Skin and Subcutis

15

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Introduction

Fine-needle aspiration cytology (FNAC) plays a limited roll in the examination of primary cutaneous neoplasms. Morphologic diagnosis of skin lesions is traditionally performed with punch biopsies or incisional biopsies. Superficial location of skin nodules facilitates excision for both curative and diagnostic purposes without significant morbidity. FNAC offers the possibility of avoiding surgical biopsy and provides rapid diagnosis making it a valuable examination tool especially in cases of metastatic depositions in the skin and subcutaneous tissue [1–7].

Although major indications for FNA of skin and subcutis nodules are metastatic lesions, parasitic, fungal, and bacterial infections, lymphoproliferative disease, depositions in some systemic lesions, and primary skin neoplasms can also be targets for FNA [8–20].

Sampling and Preparation Techniques

Skin and subcutaneous FNA are most often performed on palpable masses without radiographic guidance. Even very small nodules can be successfully aspirated and diagnosed (see Fig. 15.1). 27 to 22 gauge (0.4–07) needles are suitable, either using a capillary technique without aspiration or a syringe holder with a plastic disposable syringe attached to the needle when suction is desired. Capillary technique improves precision and reduces contamination of the specimen with blood when sampling small skin lesions. A plastic or metal syringe holder gives better control for needle placement in aspiration of deep and cystic lesions. For palpable lesions, ultrasound guidance in some circumstances provides more information regarding possible necrotic areas in subcutaneous masses and their proximity to larger blood vessels and nerves. Local anesthetic cream - application in the skin over the area of the procedure may be necessary before performing FNA in children.

Needle samples from the first puncture should be stained using Diff-Quik or rapid hematoxylin and eosin (H&E) or Papanicolaou staining. Rapid on-site evaluation (ROSE) makes it possible for the cytopathologist to assess lesion type (inflammatory, neoplastic, primary, or metastatic) and, in many cases, suggest a range of differential diagnoses and decide whether more material is required or if ancillary techniques might be helpful.

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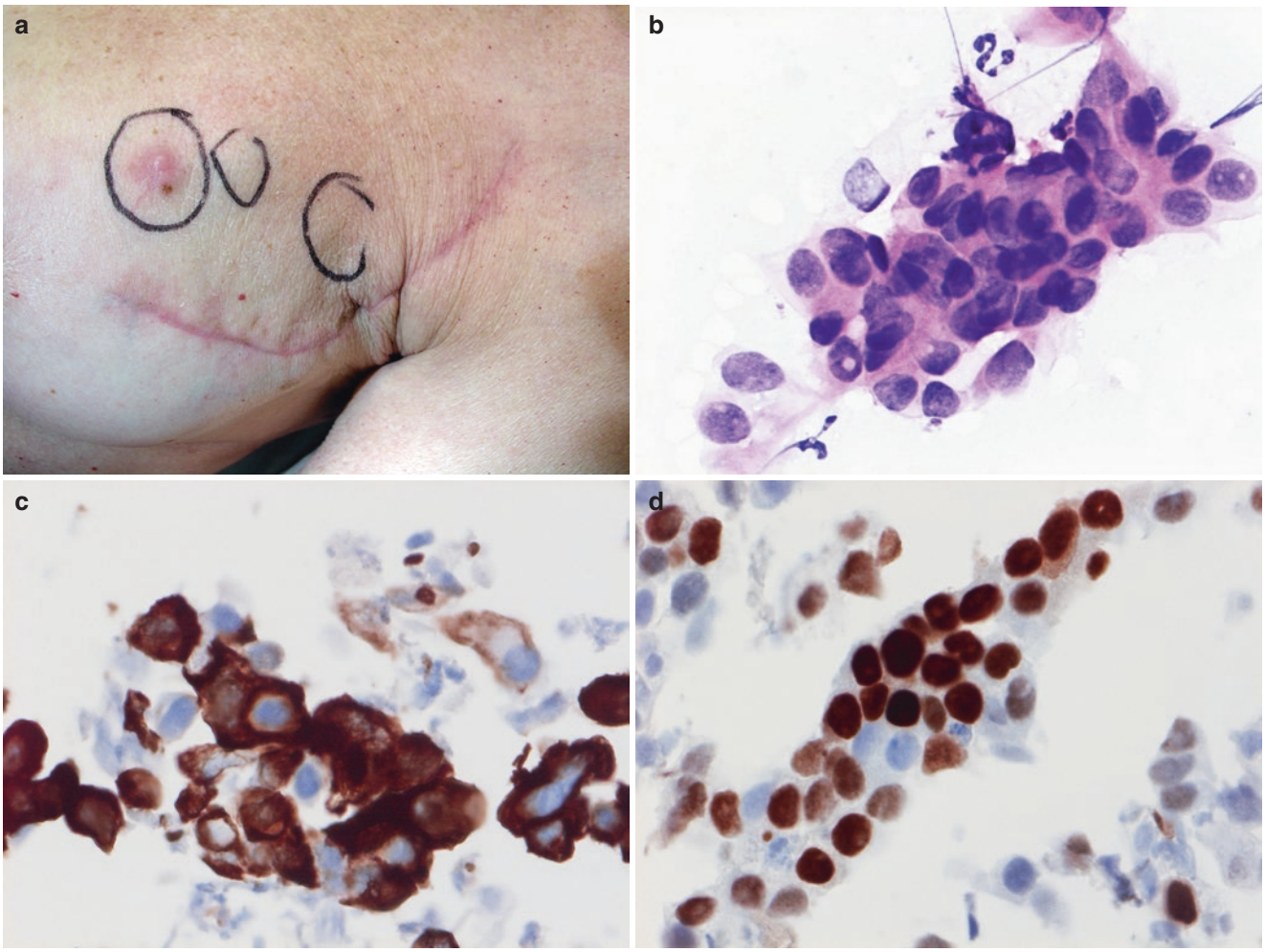


Fig. 15.1 (**a**) FNA of a small skin nodule suspicious of metastasis from breast carcinoma. (**b**) FNA smears showing cohesive sheets of carcinoma cells (H&E). Positive immunostains for (**c**) cytokeratin CK7 and (**d**) estrogen receptor confirms a diagnosis of metastatic breast carcinoma (cell block; Cellient; Hologic; Bedford, MA, USA)

Diagnostic Accuracy

Few series of accuracy of skin neoplasm have been reported [11, 12]. Diagnostic accuracy varies between 80% and 95%. In one series of primary skin tumors reported by Layfield et al., 89% of cases were correctly diagnosed as benign or malignant, while histologic diagnosis was possible in 81% of cases [15]. One study indicated that cytological examination of basal cell carcinoma (BCC) had a diagnostic accuracy of 95.65% with no false-positive and one false-negative case in 22 patients examined by FNA [21]. In another study of cutaneous neoplasm, FNA established the nature of skin tumors in 16 of 18 patients (88.9%), whereas subtyping was possible in 12 of 18 cases (66.7%) [22]. Some skin adnexal tumors, particularly pilomatrixoma, have been reported as a common cause of false-positive cytological diagnosis [23, 24].

Nonneoplastic Entities

Inflammatory Lesions

FNA is of value in the diagnosis of cutaneous manifestations of mycobacterial and protozoan lesions [16]. In addition, some parasitic, fungal, and bacterial infections have been described cytologically in small series and case reports [9, 17, 25–27].

Calcinosis Cutis

The deposition of insoluble calcium salts in the skin and subcutaneous tissue (calcinosis cutis) occurs as dystrophic, metastatic, idiopathic, or iatrogenic calcification in different systemic and local conditions. In addition, some skin tumors present with calcifications. The most common is pilomatrixoma, pilar cyst, basal cell carcinoma, and desmoplastic trichoepithelioma. Calcinosis cutis may be diagnosed by FNA in the appropriate clinical setting (see Fig. 15.2) [28–32].

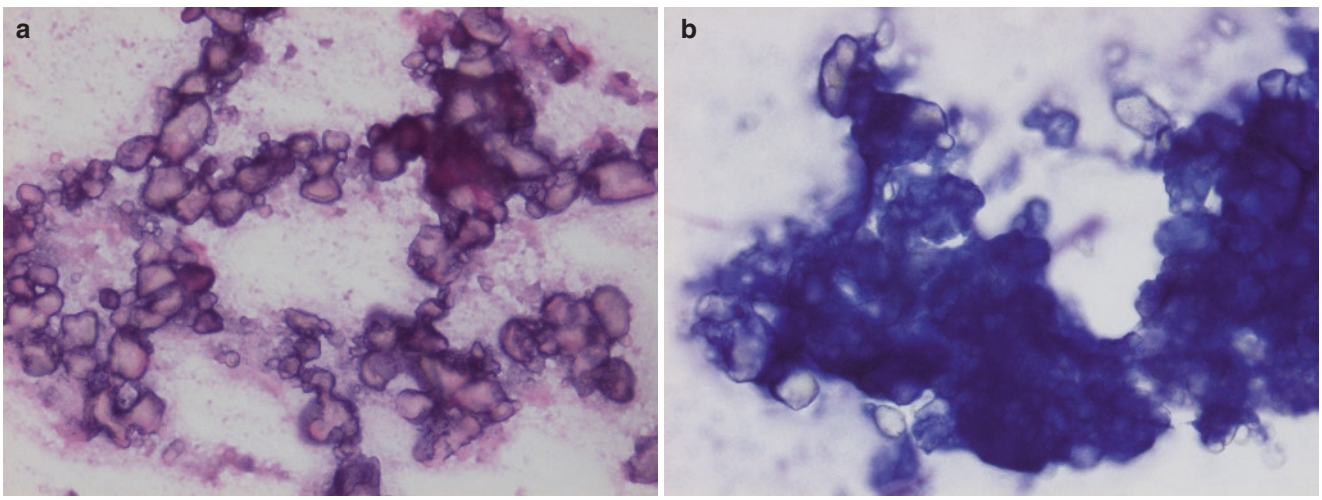


Fig. 15.2 Calcinosis cutis. (**a**, **b**) FNA smears from cutaneous nodule show calcified material (H&E; MGG)

Amyloidosis

FNA of the subcutaneous fat for examination of amyloid deposition is a sensitive method that may be used as an alternative technique to rectal biopsy [33–35]. Deposits of amyloid are detectable with the use of different techniques, i.e., the examination of Congo red-stained smears in polarized light. Amyloid is visible in bright-field microscopy as salmon-pink/red-stained areas with apple-green birefringence under polarized light (see Fig. 15.3). Systemic amyloidosis presenting in other organs such as lymph nodes may also be diagnosed by FNA.

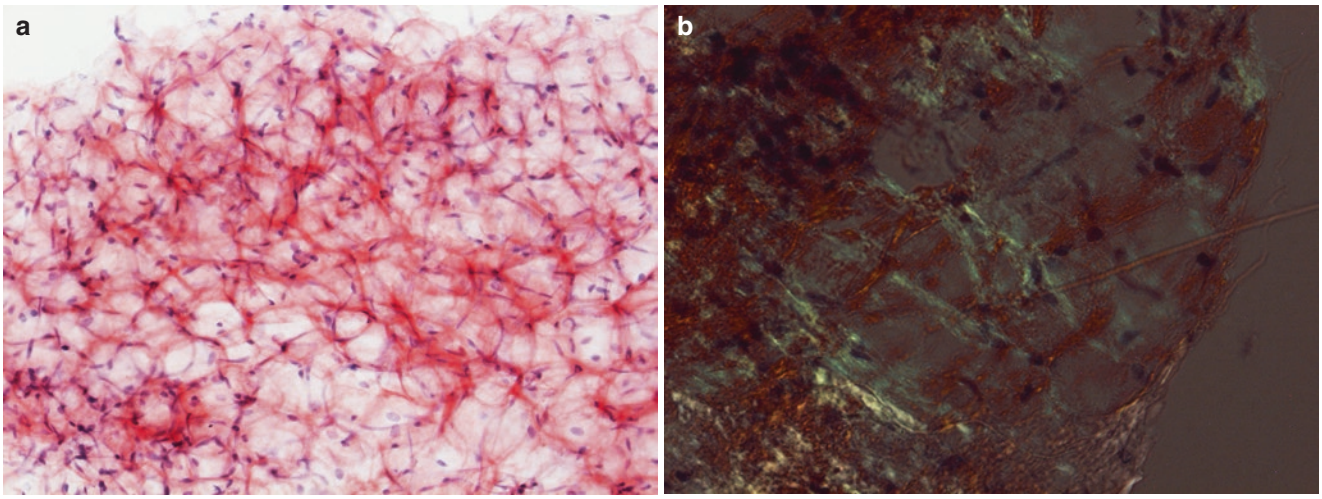


Fig. 15.3 Amyloidosis. (**a**) FNA smears from subcutaneous fat in the abdominal wall stained with Congo red. (**b**) Amyloid appears as an apple-green birefringence under polarized light

Endometriosis

A common location of endometriosis is the skin and subcutaneous tissue (e.g., the groin and abdominal wall), occasionally in the scar after a caesarian section. Endometriosis occurring in the skin and subcutaneous tissue may be sampled and diagnosed by FNA [36–38]. Smears from endometriosis are commonly cellular and correspond to histological sections that contain two main components: (1) sheets of epithelial cells with glandular structures and (2) a stromal component. The last is often similar to endometrial stroma but occasionally contains proliferating myofibroblasts and macrophages/inflammatory cells as a reaction to the periodically bleeding (see Fig. 15.4).

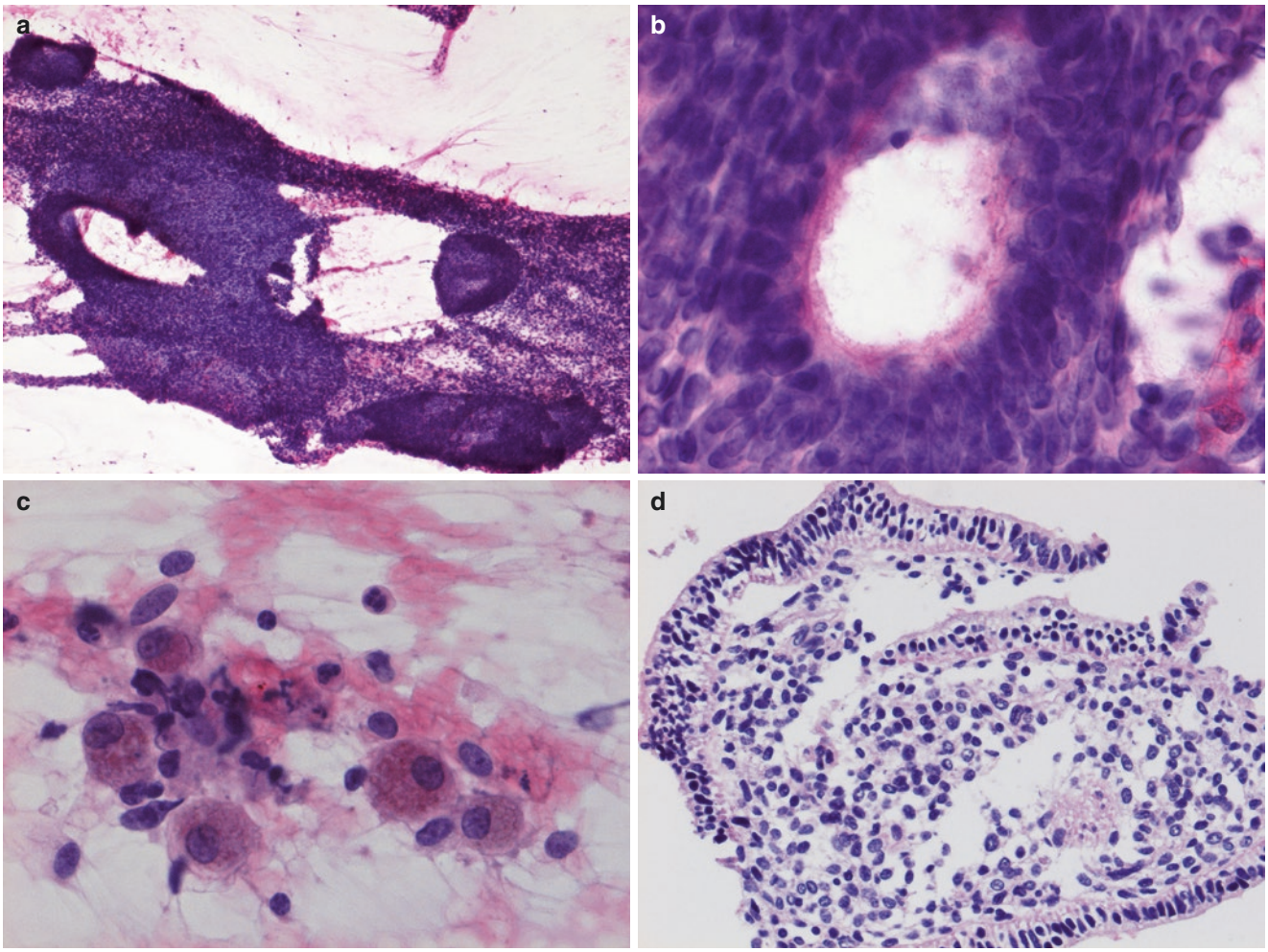


Fig. 15.4 Endometriosis. (**a**) Sheets of epithelial cells and stromal component (H&E). (**b**) Sheets of epithelial cells with glandular structures resembling endometrial epithelium (H&E). (**c**) Myofibroblasts, macrophages, and inflammatory cells commonly seen in the smears from endometriosis as a reaction to periodic bleeding (H&E). (**d**) Cell block section with clearly visible stromal and epithelial components (Cellient; Hologic; Bedford, MA, USA)

Foreign Body Granulomas and Other Granulomas of the Skin and Subcutaneous Tissue

Foreign body granulomas are occasionally sampled in the aspiration of dermoid cysts and neoplasms of squamous epithelium but also in areas of previous trauma or surgery (see Fig. 15.5). Foreign body granulomas should be distinguished from granulomas occurring in different neoplastic and inflammatory skin conditions presented with giant cells and histiocytes [39, 40]. Important differential diagnoses include inflammations caused by mycobacteria (in rare cases of skin tuberculosis and much more common infections with atypical mycobacteria). Necrosis and clusters of epithelioid histiocytes visible in smears, as well as ancillary molecular techniques [41, 42], help to distinguish specific mycobacterial inflammatory conditions from other granulomas. Some authors indicate that scrape cytology is superior to FNA inflammatory and granulomatous skin conditions occurring in the skin [43].

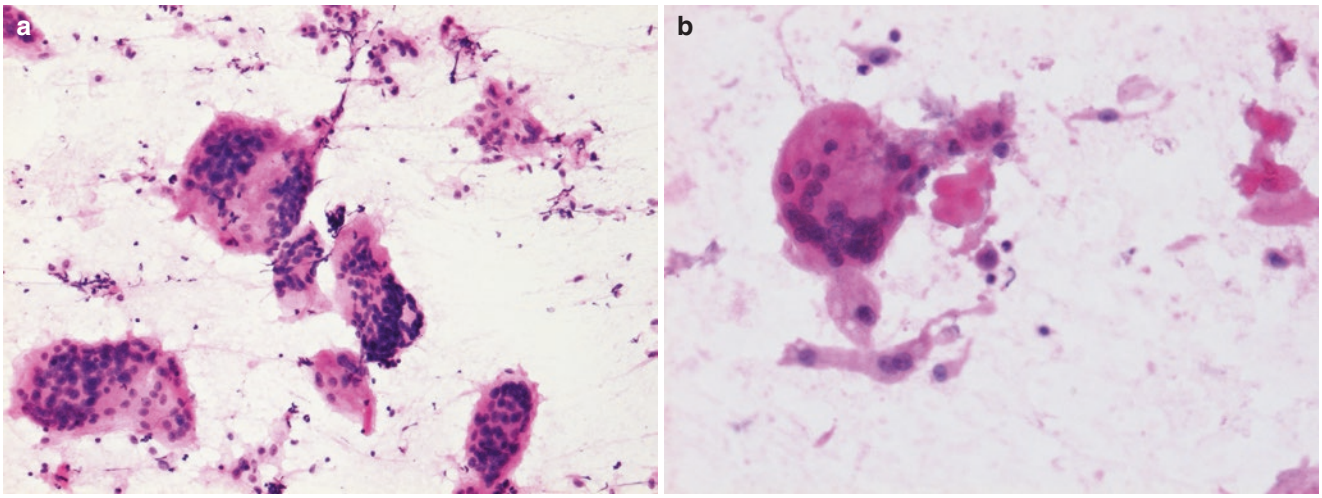


Fig. 15.5 Foreign body granuloma. (**a**, **b**) Giant cells, histiocytes, some inflammatory cells, and keratin debris (H&E)

Squamous Cysts and Other Localized Degenerative Cystic Processes

Smears from epidermal, dermoid, and pilar cysts consist of anucleated squames, often minor components of nucleated squamous epithelial cells and inflammatory cells/foreign body granulomas (see Fig. 15.6).

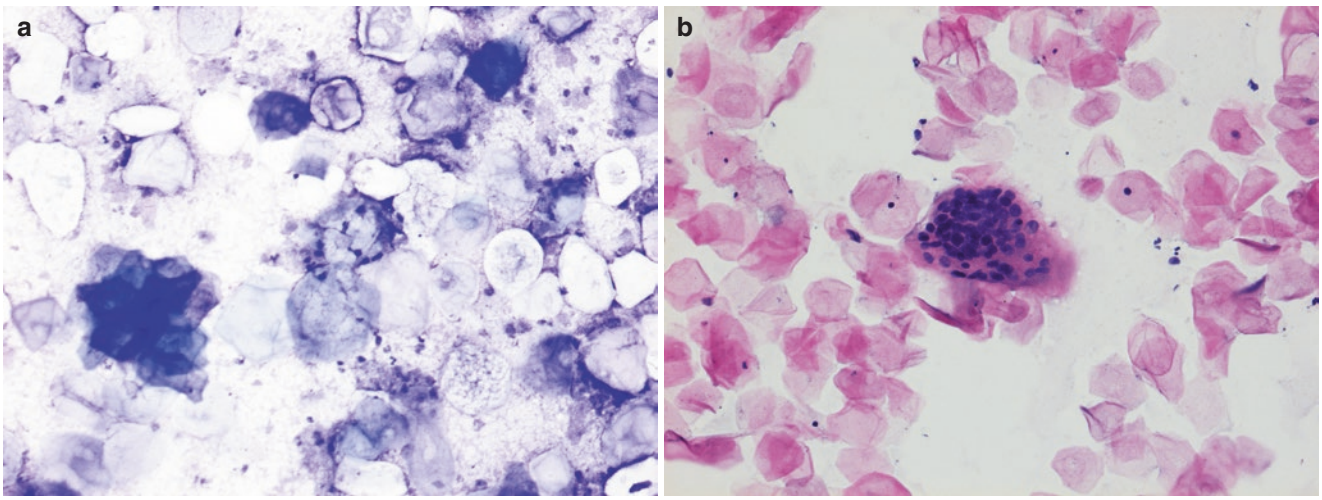


Fig. 15.6 Dermoid cyst. (**a**) Anucleated squames and inflammatory cells (MGG). (**b**) Anucleated squames, some nucleated squamous epithelial cells, and foreign body giant cells (H&E)

Verruca Vulgaris

Verruca vulgaris may be the target of aspiration when lesions are particularly exophytic. Cytologic features in smears include squamous epithelia, squamous debris, and keratohyalin-inclusion bodies (see Fig. 15.7).

