Soft Tissue

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Introduction

Evaluation of Soft Tissue Lesions by FNA

Tissue sampling is necessary for the diagnosis of soft tissue tumors when malignancy cannot be ruled out by clinical or radiographic means. Although open incisional and excisional (local excision for small and superficial lesions) biopsy is generally accepted as sampling techniques in the diagnosis of soft tissue tumors, core needle biopsy and FNA have largely replaced open biopsy as the initial diagnostic tool to establish malignancy and to assess histologic type and grade [1, 2]. CNB has become a popular diagnostic procedure since it can be performed in an outpatient setting and carries a very low risk of morbidity [2–5]. The evaluation of CNB specimens may be challenging due to limited sampling and the heterogeneity of most of soft tissue neoplasms [2–4].

Accumulated experience from Sweden and other groups with expertise in FNAC of soft tissue and bone lesions has indicated that FNAC is suitable to establish a metastatic carcinoma (see Fig. 14.1), melanoma, or lymphoma, to document a recurrence or metastasis of a previously treated sarcoma, and to diagnose a benign soft tissue lesion, as well as a primary soft tissue sarcoma [6–15]. In addition, FNAC may be used as a complementary tool to CNB in the diagnosis of musculoskeletal lesions [11, 16].

Soft tissue neoplasms comprise a heterogenous group of lesions with mesenchymal differentiation. Sarcomas are rare, constituting less than 1% of all malignant neoplasms. Benign soft tissue tumors are estimated to be approximately 100 times more frequent than sarcomas. Soft tissue tumors may occur in different planes and locations. However 99% of benign soft tissue tumors are superficial, while two thirds of the extremity and trunk wall sarcomas are deep seated. Age-specific incidence rates clearly demonstrate that soft tissue sarcomas are more common with increasing age. Gender or age-related incidence is often related to the histological type and subtype of sarcomas.

According to the guidelines of the Scandinavian Sarcoma Group, patients present with a suspicion of soft tissue sarcoma (any deep intra- or intermuscular tumors and superficial tumors >5 cm) should be referred to the centers with histopathologic and cytologic expertise and the capability for a clinical–radiologic correlation. Multidisciplinary management of soft tissue neoplasms during the past few decades favorably influenced outcomes for patients suffering from sarcoma. The best approach to a successful diagnostic evaluation of soft tissue lesions is to combine clinical data and radiographic findings with the morphology interpretation that should be accomplished with the aid of supportive ancillary techniques [10].

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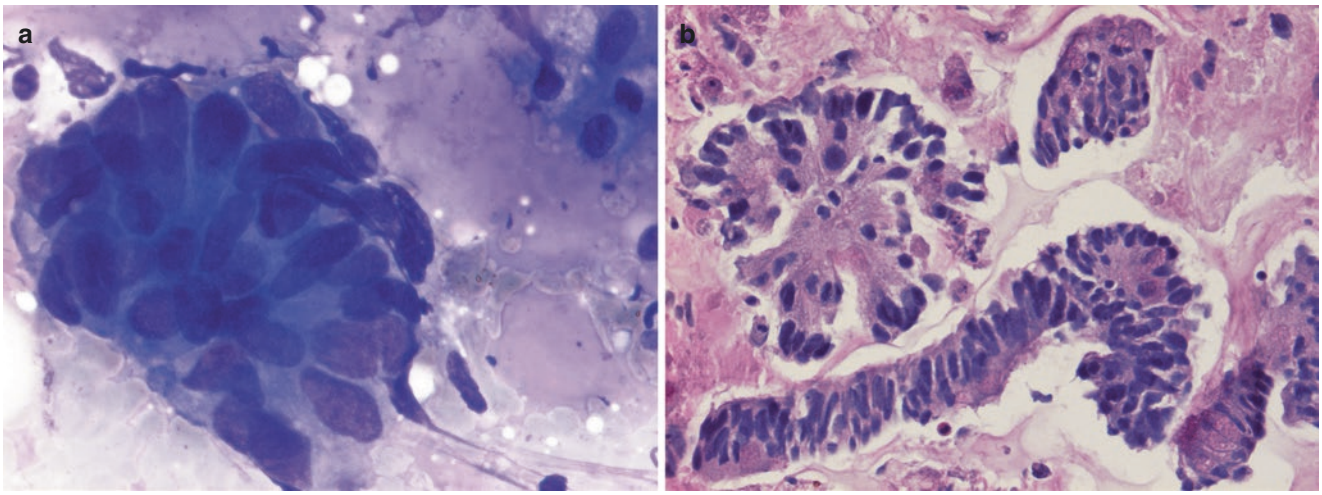

Fig. 14.1 Bone and soft tissue metastases. (**a**) Metastasis of colonic adenocarcinoma: clusters of columnar cells arranged in solid nests. Note mucinous background (MGG). (**b**) Tumor tissue architecture appears in cell block sections (H&E)

Sampling Technique

Technically, FNA biopsy of a soft tissue lesion is not significantly different from sampling a lesion from other parts of the body. Certain parameters that are particularly important in FNA of a soft tissue lesion include anatomic site, size of the target, tumor consistency, and its mobility. A syringe holder, 10 ml syringe, and needles of varying lengths are recommended. Needles wider than 22 gauge are seldom necessary. For deep-seated lesions, a needle with a stylet may be used to avoid sampling of the adjacent normal tissue. If a sarcoma is suspected, aspirating through the vertex and through a single tract is preferred. The direction of the needle should be changed with each pass to cover different parts of the tumor. The preferred areas of needle entrance are often marked by the orthopedic surgeon as part of surgery planning so as to ensure that the needle tracts are completely removed during the subsequent surgery (see Fig. 14.2) [17].

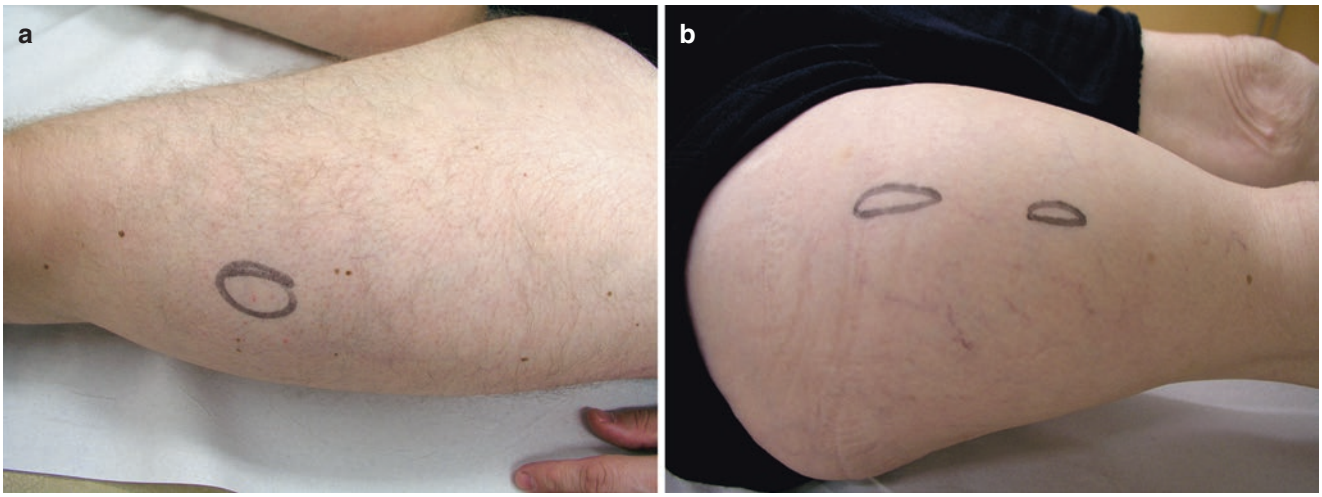

Fig. 14.2 Sampling technique. (**a**, **b**) Areas of the skin where the needle should be inserted were marked by the orthopedic surgeons

Ancillary Techniques

Ancillary techniques used in the work-up of FNA samplings have been described in section "Ancillary Techniques in FNAC" in Chap. 1. The most commonly used ancillary test is immunocytochemistry (IC), which is preferably performed on cell-block preparations [18]. Useful antibodies in the FNA diagnosis of soft tissue tumors are listed in Table 14.1. Cytogenetic and molecular techniques play an increasingly important role in the evaluation of soft tissue neoplasms. In daily practice, FNA preparations are especially suitable for molecular genetic techniques such as reverse transcriptase–polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) (Table 14.2) [19, 20]. The use of electron microscopic (EM) examination has decreased considerably because of the highly effective IC and molecular genetic techniques to determine the line of differentiation of a soft tissue tumor.

Table 14.1 Useful antibodies in the diagnosis of soft tissue neoplasm

Antibodies	Neoplasm
Muscle-specific actin	Leiomyoma; leiomyosarcoma; myofibroblastic tumors; rhabdomyosarcoma; pseudosarcomas
Smooth muscle actin (SMA)	Leiomyoma; leiomyosarcoma; myofibroblastic tumors; pseudosarcomas; PEComa
Desmin	Leiomyoma; leiomyosarcoma; rhabdomyosarcoma; PEComa; desmoplastic small round cell tumor; extrarenal malignant rhabdoid tumor (some); angiomatoid fibrous histiocytoma (some)
Caldesmon	Leiomyoma; leiomyosarcoma
Myoglobin	Rhabdomyosarcoma
MyoD1	Rhabdomyosarcoma; alveolar soft past sarcoma (cytoplasmic)
S-100 protein	Benign nerve sheath tumors; malignant peripheral nerve sheath tumor; granular cell tumor; clear cell sarcoma; round cell liposarcoma; ossifying fibromyxoid tumor; synovial sarcoma ~30%
CD34	Dermatofibrosarcoma protuberans; hemangiopericytoma/solitary fibrous tumor; epithelioid sarcoma; hemangiomas; angiosarcoma; gastrointestinal stromal tumor; spindle-cell lipoma/pleomorphic lipoma
CD31	Hemangiomas; angiosarcoma; hemangioendothelioma
Fli-1/ERG	Ewing sarcoma; angiosarcoma
CD99	Ewing sarcoma (diffuse membranous); synovial sarcoma; alveolar rhabdomyosarcoma (some); mesenchymal chondrosarcoma; solitary fibrous tumor, undifferentiated round cell sarcoma
Neuron-specific enolase (NSE)	Neuroblastoma; Ewing sarcoma (some); desmoplastic small round cell tumor
Chromogranin	Neuroblastoma (often—in undifferentiated tumors); Ewing sarcoma (some)
Synaptophysin	Neuroblastoma (often—in undifferentiated tumors); Ewing sarcoma (some)
Cytokeratin	Synovial sarcoma; epithelioid sarcoma; angiosarcoma (epithelioid angiosarcoma); epithelioid hemangioendothelioma; desmoplastic small round cell tumor; leiomyosarcoma ~30%; extrarenal rhabdoid tumor
Epithelial membrane antigen (EMA)	Synovial sarcoma; epithelioid sarcoma; epithelioid angiosarcoma; epithelioid hemangioendothelioma; low-grade fibromyxoid sarcoma (some); perineurioma; angiomatoid fibrous histiocytoma
HMB45; Melan-A; tyrosinase	Melanotic schwannoma; clear cell sarcoma; PEComa
MDM2/CDK4	Atypical lipomatous tumor; dedifferentiated liposarcoma
Claudin-1	Synovial sarcoma; epithelioid sarcoma; perineurioma; Ewing sarcoma (some)
CD117 (c-kit); DOG 1	Gastrointestinal stromal tumor
MUC-4	Low-grade fibromyxoid sarcoma; sclerosing epithelioid fibrosarcoma
ALK	Inflammatory myofibroblastic tumor
β-catenin (aberrant nuclear expression)	Desmoid fibromatosis (normal cells with cytoplasmic staining)
INI-1 (loss of expression)	Proximal-type epithelioid sarcoma, extrarenal rhabdoid tumor, epithelioid malignant peripheral nerve sheath tumor (some)
STAT6	Solitary fibrous tumor
SOX10	Melanoma, clear cell sarcoma, nerve sheath tumor, granular cell tumor, myoepithelioma
TLE1	Synovial sarcoma, nerve sheath tumor (some)
CAMTA1	Epithelioid hemangioendothelioma
TFE3	Alveolar soft part sarcoma, epithelioid hemangioendothelioma
H3K27Me3	MPNST (loss of expression)

PEComa perivascular epithelioid cell tumor

Table 14.2 Selected soft tissue tumors with cytogenetic alterations and fusion gens that can be used for clinical purposes in diagnosis and/or therapy

