Pinamonti M, Zanconati F: Breast Cytopathology. Assessing the Value of FNAC in the Diagnosis of Breast Lesions.

Invasive Carcinoma

Invasive breast cancer is the most common carcinoma in women, accounting for 23% of all cancers worldwide [Ferlay et al., 2008]. Its incidence increases with age and varies markedly in different geographical areas due to different lifestyles and genetic factors. Australia, Europe, and North America are the regions with the highest incidence, where 6% of women develop invasive breast cancer before 75 years of age. Although it is a widespread disease, patient prognosis is usually good when it is discovered at an early stage. Nevertheless, some subtypes of breast carcinoma behave in a very aggressive way regardless of their size. FNAC is able to identify most breast cancers with high accuracy, and there are also grounds for its routine use in the molecular and genetic characterization of tumor cells without resorting to more invasive techniques [see Chapter 11, this vol., pp. 108–111].

This chapter illustrates the main forms of breast cancer, setting the basis for the diagnosis of malignancy on FNAC and providing some hints to direct the cytological interpretation towards one or the other specific type of carcinoma.

Invasive Ductal Carcinoma and High-Grade Ductal Carcinoma in situ

Introduction/Epidemiology

Invasive ductal carcinoma of no special type (NST) is the prototype of breast cancer and accounts for approximately 40–75% of all invasive carcinomas in published series, with a wide range of variation based mostly on the strictness of the criteria used for inclusion in the other "special" types [Lakhani et al., 2012]. It is actually a heterogeneous category gathering all the invasive epithelial neoplasms lacking the characteristics to be diagnosed as a specific histological type, such as tubular or lobular. The epidemiology of ductal carcinoma NST reflects the general distribution of the breast cancer group as a whole, being rare in women younger than 40 years without a familiar or genetic predisposition and increasing in incidence with advancing age. Invasive ductal carcinomas are part of a multifocal lesion in approximately 20% of cases.

Invasive ductal carcinoma can be seen on mammography as an opacity with irregular, stellate, or nodal configuration and moderately or ill-defined contours, commonly showing calcifications. Ultrasound typically shows a hypoechoic mass with irregular shape, spiculated, indistinct, or microlobulated margins and posterior acoustic shadowing or enhancement (Fig. 1) [Blaichman et al., 2012]. Lesions larger than 2 cm, or even smaller if localized superficially or in a small breast, are often palpable and clinically detected as hard nodules. Advanced tumors may drastically alter the breast consistency and appearance, cause skin and nipple retraction or ulceration, and eventually result in the dramatic clinical presentation of inflammatory carcinoma, resembling acute mastitis.

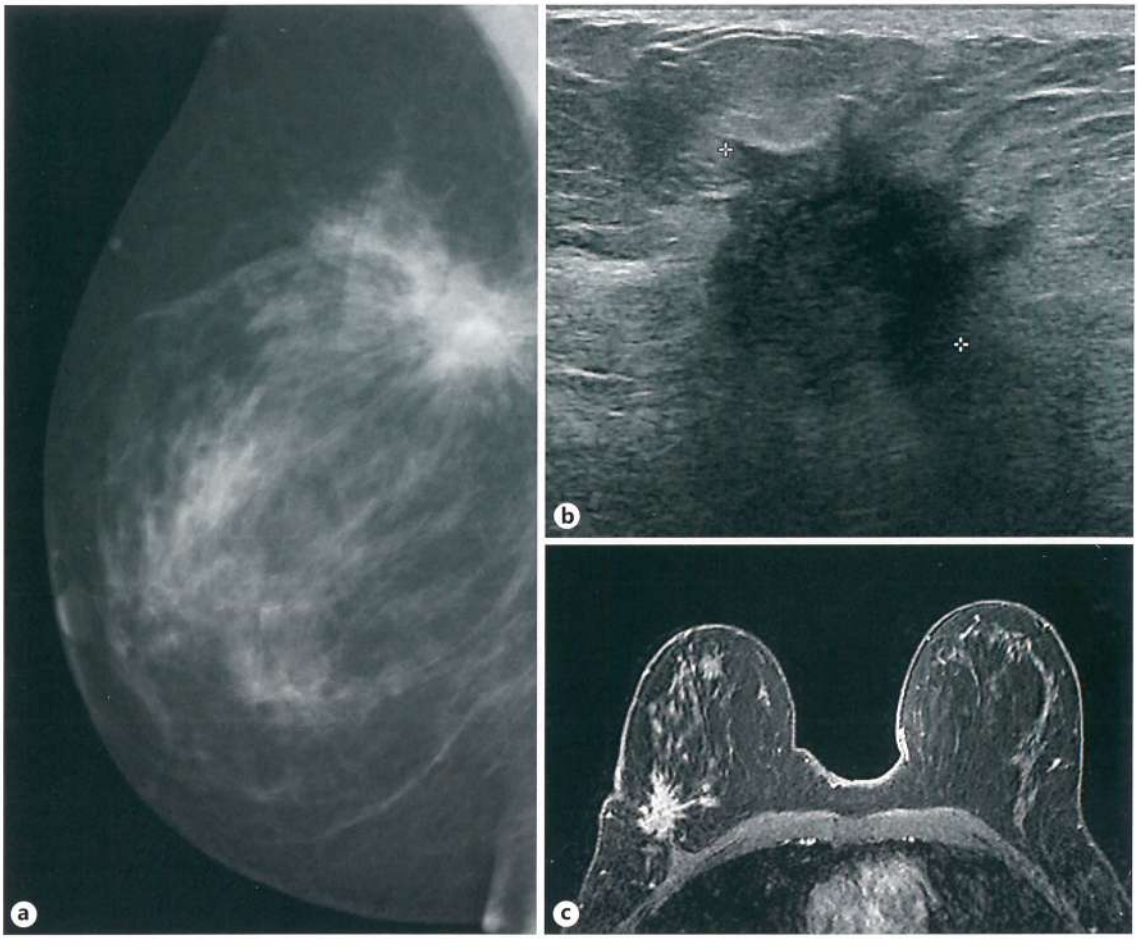


Fig. 1. Imaging of invasive ductal carcinoma. This lesion is located in the upper-outer quadrant of the right breast and is visible as a stellate opacity on mammography (**a**). Ultrasound shows a hypoechoic lesion with irregular borders and posterior acoustic shadowing (**b**). The lesion is highly suspicious also on magnetic resonance imaging (**c**).

High-grade ductal carcinoma in situ (DCIS) is a noninvasive neoplastic proliferation of ductal cells characterized by marked cytological atypia and frequently by the presence of necrosis and calcifications. Pure DCIS was considered a rare entity in the past, but, recently, its incidence has increased from 4 to nearly 25% of all breast malignancies, since the more widespread introduction of mammographic screening [Patnick, 2010]. Indeed, DCIS seldom gives rise to a palpable mass and does not generate a desmoplastic reaction, so it can only be detected by mammography in the presence of coarse, pleomorphic, and branched microcalcifications. The lack of both a palpable mass and an ultrasound-detectable nodule renders a subsequent FNAC unlikely and makes other diagnostic techniques more suitable, such as vacuum-assisted core needle biopsy under stereotaxic guidance [Jackman and Rodriguez-Soto, 2006].

Histological Features

Invasive ductal carcinoma NST may show a variety of morphological aspects encompassing different degrees of cell differentiation and architectural patterns. The tumor cells may be arranged in tubular structures, cords, clusters, or trabeculae, or occasionally infiltrate the surrounding stroma in single-cell-thick Indian files (Fig. 2). Cells may have abundant eosinophilic or scant cytoplasm, and nuclei can be regular and uniform or highly pleomorphic with prominent, multiple nucleoli. Mitotic activity may be virtually absent or extensive. The modified Bloom-Richardson-Elston grading system (also called the Nottingham system) can be used to classify invasive ductal carcinomas into 3 grades of differentiation that correlate with their aggressiveness [Elston and Ellis, 1991]. It is based on architectural criteria (rate of tubule formation/resemblance to normal breast

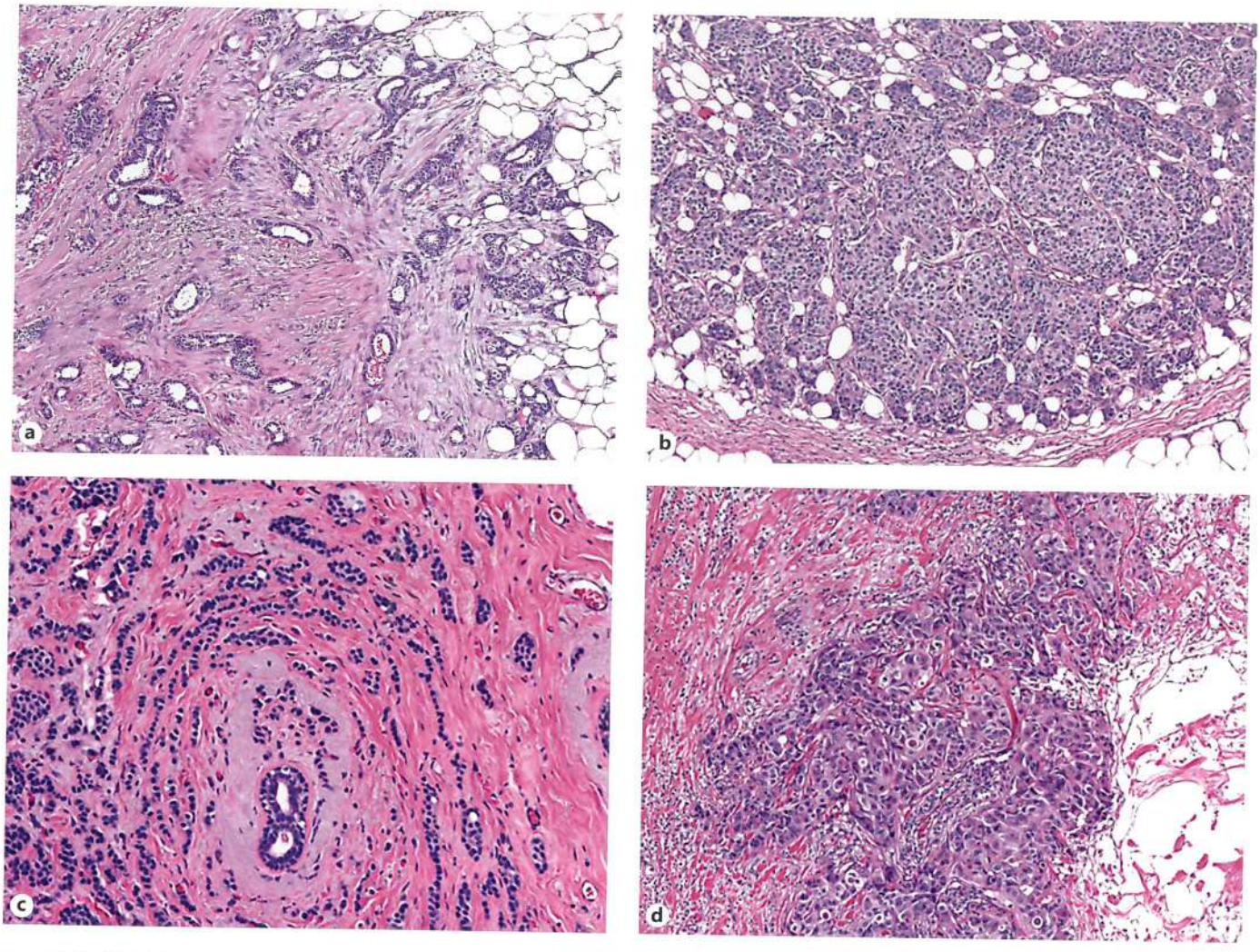


Fig. 2. Histological aspects of invasive ductal carcinoma. Well-differentiated ductal carcinomas are composed predominantly of tubular and acinar structures lined by a single layer of cuboidal cells lacking the myoepithelial component, immersed in a desmoplastic stroma (**a**). Moderately differentiated carcinomas may have a solid/trabecular architecture (**b**) or grow in single cells that infiltrate the stroma and surround normal ducts creating a sort of "target" image (**c**). Poorly differentiated cancers have solid architecture and show marked cellular atypia (**d**). H&E. Low power.

gland), combined with cytological features (nuclear atypia), and the mitotic index. Intratumor necrosis, desmoplastic reaction, and chronic inflammation are variably present in invasive ductal carcinomas and have a lesser role in defining its prognosis.

Immunohistochemistry is necessary to determine the prognosis and response of invasive ductal carcinomas NST to treatment. Hormonal receptors (estrogen and progesterone) are positive in 70–80% of cases, while human epithelial growth factor receptor 2 (HER2) is overexpressed in approximately 15% of all invasive ductal carcinomas NST [Lakhani et al., 2012].

High-grade DCIS is a proliferation of markedly atypical neoplastic cells lining the walls of breast milk ducts that may have a *solid*, *cribriform*, *papillary*, or *micropapillary* configuration. The term *comedo* is used for high-grade DCIS showing abundant necrotic debris in duct lumina (somewhat like skin blackheads or *comedones*), which may calcify (Fig. 3). Unlike the low-grade form, high-grade DCIS shows pleomorphic and poorly polarized nuclei with irregular contours, coarse, and clumped chromatin, and prominent nucleoli. In a considerable percentage of cases, high-grade DCIS is associated with an invasive component [Lakhani et al., 2012].

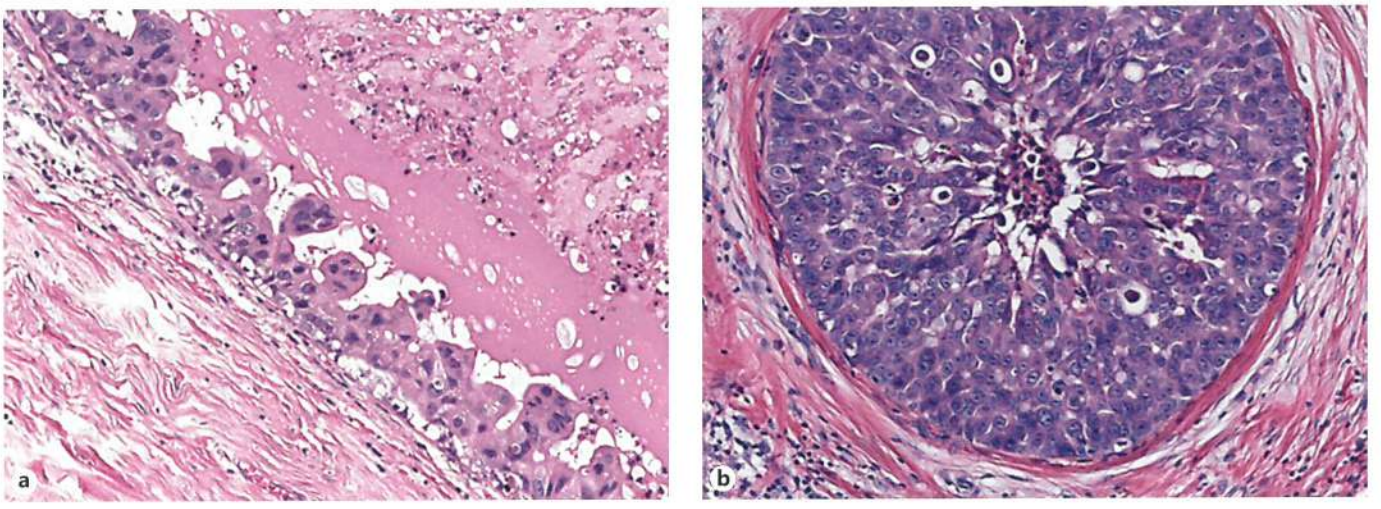


Fig. 3. High-grade ductal carcinoma in situ (DCIS). The lesion is composed of markedly atypical cells confined to the basal membrane and may show different architectural patterns: small projections of cancer cells without fibrovascular cores characterize the micropapillary variant of DCIS (**a**), while *comedo* DCIS is made up of solid nests with necrotic material in the center (**b**). H&E. Intermediate power.