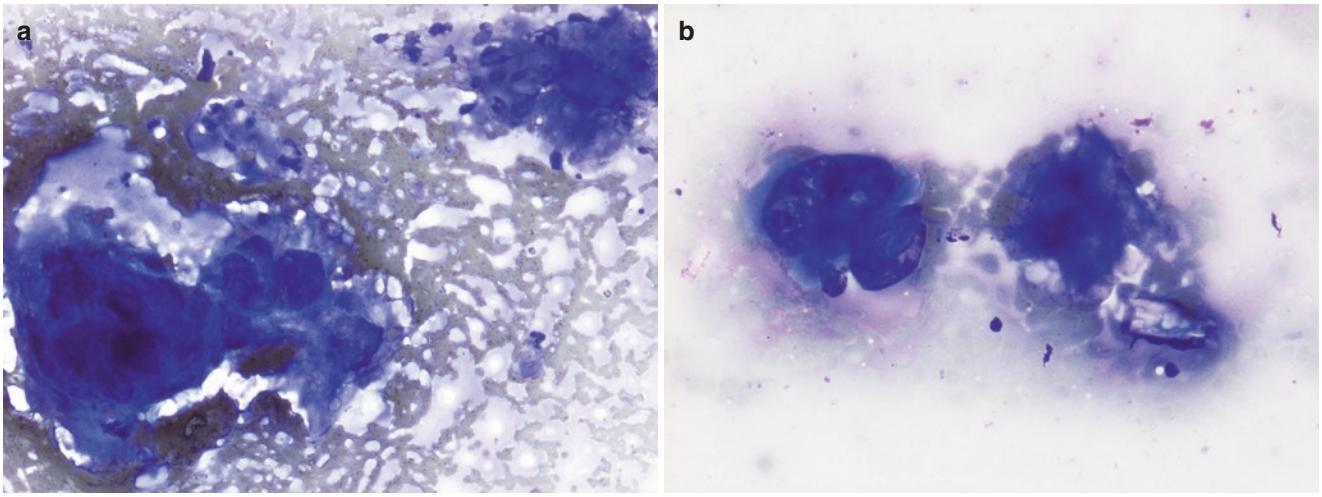


Fig. 15.7 Verruca vulgaris. (**a**, **b**) Squamous epithelial cells, squamous debris, and keratohyalin bodies (MGG)

Neoplasms of Surface Epithelium

Keratoacanthoma and Seborrheic Keratosis

Keratoacanthoma may occasionally resemble squamous cell or basal cell carcinoma. Similarly, seborrheic keratosis typically presents a clinical picture of a circumscribed skin lesion, which may be mistaken for basal cell carcinoma when ulcerated and flattened.

Cytologic findings of keratoacanthoma and seborrheic keratosis include mixtures of anucleate and nucleated squamous cells and cell clusters, while smears from keratoacanthoma present with mild-to-moderate nuclear pleomorphism. It can be difficult to distinguish keratoacanthoma from well-differentiated squamous carcinoma in FNA smears (see Fig. 15.8). Cell block material is not helpful, except for poorly differentiated squamous carcinoma presenting considerable cellular–nuclear pleomorphism and mitoses.

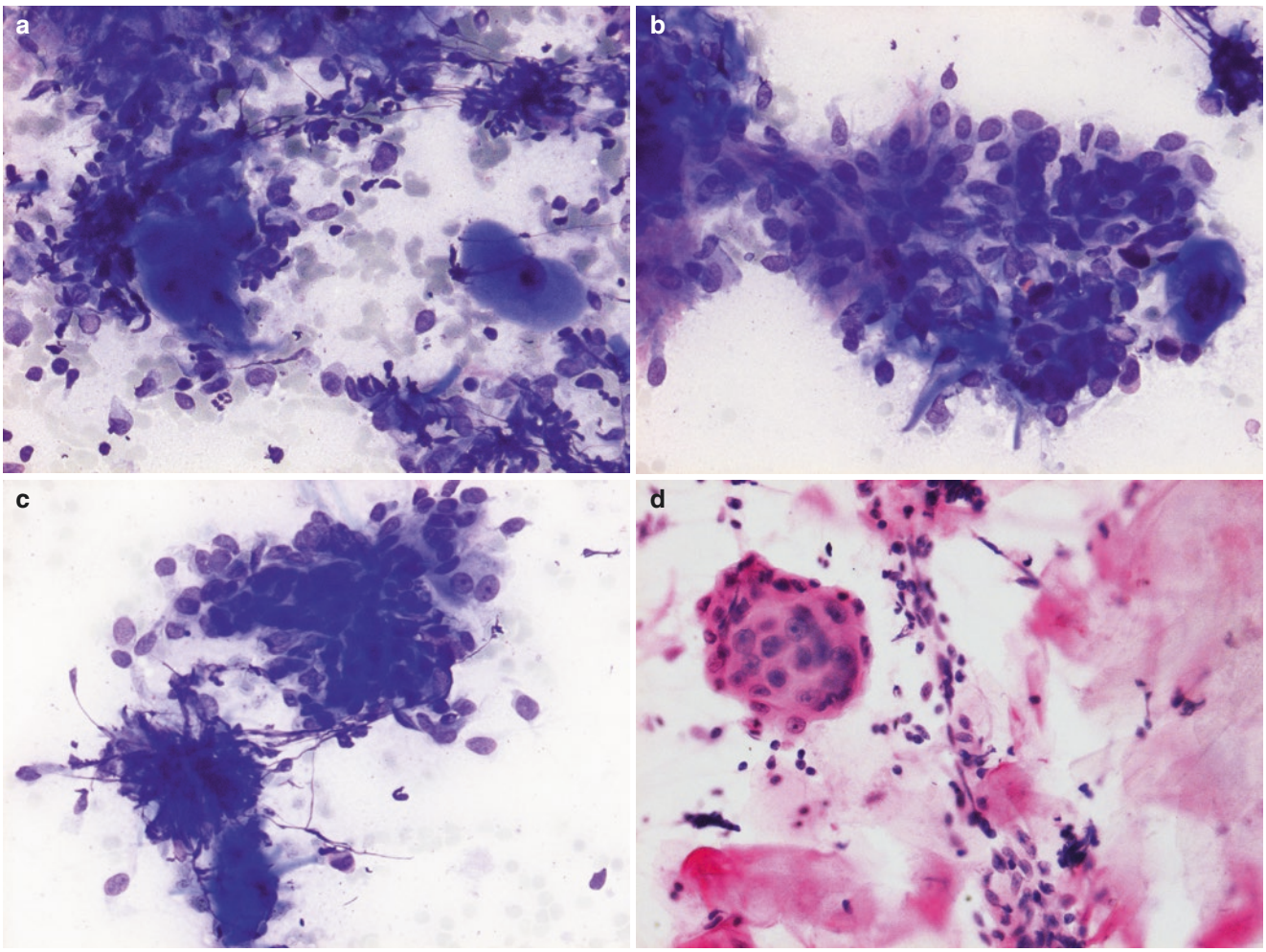


Fig. 15.8 Keratoacanthoma. (**a**–**d**) FNA smears show a mixture of keratin debris, anucleated and nucleated squamous cells, cell clusters, and mild-to-moderate nuclear pleomorphism. It is difficult to distinguish keratoacanthoma from well-differentiated squamous carcinoma (MGG, H&E)

Squamous Cell Carcinoma (SCC)

Microscopically, the majority of smears show unequivocal malignant cells with signs of keratinization and intercellular bridges (see Fig. 15.9). The few lesions presenting problems in differential diagnosis are small cell-type SCC, which is difficult to distinguish from basal cell carcinoma (BCC) [44]. Smears from BCC show commonly cohesive clusters and sheets of relatively uniform cells without intercellular bridges (see Figs. 15.11 and 15.12). Bowen's disease and keratoacanthoma show some features of SCC and are difficult to distinguish from invasive SCC (see Fig. 15.10).

Cytologic features:

- Single cells and sheets of cells
- Large- or medium-sized cells with a high nuclear–cytoplasmic (N/C) ratio and nuclei with coarsely or granular chromatin
- Hyperchromasia and occasional macronucleoli and mitoses
- Bizarre, occasionally spindled cells in poorly differentiated SCC
- Keratinized malignant cells (dense organophilic in Papanicolaou stain, eosinophilic in HTX, and pure blue turquoise in May–Grünwald–Giemsa or Diff-Quik) and keratin debris
- Necrosis common with varying numbers of inflammatory cells, histiocytes, giant cells, calcium deposits, and keratin debris

Differential diagnosis and problems in diagnosis:

- Poorly differentiated carcinomas with necrosis simulating keratinization
- Basal cell carcinoma
- Keratoacanthoma
- Other malignancies metastatic to the skin
- Pilomatrixoma
- Benign cystic lesions, cysts with necrosis and inflammation, benign cystic neoplasm of squamous epithelium, and skin adnexal structures

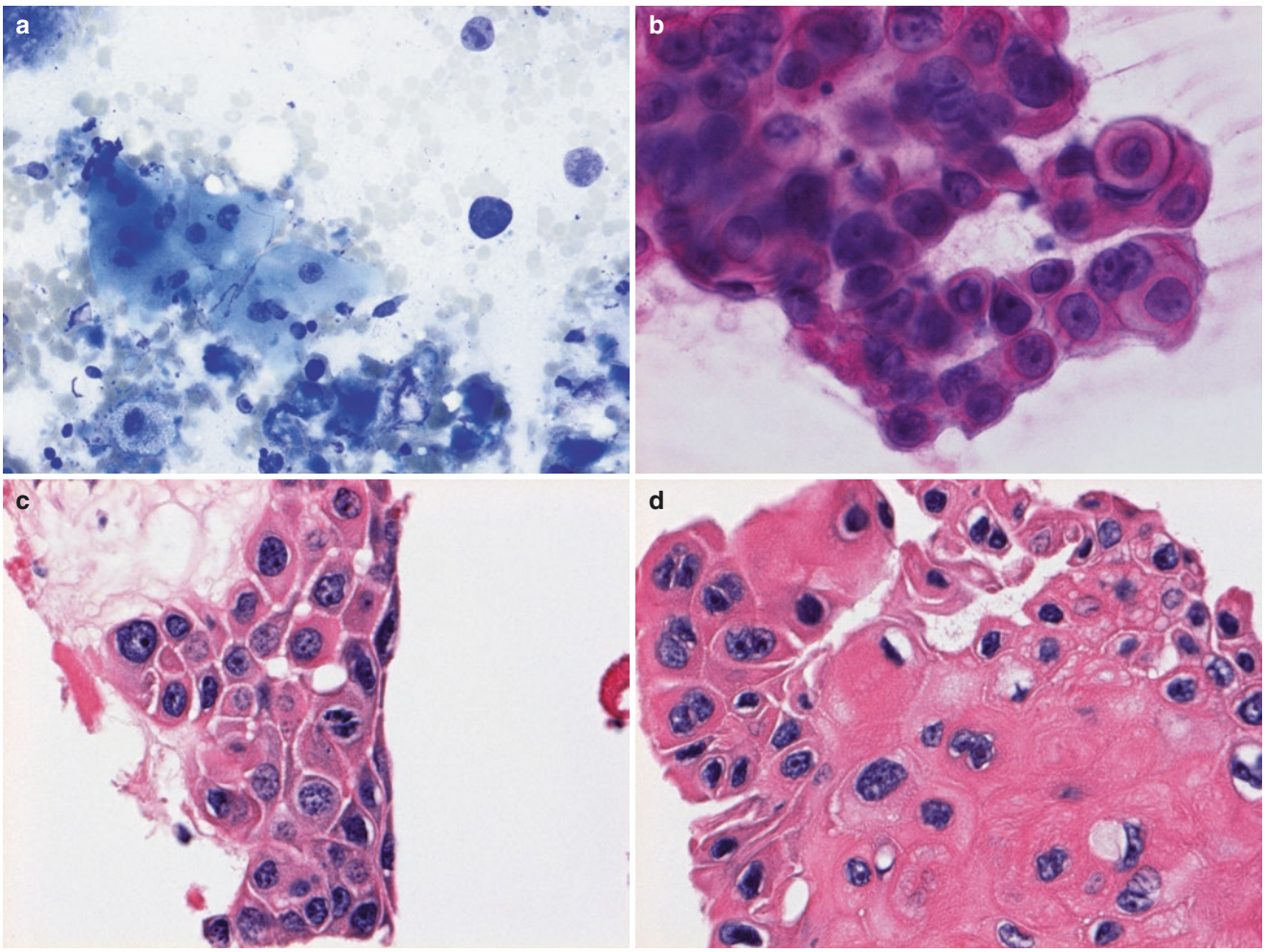


Fig. 15.9 Squamous cell carcinoma. (**a**, **b**) Sheets and dispersed malignant cells with dense cytoplasm, distinct cell borders, keratinization, and molding (MGG; H&E). (**c**, **d**) Cell block section demonstrates well the architecture of the tumor and, in a high-power view, intercellular bridges, which are features diagnostic of squamous cell carcinoma (Cellient; Hologic; Bedford, MA, USA)

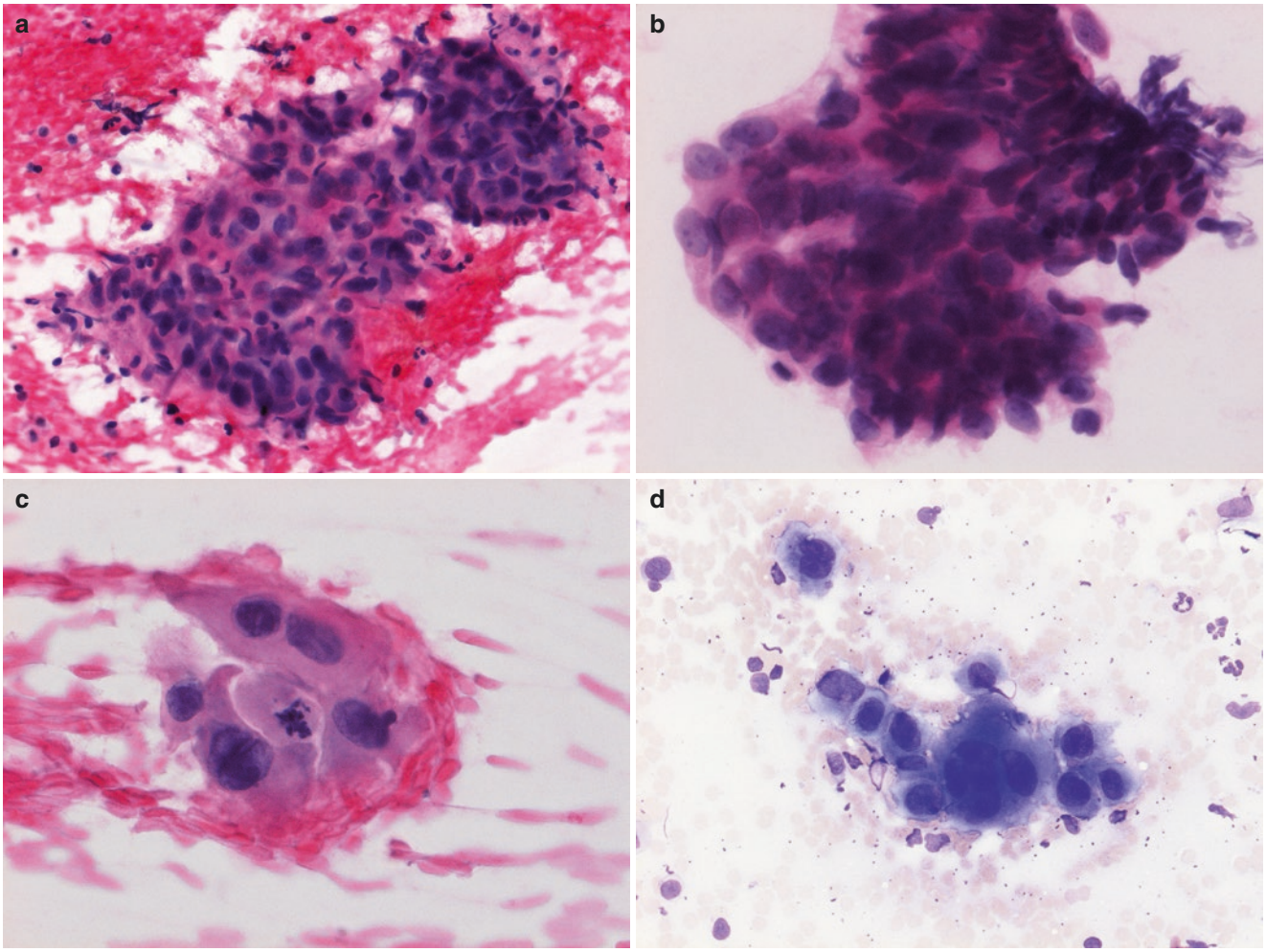


Fig. 15.10 Squamous cell carcinoma. (**a**–**c**) FNA smears from Bowen's disease (squamous cell carcinoma in situ): clusters and sheets of malignant cells with dense cytoplasm and distinct cell borders (H&E) indistinguishable from invasive squamous cell carcinoma (**d**) (MGG)

Basal Cell Carcinoma (BCC)

FNA of BCC may provide diagnostic specimens, especially when FNA examination is performed on large polypoid lesions or deeply infiltrating nonulcerated BCC. Scrape cytology may be used as an alternative examination technique of BCC, especially superficially, ulcerated lesions [45, 46]. Compared to SCC, smears from BCC contain relatively small cells arranged in cohesive regular sheets, without any intracellular bridges (see Figs. 15.11 and 15.12). Sheets of tumor cells present sharp

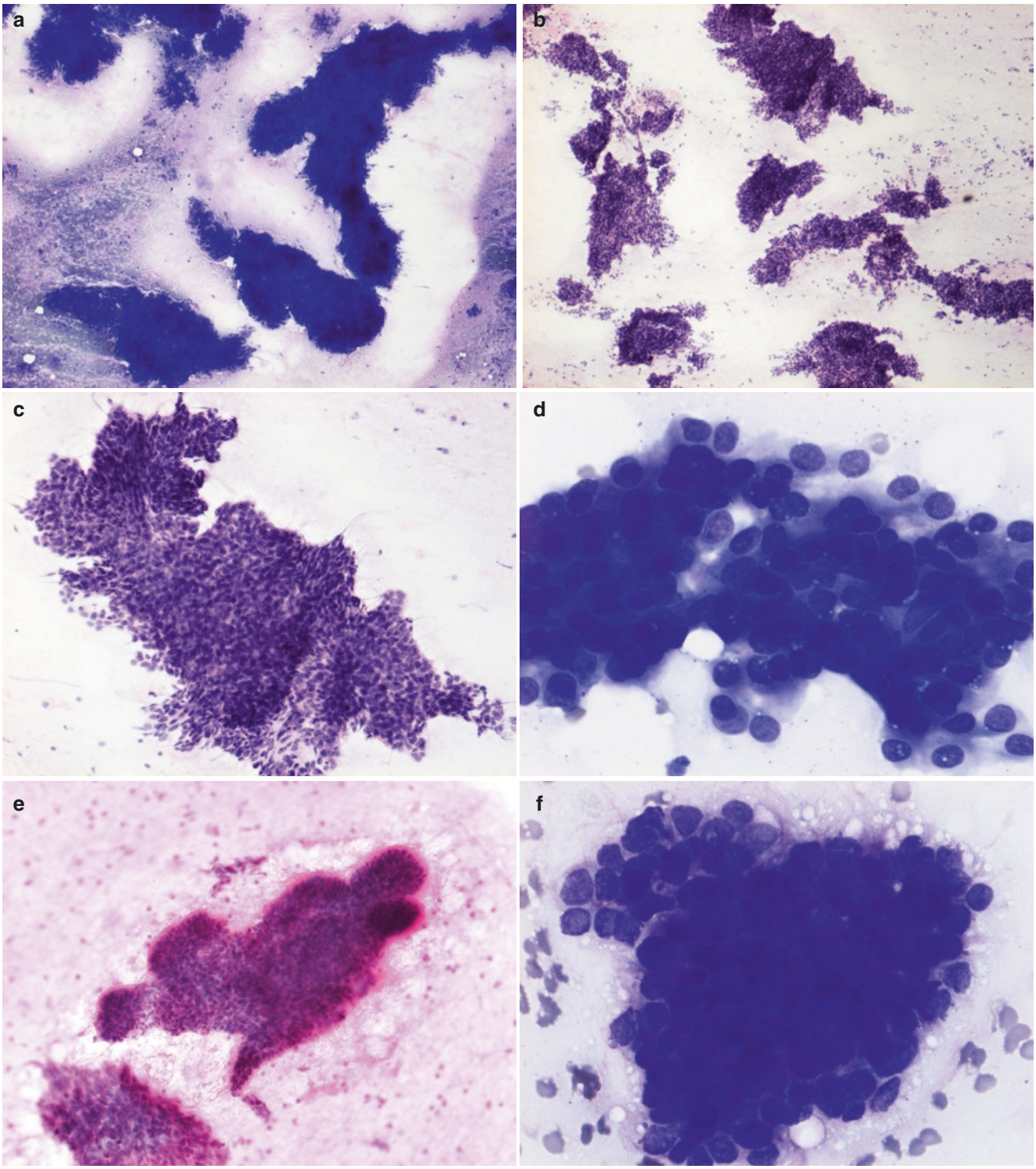


Fig. 15.11 Basal cell carcinoma. (**a**–**f**) Smears from basal cell carcinoma are usually hypercellular and show small cells arranged in cohesive regular sheets with sharp edges and palisading nuclei in the periphery (MGG; H&E)

edges with palisading nuclei in the periphery (see Fig. 15.12) [20, 21, 47]. Skin adnexal neoplasms, including pilomatrixoma (PMX) and basaloid squamous cell carcinoma, are the main differential diagnoses. Presence of pink amorphous or fibrillar matrix in the clusters of tumor cells from pilomatrixoma has been reported as being a morphologic sign helpful in distinguishing BCC from PMX. In our experience, this kind of matrix is not limited to PMX alone and may be found both in smears from BCC and other skin neoplasms (see Fig. 15.13).