Tumor	Cytogenetic aberration(s)	Genes (5′–3′)
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*EWSR1-CREB1*
	t(12;22)(q13;q12)	*EWSR1-CREB1*
	t(2;22)(q34;q12)	*FUS-ATF1*
		EWSR1-ATF1
Alveolar soft part sarcoma	der(X)t(X;17)(p11;q25)	*ASPSL-TFE3*
Clear cell sarcoma	t(12;22)(q13;q12)	*EWSR1-ATF1*
	t(2;22)(q33;q12)	*EWSR1-CREB1*
Dermatofibrosarcoma protuberans/giant cell fibroblastoma	t(17;22)(q21;q13)	*COL1A1-PDGFB*
Desmoid fibromatosis	Trisomy 8 and 20	*APC*
		CTNNB1
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
	t(21;22)(q22;q12)	*EWSR1-ERG*
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q23–25)	*WWTR1-CAMTA1*
Ewing sarcoma	t(11;22)(q24;q12)	*EWSR1-FLI1*
	t(21;22)(q22;q12)	*EWSR1-ERG*
	t(7;22)(p22;q12)	*EWSR1-ETV1*
	t(17;22)(q12;q12)	*EWSR1-ETV4*
	t(2;22)(q33;q12)	*EWSR1-FEV*
	t(16;21)(p11;q22)	*FUS-ERG*
	t(2;16) inv (22)	*FUS-FEV*
		EWSR1-ZSG
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWSR1-NR4A3*
	t(9;17)(q22;q11)	*TAF2N-NR4A3*
	t(9;17)(q22;q11)	*TCF12-NR4A3*
	t(3;9)(q11;q22)	*TFG-NR4A3*
Inflammatory myofibroblastic tumor	t(1;2)(q25;q23)	*TPM3-ALK*
	t(2;19)(q23;q13)	*TPM4-ALK*
	t(2;17)(q23;q23)	*CLTC-ALK*
	t(2;2)(p23;q13)	*RANBP2-ALK*
Infantile fibrosarcoma	t(12;15)(p13;q26)	*ETV6-NTRK3*
Atypical lipomatous tumor/well-differentiated liposarcoma	Ring chromosomes	*MDM2 amplification CDK4, HMGA2 often co-amplified*
	Giant marker chromosomes	
	Amplification 12q15 region	
Myxoid liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3*
	t(12;22)(q13;q12)	*EWSR1-DDIT3*
Low-grade fibromyxoid sarcoma	t(7;16)(tq33;p11)	*FUS-CREB3L2*
	t(11;16)(p11;p11)	*FUS-CREB3L1*
Myoepithelioma, soft tissue	t(19;22)(q13;q12)	*EWSR1-PBX*
	t(1;22)(q23;q12)	*EWSR1-POU5F1*
	t(6;22)(p21;q12)	*EWSR1-ZNF444*
Pseudomyogenic hemangioendothelioma	T(7;19)(q22;q13)	*SERPINE1-FOSB*
Rhabdomyosarcoma, alveolar	t(2;13)(q35;q14)	*PAX3-FOXO1A*
	t(1;13)(q36;q14)	*PAX7-FOXO1A*
	t(2;X)(p35;q13)	*PAX3-MLLT7*
	t(2;2)(q35;q23)	*PAX3-NCOAI*
Synovial sarcoma	t(X;18)(p11;q11)	*SS18-SSX1*
	t(X;18)(p11;q11)	*SS18-SSX2*
	t(X;18)(p11;q13)	*SS18-SSX4*
	t(X;20)(p11;q13)	*SS18L1-SSX1*
Tenosynovial giant cell tumor	t(1;2)(p13;q37)	*CSF1-COL6A3*
Undifferentiated round cell sarcoma	t(4: 19)(q35;q13.1)	*CIC-DUX4*
	t(10;19)(q26.3;q13)	*BCOR-CCNB3*

Reporting the Diagnosis and FNAC According to WHO Classification

The goal of a biopsy is to establish malignancy (sarcoma versus benign soft tissue lesion/neoplasm), to determine the histologic type (specific sarcoma versus metastasis or lymphoma), and to assess the histologic grade (dedifferentiated liposarcoma versus well-differentiated liposarcoma). Nomenclature and classification of soft tissue neoplasm used in daily clinical practice should be based on the WHO classification of soft tissue and bone neoplasms [1]. During the work-up of patients with soft tissue tumors, every effort should be made to establish a histological diagnosis and in case of sarcoma the histological grade. However, it is neither always possible nor necessary to reach a specific histology type of soft tissue sarcoma.

The necessary diagnostic level of an FNAC depends on treatment choice. For many sarcomas seated in the extremities or chest wall, primary wide radical resection is envisaged; in these instances, therefore, the most important information for treatment planning is the size and site of the mass and its proximity to vessels, nerve bundles, and bone. A correct diagnosis of sarcoma is a sufficient diagnostic level to plan surgical treatment. When neoadjuvant therapy (chemo- or radiotherapy) is the treatment option before surgery (e.g., pediatric sarcomas such as small blue round cell tumors and other high-grade sarcomas), the FNA diagnosis must include the correct histologic type and grade.

FNA diagnosis of a benign soft tissue neoplasm should also include histologic type or at least the basic histogenesis (e.g., lipomatous tumor, nerve sheath tumor, pseudosarcomas), as different benign tumors are managed differently. Most asymptomatic benign tumors (lipoma, nodular fasciitis) could be put for "wait and watch," and some are treated with limited excision (schwannoma, myxoma), whereas a few such tumors need a wider excision to prevent recurrence. At present, criteria for cytologic diagnosis have been thoroughly defined in a number of sarcomas and benign soft tissue neoplasms. To facilitate evaluation and treatment based on FNAC, a standardized reporting of FNA results is necessary. At Lund Sarcoma Centre, the following diagnostic categories are used:

- Benign (histologic type)
- Sarcoma (histologic type and grade)
- Malignancy other than sarcoma
- Inconclusive
- Insufficient

The main diagnosis of either *benign* or *sarcoma* should be given, whenever possible, supplemented with histologic type of the neoplasm and, in case of sarcoma malignancy, grade (low grade or high grade).

Inconclusive indicates inability to reliably determine whether a lesion is benign or malignant. *Insufficient* indicates a technically failed biopsy.

Grading of Soft Tissue Sarcomas in FNA

The most widely used sarcoma grading system on histology is the FNCLCC system based on tumor differentiation, mitotic rate, and tumor necrosis [21]. Recently, vascular invasion and pattern of peripheral growth (pushing/infiltrative) of sarcomas are also shown to be important prognostic parameters [22].

However, assessment of these parameters is not feasible in FNA samples. Nevertheless, in technically satisfactory specimens, it is often possible to categorize a sarcoma into morphologically low-grade or high-grade malignancy. In a subset of sarcomas, a specific histologic diagnosis rendered may determine the grade (see Fig. 14.3) [11, 23–27].

Diagnostic Accuracy

If FNA biopsy is performed in experienced hands and with adequate samples, the diagnostic accuracy is high. In a retrospective 20-year study of 517 soft tissue tumors (315 benign tumors and 202 sarcomas) from the Musculoskeletal Tumor Centre, Lund University Hospital, 28 false diagnoses (5%) were rendered including 14 false-positive and 14 false-negative diagnoses, an inconclusive diagnosis in 13 cases (3%), and insufficient for diagnosis in 29 tumors (6%) [28]. In published reports during the past 10 years, a correct classification of soft tissue tumors as benign or malignant has accuracy around 90%. In some reports, diagnostic accuracy of FNA can reach up to 97% [4, 5, 9, 29].

Limitations of FNA in the Diagnosis of Soft Tissue Tumors

The difficulties in diagnosing patients with musculoskeletal tumors stem mainly from their rarity and to the lack of experience with the microscopic appearances of soft tissue lesions on the part of most pathologists who are not subspecialized in soft tissue and bone pathology. Despite of the reported high degree of accuracy in distinguishing malignant soft tissue tumors from benign ones, FNAC has been less successful in establishing their histologic types and grades, compared to an excisional biopsy. There are three major limitations in FNA of soft tissue lesions: (1) sampling error (the tumor or the diagnostic area was missed), (2) insufficient or suboptimal material aspirated (poor yield, technically inferior

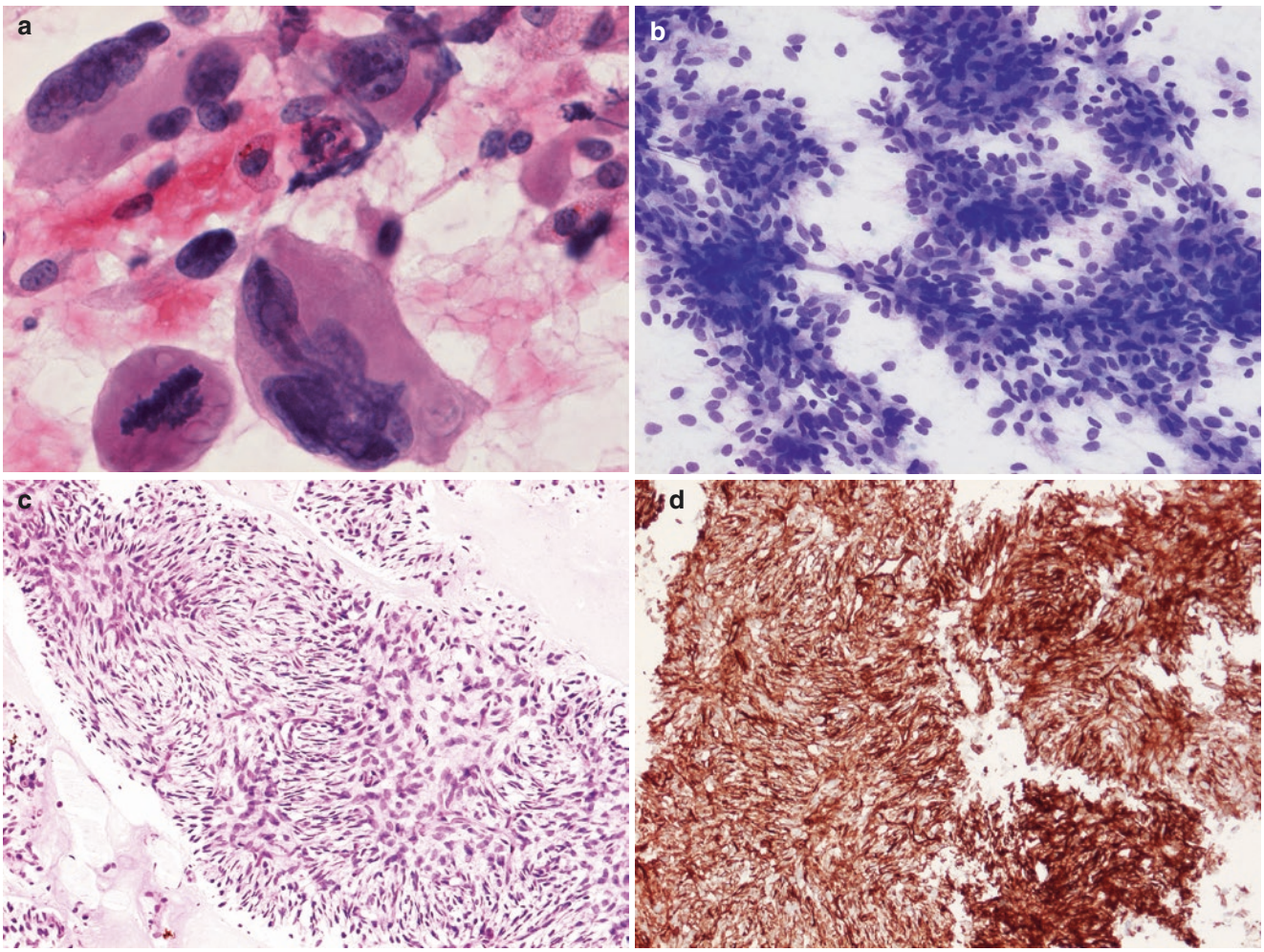

Fig. 14.3 Sarcoma grading in FNA. Grade of malignancy may be determined by histologic diagnosis. (**a**) High-grade undifferentiated pleomorphic sarcoma: high grade (grade 3/3) by definition. (**b**) Dermatofibrosarcoma protuberans: low grade (1/3) by definitions. Cell block facilitating tumor tissue architecture with typical storiform pattern (**c**) and immunoreactivity for CD34 (**d**) confirms the diagnosis (H&E; CD34)

smearing, necrosis or hemorrhage, or insufficient material for diagnostic ancillary studies), and (3) misinterpretation of the material (rare or new entities).

Complications of FNA of Soft Tissue Tumors

Complications of a correctly performed FNA in examination of soft tissue and bone lesions are minor and include small hematomas and localized tenderness. The risk of tumor cell spread in needle tracts must be addressed. This complication is strongly related to the needle size and the number of passes performed; using regular 22–25 gauge needles, for example, the incidence of this event is exceedingly low [30, 31]. To prevent this complication, the same needle insertion point is recommended for several punctures when sampling a suspected sarcoma. Tattooing of the needle insertion point helps to remove the needle track during surgery (see Figs. 1.55 and 1.56) [17].

Normal Elements

Fibroblasts/Myofibroblasts

Fibroblasts are spindle-shaped cells with slender contours, containing ovoid or rounded nuclei with fine, evenly distributed chromatin and inconspicuous nucleoli. Well-preserved fibroblasts show unipolar or bipolar cytoplasmic processes (see Fig. 14.4a). Bare nuclei are also common findings in smears. In reactive connective tissue, fibroblasts/myofibroblasts present as fusiform, rounded, or triangular cells of variable sizes, with enlarged, irregular nuclei, and occasionally coarse chromatin and prominent macronucleoli. In addition, reactive fibroblasts/myofibroblasts contain frequently abundant cytoplasm with one to several processes or angulated cytoplasmic extensions (see Fig. 14.4b–d). Binucleated cells are also common.