Cytology

The cellular material aspirated from invasive ductal carcinoma NST is typically polymorphic, showing cells with differently shaped nuclei, which can vary in size from 1.5 to 2 times the diameter of a red blood cell to even 5 times that size. Neoplastic elements are arranged in loosely cohesive monolayers or in 3-dimensional aggregates with irregular distribution and overlapping of nuclei (Fig. 4). Occasional tubular or acinar structures may be present, especially in well- or moderately differentiated cancers (Fig. 5). Myoepithelial cells are lost in the invasive component, but they might be preserved in DCIS. In such cases, great attention must be paid to nuclear abnormalities and cellular crowding. The cells within the neoplastic clusters show loss of polarity and nuclear molding; the nuclei have irregular contours and uneven distribution of the chromatin and can be eccentrically placed, giving the cells a plasmacytoid appearance. The smears are usually highly cellular and may contain a necrotic background.

Distinguishing invasive carcinoma from high-grade DCIS in cytology is challenging and most of the times not possible in daily practice. In the setting of mammographic calcifications without a tumor detectable through ultrasound, the association of necrotic background, 3-dimensional solid aggregates of markedly atypical cells, and absence of tubular aggregates are very suggestive of the presence of DCIS [Bonzanini et al., 2001]. Also, in the presence of a palpable mass or a clearly detectable hypoechoic lesion on ultrasound, the same cytological findings should remind the cytopathologist of an invasive neoplasm.

It is possible to assess grading on cytological smears, and it correlates well with the grading made on histological samples [Robinson et al., 1994]. Neoplastic cells from well-differentiated invasive ductal carcinomas are usually smaller and less pleomorphic, resembling benign ductal cells. They display mild nuclear atypia and are arranged in cohesive monolayers or in 3-dimensional clusters with tubular or finger-like appearance. Scant isolated elements might be present, while bare nuclei are rare. Nuclear chromatin is evenly distributed, and nucleoli are small or inconspicuous. The presence of scattered less-differentiated elements may be useful for the correct diagnosis, as well as the "pointed" shape of the cell layers (Fig. 6).

Poorly differentiated invasive carcinoma is easier to recognize as malignant. Cytological abnormalities are obvious, with very large cells, polymorphic naked nuclei, and unevenly distributed chromatin, often with macronucleoli (Fig. 7). In such cases, a differential diagnosis should be made with high-grade lymphomas, metastatic melanomas, or sarcomas [see Chapter 9, this vol., pp. 94–99].

Since ductal carcinoma is a heterogeneous neoplasm, many other cytological aspects are possible. Cellular clusters may show papillary features or form cribriform gland-like structures; cancer cells may be mainly isolated or display in a linear arrangement simulating that of lobular carcinoma. Signet-ring cells may occasionally be seen.

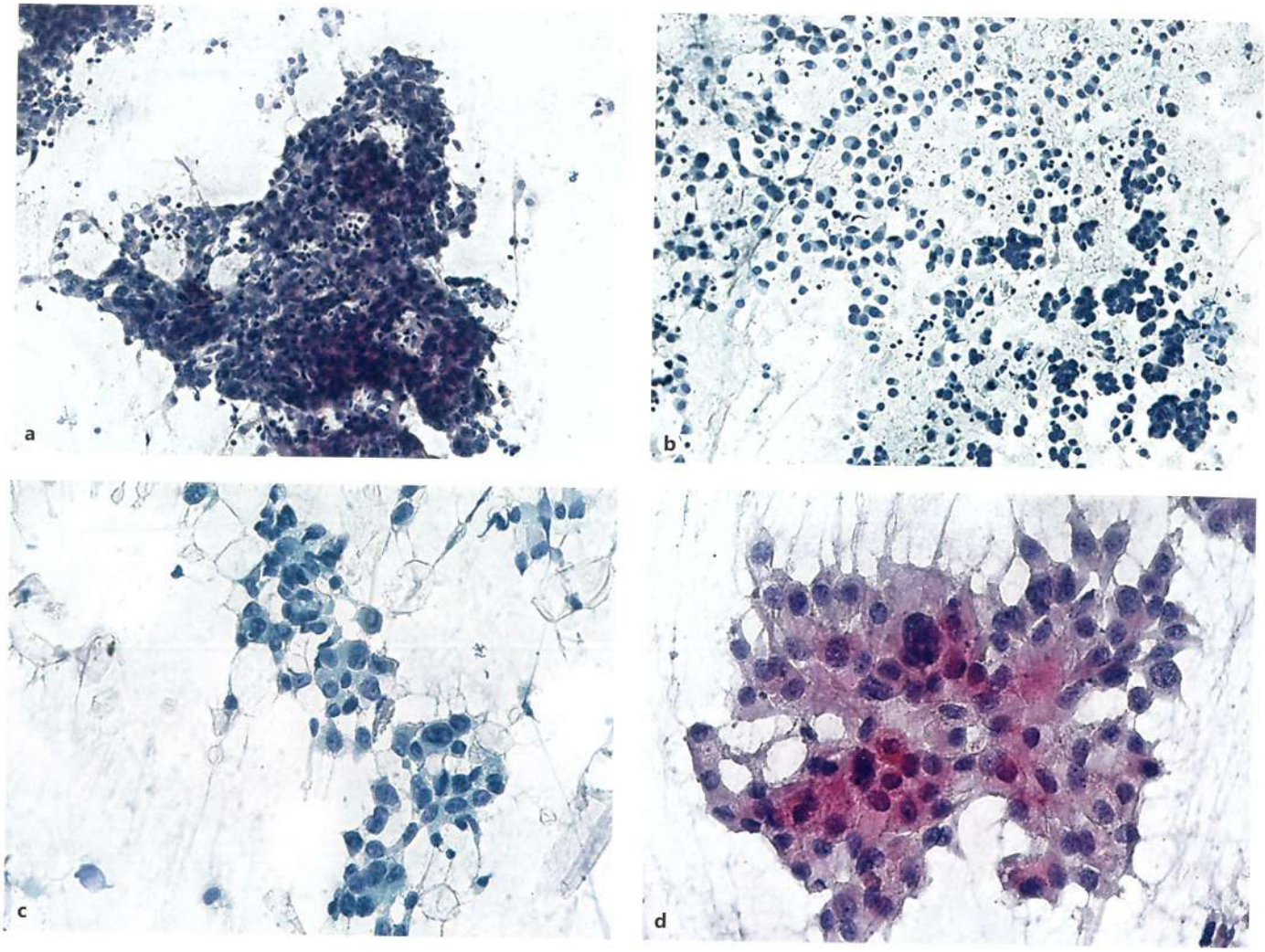


Fig. 4. Cytology of invasive ductal carcinoma of no special type. Ductal carcinoma may be suspected already at low-power magnification for the presence of irregular, 3-dimensional cell clusters (**a**) or increased cell dispersion in the smear (**b**). At higher magnification, cancer cells show a wide spectrum of nuclear abnormalities: different size and shape of nuclei, irregular chromatin distribution, and prominent nucleoli (**c**, **d**). Papanicolaou. **a**, **b** Intermediate power. **c**, **d** High power.

Summary

Key Cytological Features of Ductal Carcinoma

- High Cellularity
- Cells with different size and shape, usually large, with high nuclear/cytoplasmic ratio
- Irregular, crowded cellular clusters without myoepithelial cells
- Isolated neoplastic cells and loosely cohesive cell layers
- Hyperchromatic nuclei with irregular contours and uneven chromatin distribution

Common Pitfalls of FNA: Ductal Carcinoma

- Mild cellular atypia in low-grade cancers
- Myoepithelial cells in DCIS
- Contemporary presence of benign ductal cell layers
- Isolated cells and linear arrangement may be misleading (lobular carcinoma?)

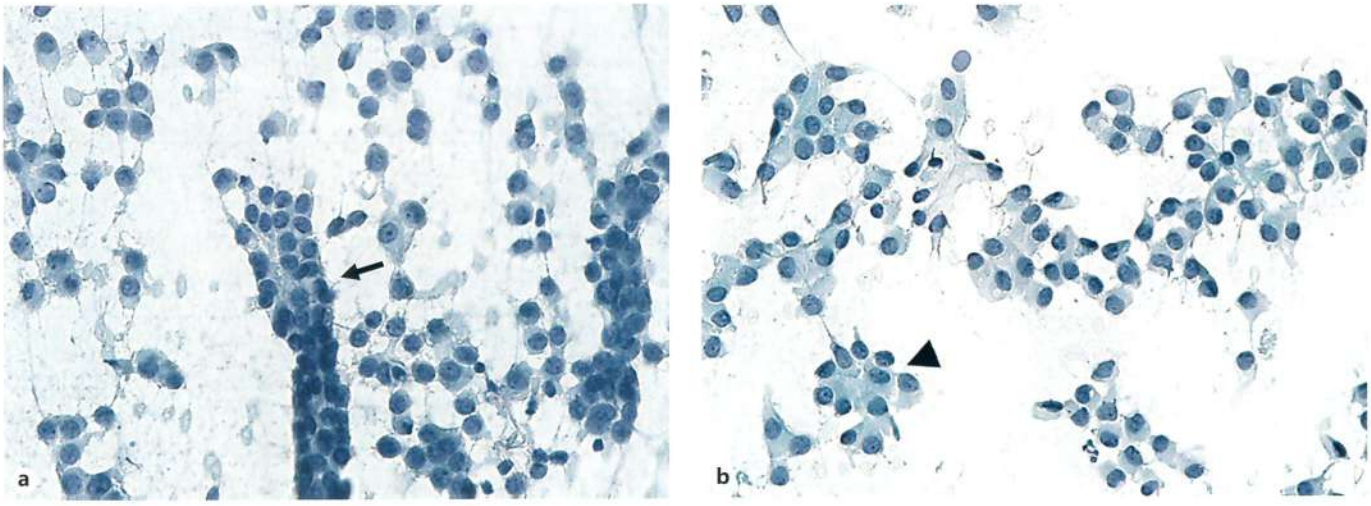


Fig. 5. Invasive ductal carcinoma of no special type. Cells of well- and moderately differentiated ductal carcinomas usually arrange in loosely cohesive small groups, tubules (arrow) (**a**), or even small, acinar-like structures (arrowhead) (**b**). Papanicolaou. High power.

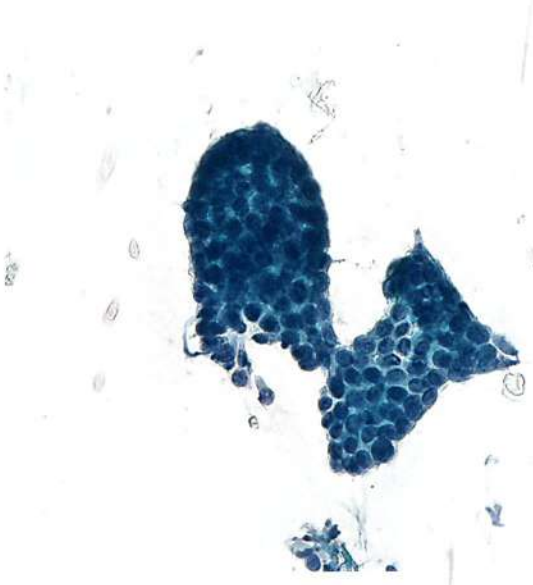


Fig. 6. Well-differentiated ductal carcinoma. It is difficult to assess this lesion as clearly malignant due to the good cohesion and monomorphism of cancer cells. Attention must be paid to the absence of myoepithelial cells and pointed edges of cellular clusters. Papanicolaou. High power.

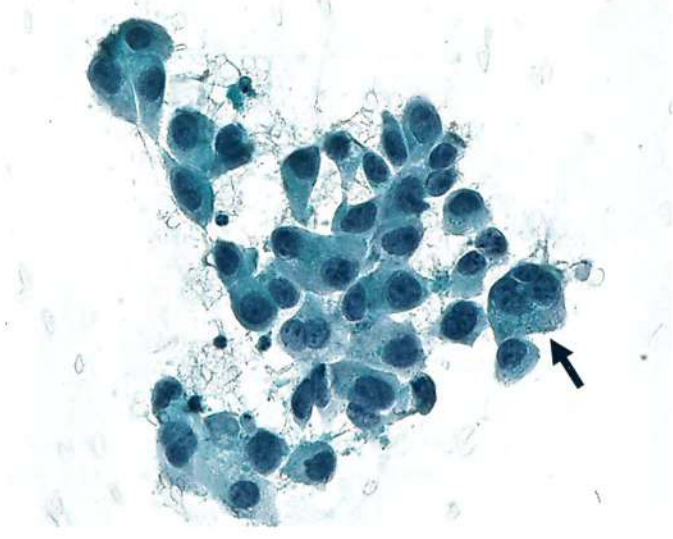


Fig. 7. Poorly differentiated ductal carcinoma. Cancer cells lack cohesion and show severe anisonucleosis and multiple, prominent nucleoli. Some cells also show binucleation (arrow). Note that the presence of abundant cytoplasm, resulting in a normal nuclear/cytoplasmic ratio, is not a reliable sign of benignity. Papanicolaou. High power.

Invasive Lobular Carcinoma

Introduction/Epidemiology

Invasive lobular carcinoma is the most common special histotype of breast carcinoma and accounts for 10–15% of all breast malignancies [Fu et al., 1998]. It usually appears in women aged 45–55 years as an ill-defined palpable mass in any of the breast quadrants and can be seen at mammography as a spiculated opacity or an architectural distortion of breast tissue [Helvie et al., 1993]. Calcifications are infrequent. Lobular carcinomas are more frequently multifocal and bilateral than ductal carcinomas, and magnetic resonance imaging can be helpful to identify multiple neoplastic foci [Hofmeyer et al., 2012].

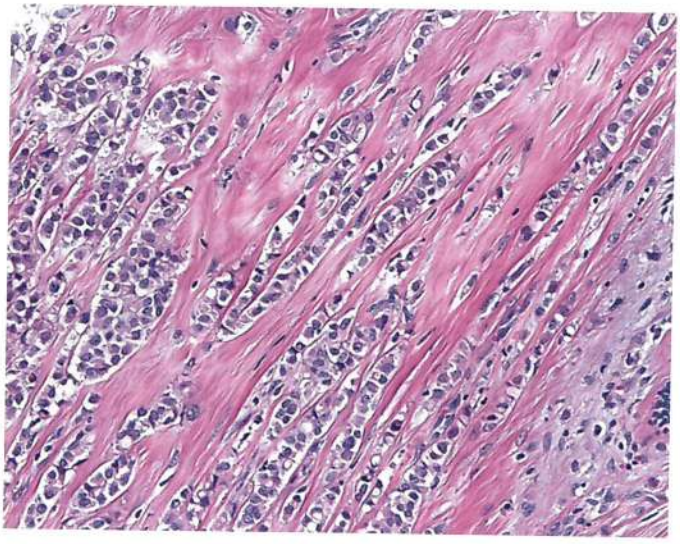


Fig. 8. Histology of invasive lobular carcinoma. Neoplastic cells infiltrate the fibrous stroma in cords or single-cell-thick Indian files. The architecture is that of a grade 3 ductal carcinoma (no duct formation), but nuclei are rather small and monomorphic, and mitotic activity is inconspicuous. H&E. Intermediate power.