Cytologic features:
- Cellular smears
- Cohesive sheets or clusters of small- or medium-sized cells with a high N/C ratio and hyperchromatic nuclei with granular chromatin and indistinct nucleoli
- Uniform or slightly atypical cells
- Some tumor cell sheets with sharp edges, occasionally palisading nuclei along the edges

Differential diagnosis and problems in diagnosis:
- Nonkeratinizing SCC
- PMX
- Skin adnexal neoplasm

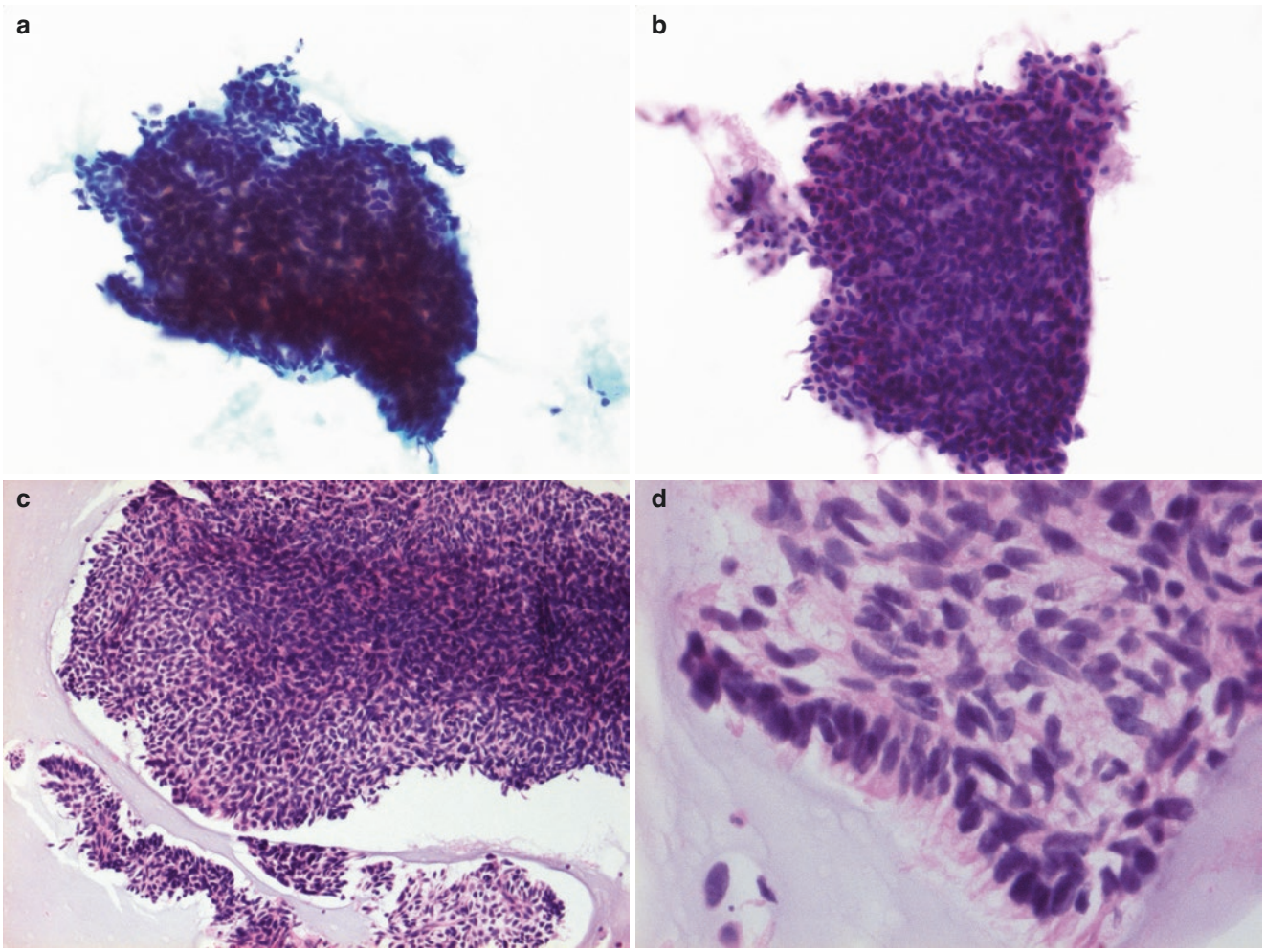


Fig. 15.12 Basal cell carcinoma. (**a**, **b**) Corresponding to routinely prepared smears, liquid-based slides show cohesive sheets of uniform, basaloid cells (Papanicolaou; H&E). (**c, d**) Palisading nuclei in the periphery of tumor sheets are better appreciated in the cell block sections (Cellient; Hologic; Bedford, MA, USA)

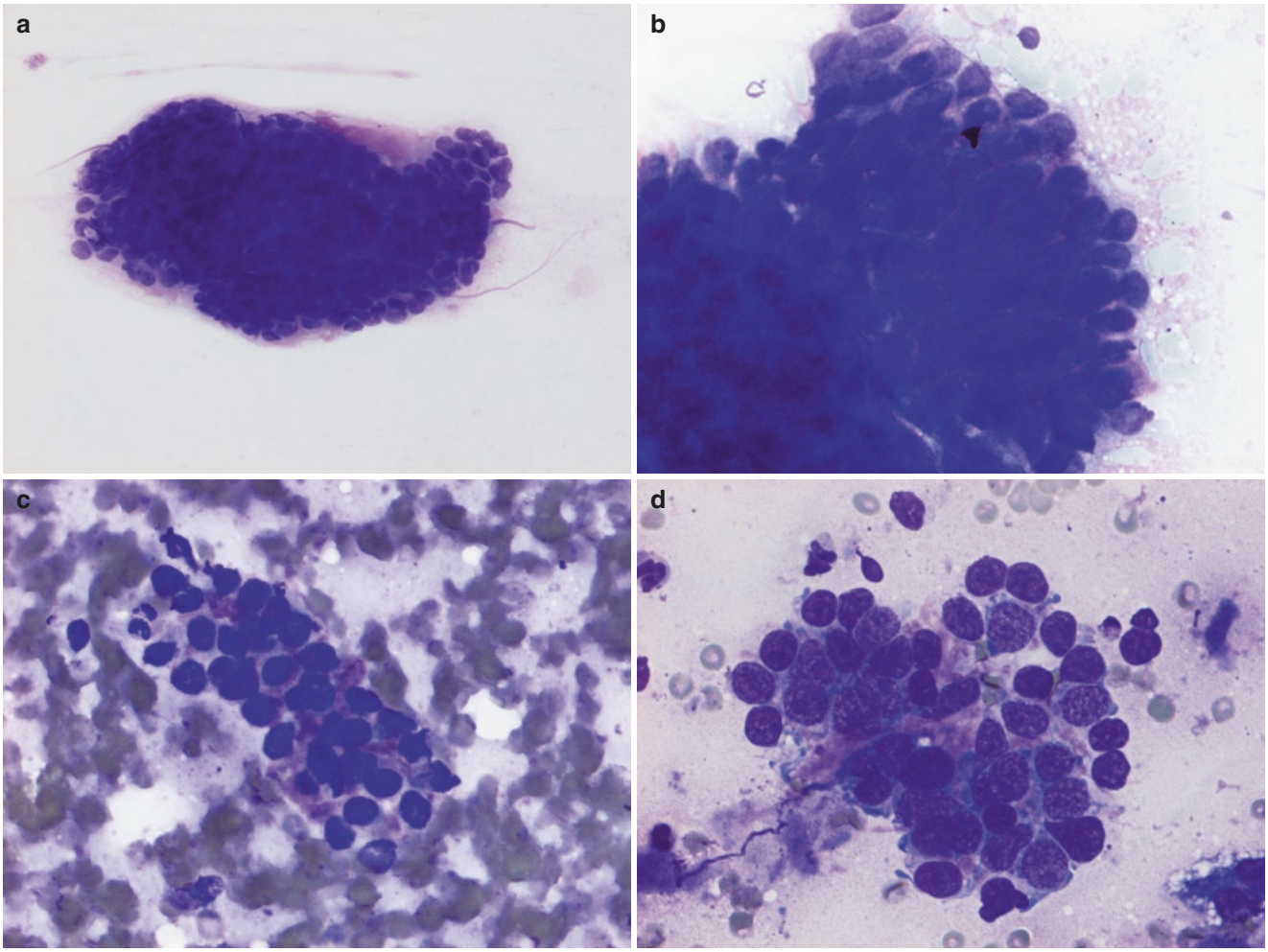


Fig. 15.13 Basal cell carcinoma. Presence of pink amorphous or fibrillar matrix in the clusters of tumor cells may be found both in smears from basal cell carcinoma (**a**, **b**) and pilomatrixoma (**c**, **d**) (MGG)

Paget Disease

Paget disease is commonly diagnosed by skin biopsy or brushing cytology. FNA is only occasionally used as a diagnostic tool.

A microscopic feature of Paget cells includes pleomorphic cells with enlarged nuclei and pale cytoplasm (see Fig. 15.14) [48]. In routinely stained smears, they can be confused with SCC and in rare cases with BCC (see Fig. 15.15). The clinical presentation renders the correct diagnosis.

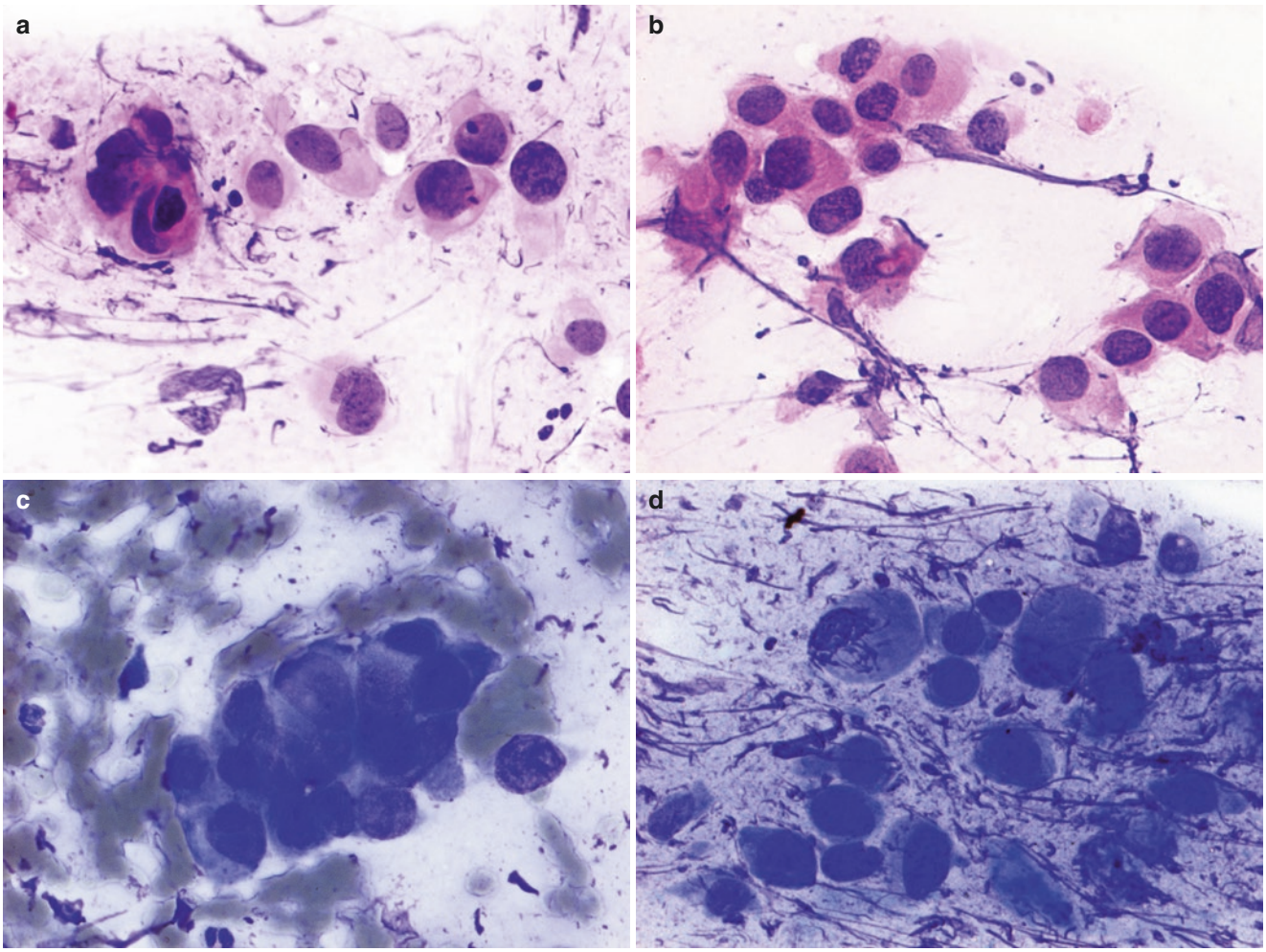


Fig. 15.14 Paget disease. (**a**–**d**) Microscopic features of brushing and FNA cytology of Paget disease of the nipple include loosely cohesive sheets and clusters and dispersed malignant cells with enlarged nuclei, granular chromatin, and pale cytoplasm (H&E; MGG)

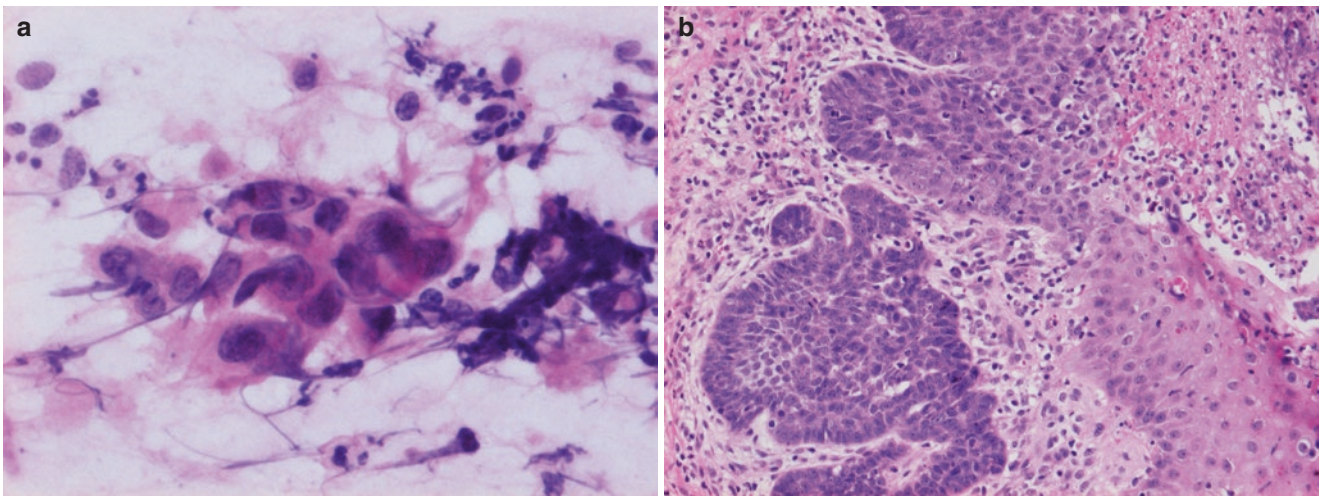


Fig. 15.15 Basal cell carcinoma of the nipple. (**a**) FNA smears erroneously interpreted as Paget disease of the nipple (H&E). (**b**) Histological section from excisional biopsy shows classical features of basal cell carcinoma (H&E)

Primary Skin Neoplasm and Skin Adnexal Neoplasms

Skin Neoplasms Rarely Stated by FNA

Most adnexal neoplasms behave nonaggressively with the exception of a small subgroup of malignant adnexal tumors. With the exception of pilomatrixoma (PMX), most adnexal neoplasms are rare targets for FNA cytology. In FNA smears, adnexal neoplasms quite often display noncharacteristic cytologic features, usually including clusters or sheets of monomorphic or slightly pleomorphic epithelial cells with occasional differentiation toward eccrine or apocrine cells [49]. Other common components of smears, especially in cystic or partly cystic neoplasms, are histiocytic cells occasionally containing intracytoplasmic hemosiderin pigment depositions.

Aspiration smears from skin adnexal neoplasms display cytologic features which are sufficient to suspect primary adnexal neoplasm and to exclude malignancy (see Figs. 15.16, 15.17, and 15.18) [50, 51]. With exception of cylindroma, pilomatrixoma, and chondroid syringoma [52], rendering of the specific histologic diagnosis from FNA of benign cutaneous tumors is difficult because of the rarity of such aspirates and lack of clear cytologic diagnostic criteria.

Benign neoplasms that display diagnostic morphologic features are dermal cylindroma and chondroid syringoma. Smears from cylindromas resemble smears from adenoid cystic carcinoma of the parotid gland, presenting as a cribriform or solid clusters of uniform cells with metachromatic background matrix and alveolar-like or acinar structures containing either collagenous or myxoid matrix (see Fig. 15.18). Smears from chondroid syringoma are almost identical to those of pleomorphic adenoma of salivary glands. FNA smears are usually cellular with sheets and clusters as well as dispersed epithelial/myoepithelial cells with plasmacytoid morphology embedded in the abundant chondromyxoid background matrix (see Fig. 15.19).

Adnexal carcinomas are rare neoplasms that display cytologic signs of malignancy (see Fig. 15.20) [53–55]. In rare conditions, differentiation toward mesenchymal cells may occur, i.e., malignancy arising in spiradenomas (see Fig. 15.21) [56].

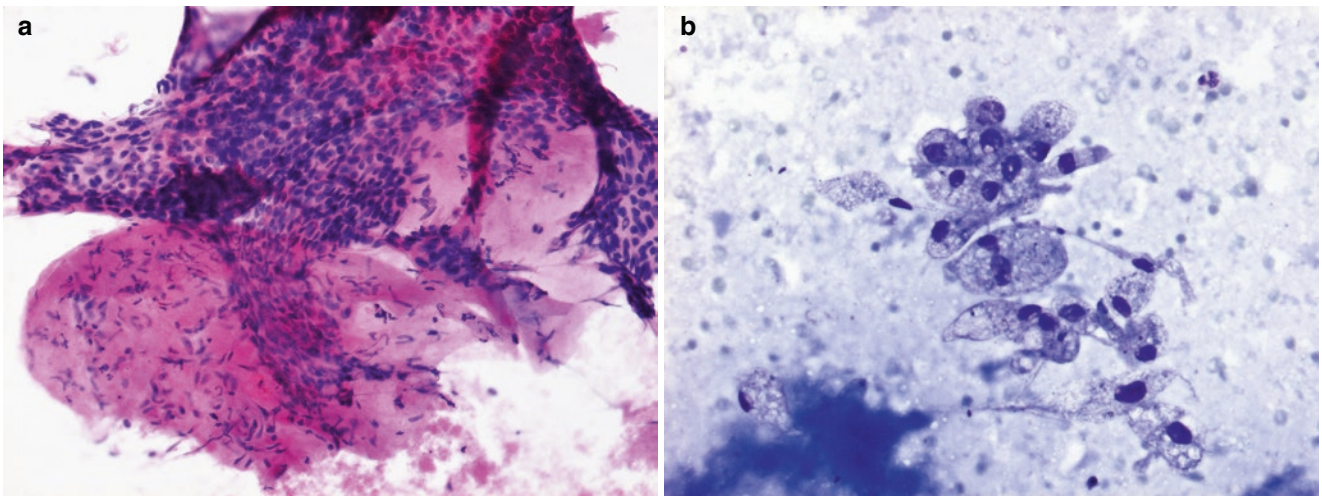


Fig. 15.16 Poroma. (**a**) Smears from poroma with sheets of bland or slightly atypical epithelial cells mixed with mesenchymal fragments (H&E). (**b**) Histiocytes and background debris indicative of a cystic component (MGG)

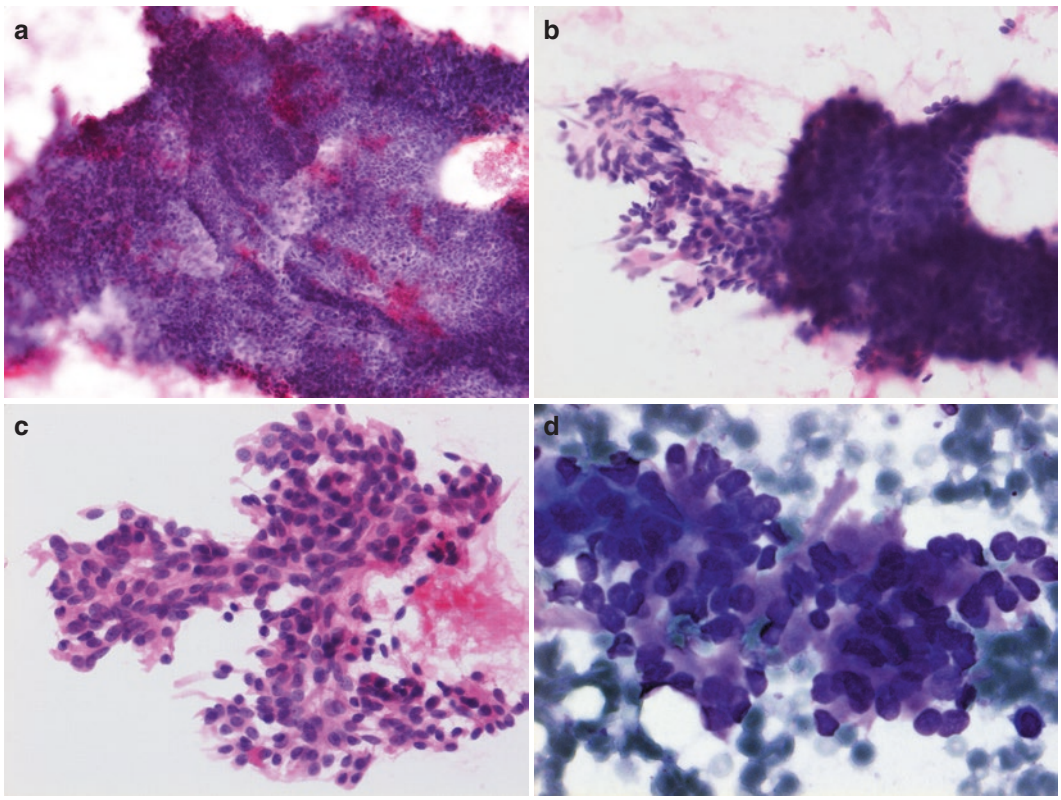


Fig. 15.17 Eccrine spiradenoma. (**a**–**c**) Large sheets and clusters of bland-looking basaloid cells with small to medium, round to oval nuclei and occasional glandular formation and collagenous matrix (H&E). (**d**) Poorly cohesive cluster of tumor cells with bland round to oval nuclei remaining acinar structures and with hyaline matrix, better appreciated in the air-dried smears (MGG)

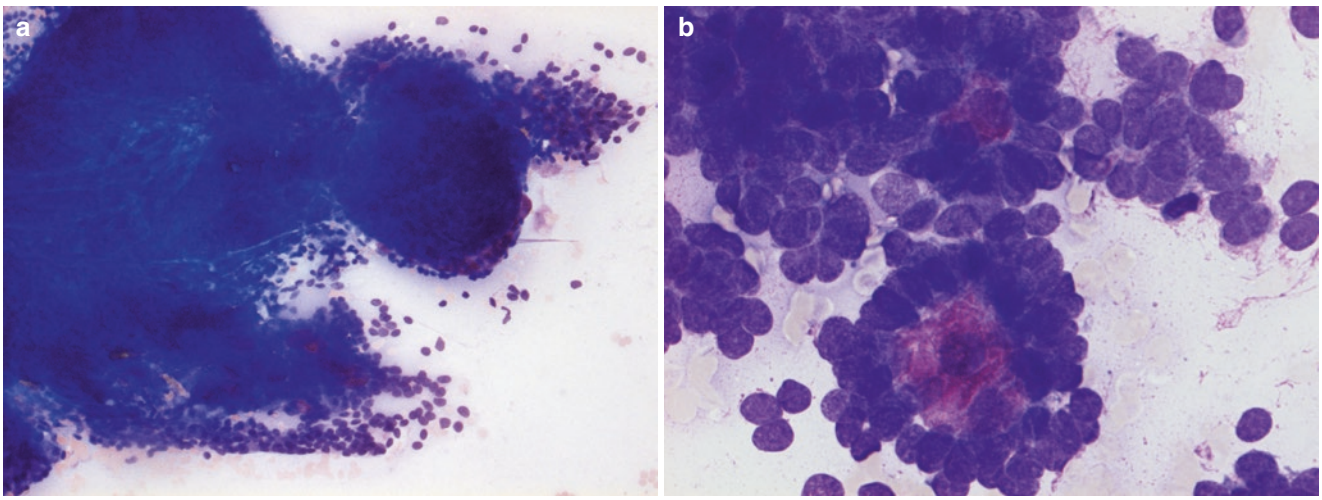


Fig. 15.18 Dermal cylindroma. (**a**, **b**) Hypercellular smears with solid and cribriform clusters of uniform cells with round, somewhat hyperchromatic nuclei without nucleoli. There are metachromatic background matrix and alveolar-like or acinar structures containing collagenous hyaline globules (MGG)