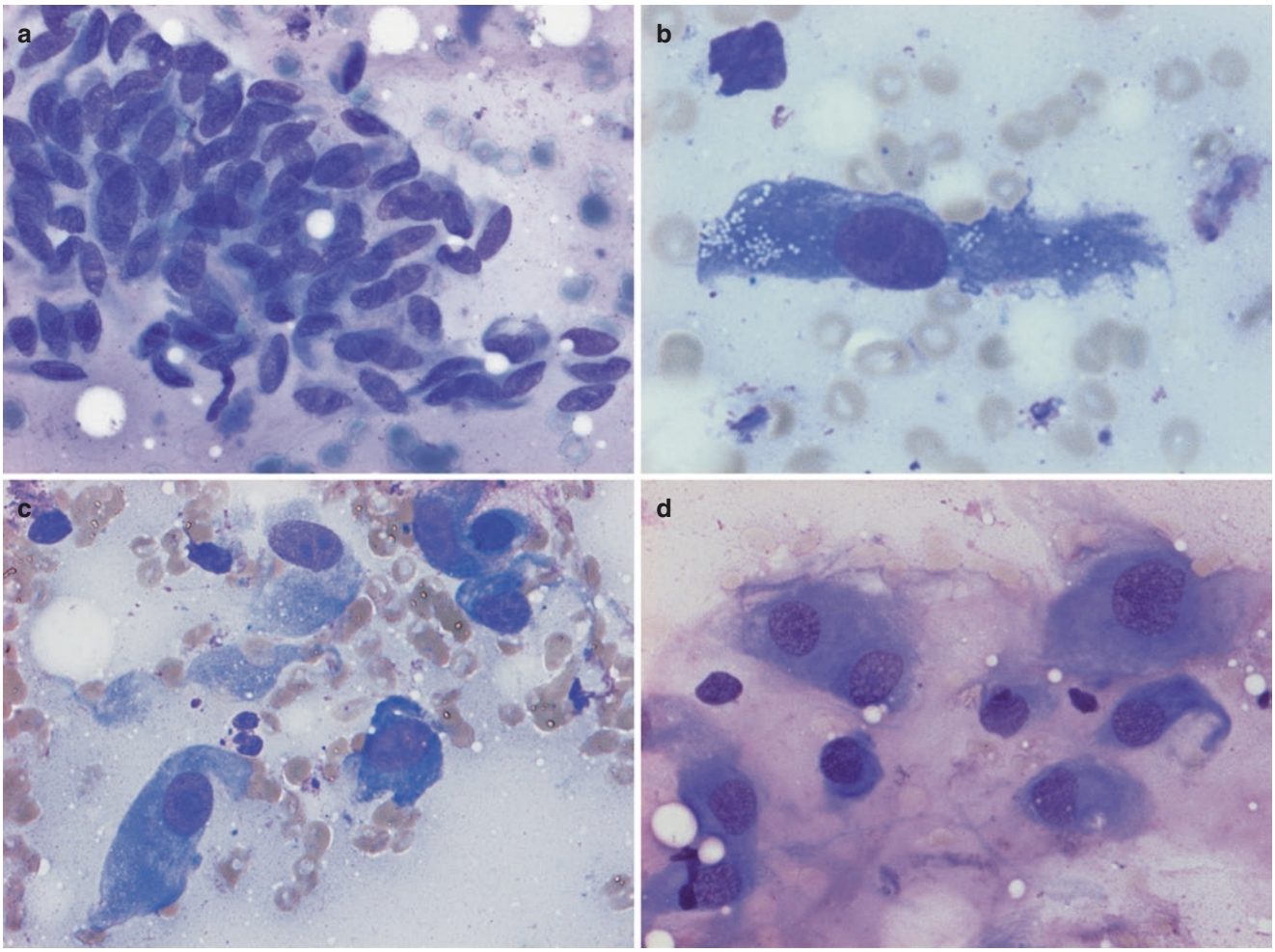

Fig. 14.4 Fibroblasts/myofibroblasts. (**a**) Loose cluster of well-preserved fibroblasts with uniform spindle-shaped nucleoli and cytoplasmic processes (MGG). (**b–d**) Reactive fibroblasts/myofibroblasts with enlarged nuclei, macronucleoli, and abundant cytoplasm with one to several processes or angulated cytoplasmic extensions (MGG; H&E)

Fat Tissue

Normal fat tissue in FNA smears occurs as clusters of fat cells with abundant univacuolated cytoplasm and peripherally situated small nuclei. Slender capillaries are frequent findings in the clusters (see Fig. 14.5a). Smears from reactive fat tissue may show a myxoid background, increasing numbers of fibroblasts and endothelial cells, and occasionally adipocytes with a multivacuolated cytoplasm resembling lipoblasts (see Fig. 14.5b–e). Histiocytes with vacuolated or foamy cytoplasm seen in reactive fat or fat necrosis may be occasionally difficult to distinguish from hibernoma cells.

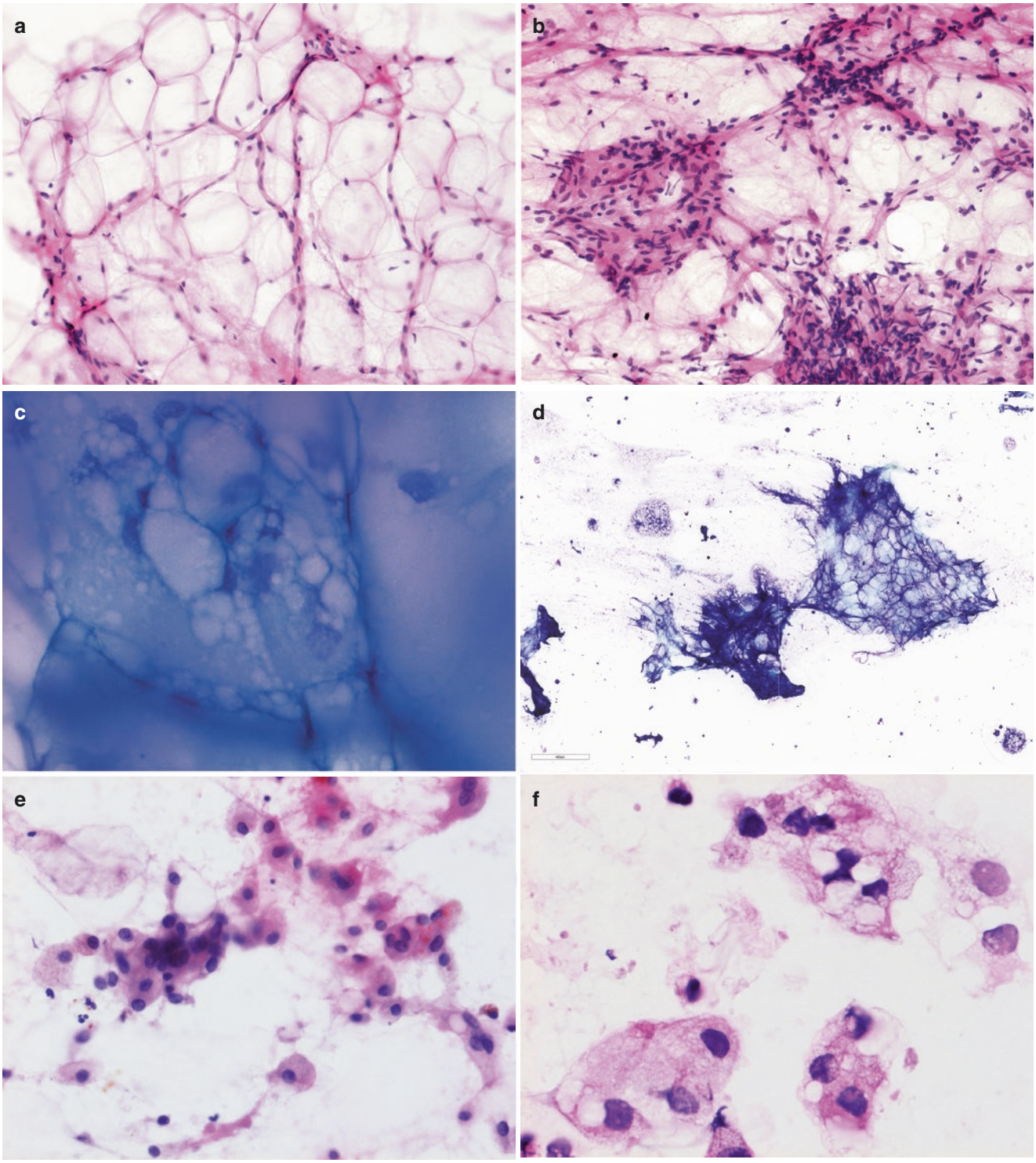

Fig. 14.5 Fat tissue. (**a**) Normal fat tissue. Clusters of adipocytes with abundant univacuolated cytoplasm and peripherally situated small nuclei. (**b**) Smears from reactive adipose tissue: an increasing number of fibroblasts and endothelial cells (H&E). Occasional myxoid background (**c**, **d**) (MGG) histiocytes (**e**) and adipocytes (**f**) with a multivacuolated cytoplasm resembling lipoblasts (H&E)

Striated Muscle

Muscle fibers are pink or amphophilic on Papanicolaou staining, eosinophilic with hematoxylin and eosin (H&E), and deep blue in May–Grünwald–Giemsa (MGG)-stained preparations. Peripherally placed small nuclei and cross-striations may be observed occasionally (see Fig. 14.6). Damaged and regenerating striated muscle fibers appear in smears as multinucleated cells with varying shapes of "muscle giant cells," which have nuclei arranged in rows or eccentrically placed. Nucleoli may be large and prominent (see Fig. 14.7).

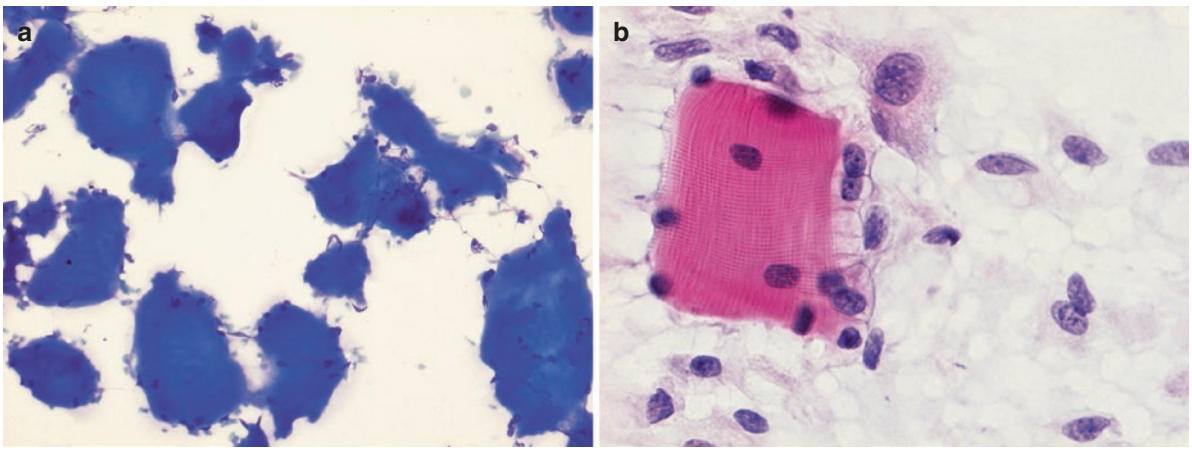

Fig. 14.6 Striated muscle. (**a**, **b**) Muscle fibers are deep blue in MGG and eosinophilic in H&E stainings. Note peripherally placed small nuclei and cross-striations (MGG; H&E)

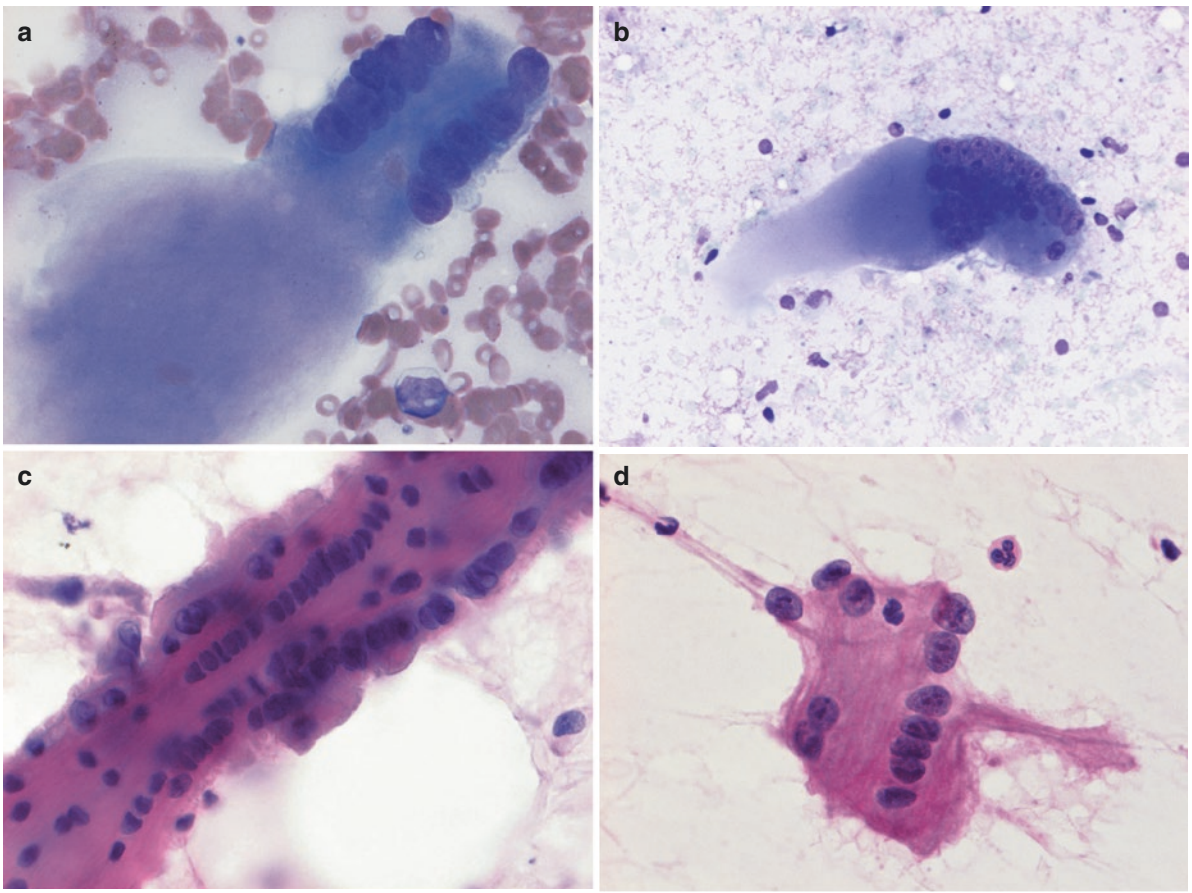

Fig. 14.7 Damaged and regenerating striated muscle. (**a**–**d**) "Muscle giant cells" with nuclei arranged in rows or eccentrically placed and prominent nucleoli (MGG; H&E)

Nonneoplastic Soft Tissue Tumors

Pseudosarcomatous Proliferations

Relatively common soft tissue lesions constitute several entities, which are mimics of malignant spindle-cell and pleomorphic neoplasms. These benign proliferations can pose considerable diagnostic difficulties in FNAC [32], as smears are usually cellular and contain proliferating fibroblasts and myofibroblasts with a wide variation in size and shape of the nuclei. Spindle-shaped cells with cytoplasmic processes and fusiform nuclei are the most common cell type, but plump cells with ovoid, rounded, or irregular nuclei are also present. Despite hypercellularity and nuclear pleomorphism throughout the smears, the chromatin in all cells is finely granular. Another typical finding is the presence of polyhedral or triangular cells with abundant cytoplasm and one or two rounded nuclei at the periphery near the cytoplasmic membrane, resembling ganglion cells.