Histological Features

Invasive lobular carcinoma is composed of a monotonous population of small- to medium-sized round cells with a thin rim of cytoplasm infiltrating the stroma as Indian files, small nests, and single cells lacking cellular cohesion (Fig. 8). It is typical for these linear cords of neoplastic cells to grow in a concentric pattern around normal ducts designing a sort of "target." Necrosis is usually absent, and mitotic figures are rare [Toikkanen et al., 1997].

The rare *pleomorphic* variant of lobular carcinoma has a greater degree of cellular atypia and pleomorphism and a higher mitotic activity. It may show apocrine or histiocytoid differentiation and may be composed of signet-ring cells [Eusebi et al., 1992; Walford and ten Velden, 1989].

Cancer cells from lobular carcinoma do not express E-cadherin on their membrane and are thus recognizable through immunohistochemistry [Pai et al., 2013]. Lobular neoplasms are typically moderately differentiated (grade 2), express hormonal receptors, and are HER2 negative (0) or weakly positive (1+), except for the pleomorphic variant, which is more frequently progesterone negative and HER2 positive [Arpino et al., 2004].

Cytology

Invasive lobular carcinoma is often difficult to recognize in cytological preparations due to the small size and monomorphism of cancer cells, which may not form crowded clusters and may be extremely few and dispersed throughout the smear. Since cancer cells may surround and mingle with normal breast ducts, it is possible to be misled by the presence of completely benign ductal layers with rare single tumor cells in the background. Thus, isolated atypical cells must not be ignored. Lobular carcinoma is often a highly fibrotic and poorly cellular lesion. Thus, cellularity in the cytological smear may be scarce, and the aspirate could be inadequate. For these reasons, the false-negative rate in FNA of lobular carcinomas is high (8–22%) [Abdulla et al., 2000; Robinson et al., 1995].

Lobular carcinoma cells are typically small in size (10–15 μm) with a very high nuclear/cytoplasmic ratio. They are isolated and dispersed, or are grouped together in small and poorly cohesive clusters with occasional alignments of single cells [Menet et al., 2007]. Nuclei are round or mildly dysmorphic, with homogeneously distributed and finely granular chromatin. The cytoplasm is light and may contain mucin vacuoles, sometimes with a small dense stain in the center that gives the cell the characteristic "target-like appearance" (Fig. 9). This vacuole may compress and indent the nucleus or push it at the periphery of the cell, defining the so-called "signet-ring cells." Signet-ring cells are often present in lobular carcinomas but only rarely represent the majority of the cancer cell population [Tsuchiya, 2008].

Aspirates from lobular carcinomas of the pleomorphic variant may display markedly atypical cells with evident nucleoli, mitotic figures, and larger, indented, and budding nuclei. These neoplasms are difficult to recognize as lobular on cytology and are usually diagnosed as moderately or poorly differentiated ductal carcinomas NST (Fig. 10).

Summary

Key Cytological Features of Lobular Carcinoma

- Scarce and scattered cellularity
- Small, monomorphic cells
- Isolated cells or poorly cohesive clusters; occasional alignments of single cells (Indian files)
- Round, mildly irregular, nuclear contours; homogeneous and finely granular chromatin
- Inconspicuous nucleoli
- Cytoplasmic vacuoles with targetoid appearance, occasional signet-ring features

Common Pitfalls of FNA: Lobular Carcinoma

- Scarce cellularity
- Mild atypia
- Small nuclei, similar to those of normal cells or histiocytes
- Presence of benign ductal cell layers

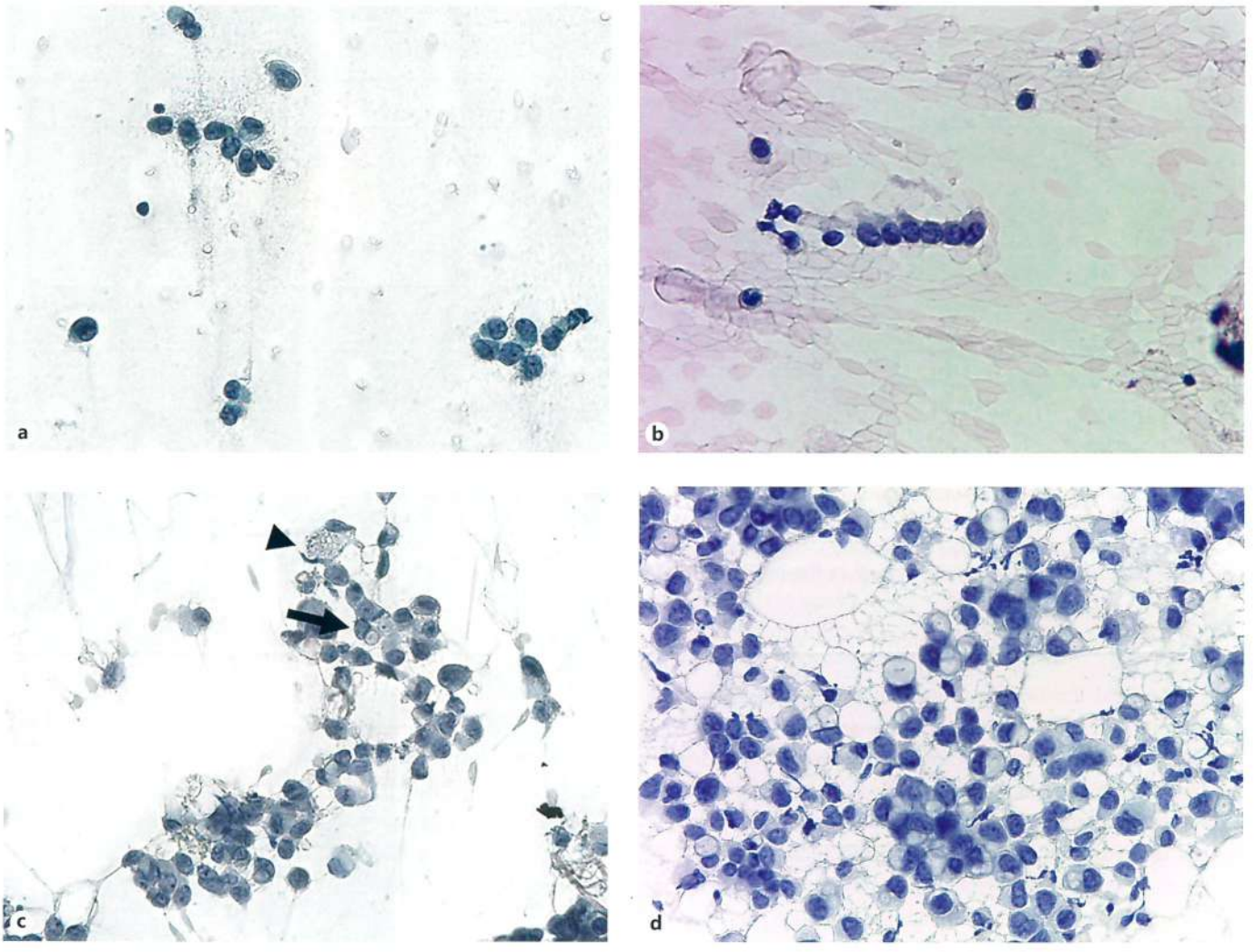


Fig. 9. Cytology of lobular carcinoma. Aspirates from lobular carcinomas are often scarcely cellular, displaying a population of dispersed, small, neoplastic cells with high nuclear/cytoplasmic ratio and vesicular nuclei (**a**), which may sometimes be arranged in short Indian files (**b**). The cytoplasm is commonly occupied by a single mucin vacuole containing a central dot of dense material (arrow) (**c**). Note the difference with the microvacuolated cytoplasm of foamy cells (arrowhead) (**c**). The cytoplasmic vacuole may be prominent, pushing the nucleus at the periphery of the cell and giving the "signet-ring-cell" aspect (**d**). Papanicolaou. High power.

Tubular Carcinoma

Introduction/Epidemiology

Tubular carcinoma is a specific type with a particularly favorable prognosis accounting for approximately 2% of all invasive cancers and presenting almost always at an early stage as a small, spiculated, mammographic opacity (Fig. 11). It can be multifocal in approximately 10–20% of cases and is seen at ultrasound as a hypoechoic lesion with ill-defined margins and posterior acoustic shadowing [Sheppard et al., 2000].

Histological Features

Tubular carcinoma is composed of well-differentiated tubular structures with open lumina lined by a single layer of cells in a fibrous and desmoplastic stroma (Fig. 12). The cells are small to moderate in size and rather monomorphic, with small, inconspicuous nucleoli and scanty mitotic figures. Many well- or moderately differentiated ductal carcinoma NST may show some sort of tubular differentiation without being classified as tubular carcinomas. Actually, there is a lack of consensus concerning the proportion of tubular structures necessary to classify a tumor as tubular carcino-

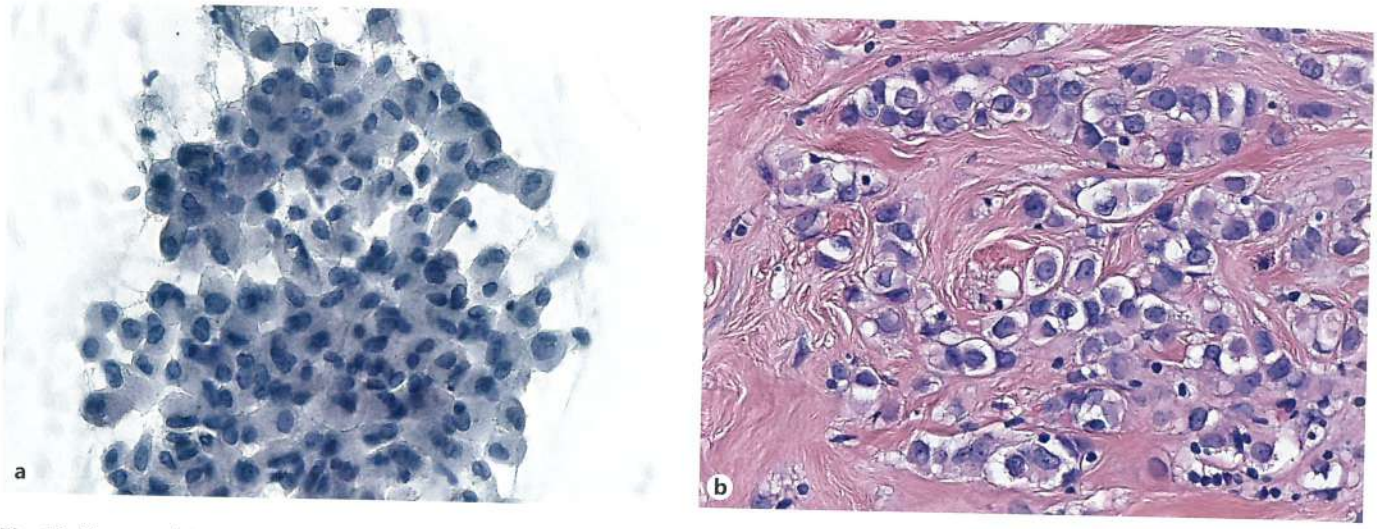


Fig. 10. Pleomorphic variant of lobular carcinoma. Cancer cells are arranged in clusters and show irregular nuclear shapes and a wide amount of granular (apocrine) cytoplasm (**a**). These are unusual features for a lobular carcinoma, and the only clue that might give a hint to the nature of these cells is the quality of nuclear chromatin. This case was assessed as "carcinoma" (C5), and the correct diagnosis was made on the histological section after immunostaining for E-cadherin. Papanicolaou (**a**) and H&E (**b**). High power.

ma, with the requirements being set between 75 and 100% [Lakhani et al., 2012].

Tubular carcinoma is almost always positive for hormonal receptors and negative for HER2 [Papadatos et al., 2001].

Cytology

Since this neoplasm shares many morphological features with well-differentiated invasive ductal carcinoma, it is not possible to make a definite diagnosis of tubular carcinoma on the cytological specimen. It is still possible to suspect and suggest this neoplasm in the presence of a monomorphic population of slightly atypical cells arranged in cohesive tubular aggregates lacking myoepithelial cells, assessing it as "well-differentiated carcinoma" or "suspicious for carcinoma" if the radiological findings are discordant. The tubular clusters have a peculiar angular or "comma-like" appearance and very neat borders, but myoepithelial cells and bare nuclei are missing or are extremely few. Some scattered isolated cells with intact cytoplasm may be present, and the background is typically clean (Fig. 13).

The high cohesiveness of cellular aggregates and minimal cytological atypia put this lesion in the differential diagnosis with some benign proliferative lesions, such as sclerosing adenosis and fibroadenomas (Fig. 14). The radiological appearance of a spiculated mass is usually sufficient to suggest the presence of this lesion to the cytopathologist. Then, a careful analysis of nuclear polarization in the clusters, together with the absence of myoepithelial cells and bare bipolar nuclei allow to correctly assess the specimen as malignant.

Summary

Key Cytological Features of Tubular Carcinoma

- Moderate to marked cellularity
- Highly cohesive tubular aggregates of monomorphic cells with angular shapes and neat borders
- Absence of myoepithelial cells
- Clean background

Common Pitfalls of FNA: Tubular Carcinoma

- Very mild cytological atypia
- Occasional myoepithelial cells or bare nuclei

Mucinous Carcinoma

Introduction/Epidemiology

Mucinous carcinoma (also known as colloid or gelatinous carcinoma) accounts for 1–6% of all breast carcinomas [Di

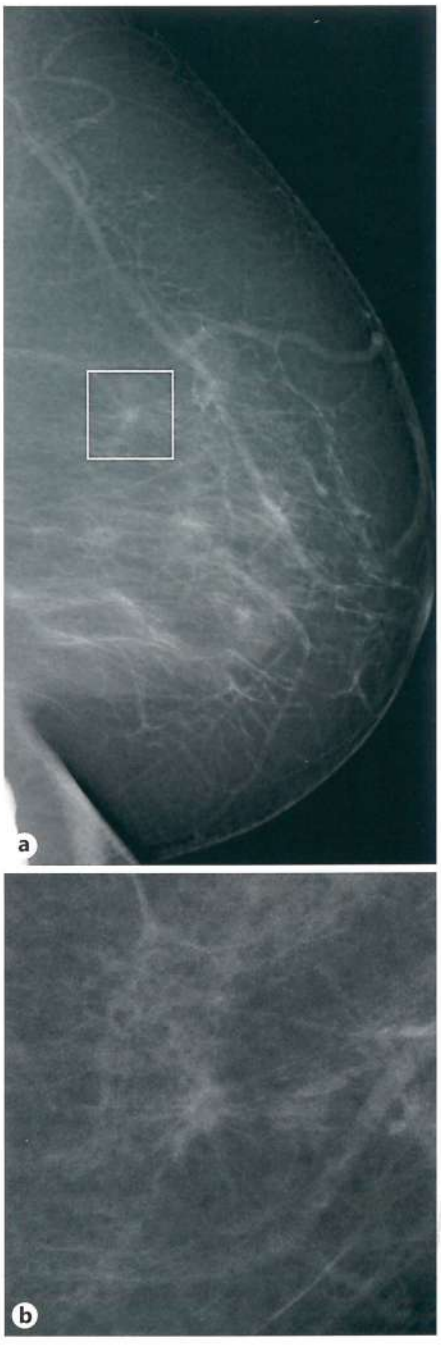


Fig. 11. Mammogram of tubular carcinoma. This lesion is visible as a small, stellate opacity in the upper-outer quadrant of the right breast (**a**). Such a small lesion can be difficult to detect, but the spiculated contours, better appreciated at higher magnification, are highly suspicious (**b**).

