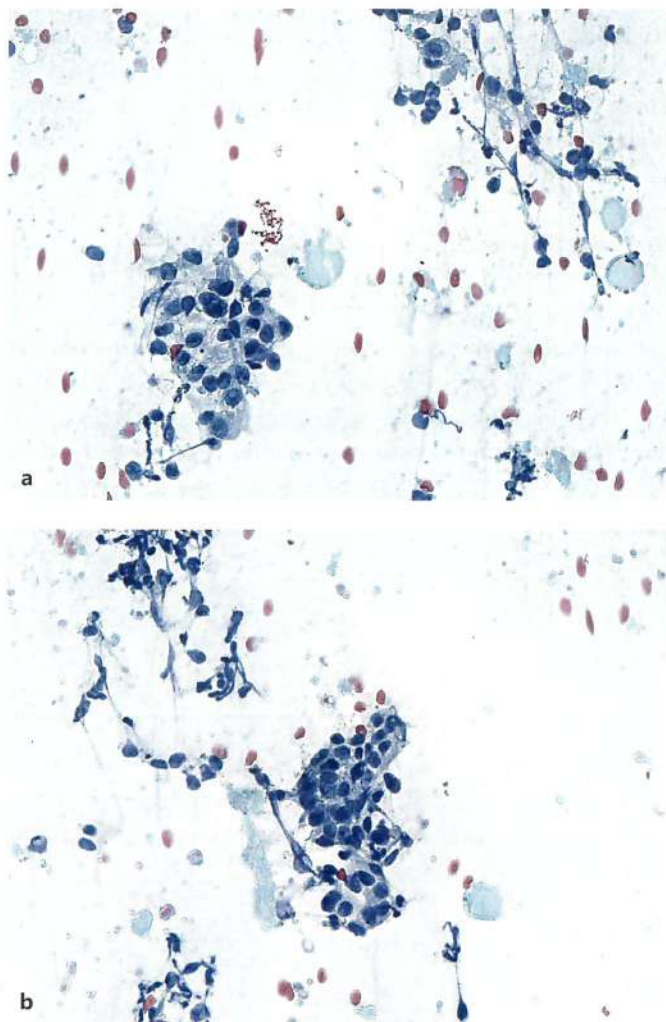


Fig. 22. Cytology of lactating adenoma. The cytological findings of this lesion might be regarded as suspicious or even malignant if the cytopathologist were not aware of the pregnancy or lactating status of the patient. Epithelial cells are arranged in small clusters with a tendency to lose cell-to-cell cohesion and may be present also isolated (a, b). Nuclei are enlarged and display prominent nucleoli, but have round or oval shape and evenly distributed chromatin. The cytoplasm is wide and pale, containing fine vacuoles (a). Papanicolaou. a, b High power.

background. Sheets of ductal cells may occasionally show a staghorn pattern like that of fibroadenoma, but the stromal component is typically scant or absent in tubular adenomas (Fig. 20).

The presence of cohesive 3-dimensional ball-like clusters and tubular structures might lead to the suspicion of a tubular carcinoma, but myoepithelial cells are typically present in the adenoma. Moreover, the tubules of tubular adenoma

are small, round, and uniform, while in tubular carcinoma they tend to be irregular in size and shape, and may sometimes show mild atypia and cellular pleomorphism [Kumar et al., 1998].

Lactating Adenoma

Introduction/Epidemiology

Lactating adenoma is an uncommon benign tumor of the breast occurring in pregnant and lactating women. Its origin is controversial, probably representing the morphological changes of a preexisting tubular adenoma or fibroadenoma during pregnancy or a coalescence of hyperplastic lobules rather than a true neoplasm [Choudhuri and Singal, 2001; Heyman et al., 2014]. It is the most prevalent breast mass in young pregnant females and commonly raises issues concerning the management of breast lesions during pregnancy.

Histological Features

Histologically, lactating adenoma is a nodular mass consisting of densely packed glands composed of actively secreting cuboidal cells with intracytoplasmic vacuoles, vesicular

nuclei, and evident nucleoli (Fig. 21). It might resemble a tubular adenoma or a fibroadenoma with lactation changes of the glandular component.

Cytology

FNAC of lactating adenoma shows a consistent cellular yield of epithelial cells, scattered and in small groups, with foamy to vacuolated cytoplasm and vesicular nuclei with prominent nucleoli (Fig. 22). The background shows typically abundant foamy lipoproteinaceous material [Choudhuri and Singal, 2001]. These cytological findings must be considered in the light of the pregnancy or lactating status of the woman in order not to overestimate their "atypical" appearance. On the other hand, the eventuality of a carcinoma during pregnancy must be excluded, and a histological confirmation through core needle biopsy is advisable in the presence of suspicious elements in the aspirate.

Secretory carcinoma might resemble almost completely lactation changes on cytology. An important diagnostic clue in these cases is the absence of bipolar bare nuclei in the cancer. Moreover, great importance should be given to the clinical and imaging features of the lesion [Vesoulis and Kashkari, 1998].

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