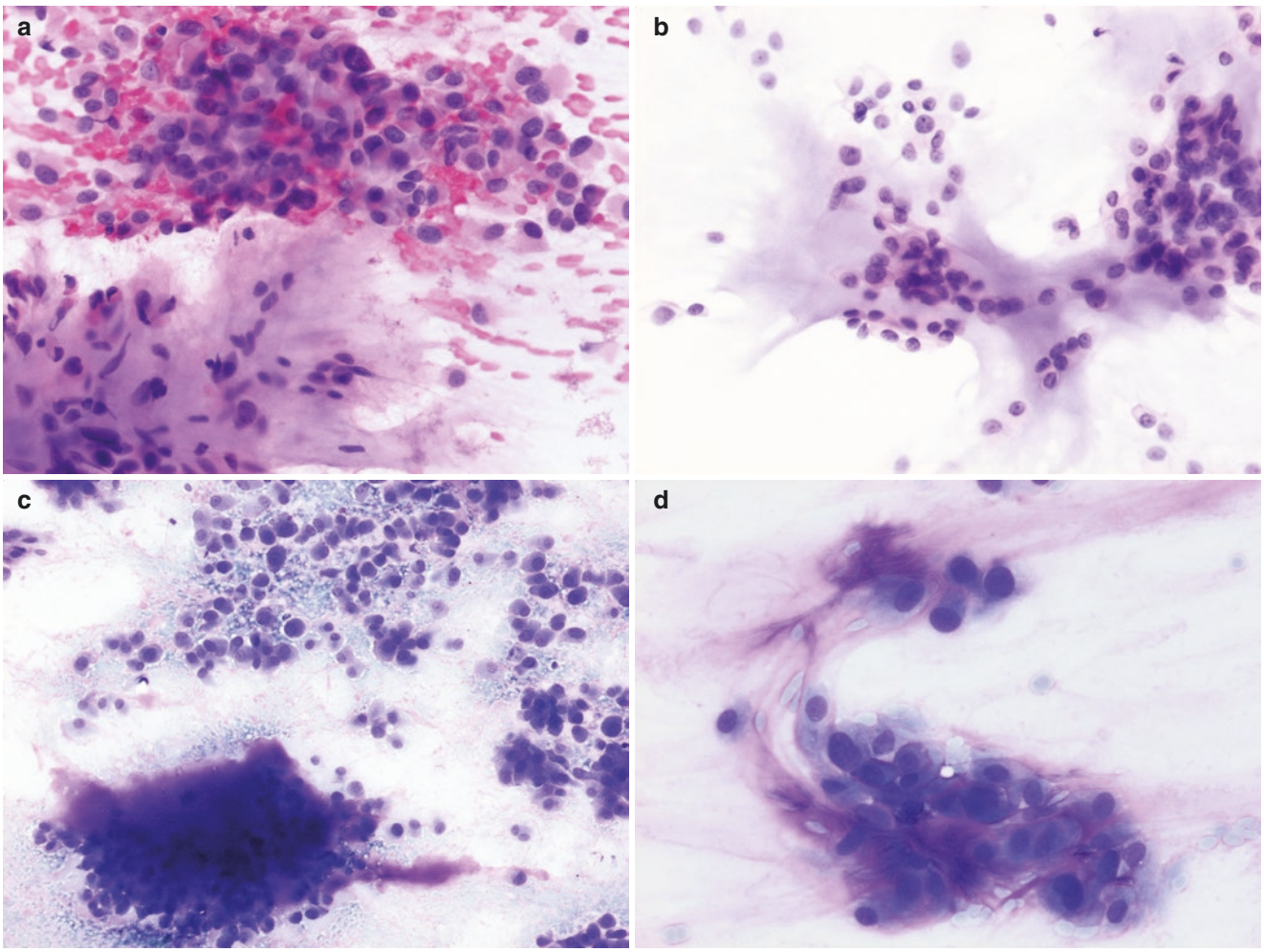


Fig. 15.19 Chondroid syringoma. Hypercellular smears with solid, poorly cohesive clusters and dispersed bland plasmacytoid epithelial–myoepithelial cells and abundant chondromyxoid matrix (**a**, **b**) (H&E) and (**c**, **d**) (MGG)

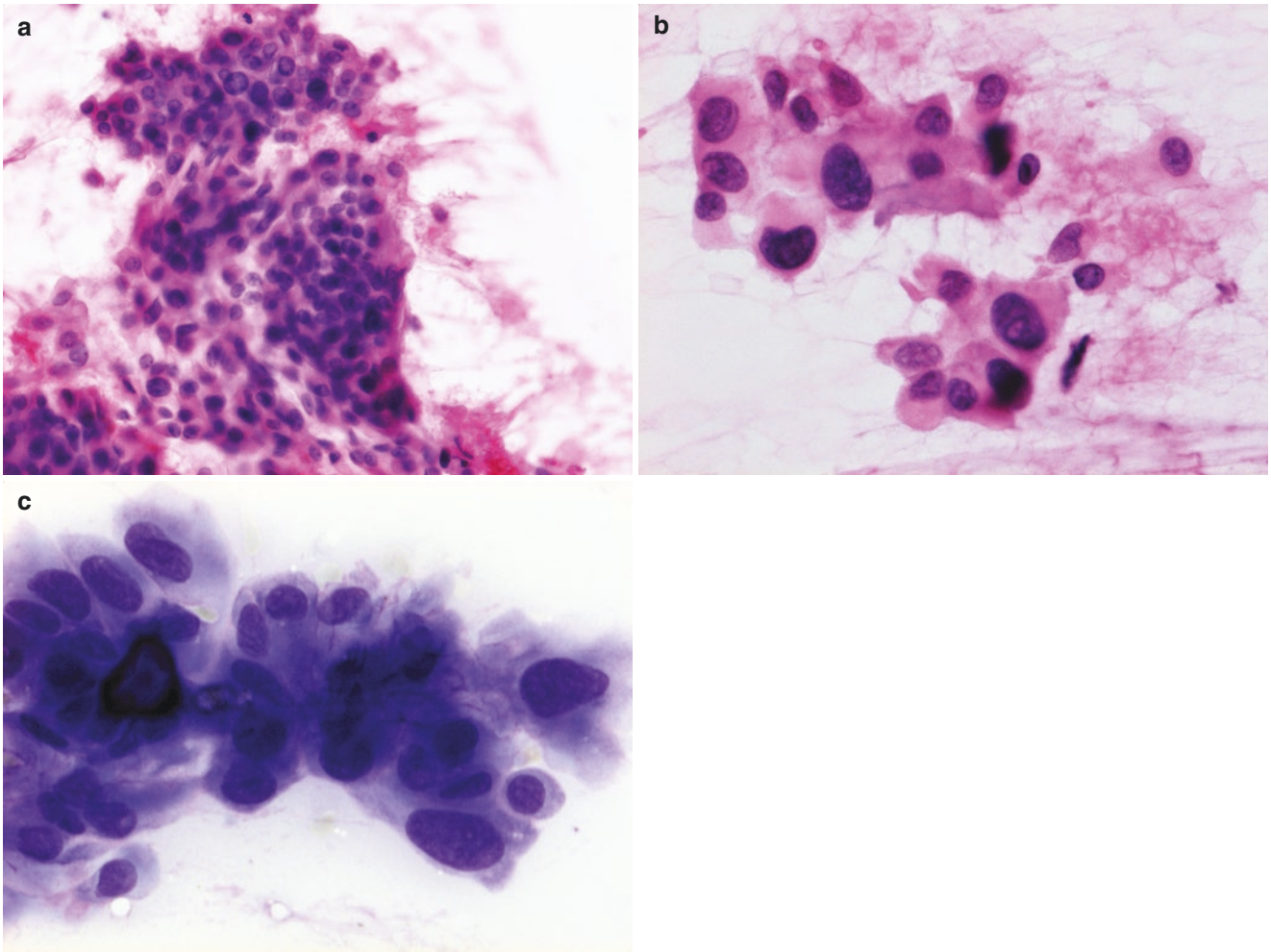


Fig. 15.20 Porocarcinoma. (**a**, **b**) Hypercellular FNA smears show clusters and sheets of pleomorphic cells with variably enlarged nuclei with granular chromatin, indicative of malignancy, and moderate to abundant poorly delineated cytoplasm (H&E). (**c**) Occasional sheets of moderately atypical cells with eccrine differentiation and calcification (MGG)

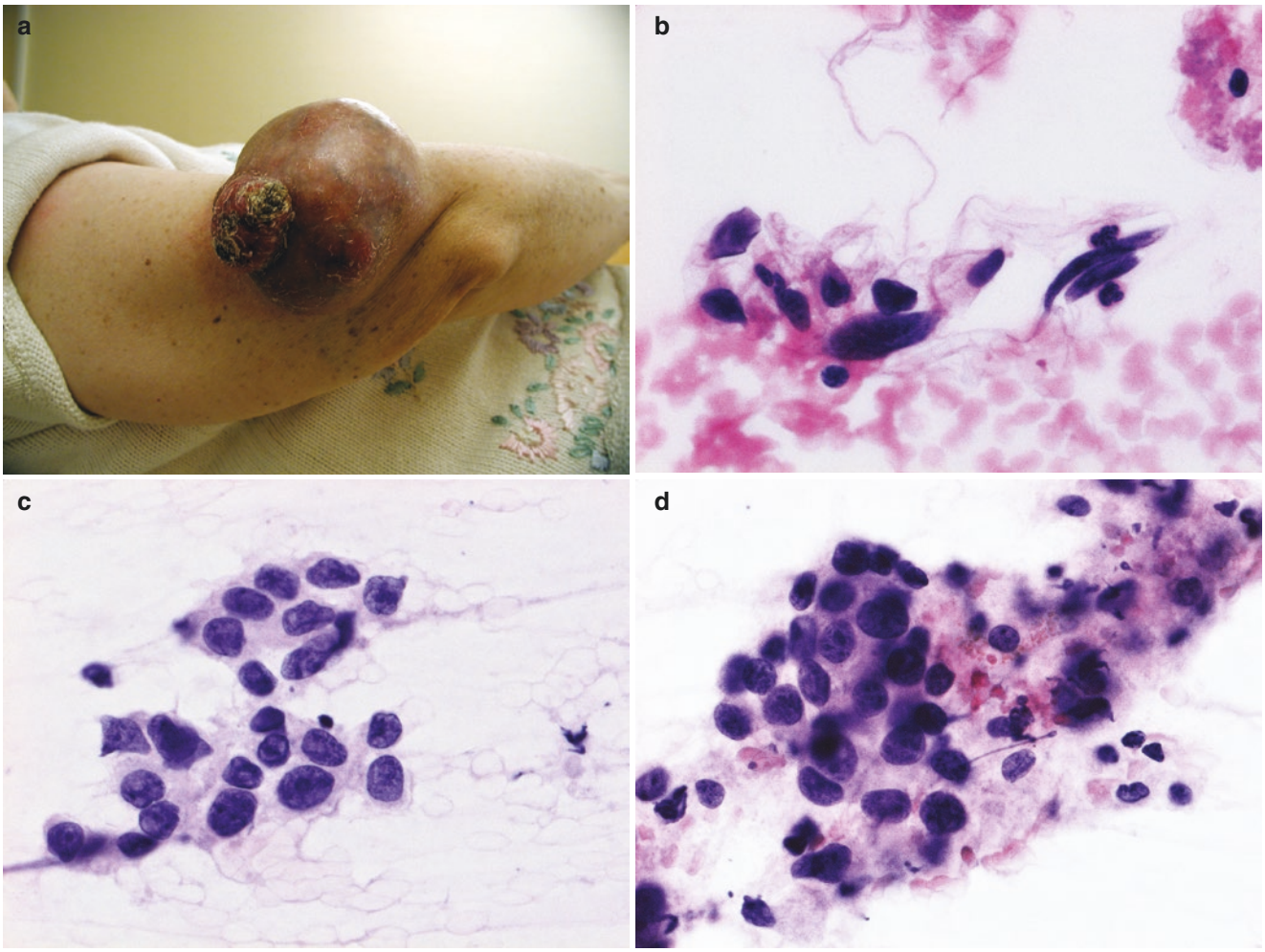


Fig. 15.21 Malignancy arising in spiradenoma (malignant spiradenoma). (**a**) A 42-year-old woman with a 15-year history of a slowly growing cutaneous mass adjacent to the right elbow. (**b**) Rare differentiation toward the mesenchymal tissue. (**c**, **d**) Clear signs of malignancy such as nuclear pleomorphism, hyperchromasia, macronuclei, and necrosis visible in smears from malignant spiradenoma (H&E)

Pilomatrixoma

Pilomatrixoma (PMX) is a benign skin neoplasm of hair matrix origin. It usually presents as a solitary, firm, dermal, or, less frequently, subdermal nodule. The most frequent presentation is on the head, neck, and limbs, but PMX may occur on any part of the body. It develops often in children and young adults but may be seen at all ages.

Clinically, PMX may mimic primary and metastatic skin deposits and dermal appendage tumors (see Fig. 15.22) or even masquerade as a breast or parotid tumor. In addition, FNA aspirates of PMX share some cytologic features with those of malignant neoplasms [23, 24, 57–61]. Smears of PMX contain distinctive cellular and noncellular components: basaloid cells, small- or medium-sized cells with a high N/C ratio, poorly defined cell borders, and nuclei with coarsely or granular chromatin. These cells may be arranged in compact sheets and clusters of varying size and shape but may occur as scattered single cells or naked nuclei (see Fig. 15.23). Hyperchromasia, macronucleoli, and occasional nuclear molding and mitoses may cause diagnostic difficulties (see Fig. 15.24) [62]. Other distinctive components of smears include ghost cells, pale-staining polyhedral cells with distinct cell borders, and a central unstained area (see Figs. 15.23 and 15.25). Varying numbers of inflammatory cells, histiocytes, and giant cells, as well as calcium deposits and amorphous eosinophilic keratin debris, are commonly present in smears (see Fig. 15.26).

Cytologic features:

- Cellular smears
- Basaloid cells, small- or medium-sized with a high N/C ratio, poorly defined cell borders, and nuclei with coarsely or granular chromatin
- Hyperchromasia and occasional macronucleoli, nuclear molding, and mitoses in basaloid cells
- Ghost cells: pale-staining polyhedral cells with distinct cell borders and a central unstained area
- Varying numbers of inflammatory cells, histiocytes, giant cells, calcium deposits, and keratin debris

Differential diagnosis and problems in diagnosis:

- Squamous cell carcinoma.
- Basal cell carcinoma.
- Other skin malignancies such as Merkel cell carcinoma, lymphoma, and tumors metastatic to the skin.
- A problem with cytological diagnosis of PMX occurs when only one or two main components are visible in smears: basaloid cells or basaloid cells in conjunction with ghost cells and keratin debris.

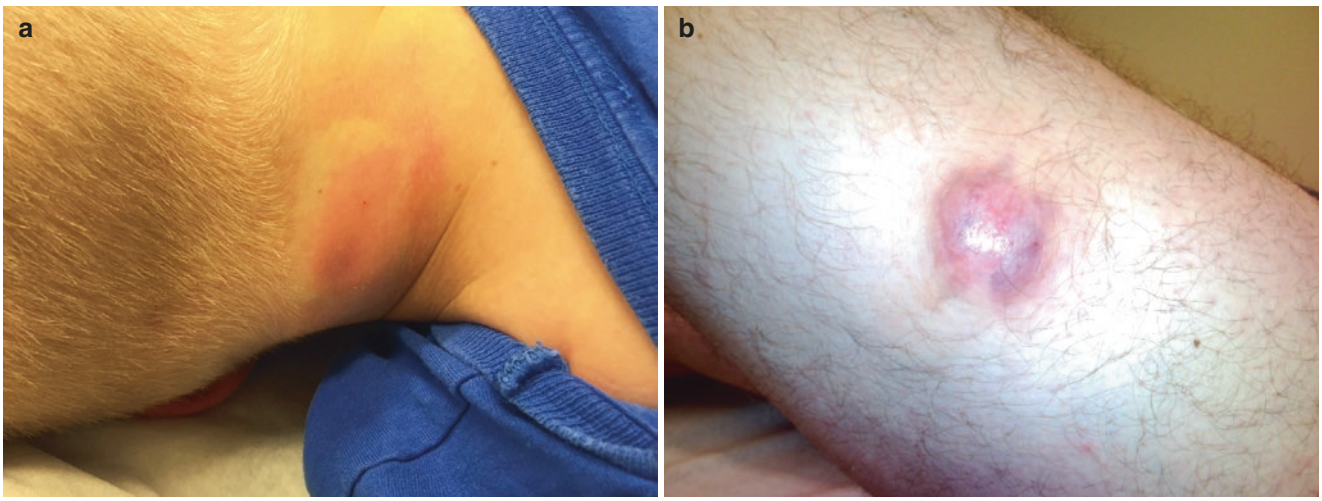


Fig. 15.22 Pilomatrixoma. (**a**, **b**) Clinically, PMX may mimic primary and metastatic skin deposits and dermal appendage tumors presenting as a skin nodule covered with discolored skin

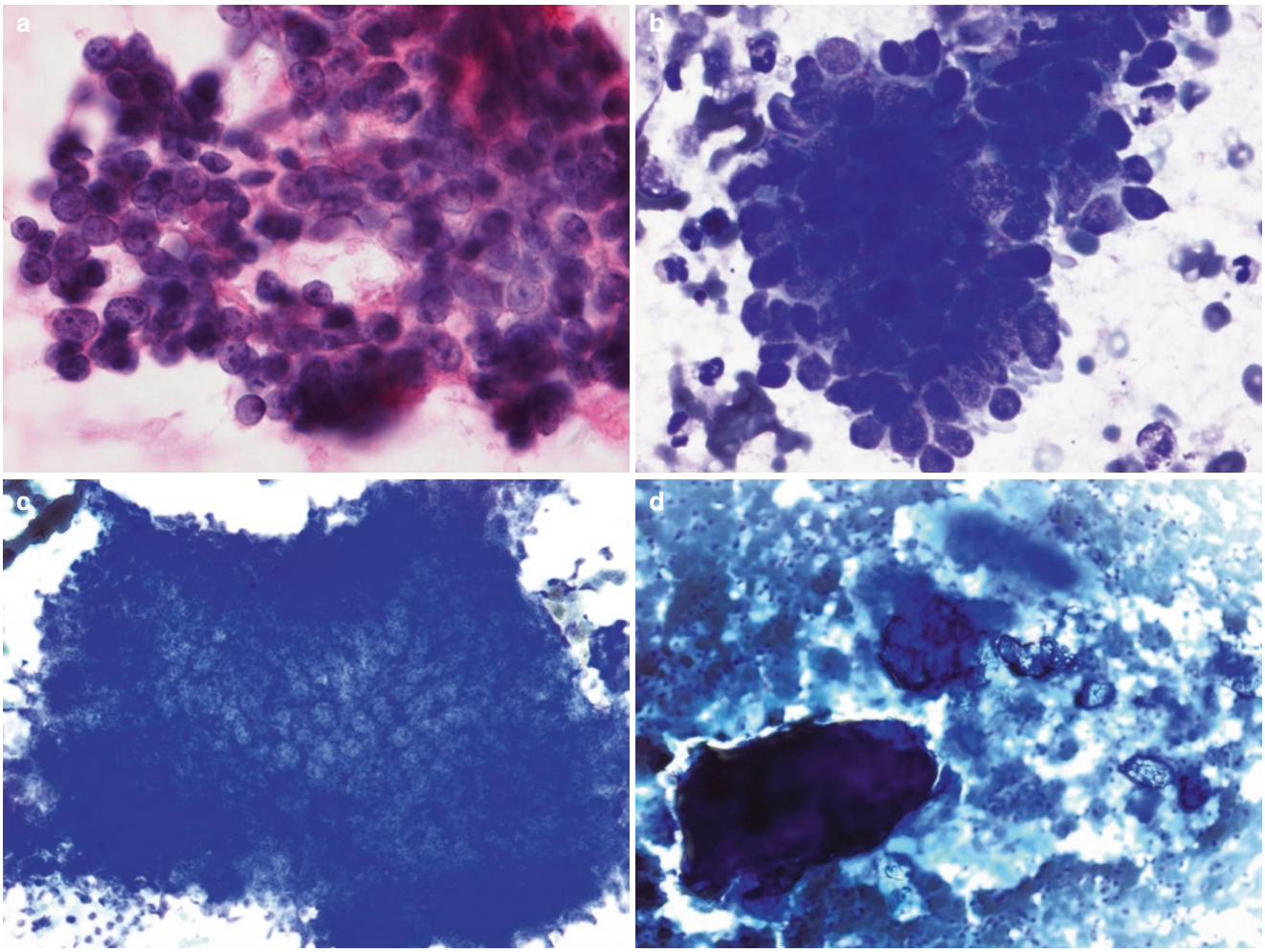


Fig. 15.23 Pilomatrixoma. (**a**, **b**) Smear shows clusters of basaloid cells: small- or medium-sized cells with a high N/C ratio (H&E; MGG). (**c**) Sheet of pale-staining polyhedral ghost cells with distinct cell borders and a central unstained area and calcifications (**d**) (MGG)

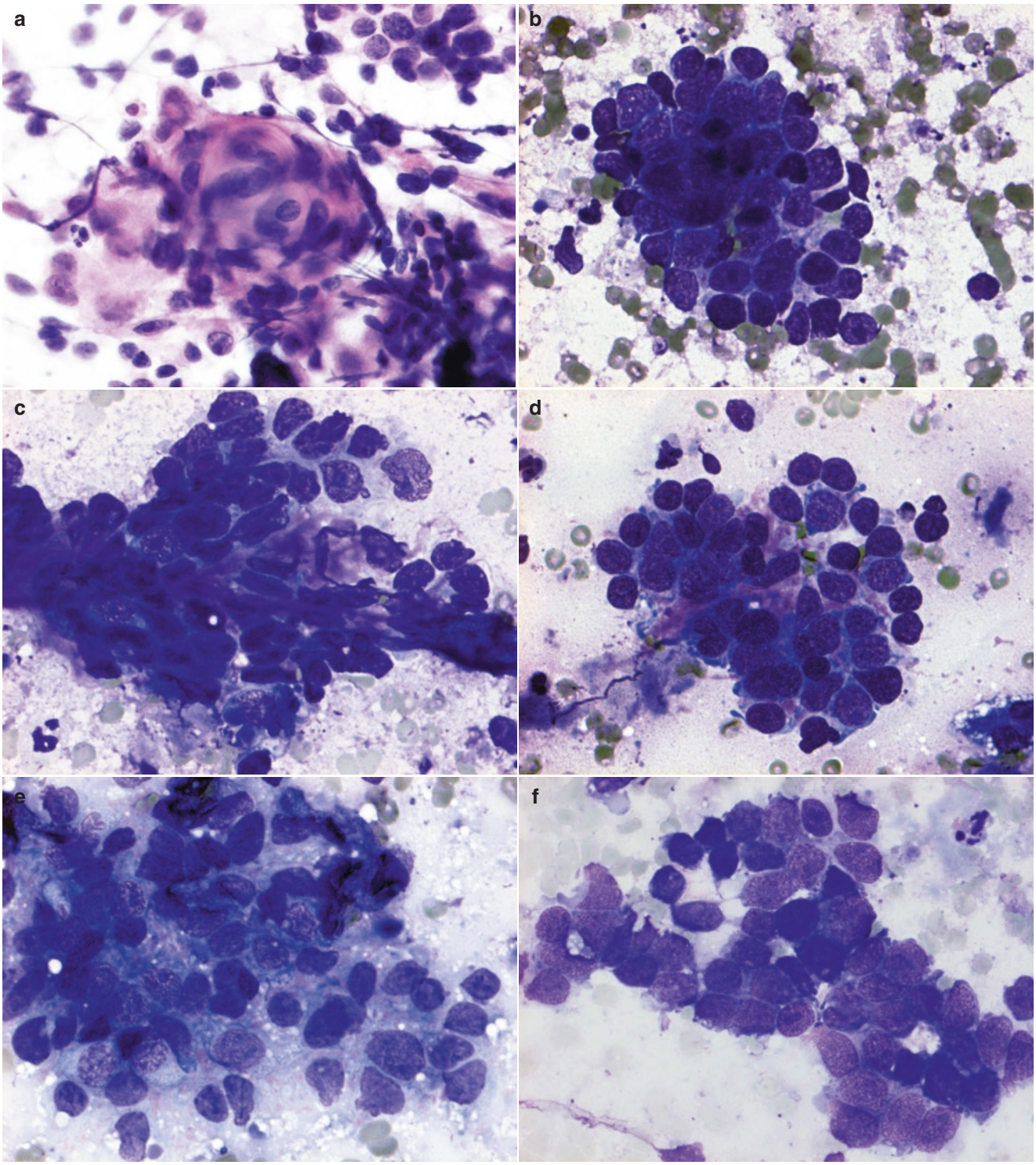
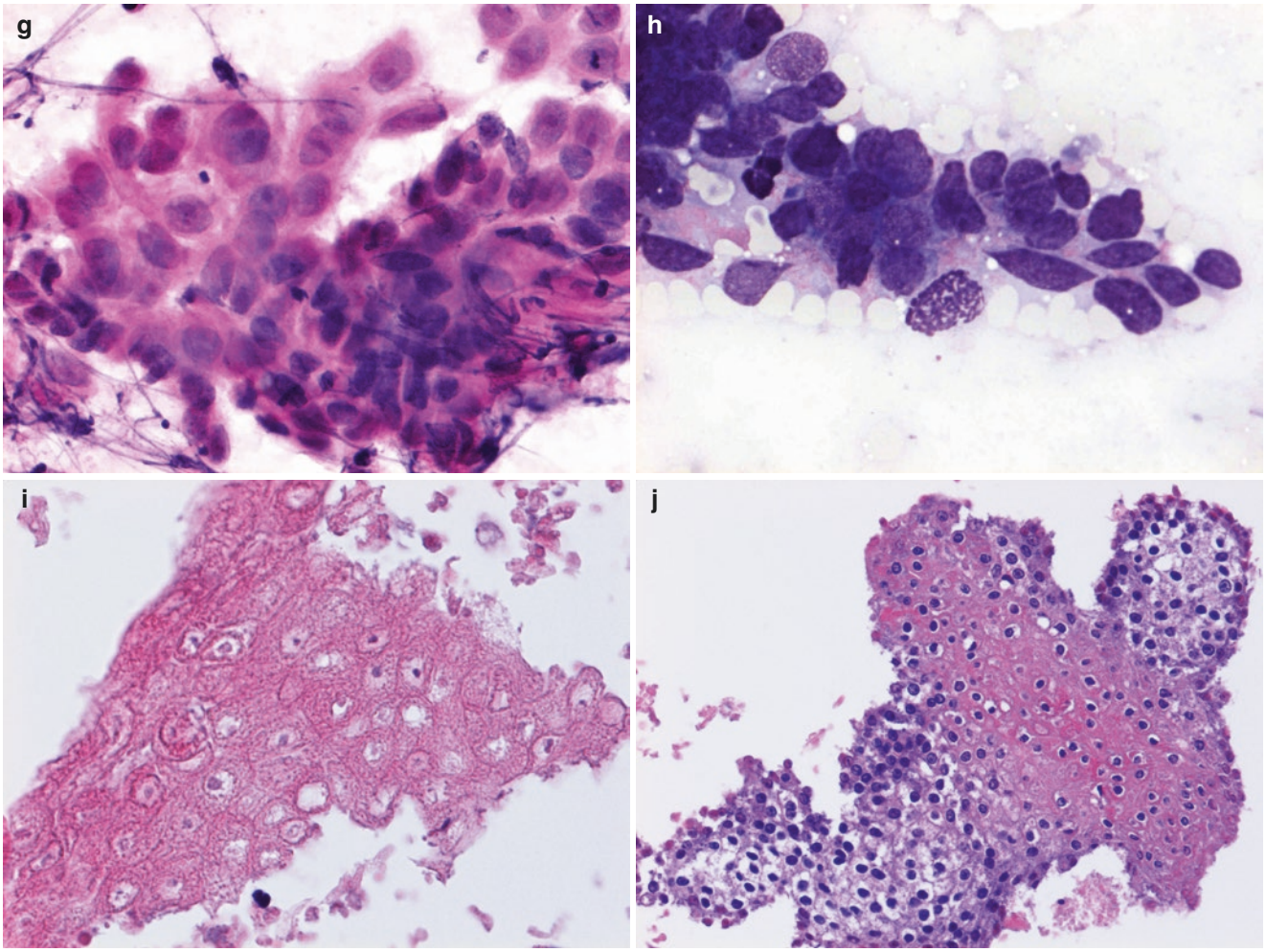