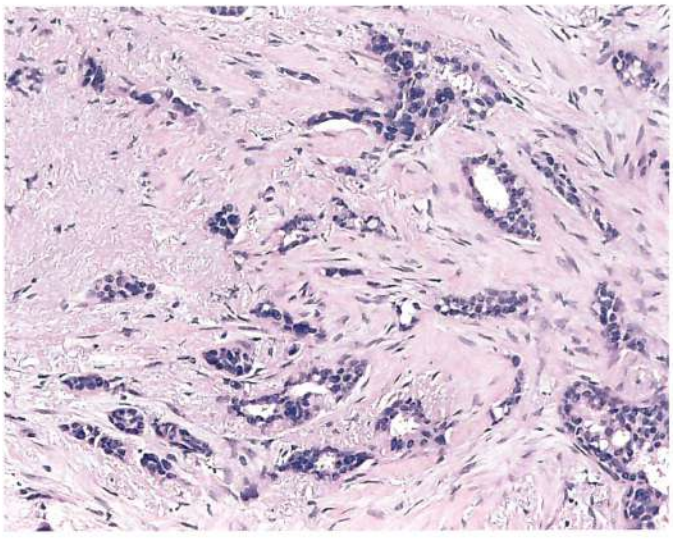


Fig. 12. Histology of tubular carcinoma. The neoplasm is composed of small tubular structures lined by a single layer of cuboidal cells with bland nuclei and without myoepithelial cells in a desmoplastic stroma. H&E. Low power.

Saverio et al., 2008]. Its pure form, which represents less than 2% of breast cancers, is known to have a very good prognosis, while the mixed form, in which a nonmucinous invasive pattern is present, carries a worse prognosis, comparable to that of patients with ductal carcinoma NST [Toikkanen et al., 1988]. Mucinous carcinoma usually presents in elderly postmenopausal women and gives rarely origin to lymph node or distant metastases. Macroscopically, it is well circumscribed and has a peculiar soft/gelatinous consistence, which could make the clinical diagnosis less reliable. Mammography and ultrasound highlight the neoplasm as a mass with well-circumscribed, round or lobular shape, or may show a less-defined, irregular mass in mixed tumors [Zhang et al., 2015].

Histological Features

Pure mucinous carcinomas can be subdivided into *cellular* and *hypocellular* variants based on the degree of cellularity and the architectural pattern. The hypocellular variant shows a tubular, cribriform, cord-like, micropapillary, or papillary growth pattern, while the cellular variant grows in solid nests (Fig. 15). Tumors with a predominantly papillary pattern tend to be more aggressive and tend to more frequently show axillary lymph node metastases at diagnosis than other pure mucinous carcinomas [Ranade et al., 2010]. The tumor cells in pure mucinous carcinomas typically show mild pleomorphism.

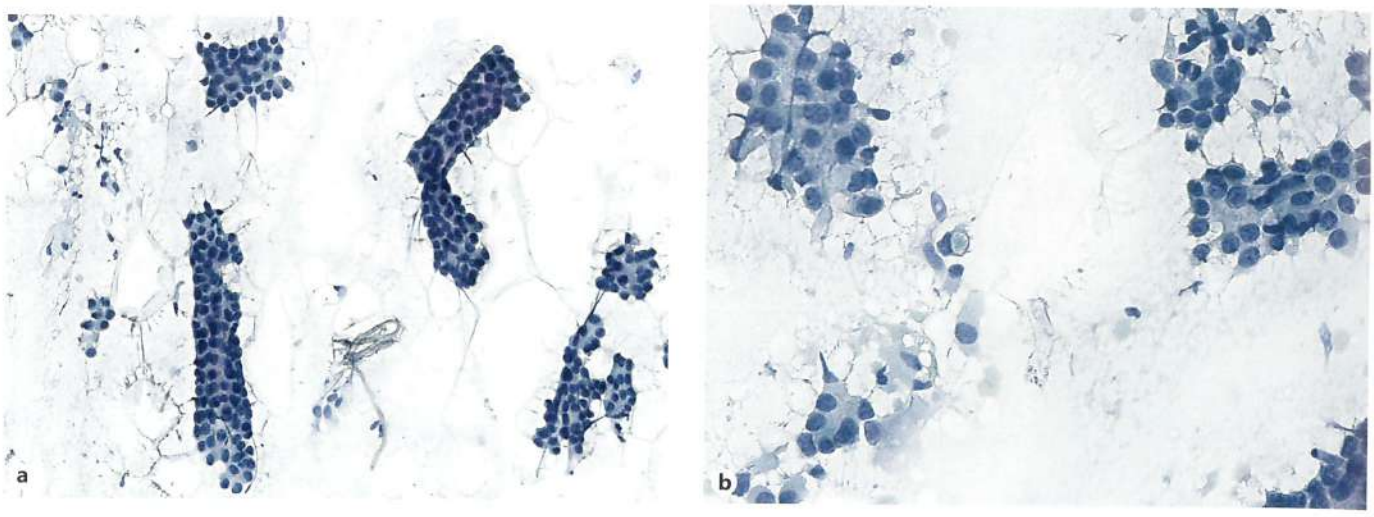


Fig. 13. Cytology of tubular carcinoma. This aspirate displays numerous medium-sized tubular aggregates of monomorphic cancer cells with round to oval-shaped nuclei in a clean background. Tubular clusters have neat borders but lack myoepithelial cells (**a**). Scattered intact cells occasionally show cytoplasmic vacuoles (**b**). Papanicolaou. **a** Intermediate power. **b** High power.

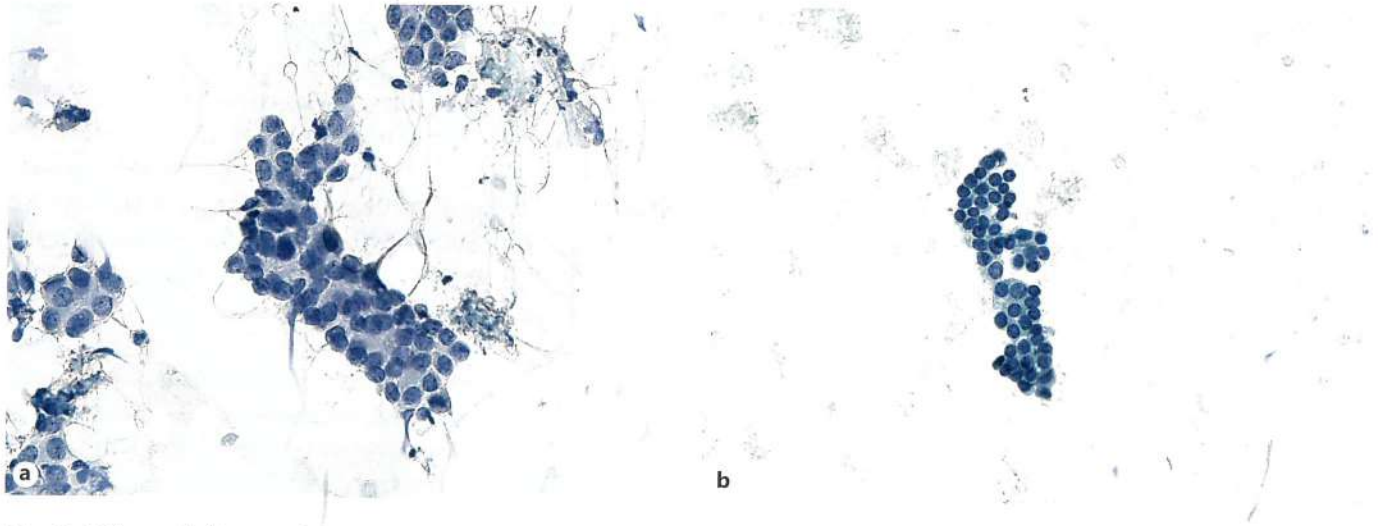


Fig. 14. Differential diagnosis between tubular carcinoma (**a**) and sclerosing adenosis (**b**). Well-differentiated carcinomas share many cytological features with some benign ductal lesions. These 2 cases are depicted at the same magnification. Note the increased nuclear size and the "railway-track" aspect with rigid borders of the tubular cluster in the first lesion (**a**) compared with those of the second one (**b**). Myoepithelial cells are not evident in any of the 2 cases. Papanicolaou. High power.

A significant portion of pure mucinous carcinomas shows neuroendocrine differentiation, which can be suspected histologically based on morphological features such as an insular or solid pattern, stippled chromatin, and a general "uniformity" of cancer cells. The confirmation of the neuroendocrine nature of cancer cells comes from immunohistochemistry, with cancer cells positive for one or more of the so-called "neuroendocrine markers" (chromogranin A, synaptophysin, neuron-specific enolase, and/or CD56). Neuroendocrine differentiation can be seen in many subtypes of breast cancer, but it is most common in pure mucinous carcinomas. Its significance in clinical practice has still not been well established, but a recent study identified the neuroendocrine variant of mucinous carcinoma as a tumor occurring later in life, with a low nuclear grade, favorable immunohistochemical features, and a lower rate of distant metastases at diagnosis [Tse et al., 2004].

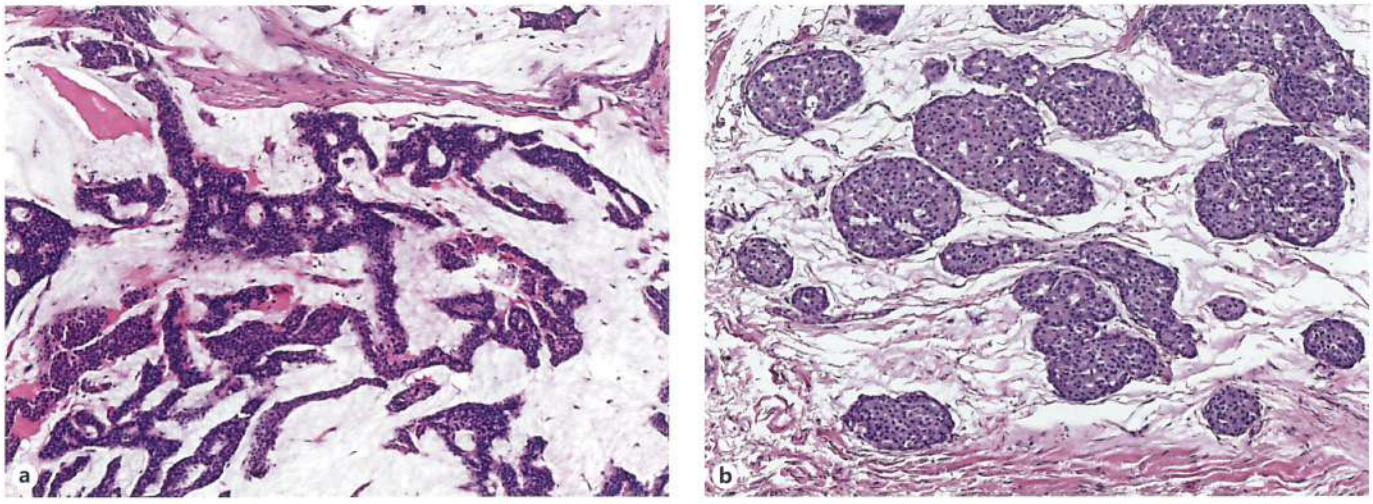


Fig. 15. Histology of mucinous carcinoma. The *hypocellular* variant of mucinous carcinoma may show a cribriform and cord-like growth pattern (**a**), while the *cellular* variant has a predominantly solid pattern (**b**). In both variants, the neoplastic cell component is immersed in abundant extracellular mucin. H&E. Low power.

Pure mucinous carcinomas are frequently (96%) estrogen (ER)/progesterone receptor (PR) positive and HER-2 negative [Kashiwagi et al., 2013].

Cytology

Despite its slight cytological atypia, FNAC is highly accurate in identifying mucinous carcinomas, even though the definitive distinction between the pure and mixed form is unreliable cytopathologically [Cyrta et al., 2013]. The most important and peculiar aspect of aspirates taken from mucinous carcinomas is the presence of extracellular mucin, which may be evident macroscopically as a translucent, slimy, and gelatinous substance that tends to dry quickly after the smear. On microscopical evaluation, mucus appears as a background gray to green-bluish transparent film in Pap-stained preparations or blue to magenta amorphous substance in Giemsa-stained preparations. Cancer cells are arranged singly or in 3-dimensional clusters with smooth borders and sometimes with evident micropapillary outline (Fig. 16). They are quite monomorphic, with plasmacytoid appearance, small nuclei (less than 2 times a red blood cell), regular nuclear membrane, and inconspicuous nucleoli. Myoepithelial cells are absent, as well as bare bipolar nuclei in the background, which is dominated by mucous substance and isolated cancer cells. Some thin-walled branching ("chicken wire") vessels might be present in the mucus, and they are fairly typical of mucinous carcinomas although not exclusive.

The finding of features such as necrosis (typically absent in pure mucinous carcinomas), large nuclei (more than 3 times a red blood cell), irregular nuclear outlines, evident nucleoli, or a scarce amount of mucin (<25%) are highly suggestive of the presence of a mixed tumor [Cyrta et al., 2013].

A neuroendocrine nature can be suspected on the cytological sample in the presence of intracytoplasmic granules in a monotonous population of plasmacytoid cells with low-grade atypia and inconspicuous nucleoli, but we do not recommend making this diagnosis based on morphology alone. In contrast to neuroendocrine carcinomas of other organs, neuroendocrine carcinomas of the breast uncommonly present the classical "salt-and-pepper" chromatin pattern [Ohashi et al., 2016].

A differential diagnosis between mucinous carcinomas and mucocele-like lesions or myxoid fibroadenoma may be difficult based on cytology due to the low-grade nuclear atypia of this neoplasm. Close attention must be paid to cellular cohesion, which is usually maintained in mucocele lesions and fibroadenomas and easily lost in mucinous carcinomas, and to the presence of myoepithelial cells and bare bipolar nuclei [Ventura et al., 2003].

In everyday clinical practice, we recommend the use of the term "carcinoma with features of mucinous differentiation," since even cases with all the typical features of pure mucinous carcinoma might have been partially sampled and might result as mixed tumors on the definitive histological specimen due to intratumor heterogeneity.