Nodular Fasciitis

Nodular fasciitis (NF) is a self-limited, benign pseudosarcomatous proliferation that arises usually in the subcutaneous tissues of the upper limbs, trunk, and head and neck but can occur at almost any anatomical location. NF is a rapidly (over a period of weeks) growing lesion which most often is painful or tender. Minority of patients report history of trauma. The lesion is usually small and rarely bigger than 5 cm. NF is most common in young adults but can affect all age groups including children, and a subset of NF-cranial fasciitis arises mostly in infants. NF is composed of fibroblasts and myofibroblasts showing variable degrees of anisocytosis and anisokaryosis (see Fig. 14.8). Because of the above mentioned clinical presentation, most nodular fasciitis is needled at its early phase. In this phase, the matrix is often myxoid, occasionally giving the impression of a low-grade myxoid sarcoma such as myxofibrosarcoma (see Fig. 14.9). Persistent NF often yields smears containing

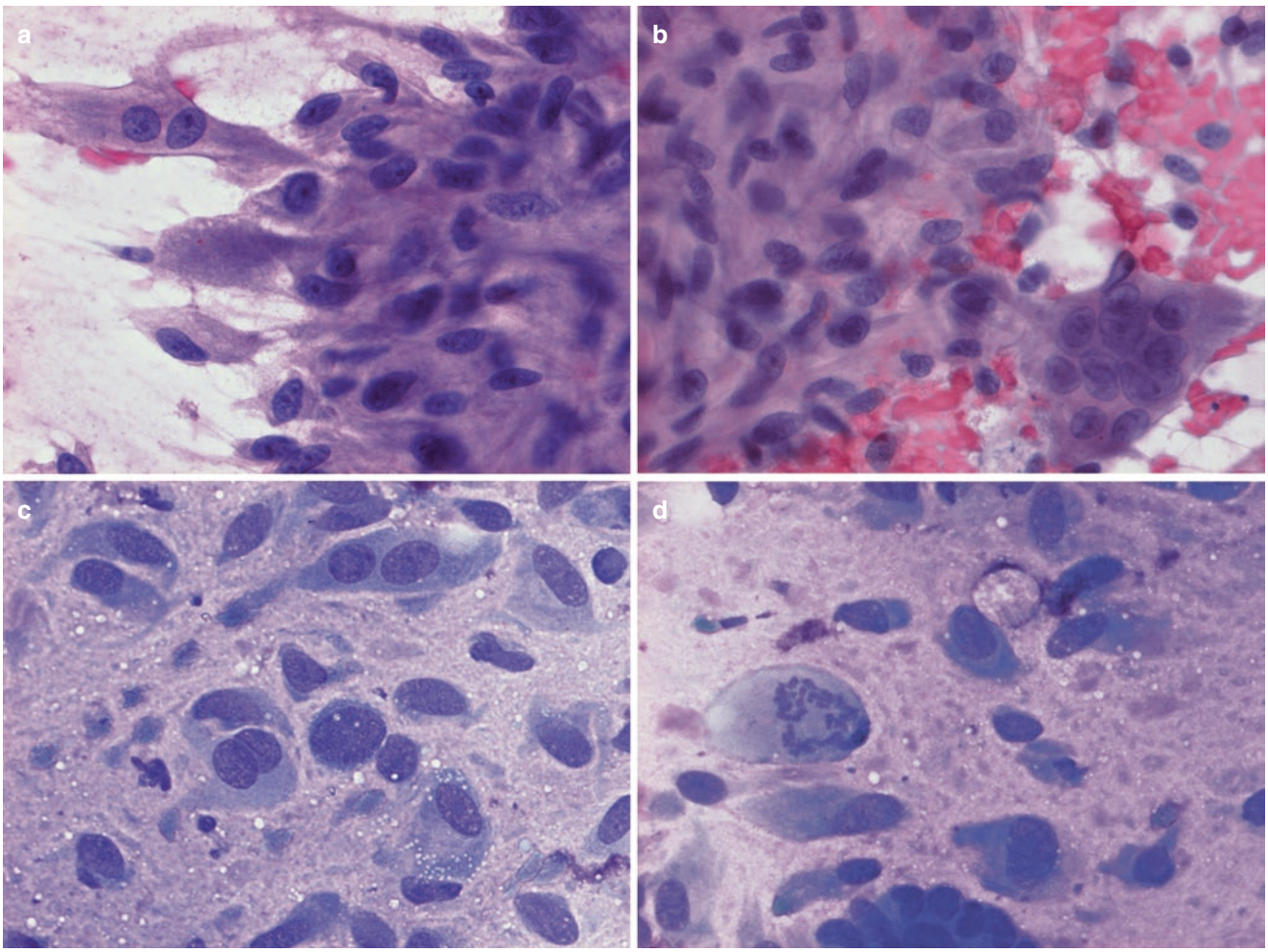

Fig. 14.8 Nodular fasciitis. (**a**) Cellular clusters of spindle-shaped myofibroblasts with cytoplasmic processes and fusiform nuclei showing variable degrees of anisocytosis and anisokaryosis. (**b**) Occasional osteoclast-like giant cells (H&E). (**c**, **d**) Dispersed spindle and plump cells with ovoid, irregular nuclei, abundant cytoplasm, and occasional mitoses (MGG)

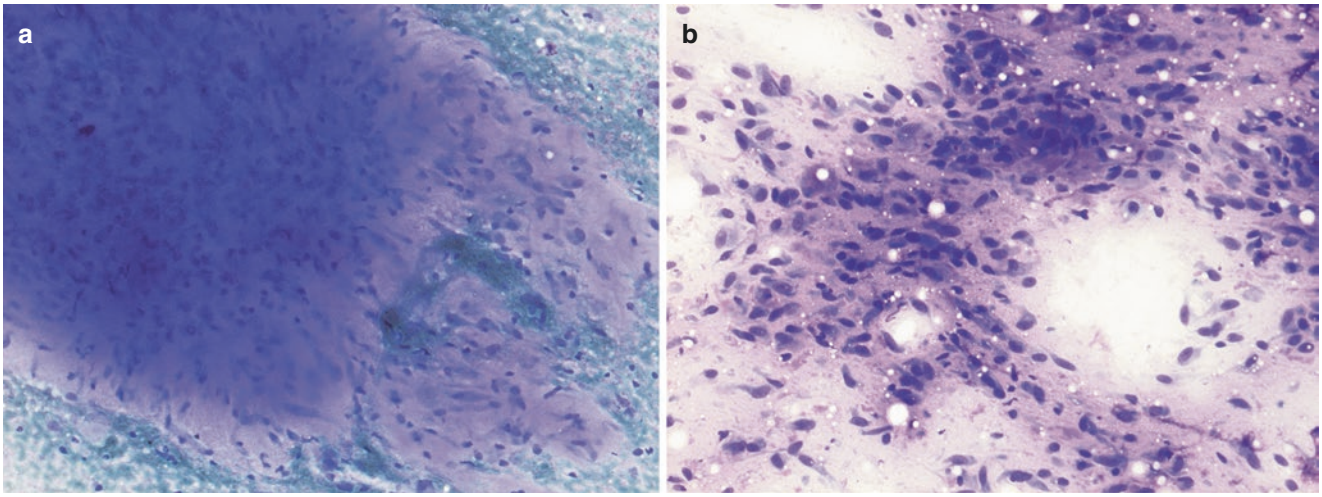

Fig. 14.9 Nodular fasciitis. (**a**, **b**) Clusters of spindle cells or dispersed spindle cells and some inflammatory cells in a prominent myxoid background (MGG)

relatively uniform, haphazardly arranged myofibroblasts producing a so-called cell culture appearance. Collagenous matrix is often present (see Fig. 14.10). The vast majority of NFs regress spontaneously, and a "wait and see" treatment option is indicated in cases with a typical clinical presentation and when characteristic cytomorphology is seen in FNA smears [32–35].

Nodular fasciitis expresses diffuse SMA and calponin positivity, occasionally focal desmin and CD68 positivity but not keratins, CD34, β-catenin, and S-100. The traditional view of nodular fasciitis as a reactive condition has been changed recently as cases of fasciitis which display a balanced translocation t(17;22)(p13;q13) resulting in a *MYH9-USP6* gene fusion have been reported. The fusion is highly indicative of the diagnosis and leads to upregulation of USP6 which is involved in cell signaling and movement and can be detected in both fresh and fixed material using cytogenetics, FISH, PCR, and NGS.

Cytologic features:
- Cellular aspirates
- Myxoid background matrix
- Dispersed spindle cells mixed with clusters and sheets of spindle cells
- Cell culture-like appearance
- Variable anisocytosis and anisokaryosis
- Ganglion-like cells
- Admixture of inflammatory cells and histiocytes
- Occasional multinucleated giant cells
- Mitoses

Differential diagnosis and problems in diagnosis:
- Pleomorphic, spindle-cell, and myxoid sarcomas
- Desmoid fibromatosis

The related pseudosarcomatous lesions include proliferative fasciitis and proliferative myositis, which develop predominantly in adults. Proliferative myositis commonly arises in the trunk, whereas proliferative fasciitis is more common in the extremities. Both proliferative fasciitis and myositis share many cytologic features with nodular fasciitis. However, the myxoid background matrix is less prominent, and the ganglion-like cells are usually numerous and often exhibit large nucleoli in proliferative fasciitis (see Fig. 14.11). In proliferative myositis, smears contain multinucleated regenerating muscle fibers in addition to the fibroblastic–myofibroblastic cells (see Fig. 14.12a, b). Mitotic figures can be found in both smears (see Fig. 14.12c).

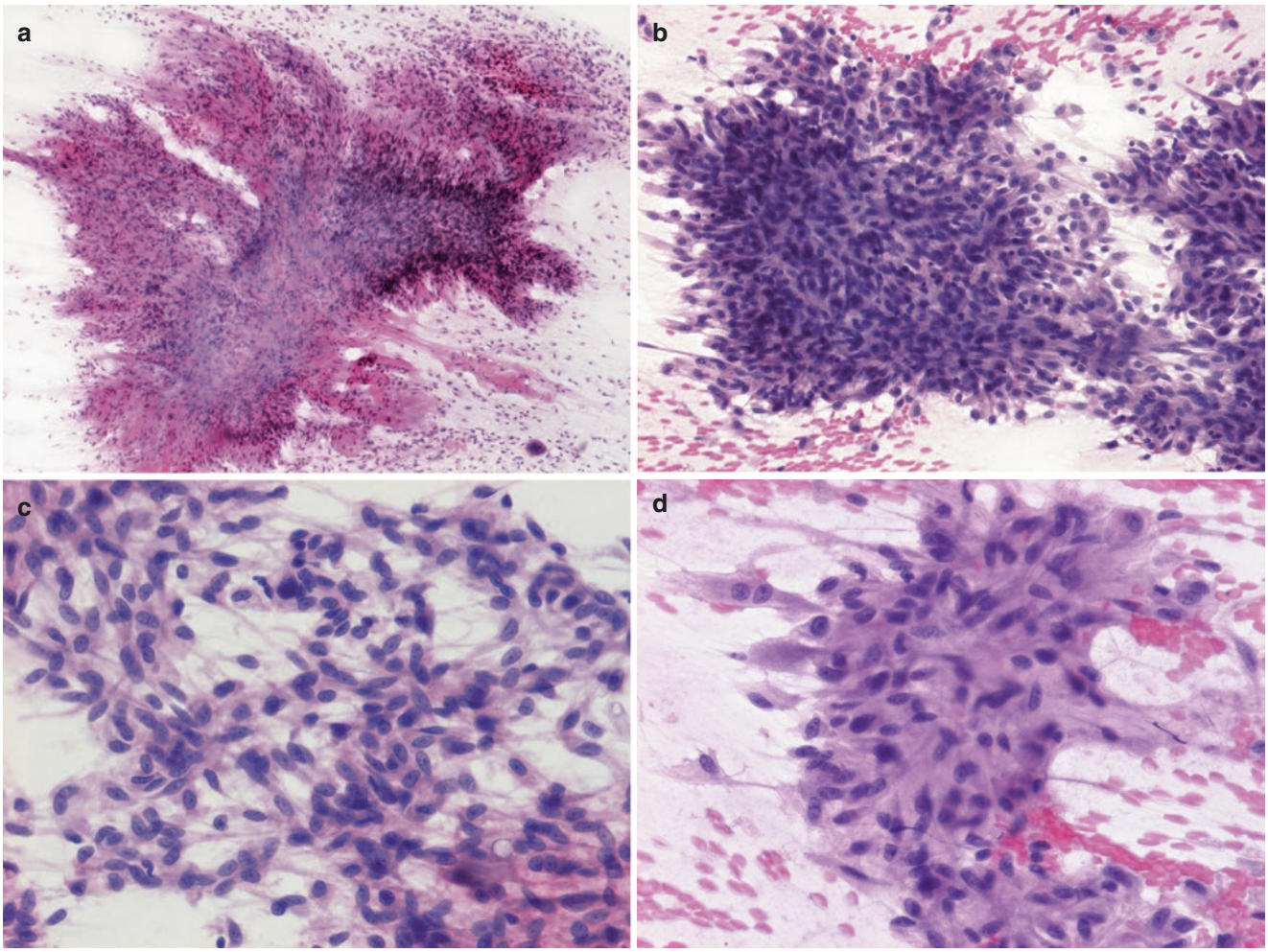

Fig. 14.10 Nodular fasciitis. (**a**) Cluster of myofibroblasts embedded in collagenous matrix. (**b**–**d**) Loosely cohesive and dispersed relatively uniformed myofibroblasts resembling the so-called cell culture appearance (H&E)