Fig. 15.24 Pilomatrixoma. (**a**–**h**) Hyperchromasia, macronucleoli, and occasional nuclear molding and mitoses may be easily confused with malignancy (H&E; MGG). Cell block sections show fragments of distinctive ghost cells (**i**) and intermediate/basaloid cells (**j**) which help to render correct diagnosis (Cellient; Hologic; Bedford, MA, USA; H&E)



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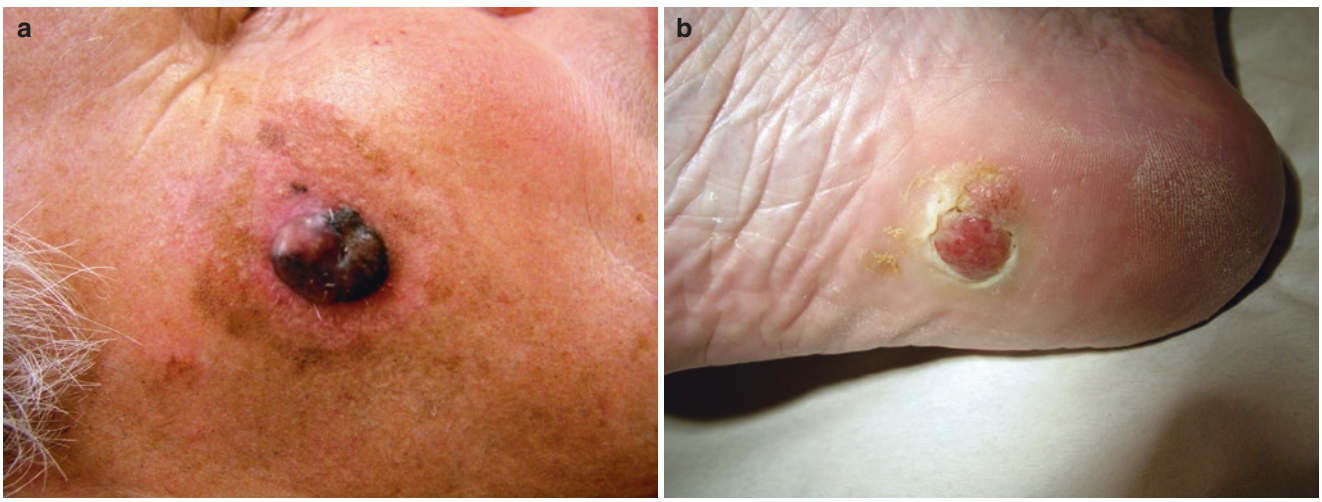

Fig. 15.25 Malignant melanoma. Clinical features of exophytic/polypoid skin melanomas (**a**) and acral ulcerated lesion clinically suspicious of pyogenic granuloma (**b**)

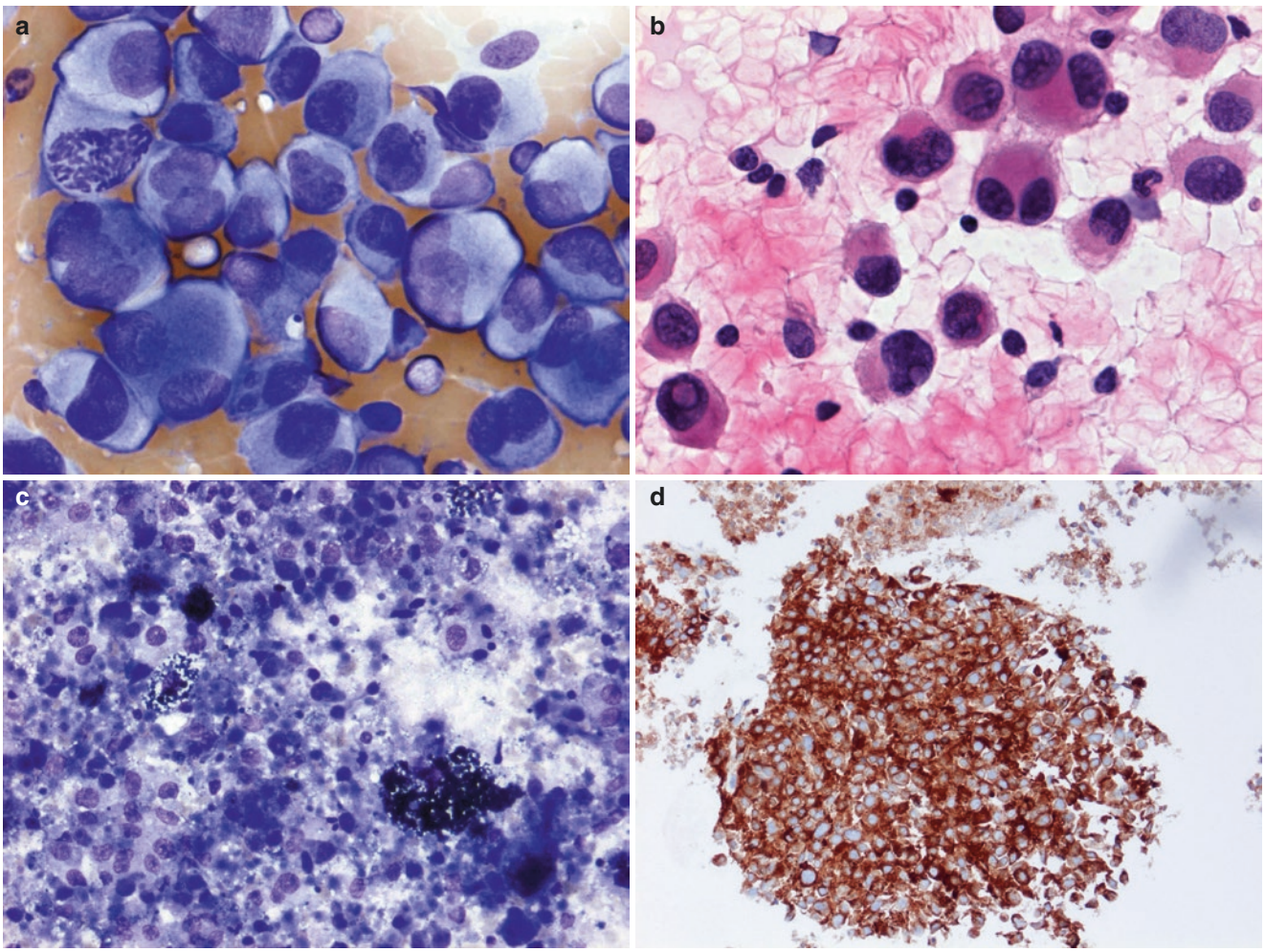

Fig. 15.26 Malignant melanoma. (**a**, **b**) Common cytological appearances of melanoma: dispersed, midsized, and moderately pleomorphic and occasionally binucleated cells with eccentrically placed hyperchromatic nuclei with intranuclear inclusions (MGG; H&E). (**c**) Melanin pigment is found in approximately 50–60% of smears from melanoma metastases (MGG). (**d**) Positive immunostains with melanin A on cell block section confirm melanoma diagnosis (Cellient; Hologic; Bedford, MA, USA)

Malignant Melanoma

Primary malignant melanomas are commonly diagnosed with excisional skin biopsy. Metastatic disease is a frequent target for FNA. In rare circumstances, skin melanomas, especially those presented as nodular/exophytic lesions, may be examined by FNA (see Fig. 15.25). The classical cytological appearance of melanoma includes dispersed, midsized, and moderately pleomorphic and occasionally binucleated cells with eccentrically placed hyperchromatic nuclei. Nuclei often contain large macronucleoli and intranuclear inclusions; bi-, tri-, and occasionally multinucleated cells are a common finding. Cytoplasm appears relatively dense, well circumscribed, and eosinophilic with H&E staining: grayish cast in MGG or Diff-Quik staining (see Fig. 15.26). In the authors' experience, melanin pigment occurs in more than 50–60% of cases, but the absence of melanin does not exclude the diagnosis of malignant melanoma. Cytologic features of melanomas may mimic other neoplasms such as carcinomas, sarcomas, or lymphomas (see Fig. 15.27). Rare cases of melanoma present smears with very pleomorphic cells, resembling high-grade pleomorphic sarcoma. Immunostains with S100, HMB45, melanin A, and SOX10 may be necessary to confirm the diagnosis of melanoma (see Fig. 15.26).

Cytologic features:

- Hypercellular smears
- Commonly dispersed cells
- Typically midsized cells with eccentrically placed hyperchromatic nuclei
- Nuclei with large macronucleoli and intranuclear inclusions
- Bi-, tri-, and occasionally multinucleated tumor cells
- Well-circumscribed, dense cytoplasm
- Occasionally rhabdoid-like appearances of cytoplasm
- Melanin pigment

Differential diagnosis and problems in diagnosis:

- Metastatic carcinoma
- Clear cell sarcoma
- Skin lymphomas

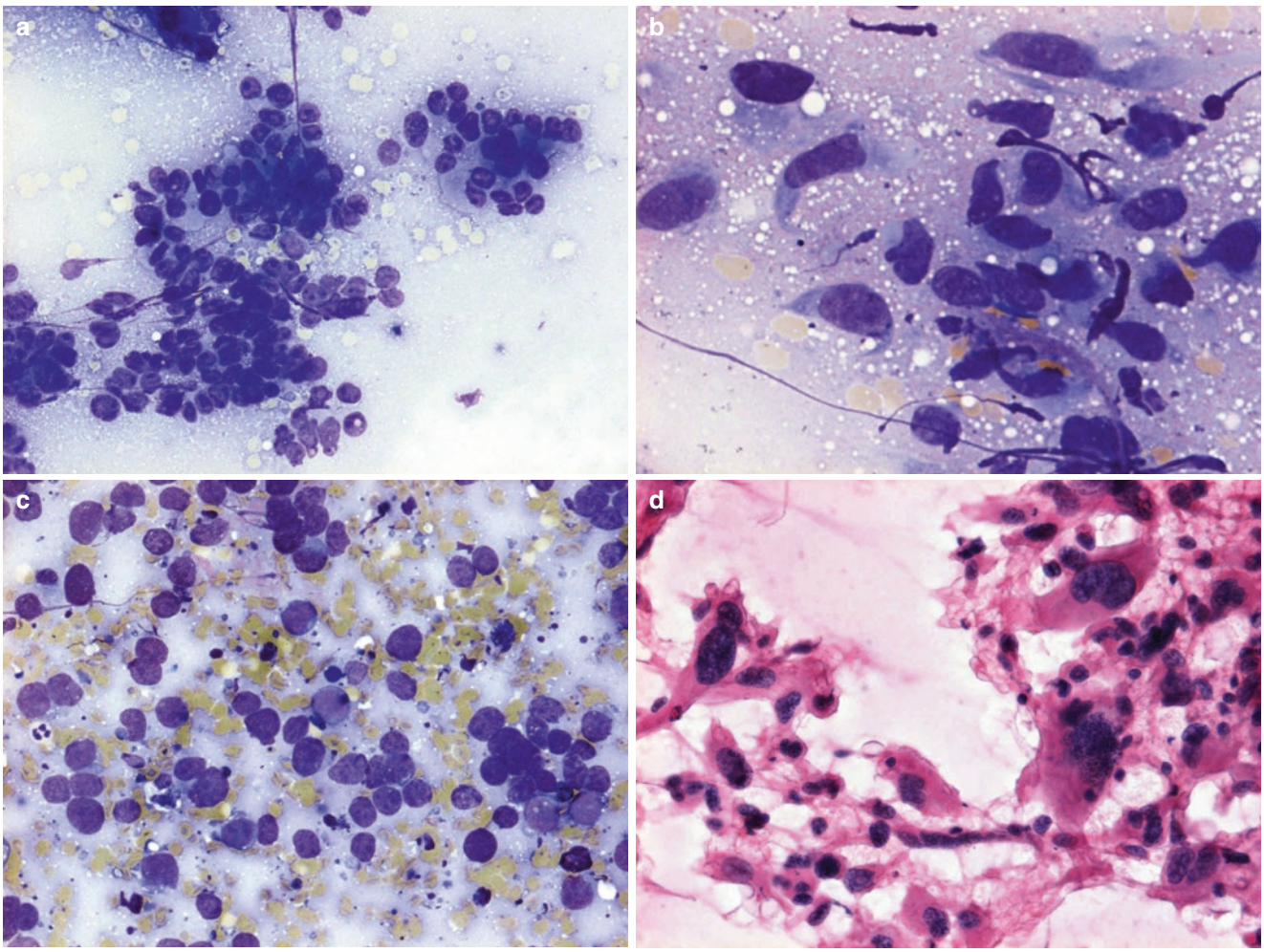

Fig. 15.27 Malignant melanoma. FNA smears from melanoma can vary widely in appearance. (**a**) Carcinoma-like melanoma. (**b**) Spindle-cell melanoma. (**c**) Lymphoma-like melanoma (MGG). (**d**) Pleomorphic melanoma resembling undifferentiated pleomorphic sarcoma (H&E)

Merkel Cell Carcinoma (Neuroendocrine Carcinoma of the Skin)

Merkel cell carcinoma (MCC), a relatively rare neoplasm, appears usually on sun-exposed areas. MCC typically appears on the head and neck area (see Fig. 15.28), but it can occur anywhere on the body. MCC is a highly malignant neoplasm that metastasizes early to the regional lymph nodes.

The diagnosis of MCC is made by a skin biopsy, but skin nodules of MCC are occasional targets for FNA [63–66]. In addition, lymph nodes and other organs containing metastases from MCC can also be examined by FNA. Although in histological sections MCC often displays characteristic trabecular architecture (trabecular carcinoma of the skin is a synonym of MCC), FNA smears display dispersed, small, round to oval tumor cells or small clusters of tumor cells that should be distinguished from non-Hodgkin lymphoma, metastasis of small cell carcinoma, olfactory neuroblastoma (esthesioneuroblastoma), desmoplastic small cell tumor, small cell melanoma, and mesenchymal chondrosarcoma and other small cell malignancies in adults (see Fig. 15.29).

MCC displays a distinctive epithelial and neuroendocrine phenotype with positivity for keratins 8, 18, 19, and 20, synaptophysin, neuron-specific enolase (NSE), and chromogranin A (Table 15.1).

Chromosomal irregularities have been documented in MCC tumors. The most common aberrations are in chromosomes 1, 6, 11, and 13, which also have been tested in FNA smears [67].

Tumor cells often lack cytoplasm, but a small rim of moderate cytoplasm with indistinct cytoplasmic borders and spherical cytoplasmic inclusions is seen in better-preserved cells. Those cytoplasmic inclusions, composed of intermediate keratin filament, give the impression of a paranuclear "dot-like" cytoplasmic staining pattern in keratin staining. Necrosis is commonly present (see Fig. 15.28).

Cytologic features:

- Hypercellular smears
- Predominantly individual, isolated tumor cells and bare nuclei
- Usually necrotic/inflammatory background with necrosis
- Minor component of poorly cohesive clusters and sheets of tumor cells
- Small to intermediate nuclei containing granular chromatin
- Nuclear overlapping and molding
- Mitoses
- Tumor cells with small to moderate cytoplasm and poorly defined cytoplasmic borders
- Cytoplasmic inclusions composed of intermediate keratin filament (paranuclear "dot-like" cytoplasmic staining pattern). Occasionally presenting as spherical cytoplasmic inclusions

Differential diagnosis and problems in diagnosis:

- Metastatic small cell carcinoma
- Metastatic malignant melanoma
- Non-Hodgkin lymphoma
- Pilomatrixoma and other skin adnexal neoplasms
- Basal cell carcinoma

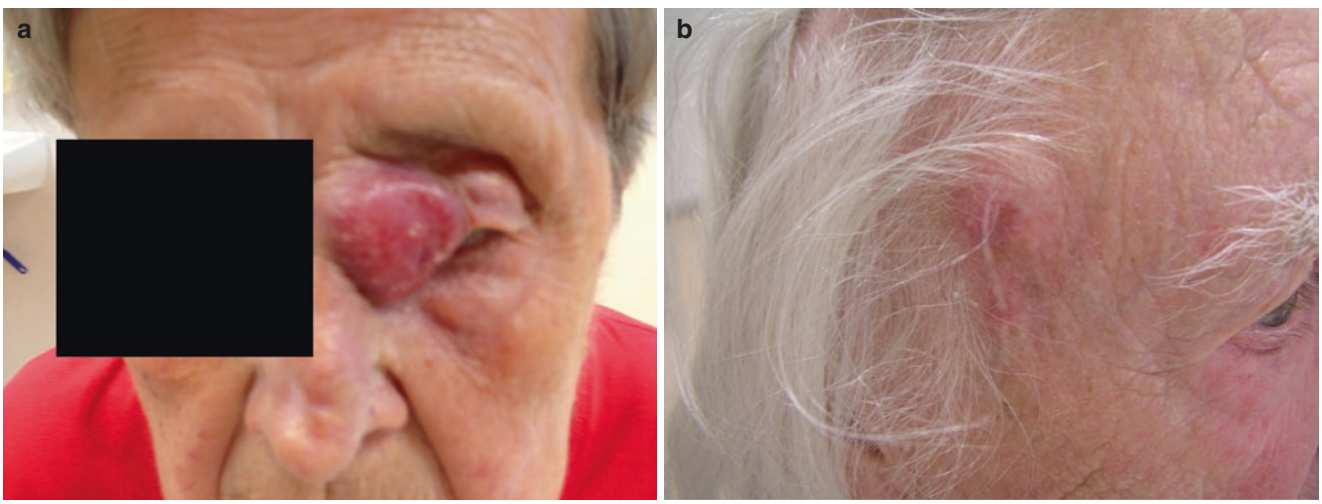

Fig. 15.28 Merkel cell carcinoma. (**a**, **b**) Clinical features of Merkel cell carcinoma growing as exophytic/polypoid tumors on the skin of the head and neck areas

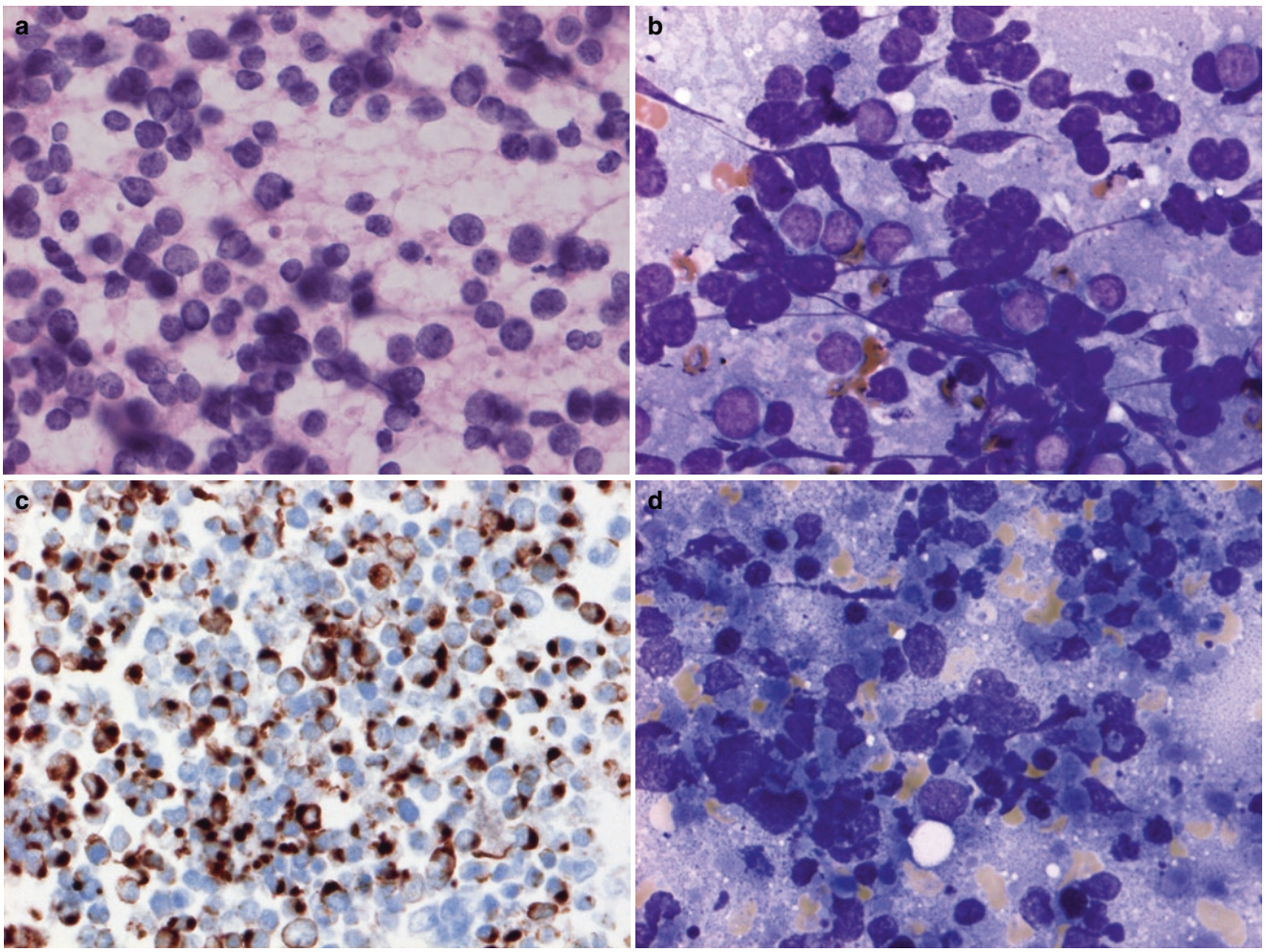

Fig. 15.29 Merkel cell carcinoma. (**a**, **b**) Cellular smears, with mostly dispersed single cells or naked nuclei. Small to intermediate cells with round to oval nuclei showing nuclear crudeness and molding and granular nuclear chromatin (H&E; MGG). (**c**) Paranuclear "dot-like" cytoplasmic staining pattern in keratin staining on cell block (Cellient; Hologic; Bedford, MA, USA). (**d**) Necrosis and apoptotic tumor cells are a common feature of Merkel cell carcinoma in FNA smears (MGG)

Table 15.1 Immunohistochemical markers in the common differential diagnosis of MCC

	CK-20	S-100	LCA	NSE	ChromA	SYP	TTF-1	CD56
MCC	+	–	–	+	±	+	–	+
SCLC	–	–	–	±	±	±	+	+
MM	–	+	–	–	–	–	–	–
Malignant lymphoma	–	–	+	–	–	–	–	–

LCA leukocyte common antigen, *MCC* Merkel cell carcinoma, *MM* malignant melanoma, *NSE* neuron-specific enolase, *SCLC* small cell lung carcinoma, *SYP* synaptophysin

Vascular Neoplasm

Hemangioma

Skin hemangiomas are rare targets for FNA, while subcutaneous and soft tissue hemangiomas are more often referred for FNA. In the majority of cases, the diagnosis of hemangioma is a diagnosis of exclusion supplemented by clinical and radiographic findings. FNA of hemangiomas is usually cell-poor, and the syringe is often filling with blood even without aspiration. In the aspiration smears, a few small, loosely cohesive sheets or clusters of spindle cells may be seen. The cells are most often poorly preserved and occasionally embedded in the collagenous matrix (see Fig. 15.30). In addition, small fragments of capillaries with uniform spindle cells and metachromatic matrix may be seen. Immunocytochemistry may be necessary to prove that the aspirate originates from a hemangioma and the spindle cells are endothelial cells. As CD34 is positive in a number of nonvascular spindle-cell tumors, other endothelial cell markers such as CD31 and factor VIII must be applied (see Fig. 15.31). In FNA smears from capillary hemangiomas in infants and young children, aspiration smears are often hypercellular, containing tight clusters of uniform spindle cells (see Fig. 15.32).