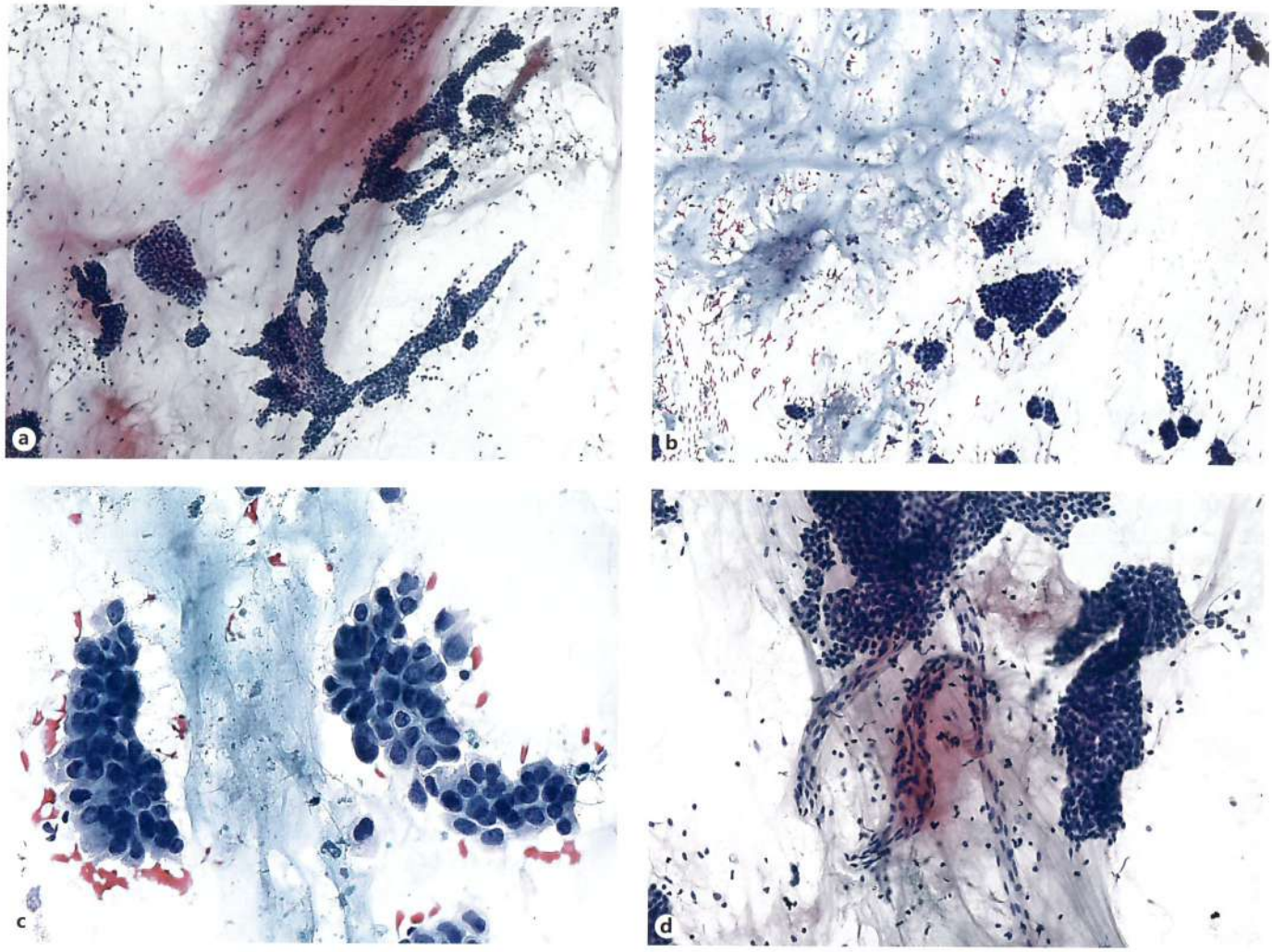


Fig. 16. Cytology of mucinous carcinoma. Aspirates from mucinous carcinomas typically show cancer cells with low-grade to moderate atypia arranged singly and in clusters in a myxoid background. Extracellular mucin may appear bluish or pink-purple in Pap-stained preparations (**a**, **b**). At higher magnification, cancer cell clusters show smooth borders and lack myoepithelial cells (**c**). Thin-walled, branching vessels might be visible in the myxoid background creating the image of a "chicken wire" (**d**). Papanicolaou. **a**, **b**, **d** Low power. **c** High power.

Summary

Key Cytological Features of Mucinous Carcinoma

- Abundant extracellular mucin
- Cancer cells with small nuclei and regular nuclear membranes
- Three-dimensional clusters without myoepithelial cells
- Absence of nucleoli
- Thin-walled, "chicken wire" vessels

Common Pitfalls of FNA: Mucinous Carcinoma

- Mild nuclear atypia
- Presence of more atypical cells and nonmucinous component (mixed type)
- Mucin-like extracellular substance in nonmucinous lesions (myxoid fibroadenoma)

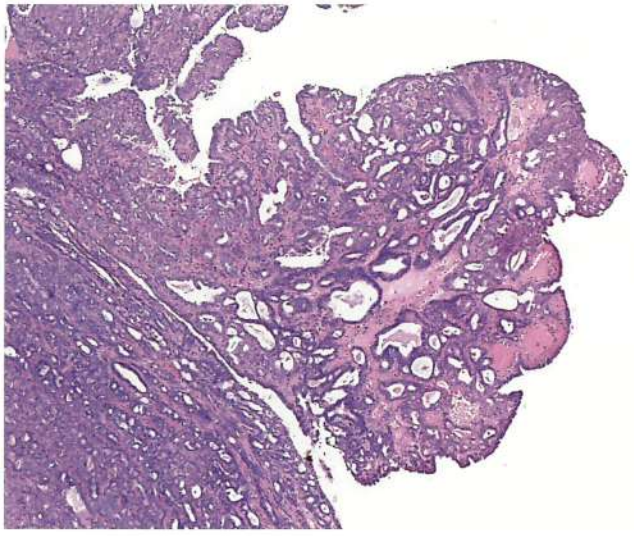


Fig. 17. Histology of papillary carcinoma. This partially cystic lesion shows complex branching papillary stalks lined by relatively monomorphic cancer cells. A clearly invasive component is present in the left lower part of the picture. Myoepithelial cells are not present, neither in the papillary nor in the invasive component. H&E. Low power.

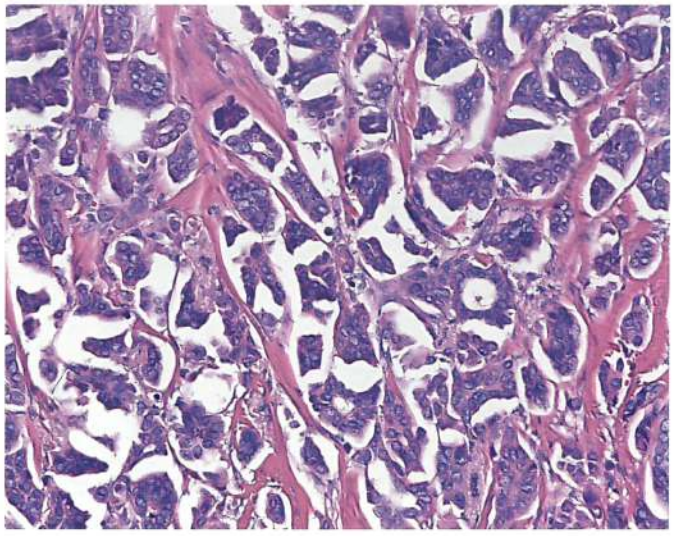


Fig. 18. Micropapillary carcinoma. Neoplastic cells are arranged in small morula-like clusters with central pseudolumina, devoid of fibrovascular cores, and surrounded by artifacts of stromal spaces. H&E. High power.

Papillary Carcinoma

Introduction/Epidemiology

Pure papillary carcinoma of the breast is a rare tumor affecting predominantly elderly postmenopausal women and has a favorable prognosis, accounting for 0.3–2% of all breast malignancies [Fisher et al., 1980]. The so-called *encapsulated* or *intracystic* papillary carcinoma is defined by the presence of papillary carcinoma within a cystically dilated duct and surrounded by a fibrous capsule. It has indolent behavior and rarely metastasizes. Papillary carcinomas are often located near the areola and may thus present as palpable masses or nipple discharge. Imaging findings of papillary carcinomas may overlap with those of benign papillary lesions or might infrequently show signs of a more obvious infiltration of the breast tissue, similarly to ductal carcinoma NST. Papillary carcinoma is more common in the male than the female breast [Reid-Nicholson et al., 2006].

Histological Features

The lesion is composed of complex branching fibrovascular cores lined by epithelial cells that usually show mild or moderate atypia (Fig. 17). The absence of an intact myoepithelial cell layer within papillary structures is an important marker to define these lesions. A papillary component may be found in association with DCIS or invasive ductal carcinoma NST.

Pure papillary carcinomas are well-differentiated neoplasms (grade 1 or 2) that usually express hormonal receptors and are negative for HER2/neu.

Invasive *micropapillary* carcinoma is an aggressive variant composed of small, morula-like clusters of cuboidal to columnar cancer cells devoid of fibrovascular cores and surrounded by clear stromal spaces (Fig. 18). It is an uncommon pure type with a tendency to vascular invasion and higher stage at diagnosis. Compared with other papillary neoplasms and with invasive ductal carcinoma NST, micropapillary carcinomas are more frequently HER2 positive [Walsh and Bleiweiss, 2001].

Cytology

As mentioned before in Chapter 6 [this vol., pp. 41–57], it is very difficult and sometimes impossible to distinguish benign from malignant papillary lesions on a cytological smear. In addition, the differentiation between noninvasive intraductal papillary carcinoma and frankly invasive papillary carcinoma is problematic due to identical cytological features [Simsir et al., 2002].

Features like marked cellularity, complex branching papillary fragments, and single atypical intact cells have been

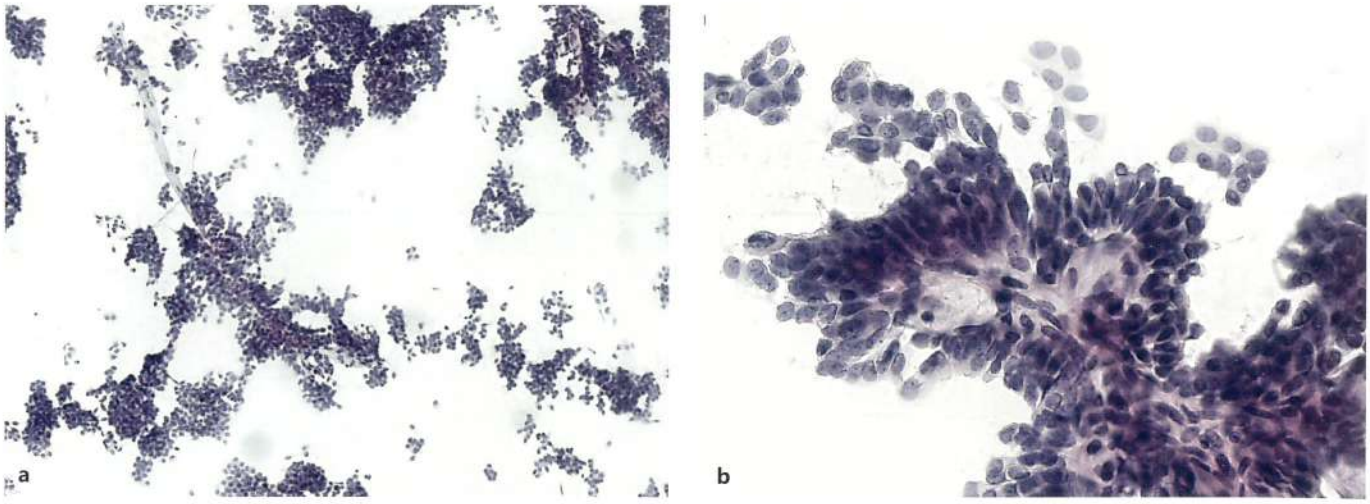


Fig. 19. Cytology of papillary carcinoma. This markedly cellular smear shows several complex and branching clusters with a stromal and an epithelial component and numerous dissociated epithelial cells. Cell clusters are hypercellular, vary widely in size and shape, and lack myoepithelial elements. Similarly, bare bipolar nuclei are relatively rare compared to the epithelial cylindrical cells with intact cytoplasm. Papanicolaou. **a** Low power. **b** High power.

suggested to point toward the malignant nature of the tumor (Fig. 19, 20) [Dawson and Mulford, 1994]. However, these features have not been found to be restricted to malignant lesions [Simsir et al., 2003]. Other features that should be examined and that could orient toward malignancy include the absence of bland columnar cells and lack of foamy or hemosiderin-laden macrophages in the background, as well as the absence of myoepithelial cells in the papillary clusters.

Sometimes the malignant nature of a lesion is more obvious, but it is still difficult to address the tumor as papillary carcinoma or any other type of carcinoma. Invasive ductal carcinoma with focal papillary areas usually shows highly cellular smears with complex crowded epithelial cell sheets displaying higher nuclear atypia and irregularities. Bare nuclei in the background are usually absent.

Micropapillary carcinoma lacks true fibrovascular cores and shows numerous well-formed angular and morular clusters of small- to medium-sized atypical cells (Fig. 21) [Khurana et al., 1997].

Distinguishing papillary carcinoma from benign papillary lesions of the breast is extremely important, and there is still an open debate about the management of papillary lesions identified by biopsy or cytology [Prathiba et al., 2010]. Much attention must be paid to the presence or absence of cytological atypia. Neither FNAC nor core needle biopsy is able to exclude malignancy with absolute certainty, and carcinoma foci have been found in 2.3% of the excised papillary lesions with pathological and radiological findings indicating a benign nature [Pareja et al., 2016]. Nevertheless, we agree that this percentage is too low to justify surgical excision in all cases of papillary lesions and suggest close radiological and cytological follow-up in women without atypia in the cytological sample and without additional risk factors. Conversely, the presence of cytological findings suspicious of malignancy, cytological-radiological discordance, or individual risk factors, such as a family history of breast cancer or the presence of predisposing genetic mutations, should lead to surgical excision.

Summary

Key Cytological Features of Papillary Carcinoma

- Marked cellularity
- Complex branching papillary clusters without myoepithelial cells
- Isolated atypical intact cells (not bare nuclei)

Common Pitfalls of FNA: Papillary Carcinoma

- Bland atypia
- Papillary component admixed with nonpapillary malignant clusters

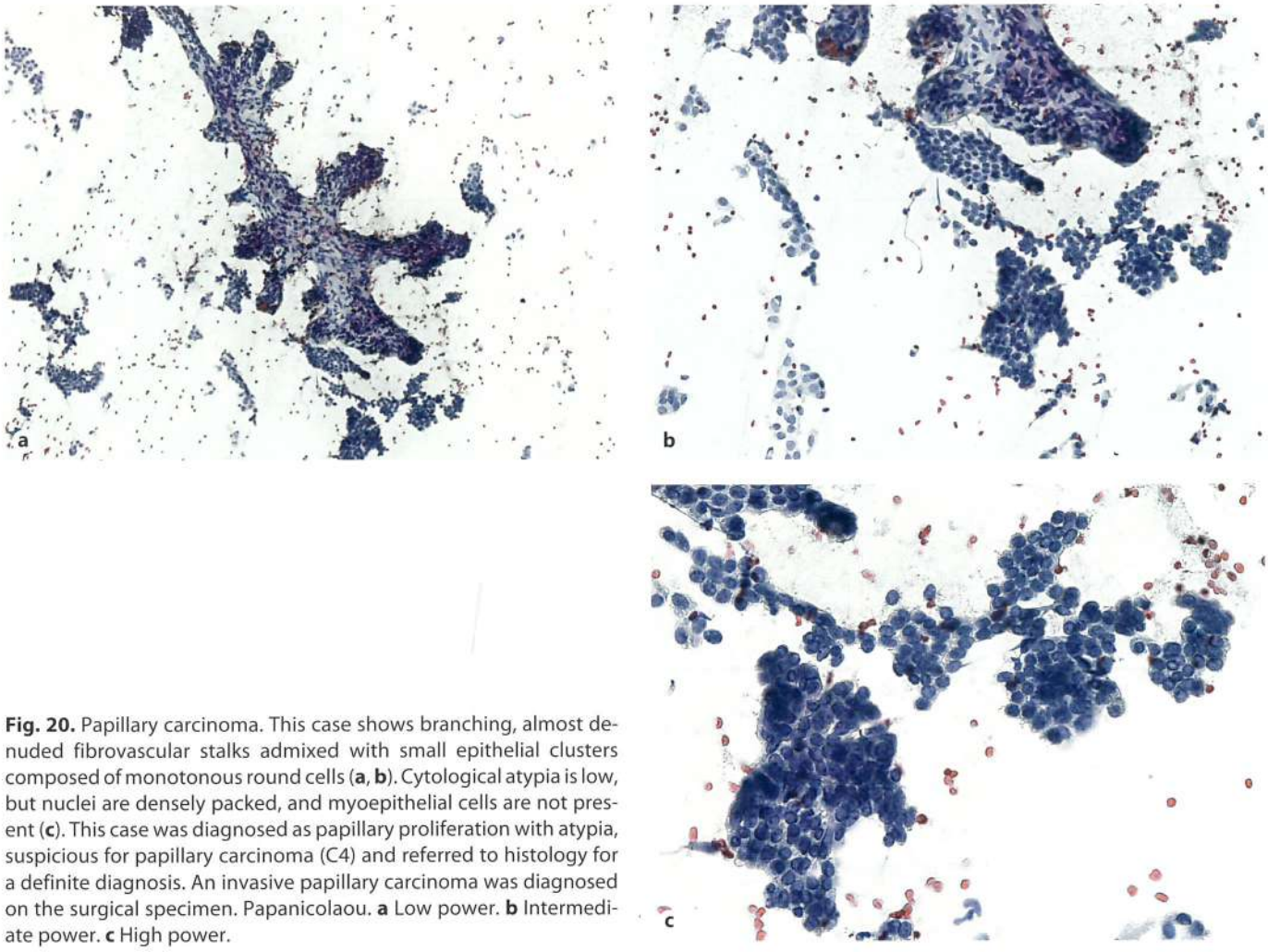


Fig. 20. Papillary carcinoma. This case shows branching, almost denuded fibrovascular stalks admixed with small epithelial clusters composed of monotonous round cells (**a**, **b**). Cytological atypia is low, but nuclei are densely packed, and myoepithelial cells are not present (**c**). This case was diagnosed as papillary proliferation with atypia, suspicious for papillary carcinoma (C4) and referred to histology for a definite diagnosis. An invasive papillary carcinoma was diagnosed on the surgical specimen. Papanicolaou. **a** Low power. **b** Intermediate power. **c** High power.