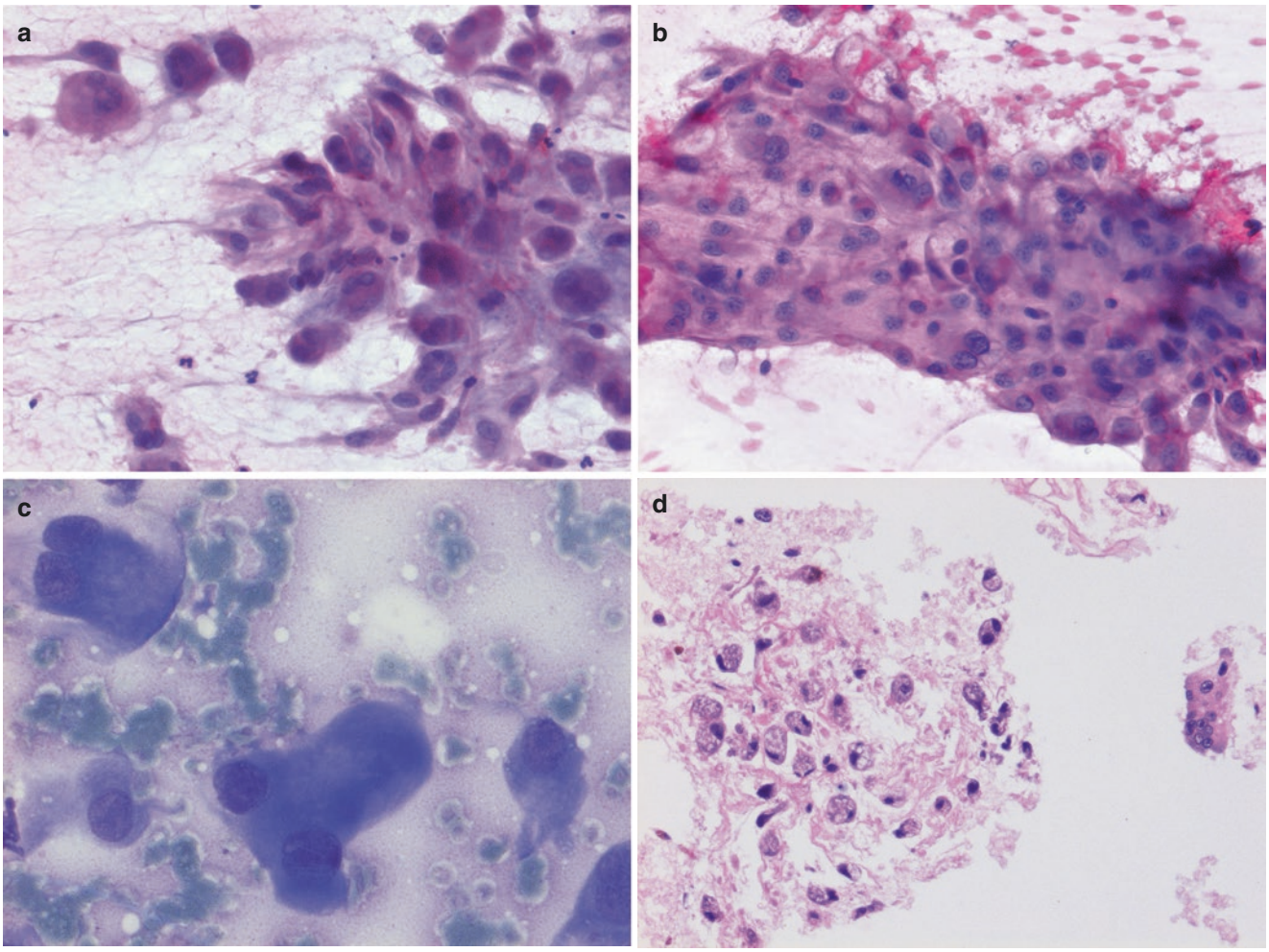

Fig. 14.11 Proliferative fasciitis. (**a–c**) Loosely cohesive clusters or dispersed relatively pleomorphic cells with round to oval and spindle-shaped nuclei. Note the admixture of numerous ganglion cell-like cells with binucleation and abundant cytoplasm (H&E; MGG). (**d**) Cell block section with ganglion-like cells and multinucleated osteoclast-like cell (H&E)

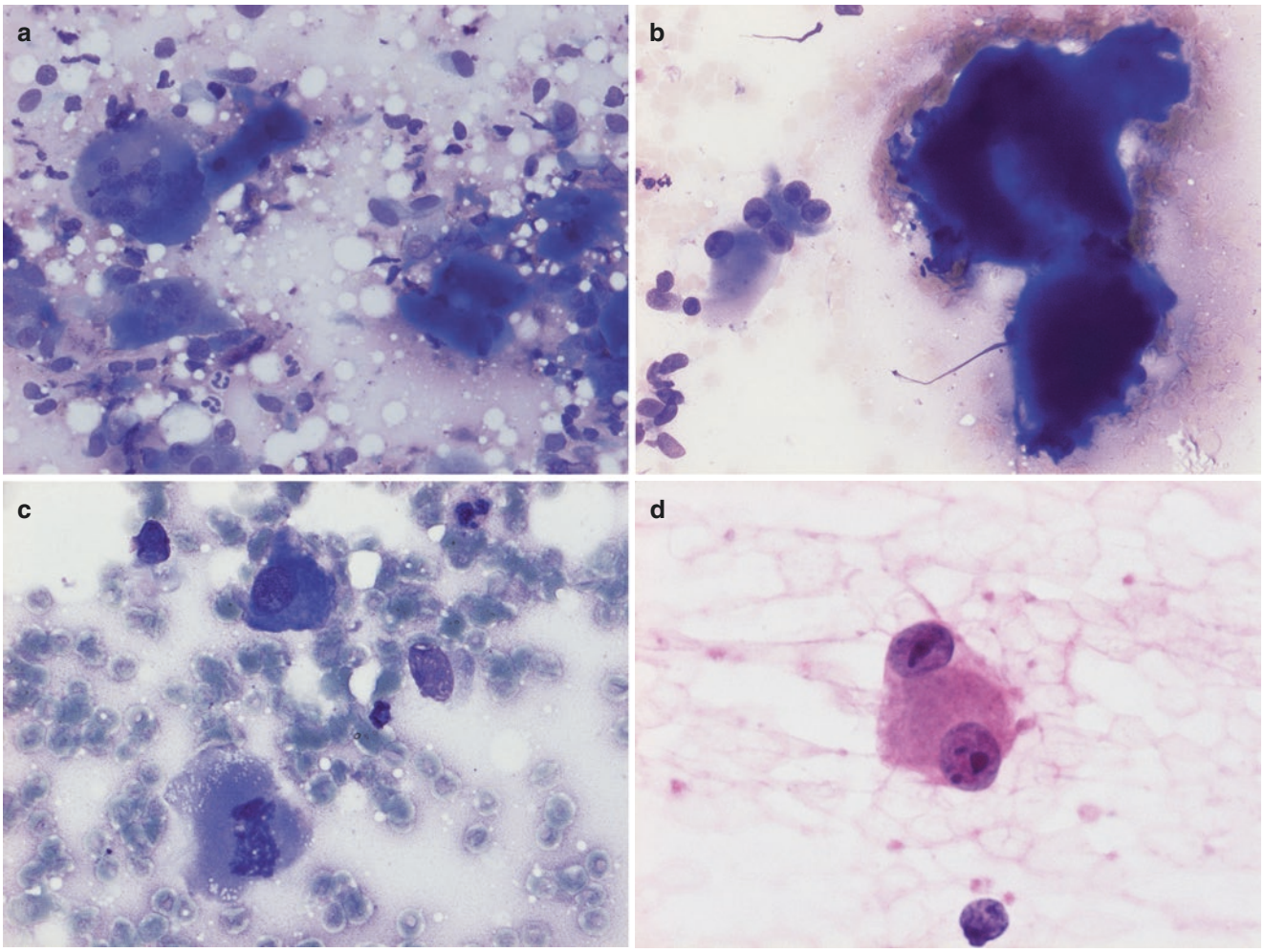

Fig. 14.12 Proliferative myositis. (**a**, **b**) Dispersed fibroblastic–myofibroblastic cells with admixture of muscle fragments, multinucleated giant cells, and regenerating muscle fibers. (**c**) Mitotic figures can be occasionally found in the smears (MGG). (**d**) Bi-nucleated ganglion-like cells (H&E)

Myositis Ossificans

Myositis ossificans (MO) is a rapidly growing soft tissue lesion, which is often mistaken clinically as sarcoma especially extraskeletal osteosarcoma. It most often arises in the subcutaneous tissue or musculature of the extremities in young adults. The mass is often tender and presents ossification in a zonal pattern. The characteristic cytologic finding is the mixture of proliferating fibroblasts/myofibroblasts, osteoblasts, osteoclast giant cells, occasionally regenerating muscle fibers ("muscle giant cells") (see Fig. 14.13), and rarely bone fragments. MO may resolve spontaneously some weeks/months after FNA examination [36].

Cytologic features:

- Proliferating spindle cells—fibroblasts/myofibroblasts with variable anisocytosis and anisokaryosis
- Osteoblasts, often with reactive changes
- Osteoclasts
- Muscle "giant cells"
- Occasionally small calcifications
- Rare mitoses

Differential diagnosis and problems in diagnosis:

- Pleomorphic soft tissue sarcoma
- Extraskeletal osteosarcoma

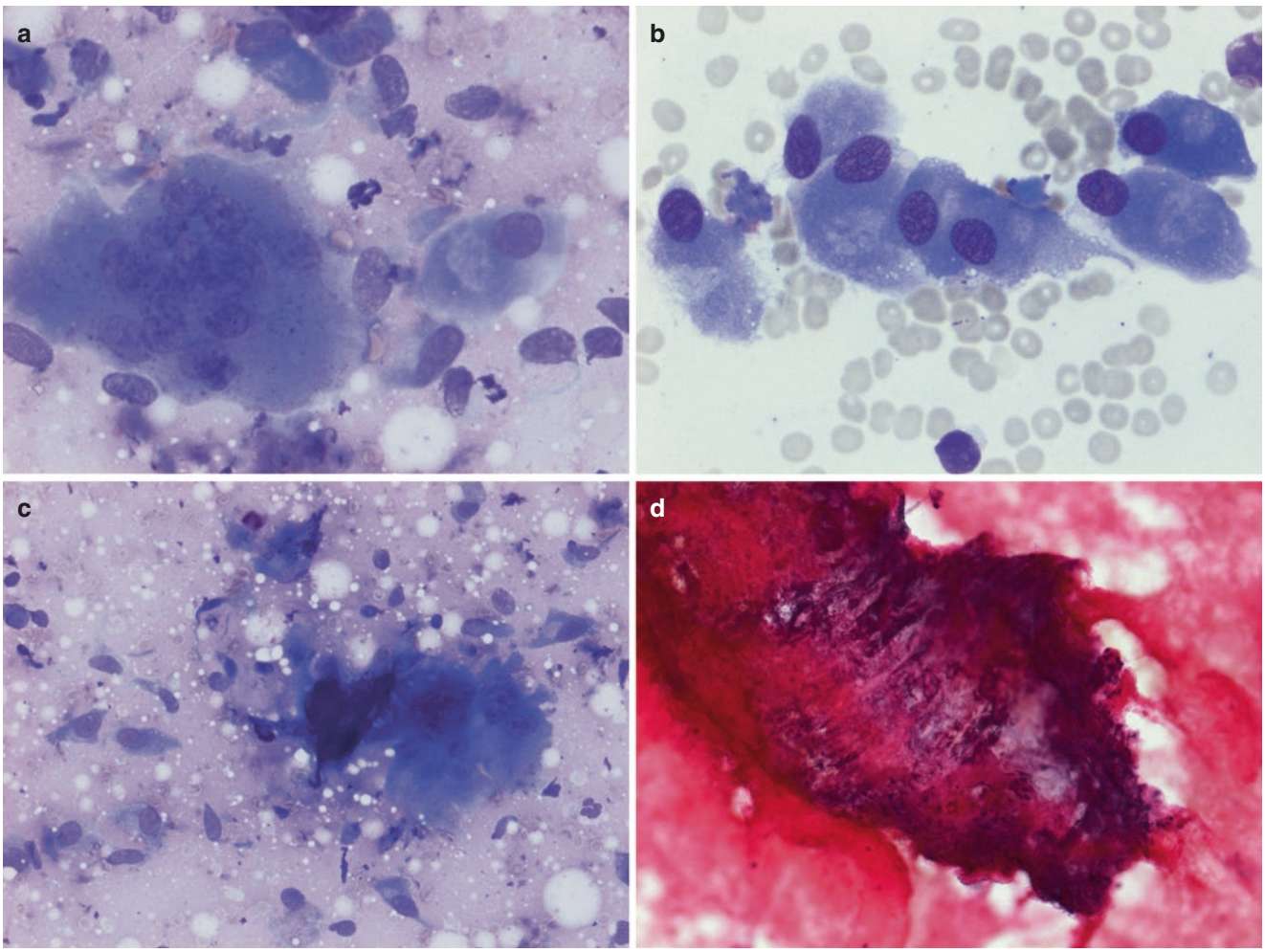

Fig. 14.13 Myositis ossificans. (**a**–**c**) Mixture of proliferating myofibroblasts, osteoblasts, and osteoclast-like giant cells (MGG) without cytologic atypia. (**d**) Rarely bone fragments (H&E)

Ischemic Fasciitis (Atypical Decubital Fibroplasia)

Ischemic fasciitis is a reactive process arising as a poorly circumscribed, non-ulcerated mass in the deep subcutaneous tissue and is usually associated with chronic pressure of areas over the bone. Ischemic fasciitis is composed of large ganglion-like cells, fibroblasts, and myofibroblasts set in a myxoid stroma. In addition, smears may contain inflammatory cells, necrotic debris, and cells with large, irregular nuclei and dense and smudged chromatin (see Fig. 1.53).