Cytologic features:

- Cell-poor, hemorrhagic smears.
- Small sheets or clusters of usually poorly preserved spindle cells.
- Cell clusters and sheets occasionally embedded in the collagenous matrix.
- Preserved cells have elongated nuclei with pointed ends and thin cytoplasmic processes.

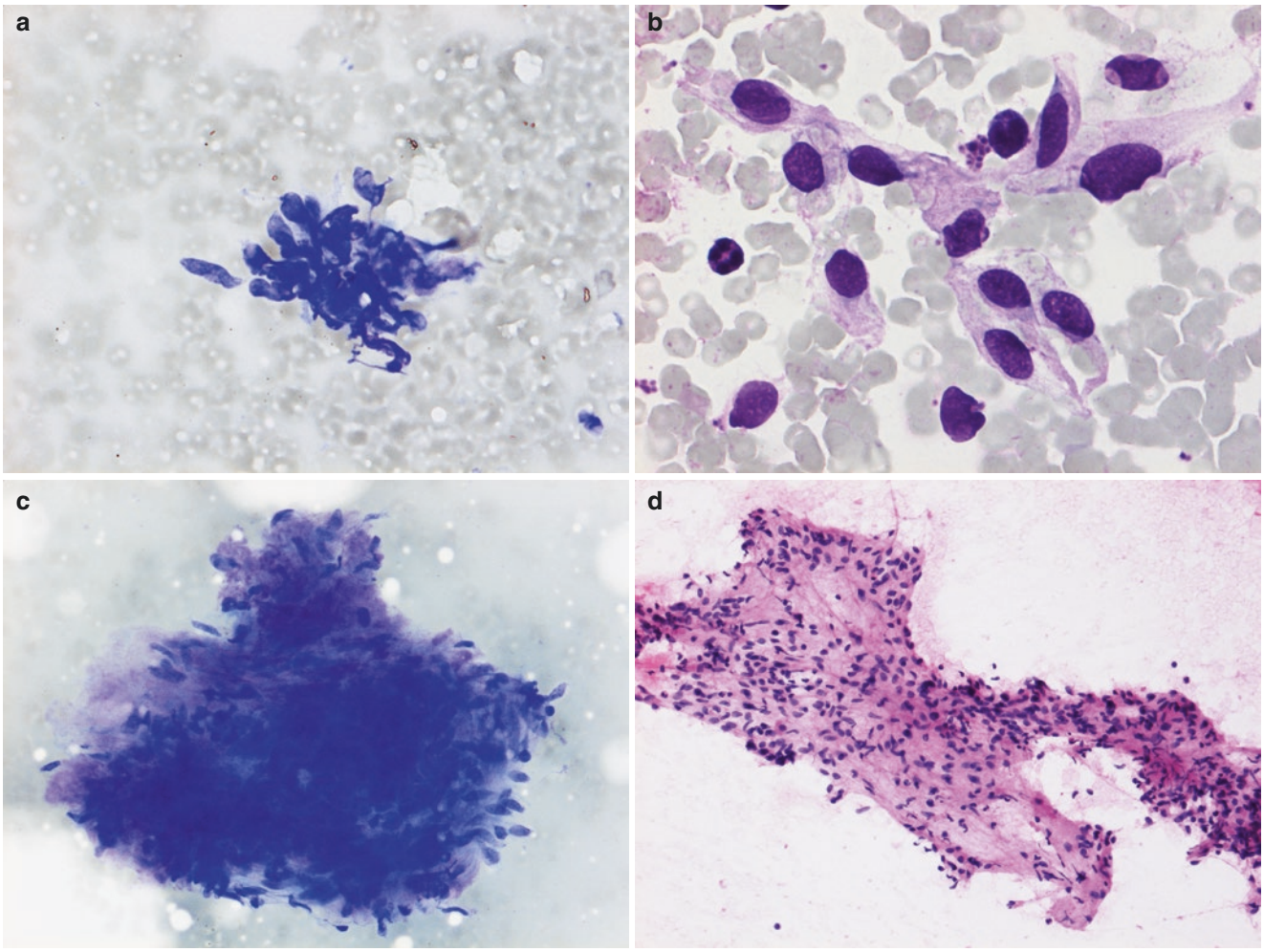

Fig. 15.30 Hemangioma. (**a**) Small sheets or clusters of usually poorly preserved spindle cells (MGG). (**b**) Better preserved cells corresponding to endothelial cells with somewhat irregular, spindle-shaped nuclei and cytoplasmic projections (H&E). (**c**, **d**) Other features of hemangioma include cell clusters and sheets occasionally embedded in the collagenous matrix (MGG; H&E)

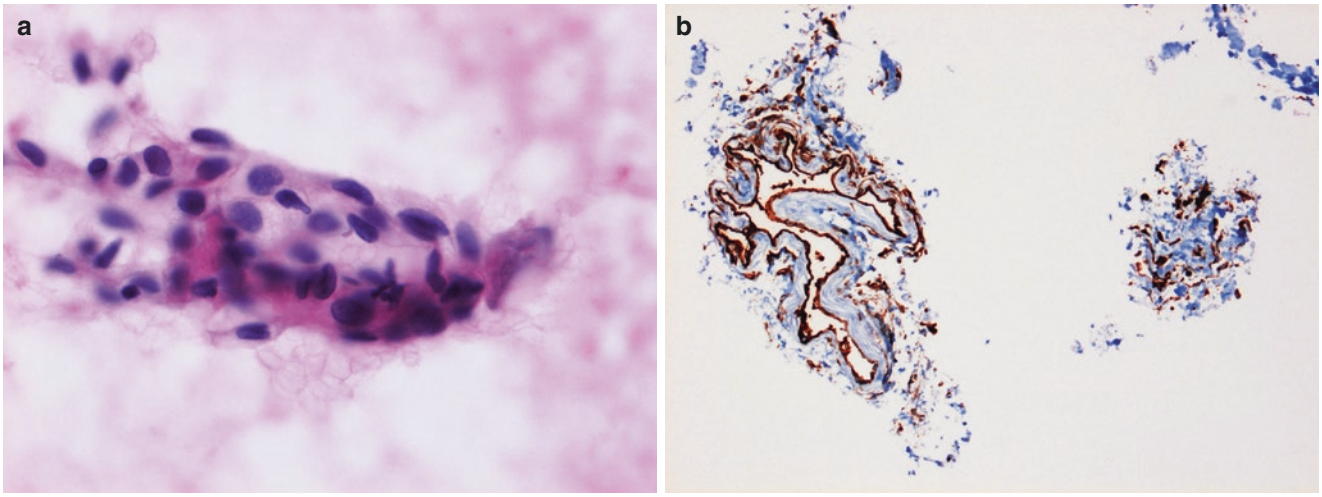

Fig. 15.31 Hemangioma. (**a**) FNA smears from arteriovenous hemangioma (H&E). (**b**) Corresponding cell block section shows positivity for CD31 in the endothelial cells and the cytoarchitecture of hemangioma (Cellient; Hologic; Bedford, MA, USA)

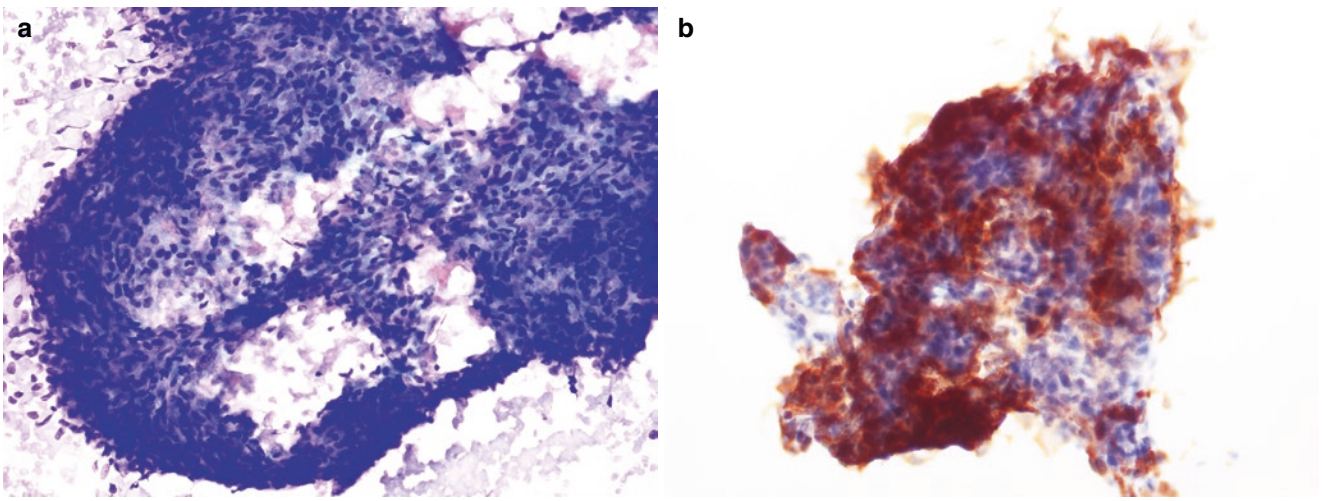

Fig. 15.32 Hemangioma. (**a**) Scanning power with smears from capillary juvenile hemangioma containing large cohesive clusters of uniform spindle cells (Diff-Quik). (**b**) Cells in cluster stains positive with endothelial marker CD31 (ThinPrep; Hologic; Bedford, MA, USA)

- Variable presence of fragments of small capillaries, occasionally with metachromatic matrix.
- Variable presence of histiocytes, some with hemosiderin pigment.
- In juvenile capillary hemangioma, thigh clusters of uniform spindle cells are a common finding.

Differential diagnosis and problems in diagnosis:

- Angiosarcoma and Kaposi sarcoma
- Angiomatoid fibrous histiocytoma
- Angioleiomyoma
- Glomus tumor

Lymphangioma

Cutaneous lymphangioma is an uncommon target for FNA. Occasionally, cavernous lymphangioma (cystic hygroma) in children and infants manifests as a subcutaneous lesion. Aspirates from such neoplasms contain liquid with benign lymphocytes, and occasional endothelial cells may be found in special preparations such as cytospins or other liquid-based techniques (see Fig. 15.33).

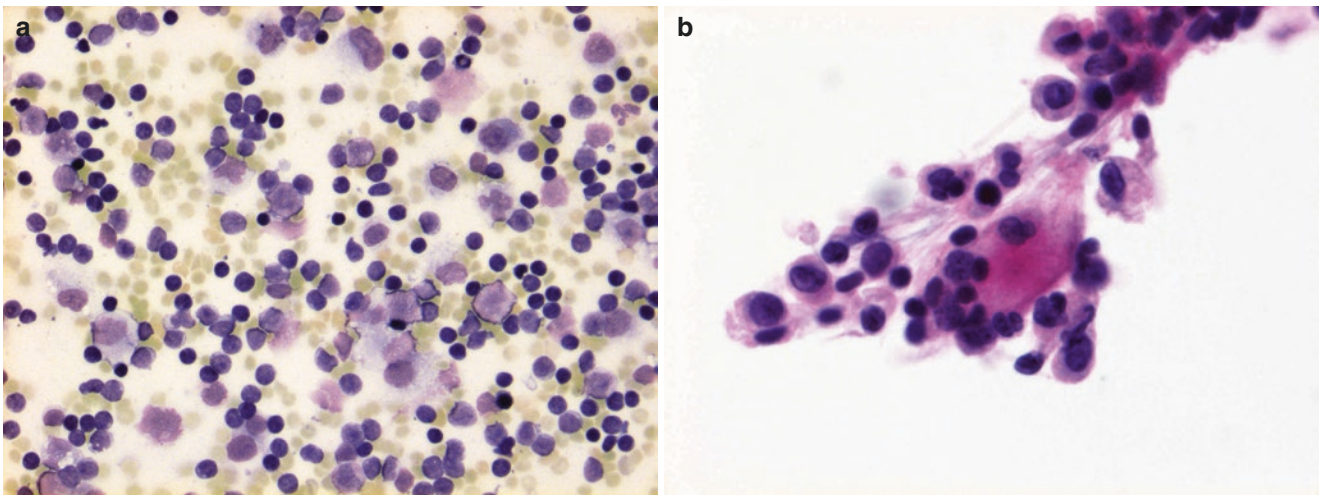

Fig. 15.33 Lymphangioma. (**a**) Smears from lymphangioma (cystic hygroma) expanding to the skin of the neck show liquid with benign lymphocytes, histocytes and erythrocytes (MGG). (**b**) Occasional endothelial cells with uniform spindle-shaped nuclei and histiocytes are seen in addition to lymphocytes in the liquid-based preparation of the FNA smears (H&E; ThinPrep; Hologic; Bedford, MA, USA)

Perivascular Neoplasm: Glomus Tumor

Most glomus tumors present as small painful nodules in the subungual region in the fingers, wrist, and foot. Glomus tumors may appear elsewhere. Only single-case reports of the cytomorphology of glomus tumors have been published. In cases of atypical sites, it may be difficult to distinguish glomus tumor from epithelial tumors and epithelioid vascular neoplasms. Smears from glomus tumor contain small- to midsized cells with poorly defined cytoplasmic borders and rounded or ovoid bland nuclei with inconspicuous nucleoli (see Fig. 15.34). Immunocytochemistry is of diagnostic help. Negative staining for cytokeratins and endothelial cell markers such as CD31 and CD34 together with positive staining for SMA suggests the diagnosis (see Fig. 15.34).

Cytologic features:

- Variable yield, often hemorrhagic aspirates
- Dispersed cells mixed with cell clusters
- Variable amount of myxoid fibrillar background matrix
- Cells are midsized with poorly defined cytoplasmic borders and rounded or ovoid bland nuclei with inconspicuous nucleoli

Differential diagnosis and problems in diagnosis:

- Angioleiomyoma
- Epithelioid vascular neoplasms
- Epithelial adnexal tumors

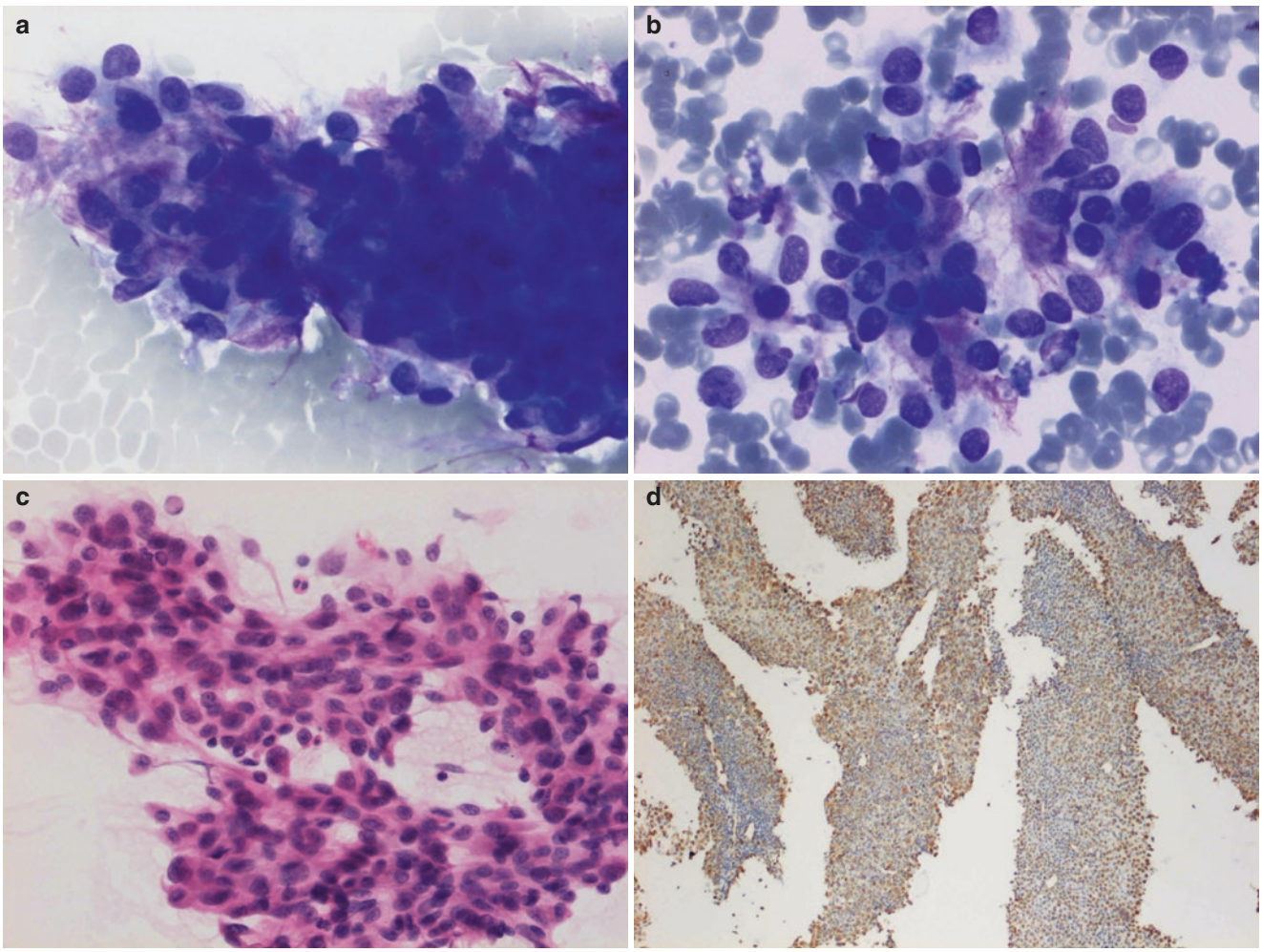

Fig. 15.34 Glomus tumor. (**a**–**c**) Cohesive or loosely cohesive clusters and sheets of small- to middle-sized cells with poorly defined cytoplasmic borders and rounded or ovoid bland nuclei with inconspicuous nucleoli. The tumor cells are often embedded in the collagenous, somewhat metachromatic matrix, which is better appreciated in the air-dried smears (**a**, **b**) (MGG), (**c**) (H&E). (**d**) Positive staining for SMA on cell block sections, in addition to FNA smears, suggests the diagnosis

Malignant Vascular Tumors

Angiosarcoma

Angiosarcoma is a cutaneous tumor, and fewer than 20% are diagnosed in deep soft tissues. Cutaneous angiosarcoma of the breast or chest wall can be a complication of irradiation [68]. The cellular population in smears of angiosarcoma displays usually clear features of malignancy, which allows a diagnosis in most cases [68–71]. Atypical spindle and polygonal cells are a common part of the smears, but epithelioid cells, variable chromatin texture and nucleolar size, and variable amount of cytoplasm in tumor cells make it difficult to render specific diagnosis of angiosarcoma from routinely stained smears (see Fig. 15.35). An exception is in those cases where small acinar-like formations with central erythrocytes or vacuolated cells with single erythrocytes are present.

Diagnosis requires immunocytochemical investigation (see Fig. 15.34). Majority of angiosarcoma stains for CD31, ERG, Fli-1, less often for CD34 and factor VIII, are variably positive. Up to half of epithelioid angiosarcoma stains for cytokeratin and some for epithelial membrane antigen (EMA). The electron microscopic demonstration of cytoplasmic Weibel–Palade bodies is yet another method to diagnose the endothelial origin of the tumor cells.

Cytologic features:
- Aspirates are often hemorrhagic.
- Mixture of dispersed cells, cell sheets, and clusters.
- Occasionally acinar structures ± erythrocytes.
- Variable presence pleomorphic/polygonal cells and spindle-cell population.
- Epithelial-like cells.
- Variable cellular and nuclear pleomorphism.
- Occasionally present signet ringlike cells with single erythrocytes in the cytoplasmic vacuole.