Carcinoma with Medullary Features

Introduction/Epidemiology

Formerly known as medullary carcinoma, it is a rare subtype of invasive breast cancer characterized by neat borders, lymphocyte-rich stroma, marked cytological atypia, and a relatively good prognosis compared with invasive ductal carcinoma NST. This neoplasm predominantly occurs in middle-aged women, but it can also be found in younger patients, since it is frequently associated with BRCA1 germline mutations [Eisinger et al., 1998]. Mammography and ultrasonography usually show a well-defined mass, which is typically soft on clinical examination.

Histological Features

The neoplasm is composed of markedly atypical epithelial cells with large, pleomorphic nuclei and prominent nucleoli, which do not form glandular structures and grow in solid nests with syncytial features. Abundant inflammatory infiltrate composed mainly of lymphocytes surrounds and permeates the tumor, clearly demarcating the neoplasm from normal breast parenchyma (Fig. 22). Foci of DCIS as well as lobular neoplasm around the tumor are uncommon findings.

Despite the presence of markedly atypical cells, which are typically ER, PR, and HER2 negative, when properly diagnosed following strict criteria, carcinoma with medullary features has a good prognosis, with low rates of lymph node or distant metastases [Pedersen et al., 1995].

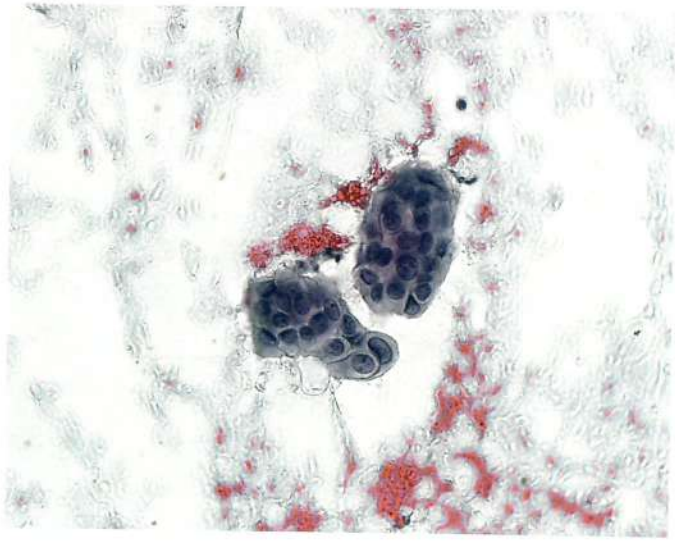


Fig. 21. Cytology of micropapillary carcinoma. The hallmarks of this lesion are small morula-like clusters with smooth margins composed of epithelial cells with round and relatively bland nuclei. These clusters lack myoepithelial cells and fibrovascular stalks. Papanicolaou. High power.

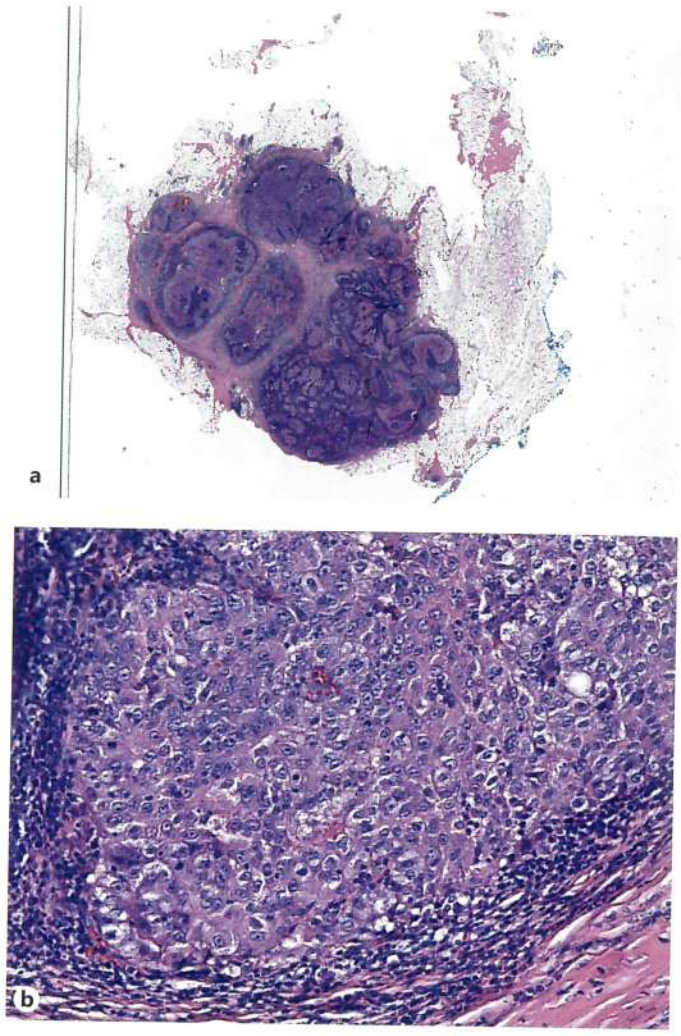


Fig. 22. Histology of carcinoma with medullary features. This neoplasm is defined as a lesion with the following histological features: solid architecture, pushing borders (**a**), rich lymphocytic intratumor infiltrate, high nuclear grade, and syncytial growth pattern (**b**). Note that lymphocytes are present also in the cytoplasm of cancer cells. H&E. **a** Slide overview. **b** High power.

Cytology

Aspirates from carcinomas with medullary features usually produce hypercellular smears with a variable admixture of markedly atypical cancer cells and chronic inflammatory cells. Neoplastic cells show one or more large pleomorphic nuclei, prominent nucleoli, and more than occasional mitotic figures, and are arranged singly or in 3-dimensional and loosely cohesive clusters (Fig. 23, 24). Tubular or acinar aggregates are typically absent, since the neoplasm has a solid-syncytial growth pattern. Many lymphocytes and plasma cells are admixed with neoplastic cells, and the background is necrotic [Galzerano et al., 2014].

A diagnosis of malignancy based on FNAC is usually easy, but it is important to differentiate this tumor from other more aggressive neoplasms in order to provide the patients with the best treatment. The presence of duct-like aggregates of cancer cells should orient the diagnosis towards ductal carcinoma NST rather than medullary carcinoma regardless of the lymphocytic infiltrate. Note that the definition of carcinoma with medullary features includes neat borders and clear circumscription of the neoplasm; therefore, a cytological diagnosis cannot be made without a careful radiological evaluation.

A large cell lymphoma could be suspected based on the aspirate, but the distinct nature of the large pleomorphic cells and the small reactive lymphocytes are usually sufficiently clear based on morphology. In selected cases, immunocytochemical stains for CD45 and cytokeratins may be helpful. Metastatic neoplasms to the breast should also be carefully excluded.

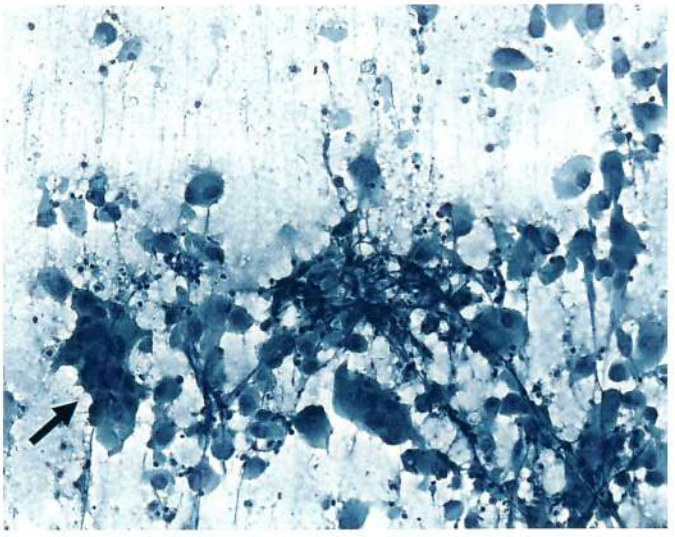


Fig. 23. Cytology of carcinoma with medullary features. A population of markedly atypical, mainly dissociated cancer cells is present in the smear. Some cells are aggregated in syncytial clusters (arrow). The background is dirty, containing cellular debris and many lymphocytes. Papanicolaou. High power.

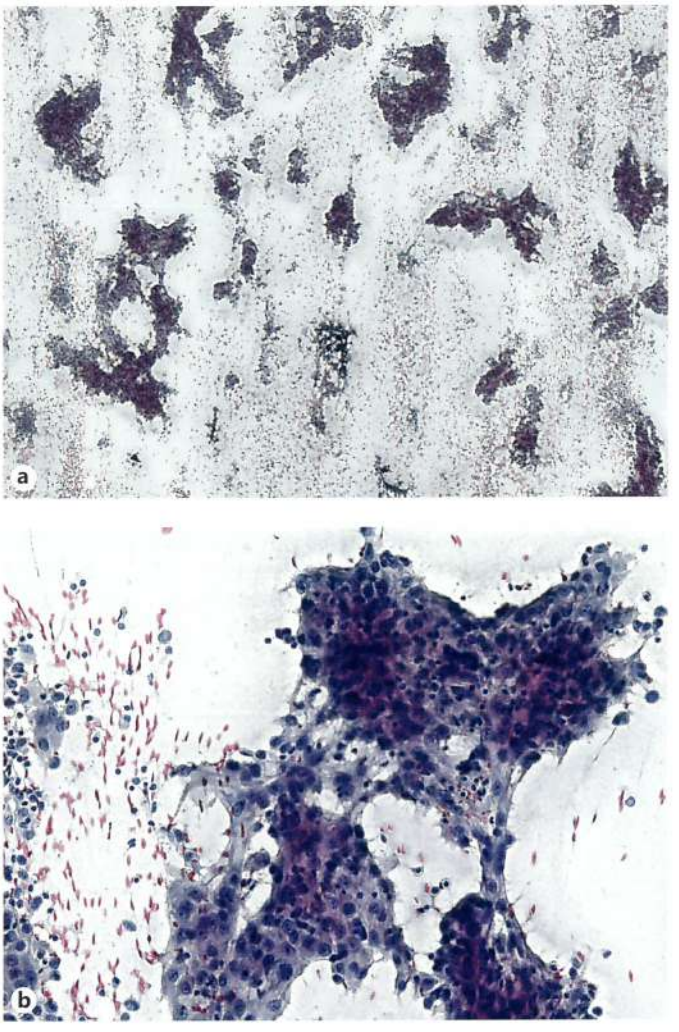


Fig. 24. Medullary carcinoma. This lesion is easily recognized as malignant already on scanning magnification (**a**). Close examination reveals hypercellular clusters of cancer cells with large nuclei, prominent nucleoli, and intracytoplasmic lymphocytes (**b**). The cytological diagnosis was high-grade carcinoma, suspicious for medullary carcinoma (C5). A definite diagnosis of medullary carcinoma is not feasible on cytology, since it relies on specific histological criteria. Papanicolaou. **a** Low power. **b** High power.

Summary

Key Cytological Features of Carcinoma with Medullary Features

- Marked cellularity
- Cancer cells with large, pleomorphic, sometimes multiple nuclei, and prominent nucleoli
- Rich lymphocytic infiltrate
- Dirty, necrotic background
- Absence of tubular and acinar structures

Apocrine Carcinoma

Apocrine carcinoma is a rare subtype of breast cancer that can pose diagnostic difficulties based on FNAC due to its morphological aspects resembling those of benign apocrine lesions, from which it must be distinguished. Clinical and radiological aspects are not different from those of invasive ductal carcinoma NST, but some peculiar cytological features can be useful to identify this neoplasm.

Aspirates from invasive apocrine carcinoma usually show numerous, predominantly dispersed, or loosely cohesive epithelial cells with abundant, dense to granular cytoplasm and round to oval nuclei, often eccentrically placed (Fig. 25). Nuclear chromatin is dispersed and a prominent eosinophilic nucleolus is present. Unlike benign apocrine lesions, malignant apocrine lesions show nuclear overlapping, nuclear pleomorphism, a raised nuclear/cytoplasmic ratio, and occasional mitotic figures (Fig. 26) [Khandeparkar et al., 2014]. A dirty, necrotic background is frequently present in aspirates from apocrine carcinomas, while benign lesions tend to show a proteinaceous cystic background with scattered foamy cells. Myoepithelial cells are not useful for this differential diagnosis, because they are frequently absent even in apocrine benign lesions.

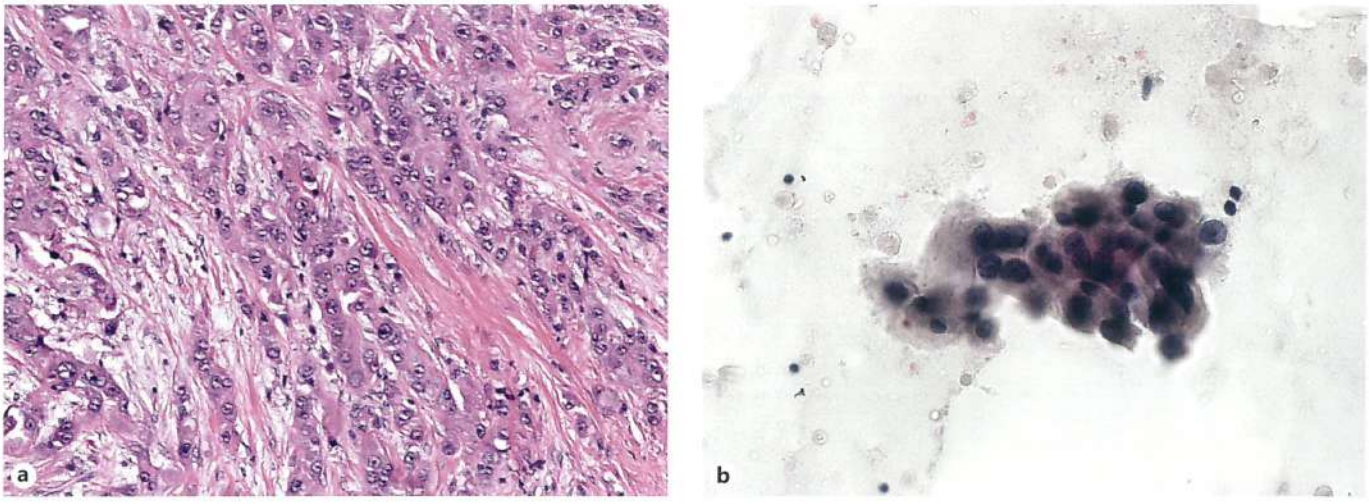


Fig. 25. Apocrine carcinoma. This invasive carcinoma is composed of cells with round nuclei, prominent nucleoli, and granular eosinophilic cytoplasm arranged in sheets and solid nests (**a**). FNAC from the same lesion shows hypercellular clusters with disordered and overlapping nuclei in a dirty background (**b**). H&E (**a**) and Papanicolaou (**b**). **a** Low power. **b** High power.