Amyloidoma (Tumoral Amyloidosis)

Amyloidoma is an uncommon lesion caused by amyloid deposition and not necessarily associated with systemic amyloidosis. Soft tissue and bone amyloidomas are very rare [37, 38]. Smears are hypocellular and contain fragments of amorphous material, with admixed bland fibroblasts and occasional calcifications (see Fig. 14.14).

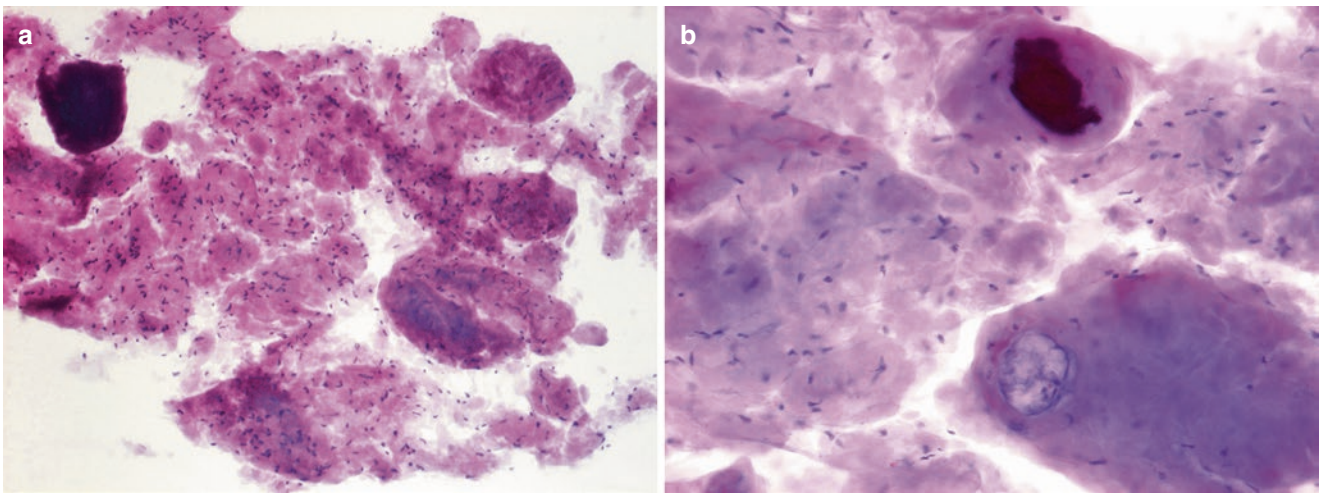

Fig. 14.14 Tumoral amyloidosis. (**a**, **b**) Deposition of amorphous material with bland fibroblasts and calcifications (H&E)

Gout

Disturbed uric acid metabolism results in gout tophi, which is defined by monosodium urate crystal deposition in the joint spaces and/or in the soft tissue adjacent to the joints. Laboratory tests showing an elevated serum uric acid level and microscopic examination of joint effusions help to establish the diagnosis. FNA cytologic diagnosis of soft tissue gout tophi can be easily rendered because monosodium urate crystals are readily identifiable on smears with or without polarized light (see Fig. 14.15) [39].

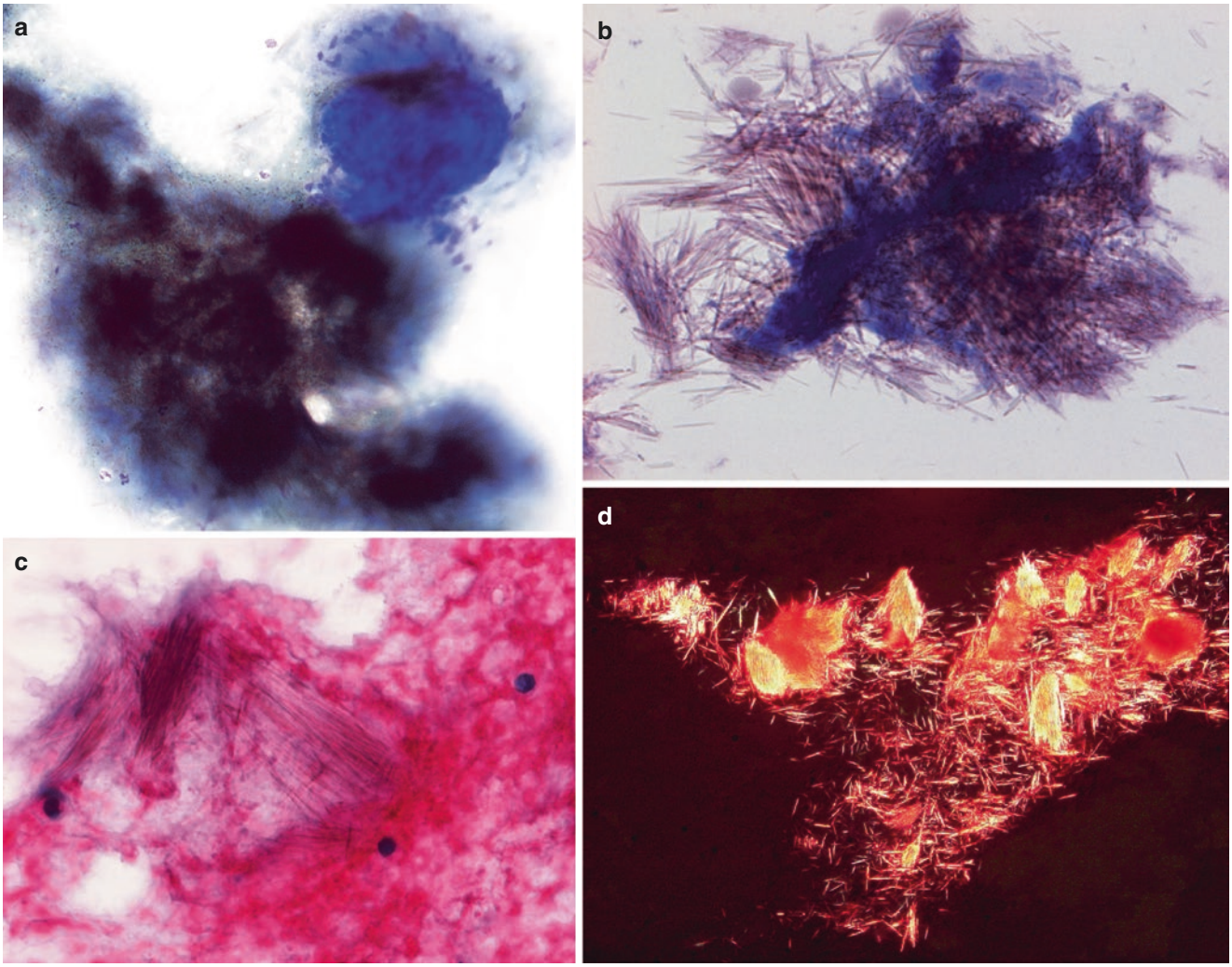

Fig. 14.15 Gout. (**a**) In low-power view, brown-stained sheath of crystals with adjacent multinucleated giant cells (MGG). (**b**–**d**) Monosodium urate crystals are easily identified in high power with (**d**) or without polarized light (MGG; H&E)

Benign Adipocytic Tumors

Lipoma

Lipomas, the most common soft tissue tumor of adults, usually present as slowly growing, solitary or multiple, subcutaneous masses and can be occasionally deeply seated (intramuscular or intermuscular lipoma). They are composed of mature adipose tissue but may include other connective tissue elements and regressive/degenerative areas, which may cause difficulties in FNA examination.

Cytologic features:
- Fatty tissue fragments composed of adipocytes containing a single fat vacuole and a small, dark, peripheral nucleus
- Variable number of capillaries within the fatty tissue fragments
- Few dissociated adipocytes
- Fragments of striated muscle or regenerating muscle in inter-/intramuscular lipoma
- Occasional myxoid matrix
- Rarely metaplastic cartilage/bone

Aspirates from lipoma are identical to those from normal adipose tissue. It is important to ensure that the needle is placed within the mass to avoid contamination with subcutaneous fat during the biopsy of a deeply seated mass.

Angiolipoma

Angiolipomas are subcutaneous lipomatous tumors. They are often multiple and tender at palpation. Most angiolipomas are smaller than 2 cm. An angiolipoma should be suspected when the tumor is small and tender at palpation, in conjunction with the FNA findings of numerous branching capillary vessels within the fat tissue fragments.

Lipoblastoma/Lipoblastomatosis

This tumor of infancy most commonly involves the extremities and presents with either a well-circumscribed subcutaneous tumor (lipoblastoma) or a deep-seated, diffusely infiltrative, ill-defined mass (lipoblastomatosis). Histologically composed of immature fat with mesenchymal, myxoid, and fibrotic areas, the tumor is thought to be capable of maturation to a common lipoma. The typical features include small uniform adipocytes with vacuolated cytoplasm and round uniform nuclei in a myxoid background matrix, admixed with branching strands of capillaries [40–42] (see Fig. 14.16). Smears may also be dominated by large ordinary univacuolated adipocytes. Although lipoblastoma mimics myxoid liposarcoma cytomorphologically, two tumors occur in different age groups: lipoblastoma in boys younger than 3 years old and myxoid liposarcoma in young adults [41].

Cytologic features:
- Fatty tissue fragments with variable amounts of myxoid matrix
- Branching strands of thin capillaries
- Few dissociated adipocytes
- Occasionally uni- or multivacuolated lipoblast-like cells
- Occasionally hibernoma-like cells

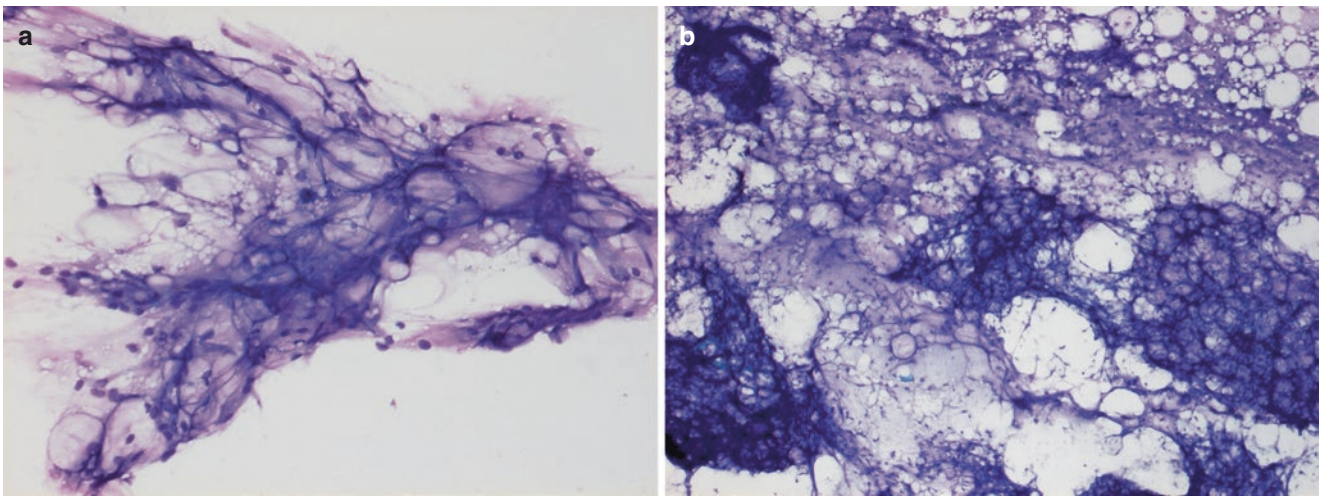

Fig. 14.16 Lipoblastoma. (**a**, **b**) FNA smears contain large fragments of fatty tissue with variable amounts of myxoid matrix and branching strands of thin capillaries (MGG)

Spindle-Cell/Pleomorphic Lipoma

These two benign lipomatous tumors share very similar clinical, morphologic, and cytogenetic features and represent a morphologic continuum. For both tumors, the typical clinical setting is a subcutaneous tumor in the posterior neck region, upper back, and over the shoulders in middle-aged men. Head and mouth areas, including tongue and orbit, are less common sites.