Differential diagnosis and problems in diagnosis:
- Kaposi sarcoma
- Spindle-cell sarcoma of various lines of differentiation
- Pleomorphic sarcoma of various lines of differentiation
- Carcinoma metastasis
- Malignant melanoma

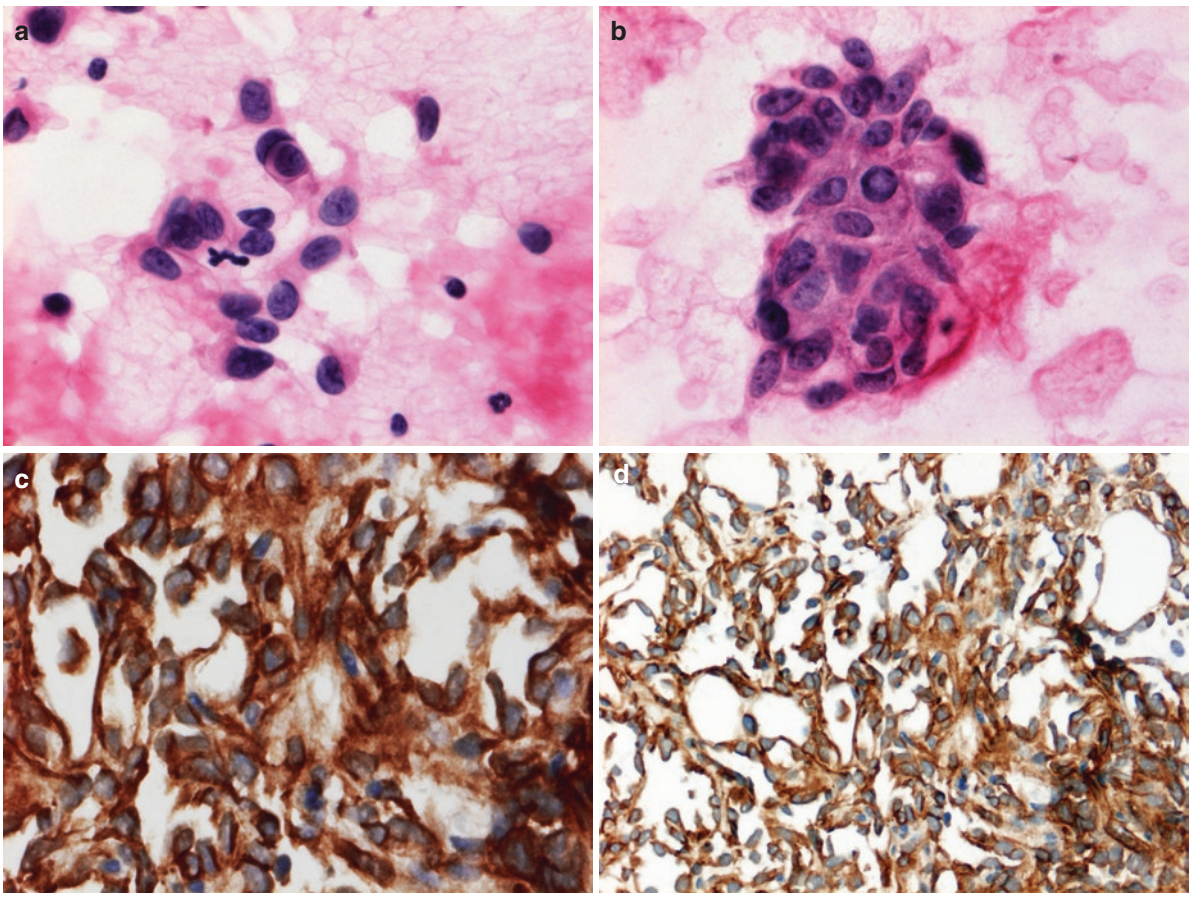

Fig. 15.35 Angiosarcoma. (**a**) Smears from epithelioid angiosarcoma show dispersed spindle cells, epithelioid cells, and naked nuclei with molding resembling smears from metastatic carcinoma (H&E). (**b**) Loosely cohesive sheets of malignant spindle – and polygonal – cells. It can be difficult to render specific diagnosis of angiosarcoma from routinely stained smears due to variable tumor cell morphology (H&E). (**c**, **d**) Immunostaining with endothelial markers such as CD31, CD34, ERG and Fli-1 may be necessary to establish final diagnosis (cell block, CD31, CD34)

Kaposi Sarcoma

Kaposi sarcoma (KS) is a locally aggressive neoplasm associated with HHV-8 infection and commonly involves the skin of distal extremities in elderly men. KS may occasionally arise in mucosal membranes, visceral organs, and lymph nodes. KS develops occasionally in patients receiving immunosuppressive treatment. An endemic form of KS occurs in children or middle-aged adults in Africa. The most aggressive form of the disease is AIDS-associated KS arising in individuals infected with HIV-1. Smears from KS display small, loosely cohesive clusters of bland-looking or slightly/moderately pleomorphic spindle cells (see Fig. 15.36) [72, 73]. Clinical presentation and positivity for HHV-8 and vascular markers help to render the correct diagnosis from FNA smears.

Cytologic features:

- Mixture of dispersed cells and small, loosely cohesive cell clusters and sheets
- Predominantly bland-looking or moderately pleomorphic spindle cells with smear artifacts
- Tumor cells positive for endothelial markers such as CD31 and CD34

Differential diagnosis and problems in diagnosis:

- Angiosarcoma
- Spindle-cell sarcoma of various lines of differentiation

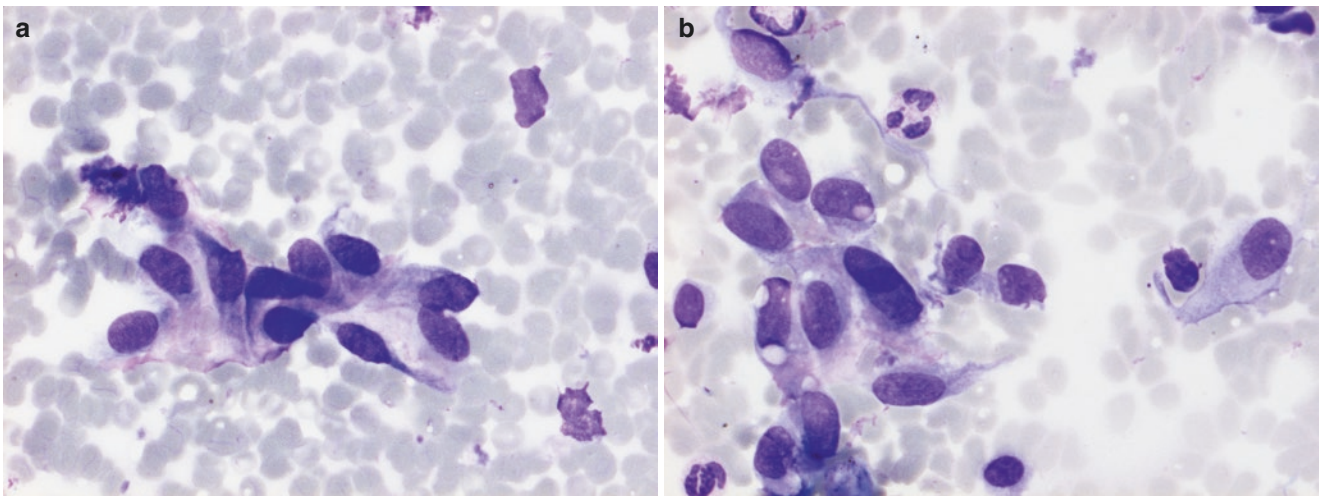

Fig. 15.36 Kaposi sarcoma. (**a**, **b**) Smears from Kaposi sarcoma showing small, loosely cohesive sheets of bland-looking spindle cells with cytoplasmic projections (MGG)

Granular Cell Tumor

Granular cell tumor is a benign neoplasm composed of relatively uniform round and polygonal cells with abundant granular cytoplasm. Granular cell tumors occur in any age group, arising commonly in the skin and subcutaneous tissue [74]; occasionally in the genital tract, tongue, and breast; and rarely in deep soft tissue [75]. Most aspirates from granular cell tumors display diagnostic features of bland-looking cells with abundant granular cytoplasm (see Fig. 15.37). The diagnostic problem occurs in atypical locations of the neoplasm such as deep tissue of the breast. Cytoplasmic positivity for S100 and PAS-positive granular cytoplasm helps to render the correct diagnosis in such cases (see Fig. 15.38).

Cytologic features:
- Mixture of single cells or bare nuclei and poorly cohesive sheets of cells.
- Cells with fragile granular cytoplasm, often stripped nuclei, and cytoplasmic granular background.
- Preserved round-, polygonal-, or spindle-shaped cells with abundant granular cytoplasm and ill-defined cytoplasmic borders.
- Small, round to oval nuclei with finely granular chromatin and small nucleoli.
- Occasionally moderately pleomorphic cells with nuclei showing coarse chromatin and macronucleoli.
- Tumor cells are positive for S-100 and contain PAS-positive cytoplasmic material.

Differential diagnosis and problems in diagnosis:
- Hibernoma
- Adult rhabdomyoma
- Alveolar soft part sarcoma

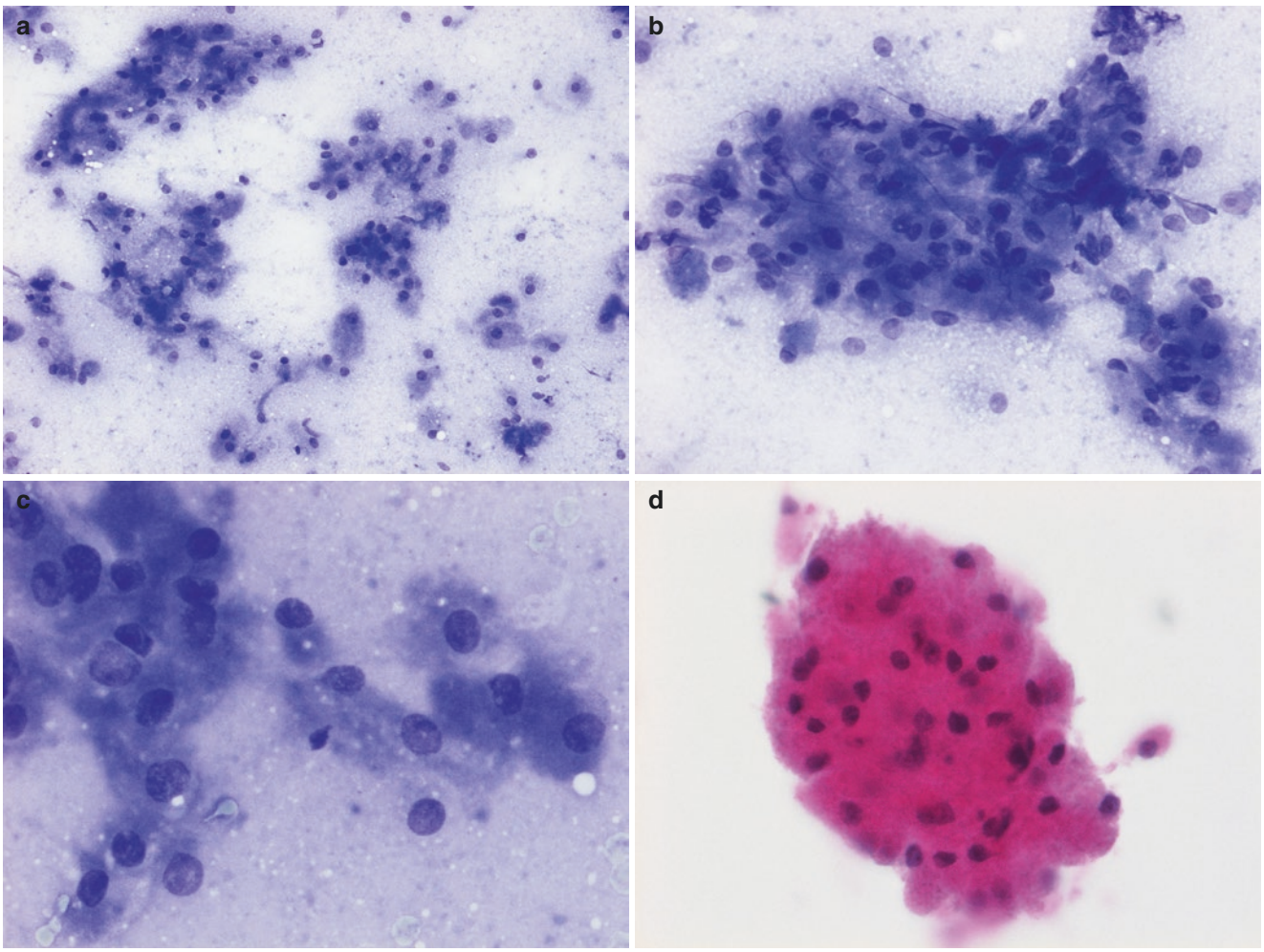

Fig. 15.37 Granular cell tumor. (**a**–**d**) FNA smears from different granular cell tumors containing poorly cohesive sheets of bland-looking cells with abundant fragile granular cytoplasm and ill-defined cytoplasmic borders (MGG; H&E)

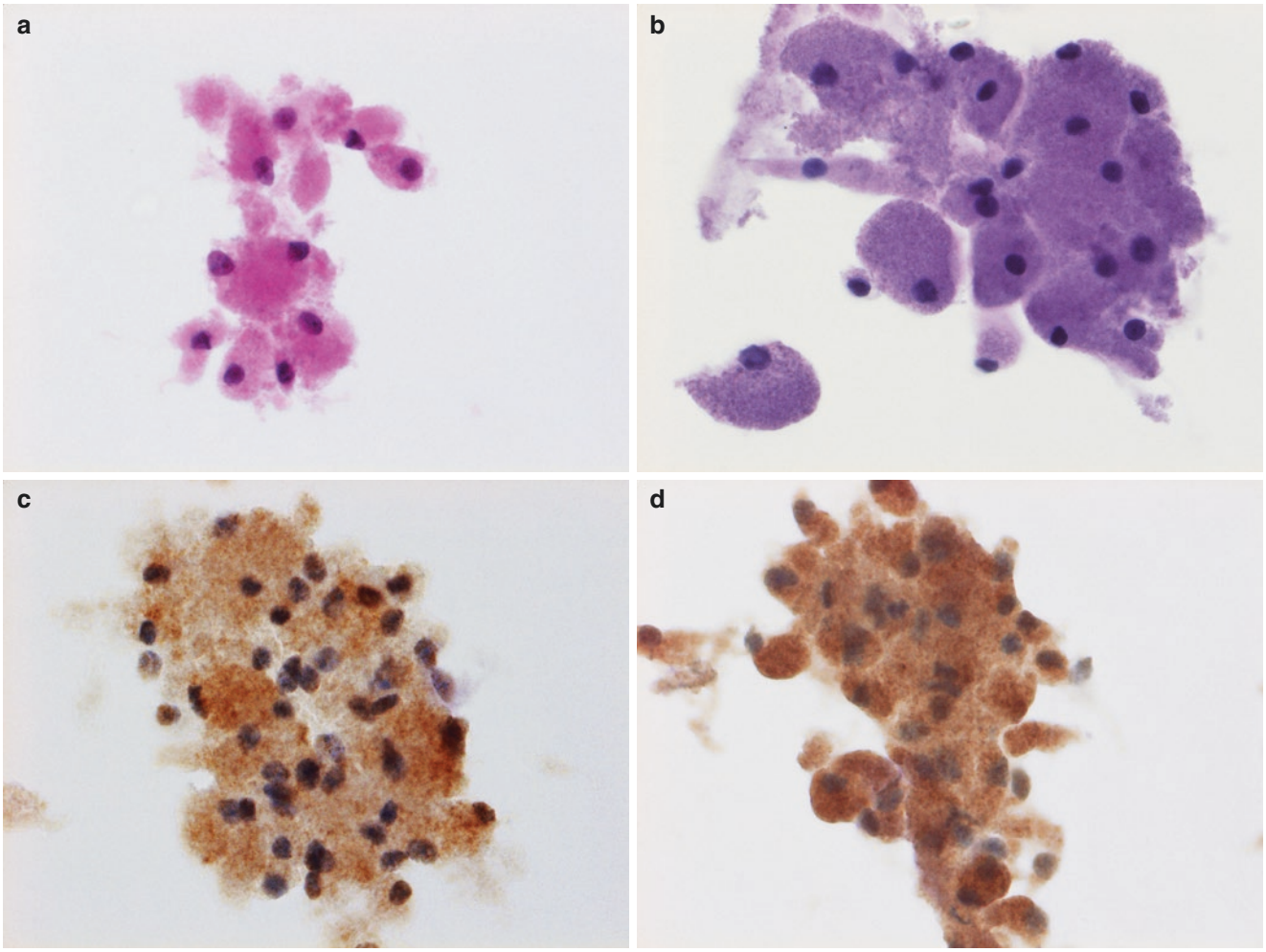

Fig. 15.38 Granular cell tumor. (**a**) Liquid-based preparation of FNA smears from granular cell tumors: cell morphology is similar to conventional smears. Adjunctive techniques in the cytological diagnosis of granular cell tumor: (**b**) Tumor cells containing PAS-positive cytoplasmic material. (**c**, **d**) Positive in immunostaining for S-100 protein (ThinPrep; Hologic; Bedford, MA, USA)

Dermatofibroma (Benign Fibrous Histiocytoma)

Dermatofibroma (DF) commonly arises in the skin of extremities but may occur in any cutaneous site. DF often presents as a skin nodule or induration in the skin. Typical smears from DF consist of fibroblasts, fragments of collagen tissue, and histiocytes, often with appearances of xanthomatous histiocytes containing iron pigment [76]. In the majority of smears from DF, one can appreciate multinucleated histiocytes consistent with Touton giant cells (see Figs. 15.39 and 15.40).

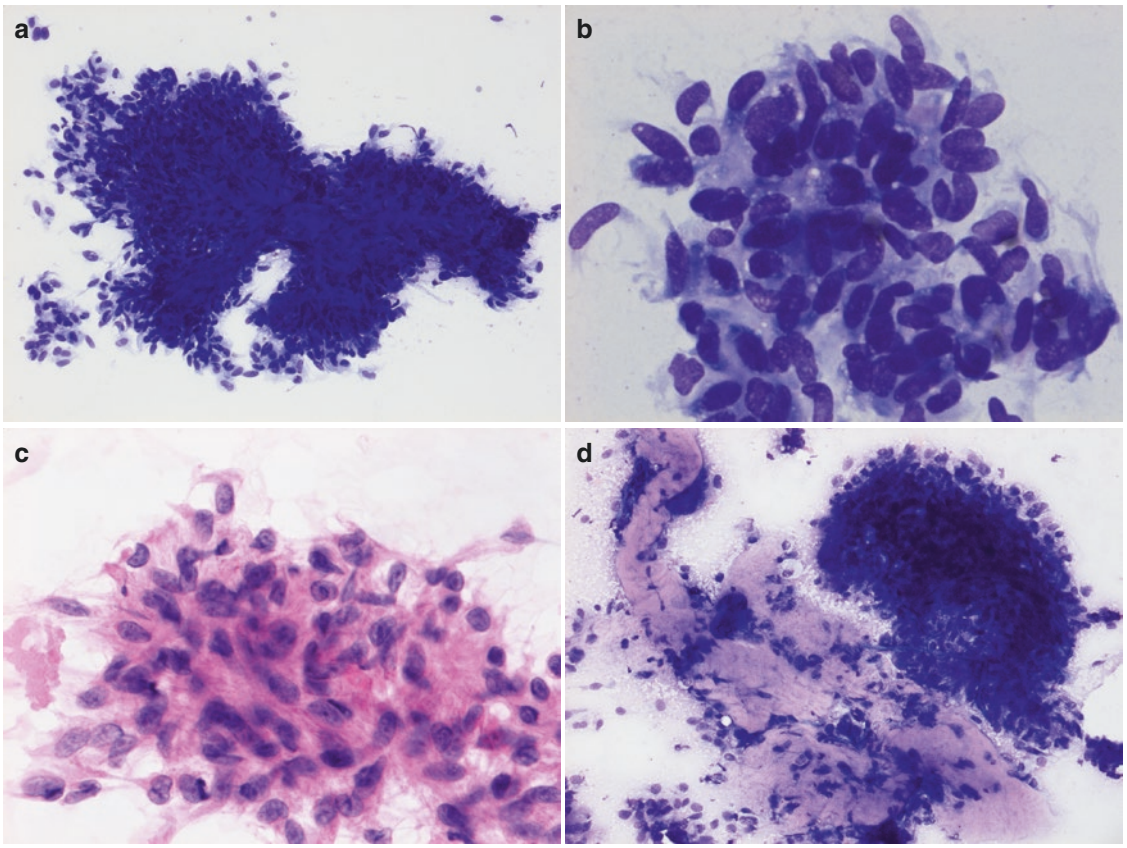

Fig. 15.39 Dermatofibroma. (**a**–**c**) FNA smears with clusters and sheets of fibroblasts with bland ovoid or spindle-shaped nuclei with short cytoplasmic processes (**a**, **b**) (MGG), (**c**) (H&E). (**d**) Admixture of fragments of collagen tissue (MGG)

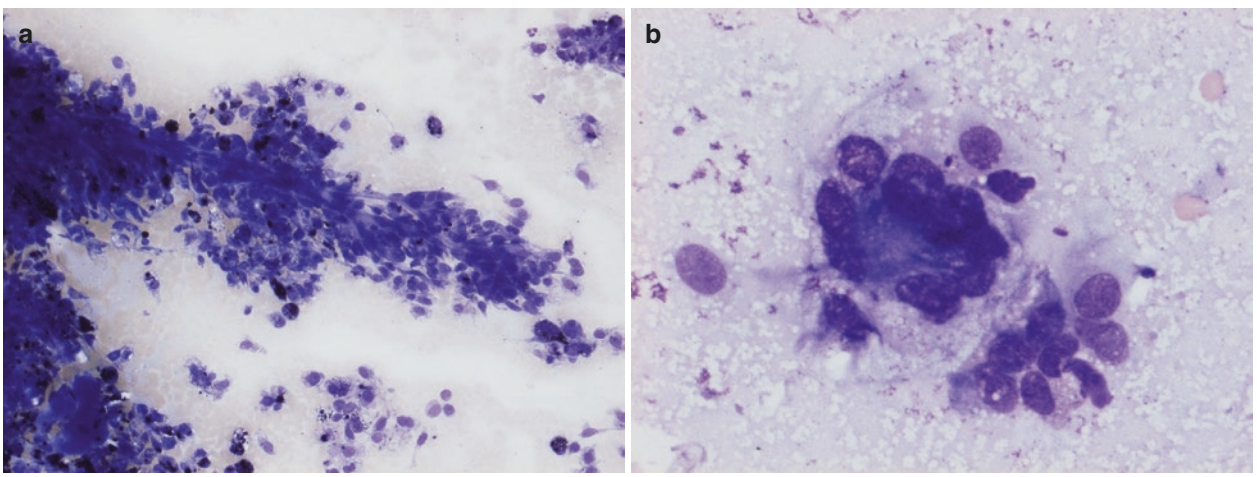

Fig. 15.40 Dermatofibroma. FNA smears show clusters of spindle cells with admixture of xanthomatous histiocytes containing iron pigment (**a**) and foreign body-type Touton giant cells (**b**) (MGG)

Dermatofibrosarcoma Protuberans

Cytomorphology of dermatofibrosarcoma protuberans is described in detail in the chapter entitled "Soft Tissue" (see Chap. 14). Cell block and immunostains for CD34 appreciate typical morphology and phenotype of these uncommon neoplasms.

Atypical Fibroxanthoma

Atypical fibroxanthoma (AFX) is a low-grade neoplasm that typically occurs as a small skin nodule at the sun-exposed areas of the skin of elderly individuals. AFX is a rare target for FNA with smears showing variety of morphologic patterns corresponding to histological sections. Smears may be easy misdiagnosed as a high-grade malignant neoplasm due to atypical pleomorphic tumor cells showing microscopic signs of malignancy (see Fig. 15.41).

Pleomorphic Dermal Sarcoma

Cytomorphology of pleomorphic dermal sarcoma is described in detail in the chapter entitled "Soft Tissue" (see Chap. 14). For correct diagnosis, histological examination of entire excised tumor is necessary to see its architecture with typically deep infiltrative growth into subcutaneous tissue and often also into the superficial muscle fascia.