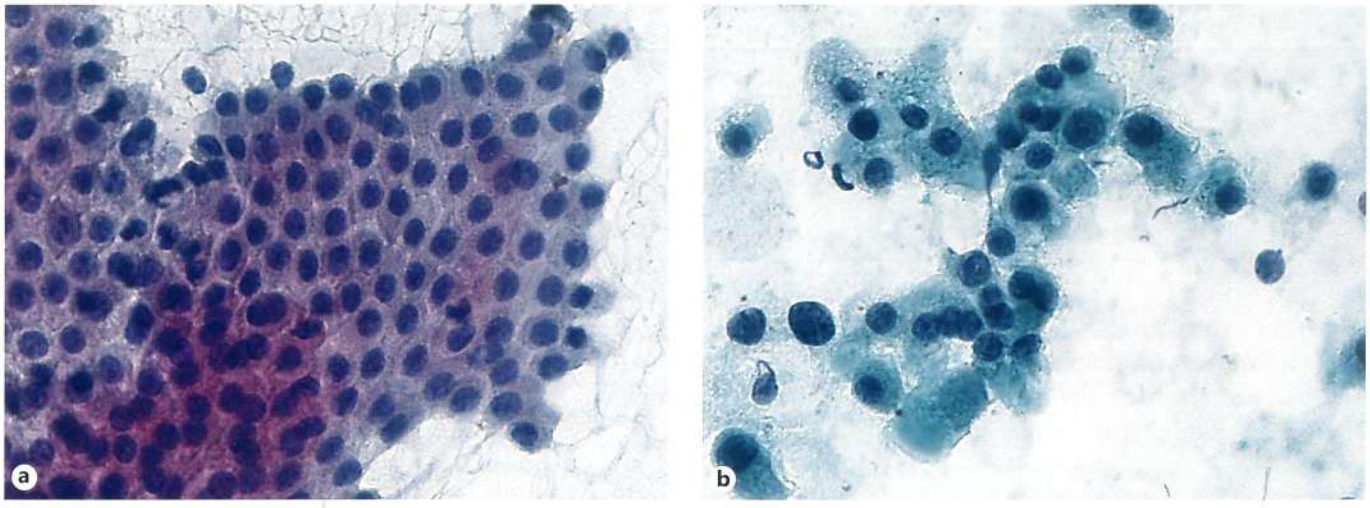


Fig. 26. Differential diagnosis between benign and malignant apocrine lesions. Compared to benign apocrine metaplastic cells (**a**), those of an apocrine carcinoma show greater nuclear pleomorphism and nuclear overlapping, and are arranged in less cohesive, disordered clusters (**b**). Intact single cells are more common in malignant lesions, but they do not represent a reliable sign of malignancy, since they are also present in many benign lesions. Myoepithelial cells, as well as bare bipolar nuclei, are typically lacking in both cases. Papanicolaou. High power.

Secretory Carcinoma

This rare neoplasm is composed of low-grade glandular elements with a solid, tubular, or microcystic architecture and a prominent production of intra- and extracellular secretory material. It may arise in both sexes with a wide age range (3–87 years), being more common in children and young adults [Rosen and Cranor, 1991]. It is more prevalent in the periareolar region and is clinically detected as a well-circumscribed, mobile mass. Histologically, it has pushing borders, and the prognosis is generally good, especially in the younger patients, although it is ER, PR, and HER2/neu negative. These tumors carry a characteristic genetic translocation t(12;15) creating an ETV6-ETRK3 gene fusion, which is considered a very specific diagnostic marker [Lae et al., 2009].

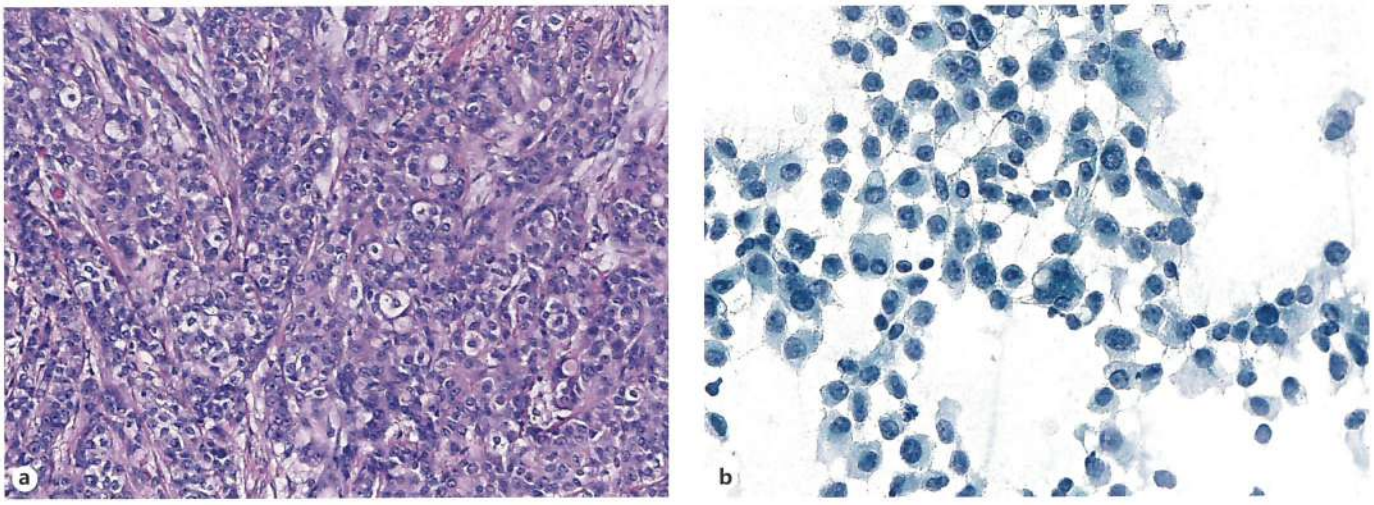


Fig. 27. Secretory carcinoma. This secretory carcinoma shows a predominantly solid architecture and is composed of round and polygonal cells with pale cytoplasm containing secretory vacuoles (**a**). The same cells are well appreciated in the aspirate, where they display singly or in loosely cohesive clusters and show vacuolated or "foamy" cytoplasm (**b**). H&E (**a**) and Papanicolaou (**b**). **a** Low power. **b** High power.

The cytological features of secretory carcinoma can be very similar to those of the normal breast during late pregnancy or lactation, showing clusters of rather uniform epithelial cells with numerous large cytoplasmic vacuoles containing proteinaceous material, which is also present in the background. Nuclei are typically round to oval, with a single, prominent nucleolus and even chromatin (Fig. 27). The absence of myoepithelial cells and bare bipolar nuclei in the background may be a useful diagnostic element to differentiate this neoplasm from lactation changes or a lactating adenoma. Actually, the clinical information is the most important element for this distinction [Vesoulis and Kashkari, 1998].

Metaplastic Carcinoma

Introduction/Epidemiology

Metaplastic carcinoma is a definition used to address a group of invasive carcinomas of the breast characterized by differentiation of the neoplastic cells towards squamous and/or mesenchymal-looking elements, such as spindle, chondroid, osseous, or rhabdomyoid cells. These are rare lesions, accounting for 0.2–5% of all invasive breast carcinomas [Stalsberg and Thomas, 1993]. The age distribution and clinical findings are similar to those of invasive ductal carcinoma NST.

Histological Features

Metaplastic carcinomas are a heterogeneous group of lesions. We find it useful to distinguish some subtypes sharing similar histological features as well as prognostic outcomes (Fig. 28).

The so-called *low-grade adenosquamous carcinomas* are neoplasms composed of well-developed glandular and tubular structures closely admixed with solid nests of squamous cells in a spindle cell background. In some studies, a group of metaplastic carcinomas with a better prognosis and lower risk of distant metastases was identified. Nevertheless, the lesion has a highly infiltrative growth pattern and frequent local recurrences [Van Hoeven et al., 1993].

Fibromatosis-like metaplastic carcinomas are composed of bland-looking spindle cells with slender nuclei and finely distributed chromatin embedded in stroma with varying degree of collagenization. Like the former group, these tumors also seem to have prevalently local aggressiveness, with a generally better prognosis compared to the others [Gobbi et al., 1999].

Pure and mixed *squamous cell carcinomas* of the breast are included among the metaplastic carcinomas. They resemble moderately and poorly differentiated squamous and adenosquamous carcinomas from other organs and have an aggressive behavior. They frequently have central cavitation and may appear as partially cystic masses on ultrasound examination.

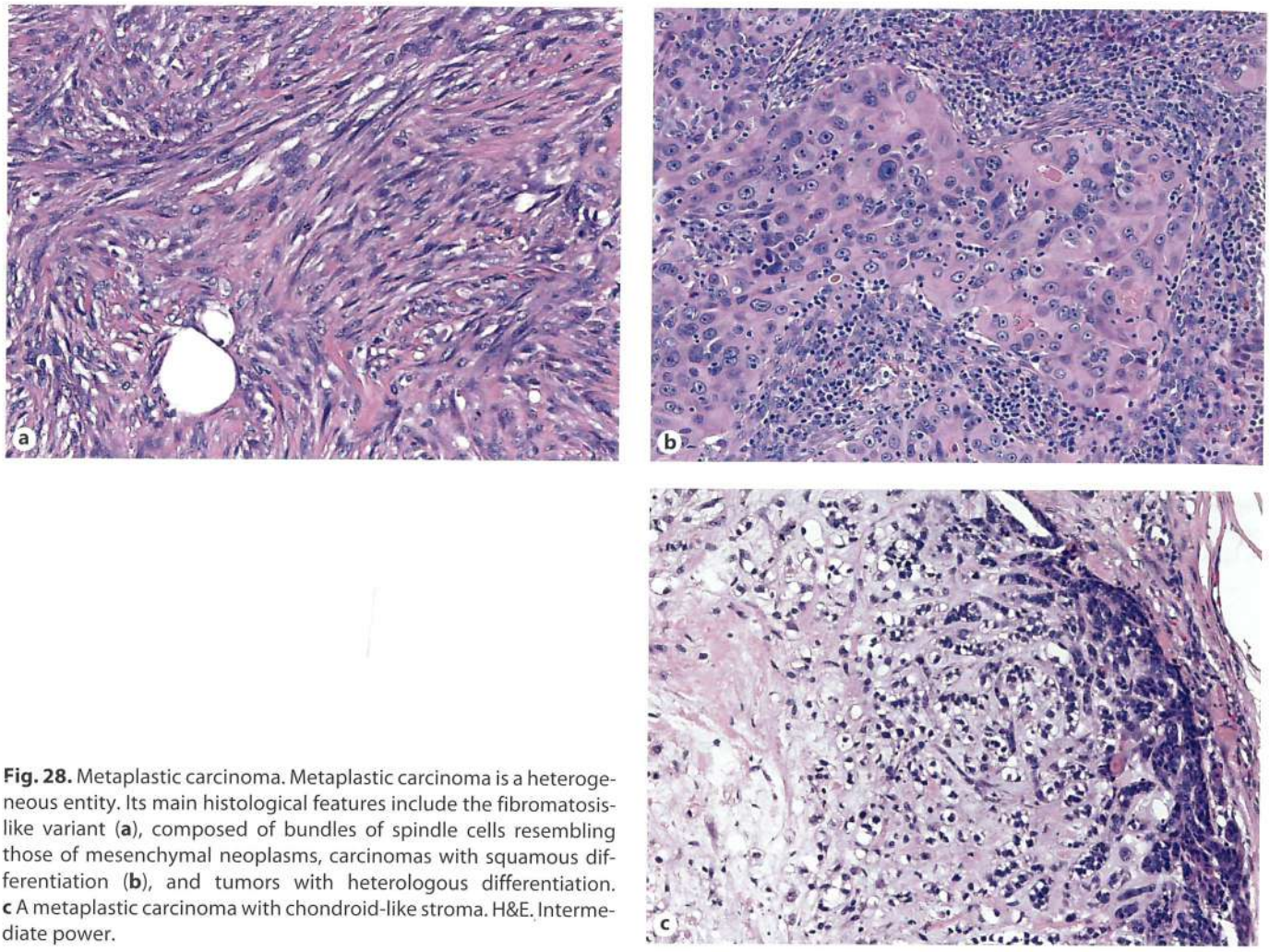


Fig. 28. Metaplastic carcinoma. Metaplastic carcinoma is a heterogeneous entity. Its main histological features include the fibromatosis-like variant (**a**), composed of bundles of spindle cells resembling those of mesenchymal neoplasms, carcinomas with squamous differentiation (**b**), and tumors with heterologous differentiation. **c** A metaplastic carcinoma with chondroid-like stroma. H&E. Intermediate power.

Spindle cell carcinomas are aggressive neoplasms composed of spindle-shaped cells with marked nuclear pleomorphism expressing at least focally epithelial markers (typically p63 and high-molecular-weight cytokeratins).

The last subtype is composed of carcinomas with other uncommon and peculiar mesenchymal differentiations, such as chondroid, osseous, rhabdomyoid, or neuroglial findings. They typically include areas resembling ductal carcinoma NST or squamous cell carcinoma. The term "matrix-producing carcinoma" is reserved to tumors that produce abundant extracellular chondroid matrix.

Metaplastic carcinomas are almost invariably ER, PR and HER2/neu negative [Reis-Filho et al., 2005; Tse et al., 2006].

Cytology

The typical aspirate from a metaplastic carcinoma shows poorly differentiated adenocarcinoma cells arranged singly or in 3-dimensional clusters, admixed with markedly atypical squamous cells, naked carcinomatous nuclei, and necrotic debris (Fig. 29). Pleomorphic spindle cells and chondroid matrix in the background may be present in tumors with mesenchymal differentiation (Fig. 30) [Lale et al., 2011].