The cytomorphology of spindle-cell lipoma is often distinct, although proportions of different elements vary from case to case. The smears contain fat fragments mixed with fascicles of uniform spindle cells with elongated, uniform nuclei and collagen fibers, often in a myxoid background matrix (see Fig. 14.17) [43]. The characteristic finding of pleomorphic lipoma is the presence of floret cells: multinucleated giant cells with hyperchromatic nuclei and a moderate amount of cytoplasm (see Fig. 14.18).

Cytologic features of spindle-cell lipoma:

- Mixture of mature adipose tissue and dispersed or clustered, bland spindle cells
- Fragments of brightly eosinophilic (H&E) collagen–hyaline fibers
- Myxoid background common
- Mast cells (particularly in cases with the myxoid background)

Differential diagnosis and problems in diagnosis:

- Schwannoma
- Dermatofibrosarcoma protuberans
- Low-grade myxofibrosarcoma
- Myxoid liposarcoma

Cytologic features of pleomorphic lipoma:

- Fragments of mature fat
- Variable number of floret cells
- Variable number of spindle cells
- Occasionally myxoid background matrix
- Occasionally mast cells

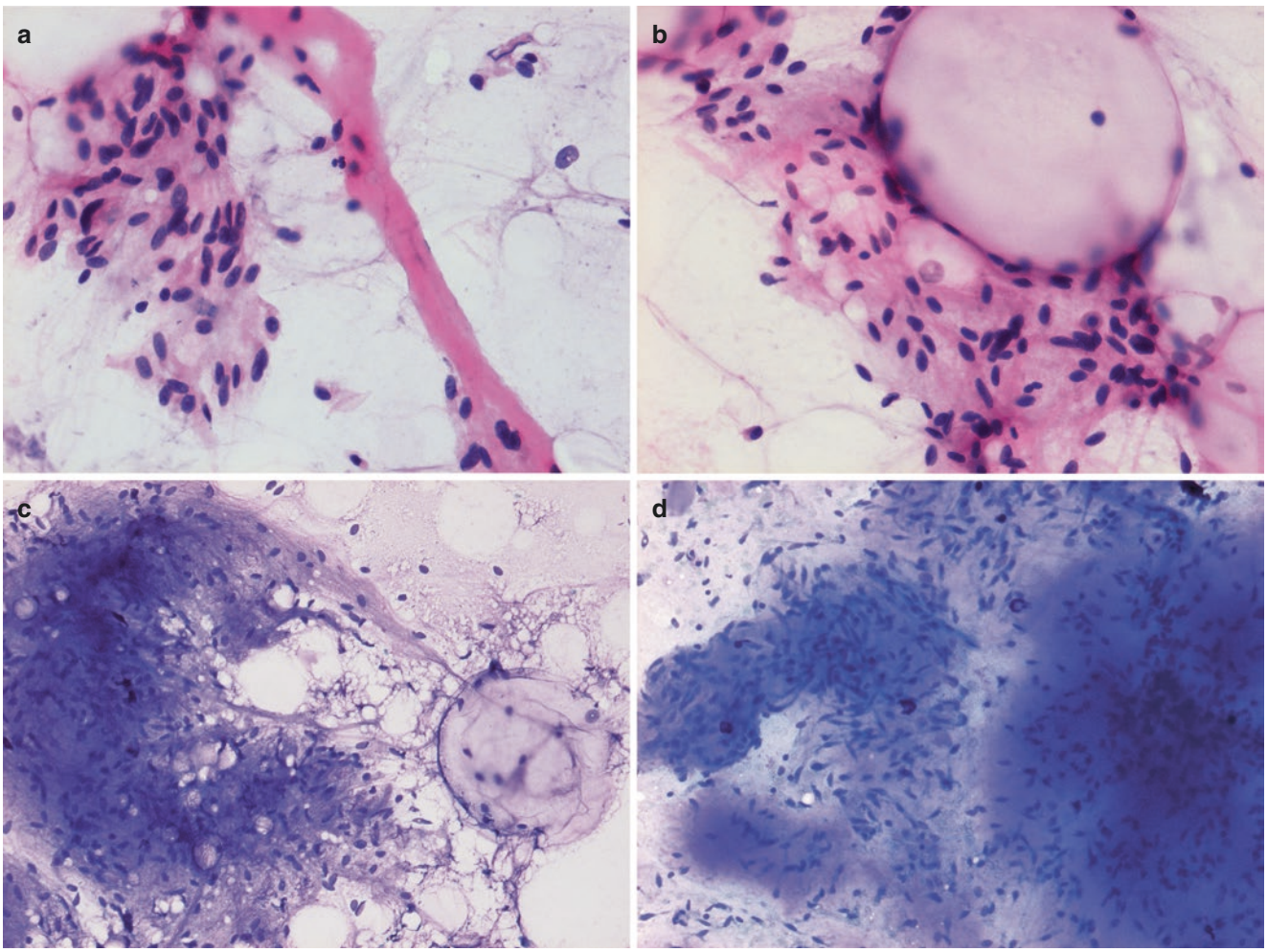

Fig. 14.17 Spindle-cell lipoma. (**a**, **b**) Mixture of loosely cohesive clusters and dispersed bland spindle cells, mature adipose tissue, and fragments of brightly eosinophilic collagen–hyaline fibers (H&E). (**c**, **d**) Myxoid background and mast cells are common (MGG)

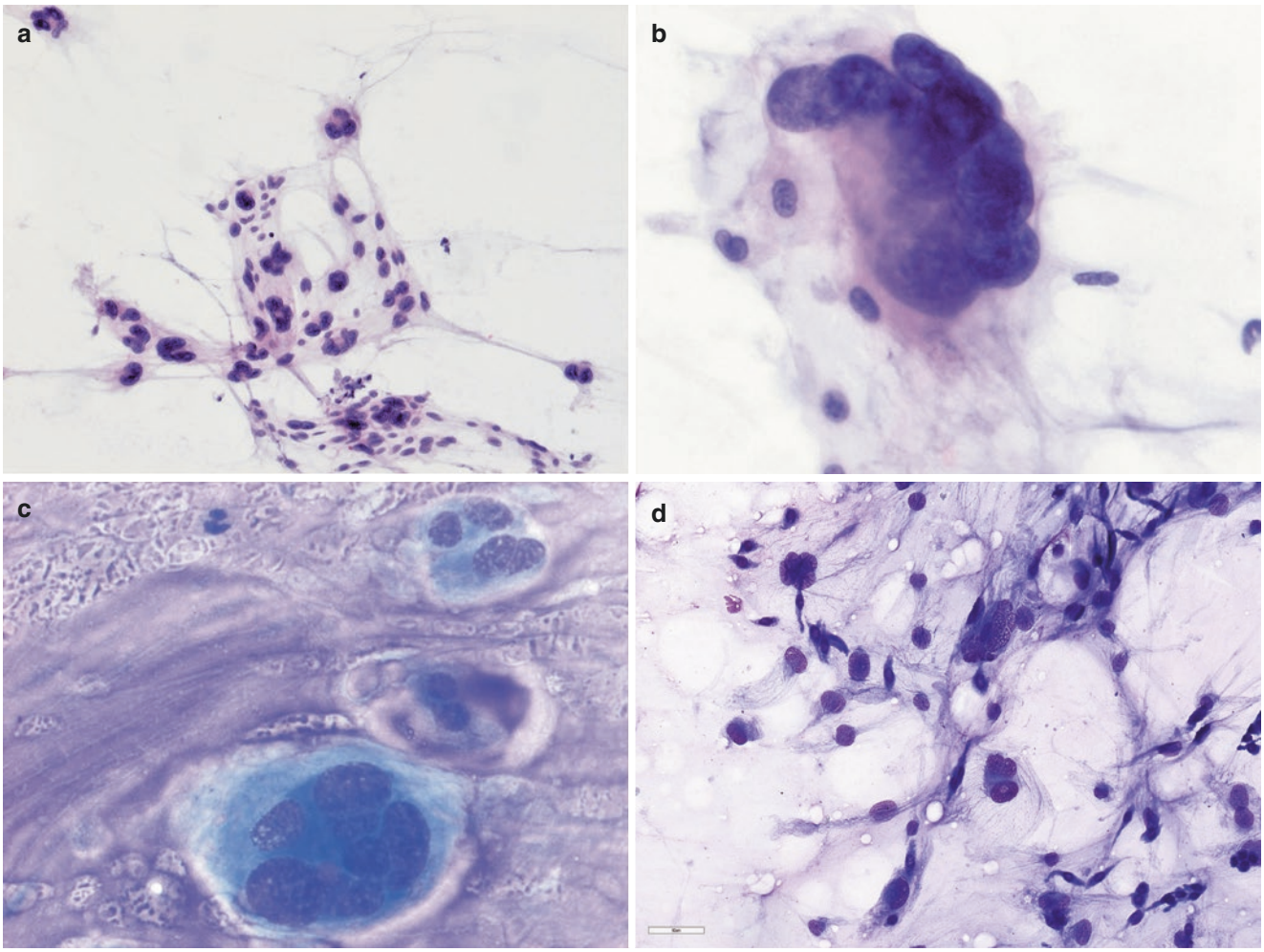

Fig. 14.18 Pleomorphic lipoma. (**a**) In scanning power fragments of mature fat, variable number of floret cells and spindle cells (H&E). (**b–d**) Floret cells and occasionally prominent myxoid background matrix (MGG)

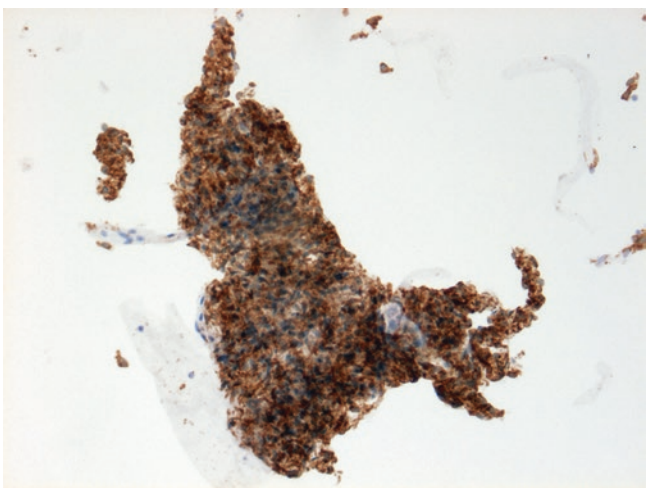

Fig. 14.19 Spindle-cell lipoma. Positive CD34 staining in the spindle-cell component (ThinPrep)

Differential diagnosis and problems in diagnosis:

- Well-differentiated liposarcoma (atypical lipomatous tumor)

A diagnostically important but variable sign in smears is the presence of fragments of eosinophilic (H&E) collagen–hyaline fibers. Depending on the areas sampled from this very heterogenous tumor, aspirates from spindle-cell lipoma may show a predominance of adipose tissue fragments or a predominance of spindle-cell fascicles or an abundant myxoid matrix. In addition to floret cells, smears from pleomorphic lipomas may contain collagen fibers and areas of myxoid stroma similar to spindle-cell lipoma. Hybrid forms with both spindle and pleomorphic lipoma features are not uncommon. The spindle cells are positive for CD34 (see Fig. 14.19) and negative for S-100 protein.

Hibernoma

Hibernoma is a rare lipomatous tumor of brown fat derivation. It is commonly situated in the interscapular region, on the back or chest wall (sites of normal deposits of brown fat), but can also occur in the extremities. Hibernomas are usually subcutaneous but may also be deep seated (intramuscular). In smears, clusters or fragments of ordinary large adipocytes are intermingled with round to oval and polygonal cells of variable sizes, with vacuolated or granular cytoplasm and centrally placed small uniform nuclei. The tissue fragments often contain numerous capillary vessels (see Fig. 14.20). Ordinary lipoma-like fat cells may dominate the smears, and the typical hibernoma cells may be in minority, thus posing challenges to diagnosis [44].