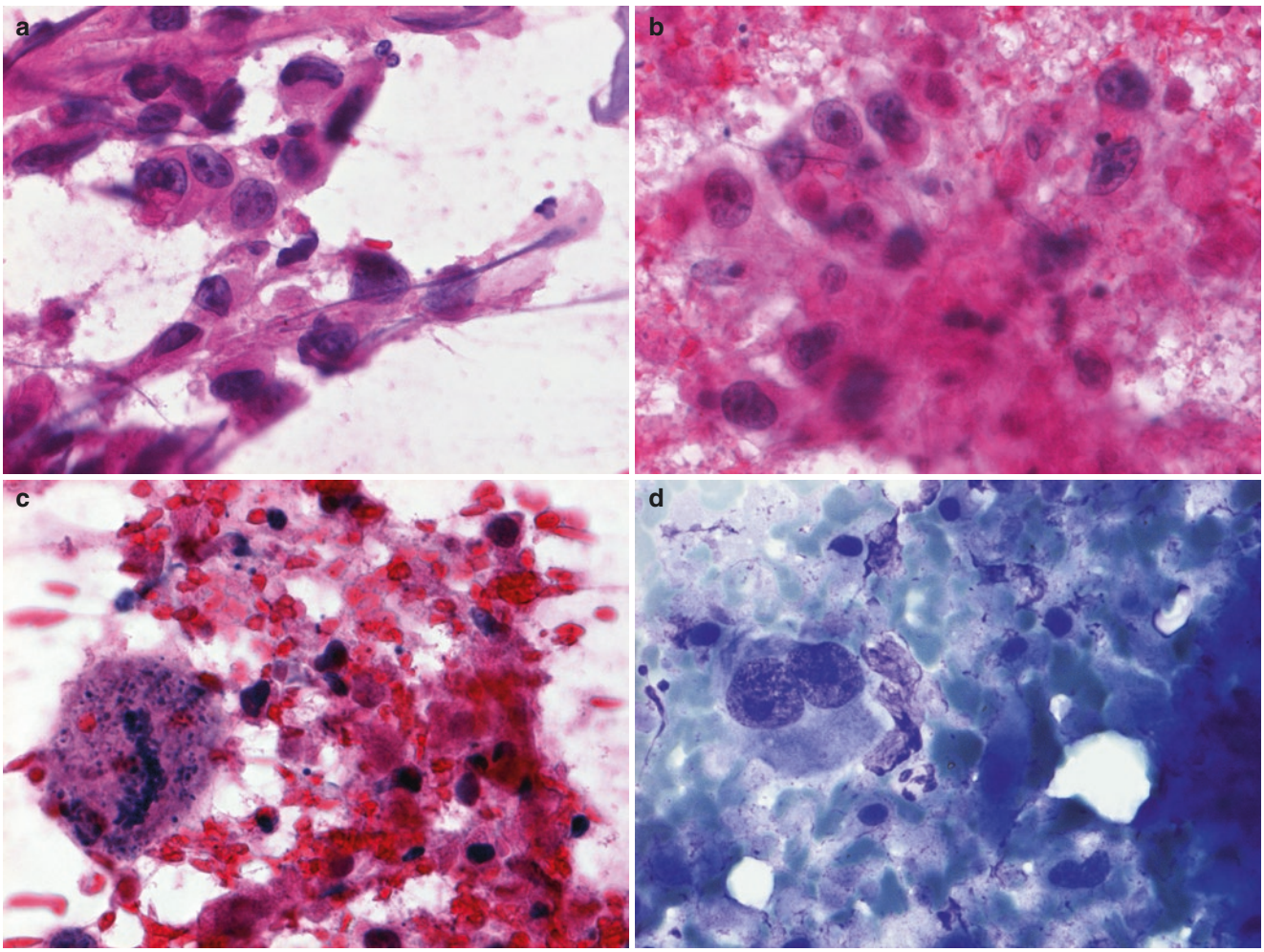

Fig. 15.41 Atypical fibroxanthoma. FNA smears show sheets and single cells with variable but often epithelioid morphology, irregular nuclei with occasional macronucleoli, coarse chromatin (**a–d**) (H&E and MGG), and (**c**) bizarre mitosis (H&E)

Lymphoproliferative Cutaneous Neoplasm

FNA is of little use in the diagnosis of cutaneous lymphoproliferative disease. FNA may successfully confirm recurrences and spread of hematopoietic malignancies. However, FNA complemented with molecular techniques and flow cytometric analysis may provide primary diagnosis of lymphoid lesions.

Cutaneous Lymphomas

Skin lesions may be presentation of systemic non-Hodgkin lymphomas (NHL) and primary cutaneous lymphomas [77]. Mycosis fungoides commonly present in the skin (see Fig. 15.42) [78, 79]. Other subtypes of NHL may be aspirated in the FNA of skin lesions. In routinely stained smears, one can appreciate lymphoid cells with atypical features (see Fig. 15.43). In most cases of cutaneous lymphoma, subtyping of these neoplasms is not possible without ancillary techniques such as flow cytometry [80] and molecular techniques (especially useful in T-cell malignancies).

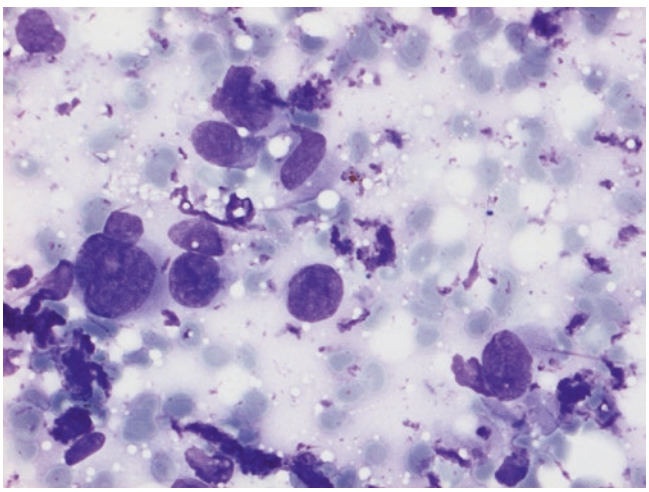

Fig. 15.42 Mycosis fungoides. FNA smears with scattered, poorly preserved, atypical lymphoid cells (MGG). The final diagnosis is difficult to render from FNA smears alone. Clinical information and ancillary techniques are required

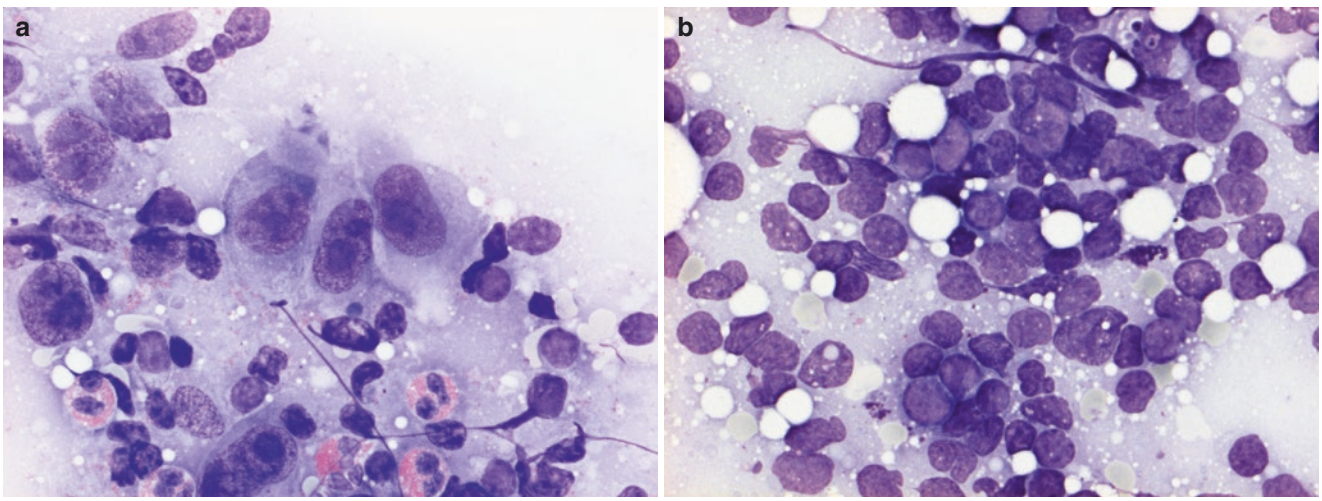

Fig. 15.43 Lymphoma of the skin. (**a**) Dissociated large pleomorphic tumor cells with abundant cytoplasm and irregular nuclei with macronucleoli and admixture of eosinophilic granulocytes. Ancillary techniques confirmed a diagnosis of large-cell anaplastic lymphoma (MGG). (**b**) Dissociated large tumor cells with scant cytoplasm. The cytomorphology is consistent with a high-grade lymphoma, and ancillary studies confirmed the diagnosis of lymphoblast lymphoma (MGG)

Myeloid (Granulocytic) Sarcoma (Extramedullary Myeloid Tumor)

Granulocytic sarcoma (GS) is a rare neoplasm commonly associated with acute myeloid leukemia and blast transformation in chronic leukemia. GS is occasionally the first presentation of chronic myeloid leukemia in the chronic phase [81]. This neoplasm is composed of primitive precursors of the granulocytic series that include myeloblasts, promyelocytes, and myelocytes. GS arise usually in the soft tissue, bone, lymph nodes, and skin but may arise in any part of the body [82]. Infiltrates of GS in the skin form nodules, papules, or plaques discolored overlying the skin [81]. In most cases, smears from granulocytic sarcoma contain cells of myeloid lineage readily recognized by intracytoplasmic granulation [82] (see Fig. 15.44). Immunostains together with flow cytometric and cytogenetic analysis constitute important ancillary techniques for a definitive diagnosis from FNA smears (see Fig. 15.44d).

Cytologic features:

- Variable morphology.
- Predominantly dispersed cells.
- Well-differentiated; myeloid differentiation is easily seen: cells with fragile granular cytoplasm and often cytoplasmic granular background.
- Poorly differentiated, mixture of large cells with vesicular nuclei, conspicuous nucleoli, and cells with lobed nuclei and granular eosinophilic cytoplasm.
- Blastic, midsized cells with inconspicuous nucleoli, scanty cytoplasm, and no eosinophilic granules.
- Tumor cells are positive for lysozyme, myeloperoxidase, CD43, CD68, CD34, and often CD117.

Differential diagnosis and problems in diagnosis:

- Cutaneous NHL
- Langerhans cell histiocytosis

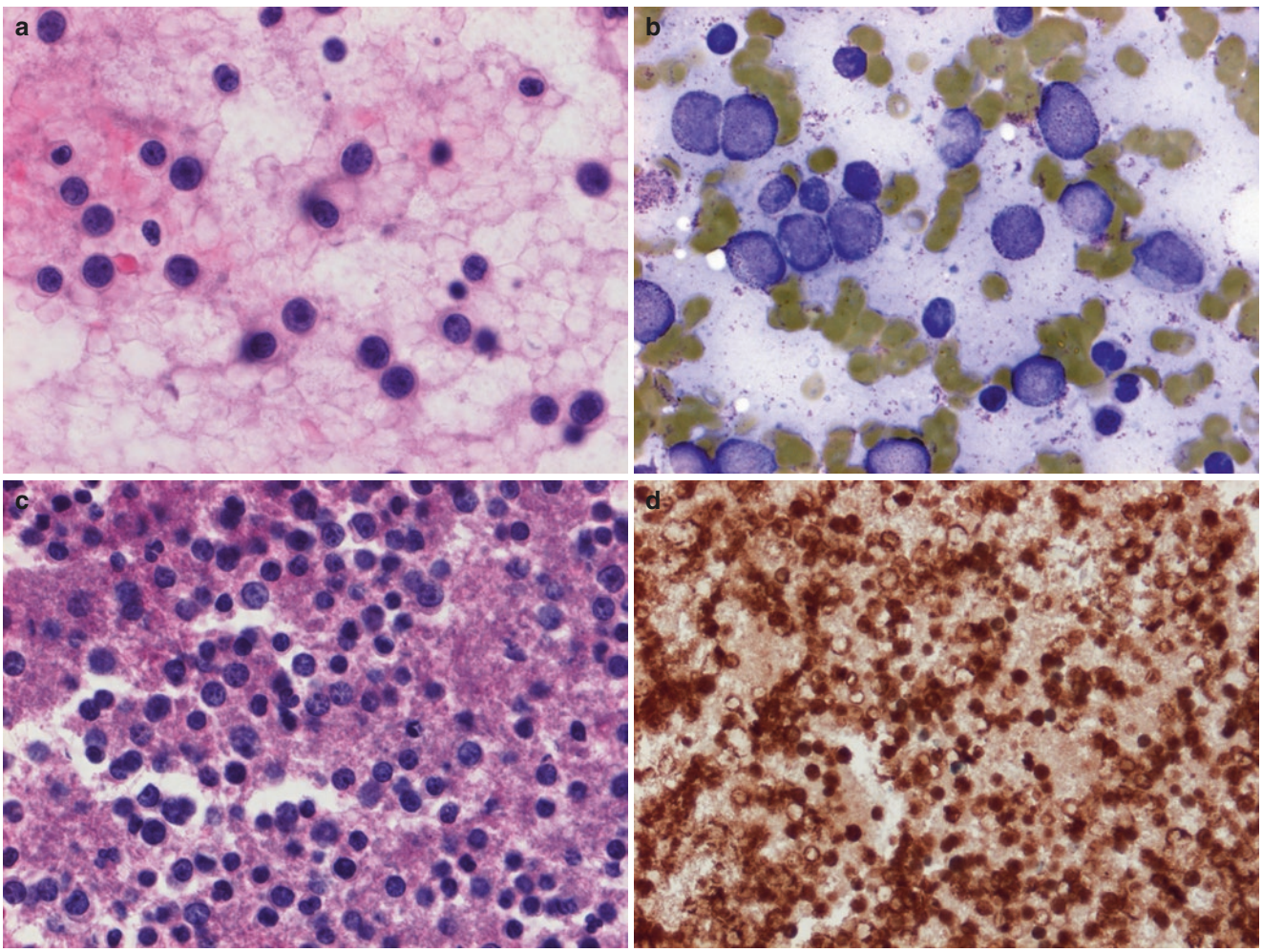

Fig. 15.44 Myeloid (granulocytic) sarcoma. (**a**) Dissociated, scattered, large, malignant cells in alcohol-fixed smears (H&E). (**b**) In air-dried and MGG-stained smears, the cells show fragile granular cytoplasm and cytoplasmic granular background indicative of myeloid differentiation (MGG). (**c**, **d**) Cell block with morphology consistent with FNA smears and positivity for myeloperoxidase (Cellient; Hologic; Bedford, MA, USA)

Metastatic Neoplasm of the Skin. Sister Mary Joseph Nodule

Cutaneous metastases appear in up to 9% of individuals, as determined at autopsy. Areas such as the scalp are the more frequent sites for metastatic malignancies (see Fig. 15.45) [83, 84]. Metastatic deposition in the umbilical area, named "Sister Mary Joseph nodule," most often spreads from the gastrointestinal or genitourinary tract (see Fig. 15.46) [85–87]. In cases of previously known malignancies, FNA is a rapid technique to confirm metastatic disease. In cases where skin metastasis is the first presentation of malignant neoplasms in internal organs, ancillary techniques are necessary to diagnose origin and histological type of malignancy (see Fig. 15.47).

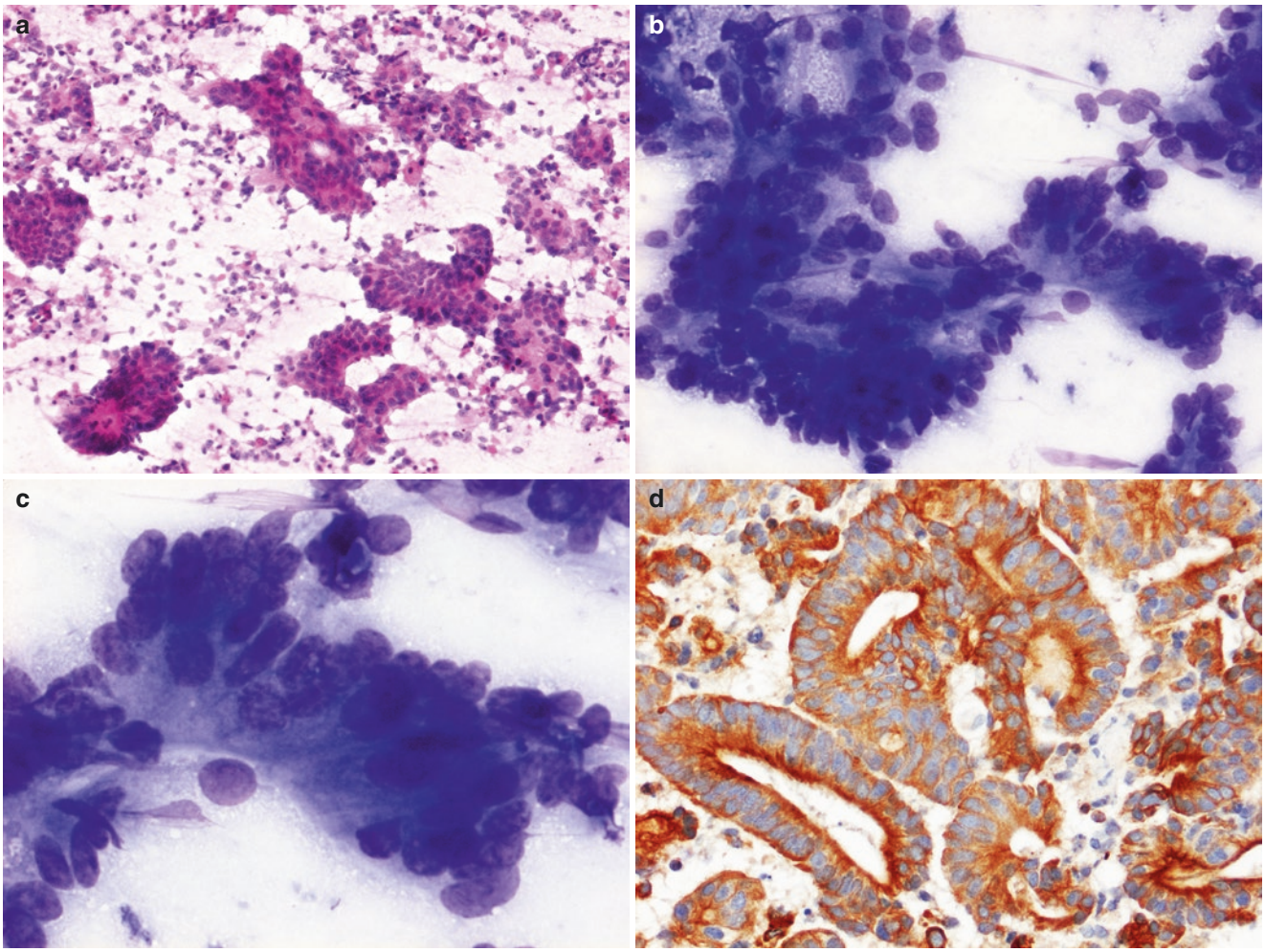

Fig. 15.45 Metastatic neoplasm to the skin. (**a**–**c**) Scalp skin metastasis in patient with history of colonic adenocarcinoma. Note micromorphology of routinely stained smears indicative of colonic carcinoma metastasis (H&E; MGG). (**d**) Micromorphology of metastasis and positive keratin stains in the sections from cell block confirm the diagnosis (Cellient; Hologic; Bedford, MA, USA)

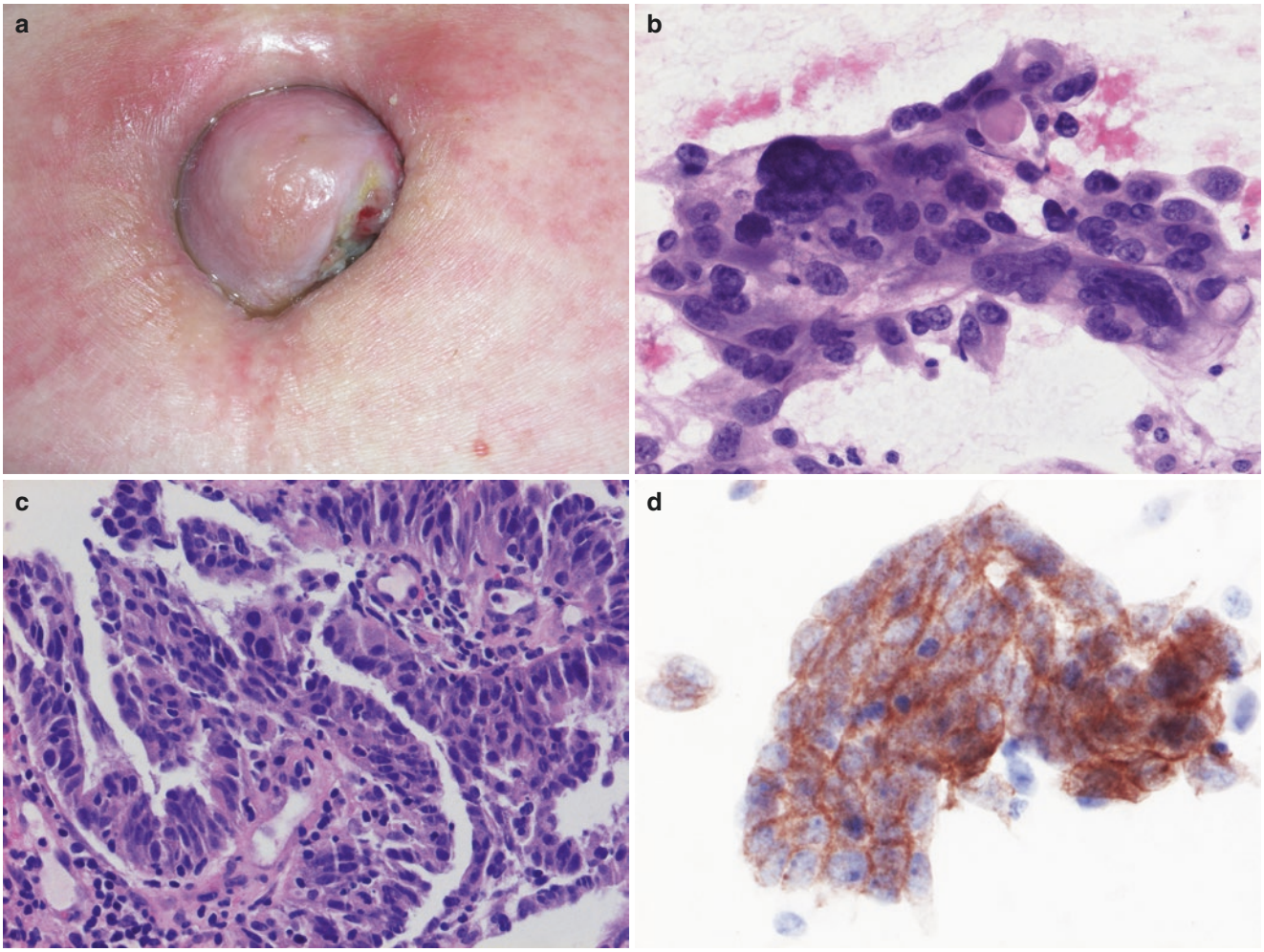

Fig. 15.46 Metastatic neoplasm to the skin. (**a**) Clinical presentation of Sister Mary Joseph nodule in a patient first diagnosed by FNA as high-grade sarcoma. (**b**) Smears of repeat FNA (H&E). (**c**) Cell block section (Cellient; Hologic; Bedford, MA, USA). (**d**) Positive result for keratin staining (ThinPrep; Hologic; Bedford, MA, USA) indicative of metastasis from adenocarcinoma. Further investigations disclosed endometrioid carcinoma developed outside of the uterine cavity in an area of endometriosis

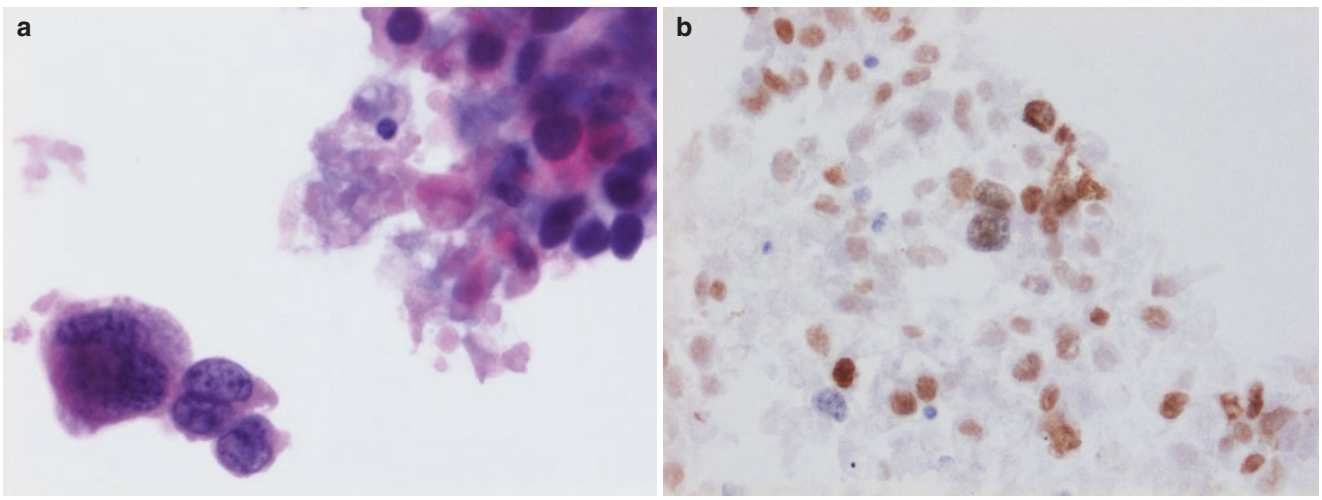

Fig. 15.47 Metastatic neoplasm to the skin. (**a**) Partly necrotic metastasis to the skin (H&E). (**b**) Immunostains with TTF1 positivity indicative of lung carcinoma (cell block; Cellient; Hologic; Bedford, MA, USA). Further investigations disclosed primary bronchogenic carcinoma in the lung

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