Metaplastic carcinomas are known to be potential mimickers of other types of lesions and may represent dangerous pitfalls of cytology depending on the examiner's experience and the type of cells that are present in the smear. Carcinomas with a glandular and a squamous component, and especially low-grade adenosquamous carcinomas, might be only partially sampled, being misdiagnosed as ductal or tu-

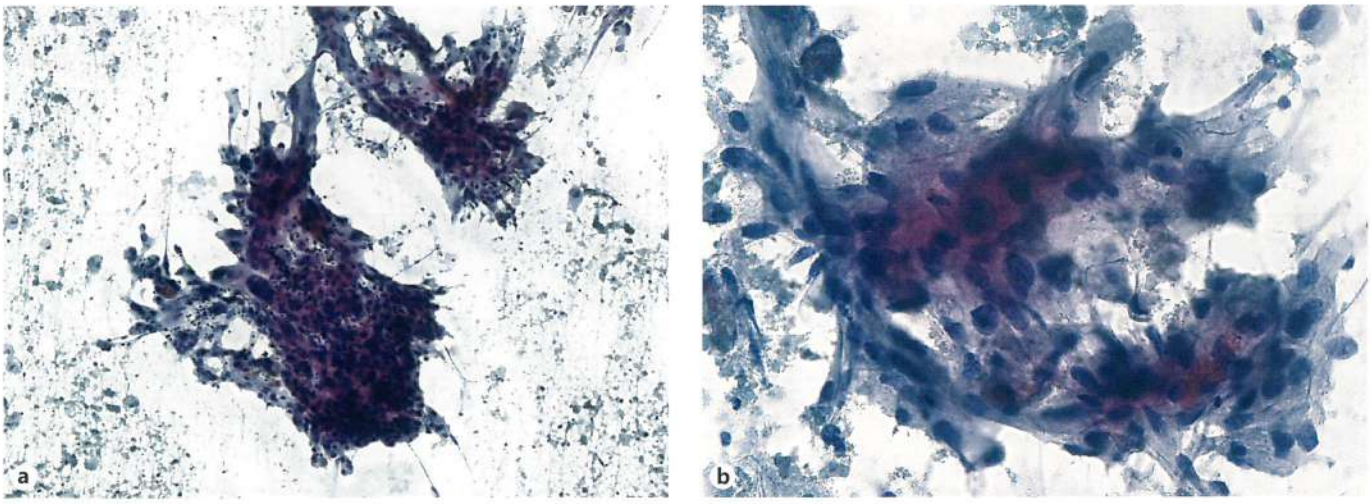


Fig. 29. Cytology of metaplastic carcinoma. The most frequent cytological aspects from metaplastic carcinomas include hypercellular clusters of severely atypical cancer cells with "squamoid" cytoplasm in a dirty, often necrotic background. Papanicolaou. **a** Low power. **b** High power.

bular carcinomas or even as benign proliferative lesions if only the well-differentiated glandular component is detected [Bataillon et al., 2014]. The finding of squamous cells in breast FNAC is highly suspicious of the presence of a metaplastic carcinoma. Nevertheless, the presence of a purely squamous cell neoplasm in the breast should raise the doubt of being a metastatic lesion, so other possible sites of origin should carefully be ruled out.

The presence of chondroid matrix in the background can pose a challenging differential diagnosis with pleomorphic adenoma, myxoid fibroadenoma, and mucinous lesions (mucinous carcinoma and mucocele-like lesions). The presence of high-grade adenocarcinoma cells is usually sufficient to remove the doubt that it might be a benign lesion. However, some cases show well-differentiated tumor cells, and a definite diagnosis might be difficult if not impossible based on morphology only [Tajima et al., 2015].

Giemsa staining can be helpful to distinguish the chondromyxoid matrix of metaplastic carcinoma from mucinous material based on its typical brightly pink color, different from the blue to magenta shade of mucus.

A differential diagnosis between spindle cell metaplastic carcinoma and malignant phyllodes tumor might be possible on FNAC if an epithelioid component is present in the smear. Actually, malignant phyllodes tumor is composed of high-grade stromal cells and a benign-looking epithelial component, consisting of cohesive staghorn clusters of ductal cells with overlapping myoepithelial cells. Conversely, metaplastic carcinomas usually display elements resembling a poorly differentiated ductal or squamous carcinoma.

Tumors displaying only spindle cells in the smear might be impossible to define without the aid of immunocytochemistry. Sometimes, a definite diagnosis of metaplastic carcinoma is possible only on the surgical specimen.

Summary

Key Cytological Features of Metaplastic Carcinoma

- Malignant squamous cells
- Pleomorphic spindle cells
- Chondromyxoid matrix
- Necrotic debris in the background

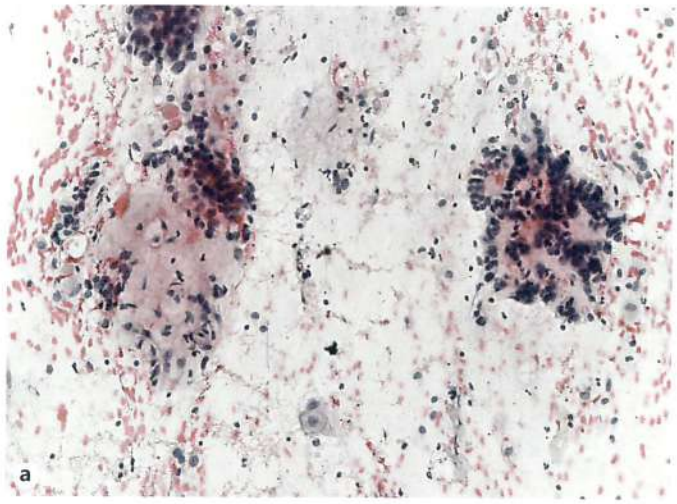
Common Pitfalls of FNA: Metaplastic Carcinoma

- Only glandular elements with mild atypia (from a low-grade adenosquamous carcinoma)
- Only adenocarcinoma cells
- Metastatic squamous cell carcinoma
- Only bland-looking spindle cells

Adenoid Cystic Carcinoma

Introduction/Epidemiology

Adenoid cystic carcinoma of the breast is a very rare variant of breast carcinoma sharing morphological features with its analogue in salivary glands. It is usually found in



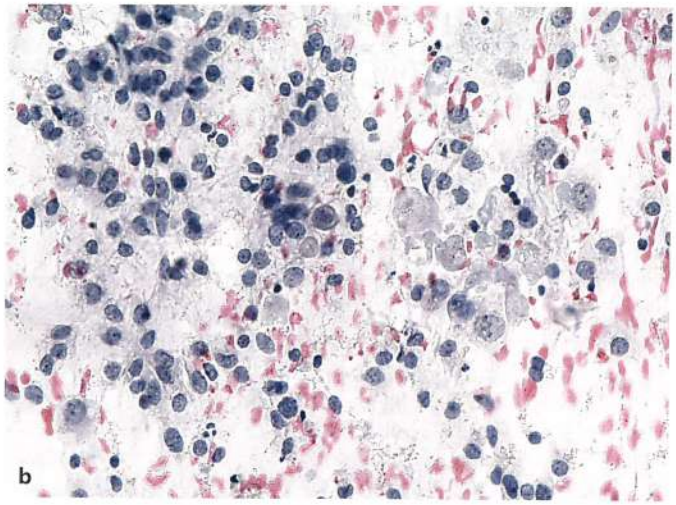


Fig. 30. Heterologous metaplastic carcinoma. Metaplastic carcinoma might be suspected on the cytological smear for the presence of chondromyxoid material in the background. Compare with Figure 28c (histology of the same case). The differential diagnosis is with myxoid fibroadenomas and mucinous carcinoma. Papanicolaou. **a** Intermediate power. **b** High power.

the sixth decade of life and seldom in premenopausal women. Tumor size may range from 0.7 to 10 cm, with an average of 3 cm in some series [Arpino et al., 2002; Peters and Wolf, 1983]. It fails to show the typical appearance of invasive ductal carcinoma on both mammogram and ultrasonography, usually presenting as a benign-appearing, smooth, round, or lobulated density or as an irregular mass (Fig. 31) [Sheen-Chen et al., 2005]. Symptoms at presentation include a breast lump and intermittent pain.

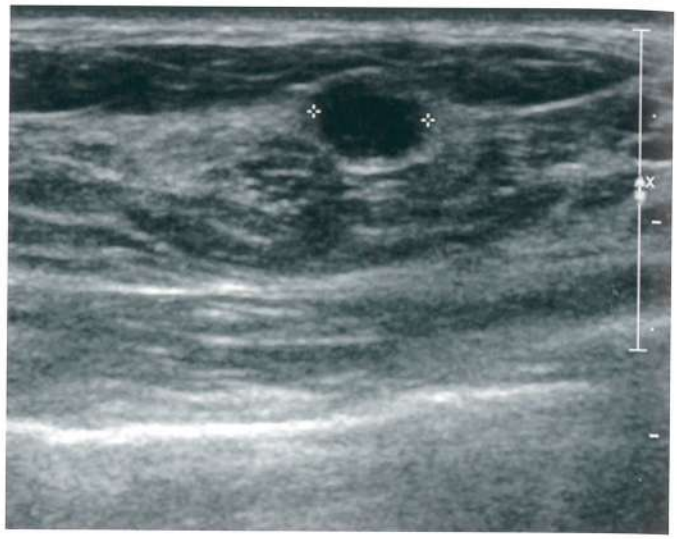


Fig. 31. Ultrasound of an adenoid-cystic carcinoma. This small lesion was initially considered benign based on radiological findings and turned out to be an adenoid-cystic carcinoma on the following cytological and pathological examination. On ultrasound, it appears as an ovoid, hypoechoic, partially cystic mass with round contours and the long axis parallel to the skin.

Histological Features

Similar to its analogue in salivary glands, adenoid cystic carcinoma of the breast is characterized by a variety of patterns that typically include small glandular lumina lined by ductal epithelium and eosinophilic "cylinders" with basement membrane material lined by basal/myoepithelial-type cells (Fig. 32). These tumors show an extremely low proliferative rate and have generally a good prognosis, with rare axillary lymph node involvement. Noteworthy, distant metastases might develop in a small number of cases, even though axillary lymph nodes are negative. For this reason, axillary lymph node dissection may not be helpful in this special type of cancer and probably should be avoided [Arpino et al., 2002].

ER and PR are variably positive, differently from adenoid cystic carcinomas of other sites, and Her2 is typically negative.

Cytology

The cytological appearance of adenoid cystic carcinoma reflects its peculiar histological aspect, showing clusters of epithelial cells oriented around solid spheres of amorphous, proteinaceous material. Cells are rather small and monotonous, with oval-shaped nuclei surrounded by a thin rim of

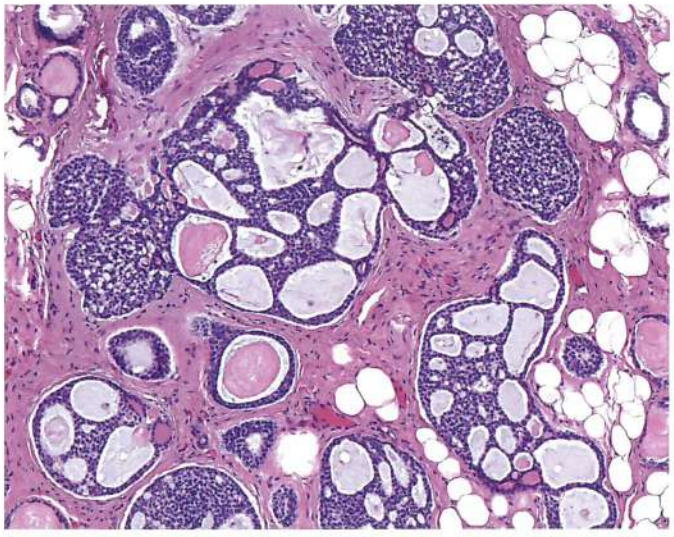


Fig. 32. Histology of adenoid-cystic carcinoma. The classical "cylindromatous" growth pattern is well represented in this case. Glandular lumina are filled with homogeneous, small, cuboidal cells lining variably sized cystic cavities with cylinders of eosinophilic material. H&E. Low power.

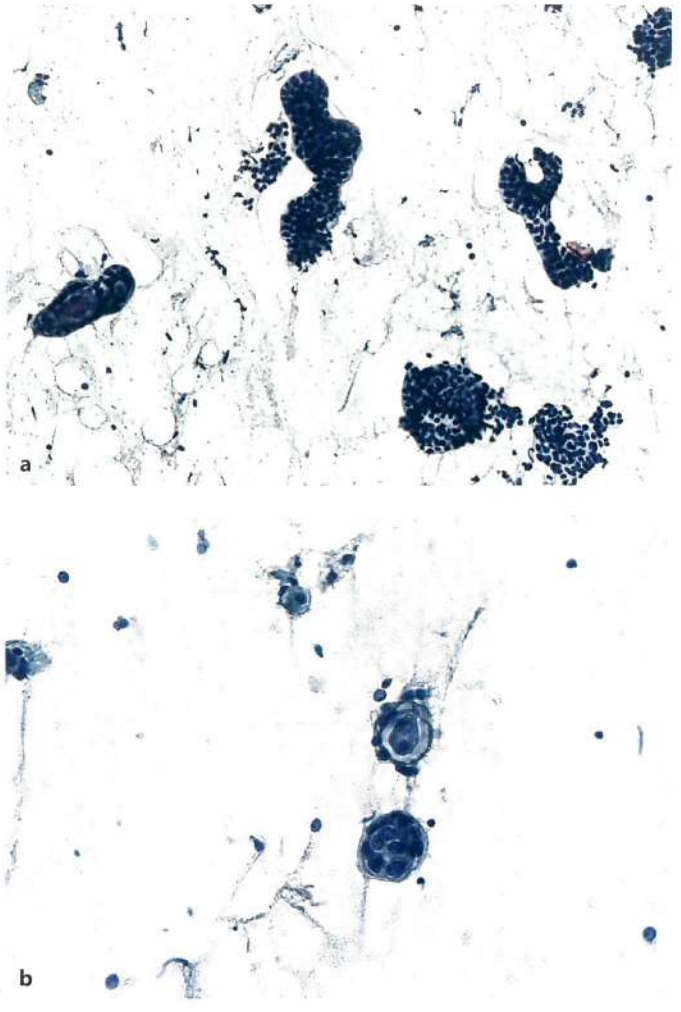


Fig. 33. Cytology of adenoid-cystic carcinoma. The typical picture of an aspirate from adenoid-cystic carcinoma includes small cellular clusters with round and neat borders composed of uniform cells with bland nuclei. Some clusters have small spheres of amorphous material in the center, around which display epithelial cells. Bare nuclei are present in the background, but they tend to be round rather than ovoid or bipolar. Papanicolaou. **a** Low power. **b** High power.

cytoplasm. Many bare nuclei are present in the background, but they tend to be round rather than oval or bipolar (Fig. 33).

The lack of cytological atypia, together with the radiological "benign" aspect, may lead to the misdiagnosis of this lesion as a benign proliferative lesion, such as microglandular adenosis or collagenous spherulosis. The latter is a peculiar condition rarely encountered in the breast, which shows collagenous spherules on cytological samples very similar to those found in adenoid cystic carcinomas. To differentiate both entities, attention should be paid to the nuclear/cytoplasmic ratio, which is very high in adenoid cystic carcinoma. Moreover, in collagen spherulosis, acellular spherules are surrounded by a single layer of cells, while in adenoid cystic carcinoma several layers may be present [Ilkay et al., 2015].

Besides the peculiar glandular aggregates with hyaline spherules in the center, a variable amount of tubular and solid clusters are often observed in aspirates from adenoid cystic carcinoma, and their presence, especially when numerous, may help in the differential diagnosis with other types of well-differentiated breast cancers. In these cases, the failed recognition of this entity may lead to a potential overtreatment of the patient, who would neither benefit from sentinel lymph node biopsy nor from axillary dissection. On the other side, the extreme rarity of this neoplasm should not lead the cytopathologist to a hurried, and potentially wrong, diagnosis. Thus, we suggest assessing aspirates suggestive of adenoid cystic carcinoma as "atypical or suspicious for carcinoma" and direct the patient to core needle biopsy to confirm the diagnosis before proceeding with the treatment.

Immunocytochemistry can be extremely useful to identify this neoplasm without resorting to core needle biopsy. Indeed, neoplastic cells are strongly positive for p63 and

CD117/c-kit, allowing a differential diagnosis with most invasive carcinomas (p63 negative) and collagenous spherulosis (CD117 negative) [Ilkay et al., 2015].

Summary

Key Cytological Features of Adenoid Cystic Carcinoma

- Moderate to marked cellularity
- Clusters of epithelial cells oriented around hyaline spherules
- Small-sized, bland cells with oval nuclei and scant cytoplasm

Common Pitfalls of FNA: Adenoid Cystic Carcinoma

- Tubular structures and solid aggregates
- Very mild cytological atypia
- Bare nuclei in the background
- Radiological "benign" aspect

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