Cytologic features:

- Fragments of adipocytes and hibernoma cells
- Hibernoma cells: abundant microvacuolated to granular cytoplasm
- Small, bland nuclei
- Numerous capillaries
- Occasionally lipoblast-like cells

Differential diagnosis and problems in diagnosis:

- Well-differentiated liposarcoma (atypical lipomatous tumor)
- Lipoma with fat necrosis
- Granular cell tumor
- Adult rhabdomyoma

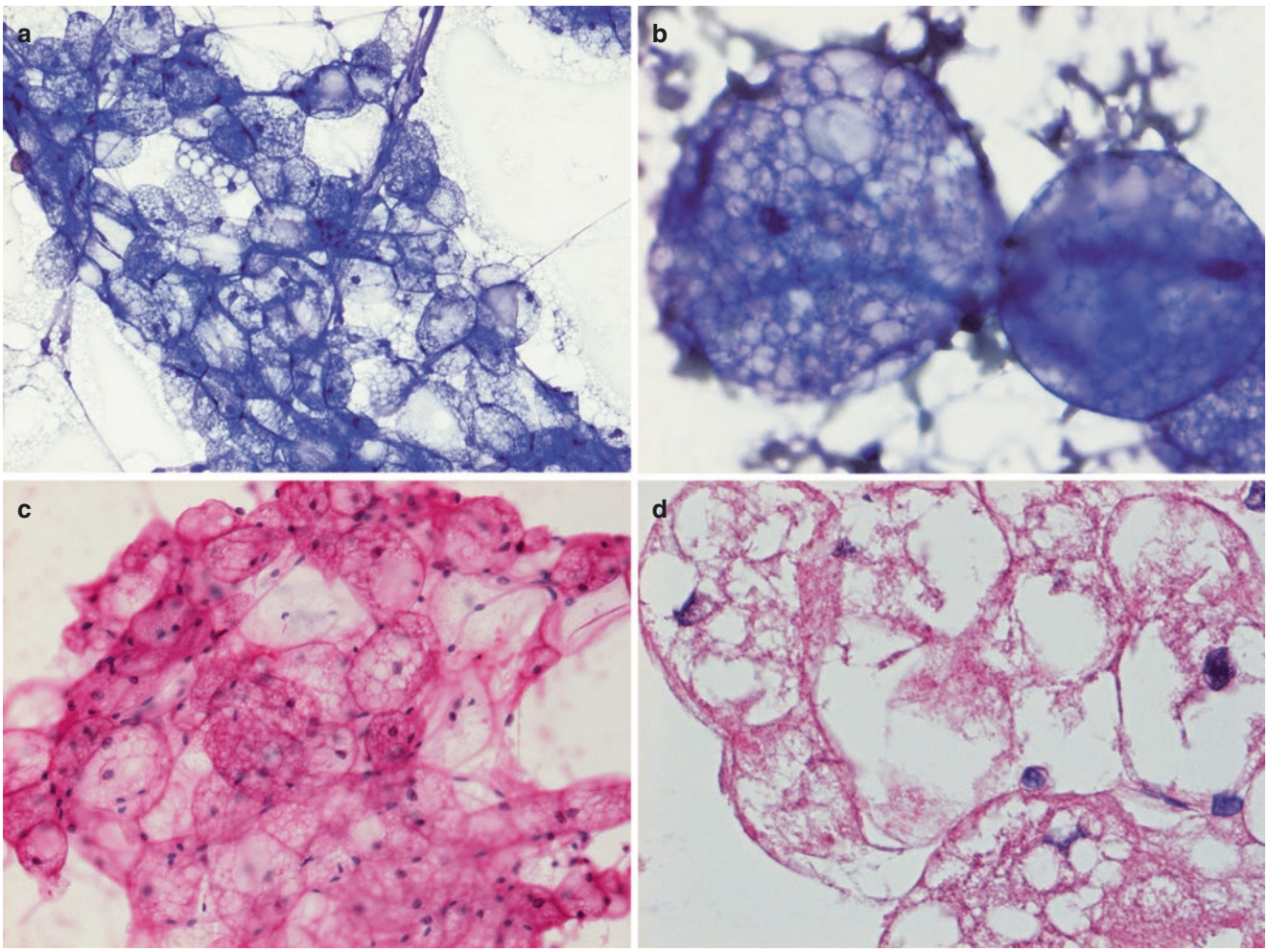

Fig. 14.20 Hibernoma. (**a**–**c**) Clusters, sheets of round to oval and polygonal cells with abundant microvacuolated or granular cytoplasm, and centrally placed small uniform nuclei, sometimes mimicking a lipoblast (**b**) (MGG; H&E). (**d**) Overall hibernoma architecture is preserved in cell block material (H&E)

Chondroid Lipoma

Chondroid lipoma is an infrequent deep-seated benign lipomatous tumor occurring in the proximal extremities, limb girdles, trunk, and head and neck region. FNA smears show clusters of mature adipocytes with admixture of lipoblasts and small chondroid cells in a background of abundant myxochondroid matrix (see Fig. 14.21) [45].

Despite variation in size and shape, the nuclei of small chondroid cells are bland appearing. One helpful feature in distinguishing it from myxoid liposarcoma is the lack of a plexiform capillary network in the cellular clusters.

Cytologic features:

- Variable but commonly abundant myxochondroid background matrix
- Sheets and clusters of ordinary adipocytes
- Sheets and clusters of uni- or multivacuolated, lipoblast-like cells
- Small chondroid cells with irregular, bland, occasionally coffee bean-shaped nuclei and granular cytoplasm
- Lack of a plexiform capillary network seen in myxoid liposarcoma

Differential diagnosis and problems in diagnosis:

- Myxoid liposarcoma
- Extraskeletal myxoid chondrosarcoma

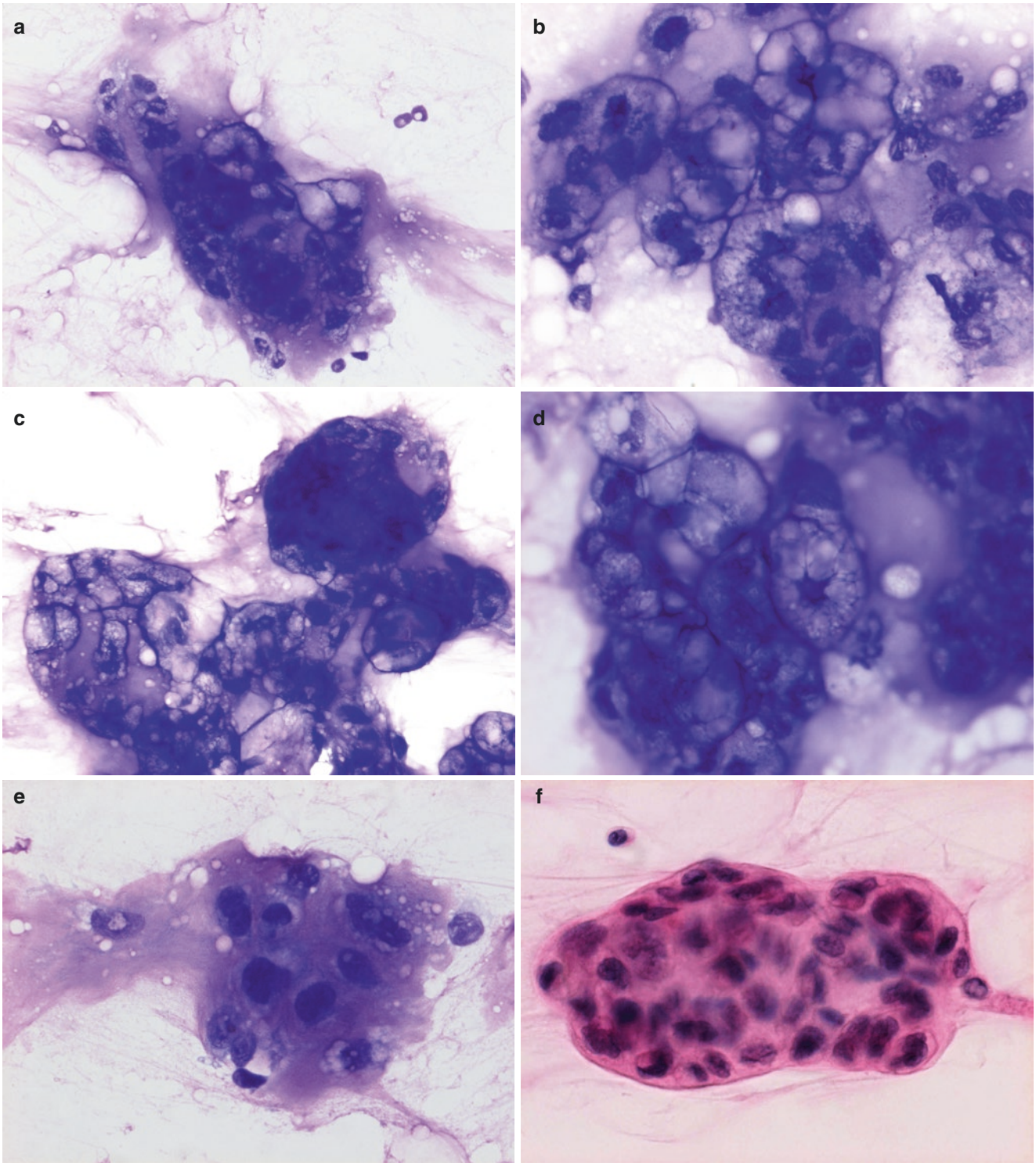

Fig. 14.21 Chondroid lipoma. (**a**–**f**) Clusters and small fragments of mature adipocytes with admixture of lipoblasts, small chondroid cells, and abundant myxochondroid background matrix (MGG and H&E). Note the lipoblast-like cells in (**a–d**)

Diagnostic Pitfalls in Benign Adipose Tumors

Distinguishing various benign lipomatous neoplasms from liposarcomas is important for proper clinical management. The main clue to a benign diagnosis is the absence of atypical lipoblasts. Clinical details such as patient age, tumor location, and size are also valuable in the differential diagnosis.

The cytologic features of variants of benign lipomatous tumors and their mimics are summarized in Tables 14.3 and 14.4.

Table 14.3 Cytologic features of benign lipomatous tumors and their mimics

Tumor	Cytologic features	Mimics
Common lipoma	Fragments of adipose tissue with large, univacuolated, mature fat cells with a small dark peripheral nucleus. Few dissociated adipocytes. Variable capillary vessels within the fatty tissue fragments. Occasional myxoid matrix, metaplastic cartilage/bone	Atypical lipomatous tumor
Inter- and intramuscular lipoma	As common lipoma + fragments of striated muscle or regenerating muscle, occasional muscle giant cells	Intramuscular angioma with prominent fat
Angiolipoma	As common lipoma + numerous branching capillary vessel fragments are in the fat tissue fragments	
Lipoblastoma/ lipoblastomatosis	Clusters of small uniform adipocytes with vacuolated cytoplasm and round uniform nuclei. Myxoid background matrix. Branching strands of capillaries. Commonly admixture of normal looking fatty cells. Occasionally hibernoma-like cells and uni-or multivacuolated lipoblast-like cells	Myxoid liposarcoma
Spindle-cell lipoma	Mixture of mature adipose tissue and dispersed or clustered, bland spindle cells in variable proportions. Fragments of brightly eosinophilic (hematoxylin and eosin) collagen–hyaline fibers. Myxoid background and mast cells common	Schwannoma
		Dermatofibrosarcoma protuberans
		Low-grade myxofibrosarcoma
		Myxoid liposarcoma
Pleomorphic lipoma	Fragments of mature fat. Variable number of spindle cells and floret cells. Occasionally myxoid background matrix and mast cells	Well-differentiated liposarcoma (atypical lipomatous tumor)
Hibernoma	Clusters and fragments of large univacuolated, mature fat cells mixed with variable proportions of "hibernoma cells" (multivacuolated or granulated cytoplasm). Capillary network. Occasionally dissociated or small groups of hibernoma cells. Smears may be dominated by large mature fat cells	Well-differentiated liposarcoma (atypical lipomatous tumor)
		Lipoma with fat necrosis
		Granular cell tumor
		Adult rhabdomyoma
Chondroid lipoma	Clusters of mature fat cells mixed with uni- or multivacuolated, lipoblast-like cells. Variable but commonly abundant myxochondroid background matrix. Small chondroid cells with irregular, bland, occasionally coffee bean-shaped nuclei and granular cytoplasm	Myxoid liposarcoma
		Extraskeletal myxoid chondrosarcoma

Table 14.4 Cytologic features in mimics of benign lipomatous tumors

Tumor	Cytologic features
Well-differentiated liposarcoma/atypical lipomatous tumor	Fragments/clusters of mature fat cells. Large atypical stromal cells with irregular, hyperchromatic, within and outside fragments/clusters. Rare atypical lipoblasts. Occasional floret cells
Myxoid liposarcoma	Tissue fragments with myxoid matrix and branching capillary network. Uniform, round to oval or spindle-shaped primitive cells. Uni- or multivacuolated lipoblasts, some with signet-ring features. No mitoses. Few dissociated tumor cells
Low-grade myxofibrosarcoma	Dispersed cells and cell clusters. Abundant myxoid background. Slight to moderate atypical spindle cells. Fragments of curved vessels embedded in the myxoid matrix. Occasional pseudolipoblasts
Extraskeletal myxoid chondrosarcoma	Dispersed cells, branching cords, strands, and cell balls. Spindle-shaped, fusiform, or round cells with ovoid or rounded nuclei. Bland nuclear chromatin and small nucleoli. Myxoid background matrix. Chondroblast-like lacunar structures. Lack of significant vascularity
Schwannoma	Cohesive fragments of different sized, often with irregular borders ("of a jigsaw puzzle pieces"). Rare dispersed cells. Cells with indistinct cytoplasm and elongated, slender nuclei with pointed ends, boomerang-shaped or comma-like nuclei. Fibrillary background. Occasional nuclear palisading and Verocay bodies. Occasionally small lymphocyte-like nuclei or slight to moderate nuclear pleomorphism
Adult rhabdomyoma	Large, rounded, polygonal, or elongated cells, dispersed or arranged in cohesive, syncytial clusters. Abundant eosinophilic (hematoxylin and eosin) granular cytoplasm. Small nuclei with prominent nucleoli. Stripped nuclei occasionally. Rarely visible cross-striation
Granular cells tumor	Mixture of poorly cohesive sheets and single cells or bare nuclei. Cells with fragile granular cytoplasm, often stripped nuclei and cytoplasmic granular background. Preserved cells with abundant granular cytoplasm and ill-defined cytoplasmic borders. Small, rounded to oval nuclei with finely granular chromatin and small nucleoli. Occasionally moderately pleomorphic cells

Malignant Adipocytic Tumors

It has been estimated that about 20% of soft tissue sarcomas in adults are liposarcomas. Most liposarcomas are deep seated, intra- or intermuscular, and the most common sites are the lower extremities, trunk, and retroperitoneum. There are three clinically, morphologically, and cytogenetically distinct entities: well-differentiated/dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma [1].

Atypical Lipomatous Tumor/ Well-Differentiated Liposarcoma

Well-differentiated liposarcoma is a locally aggressive, nonmetastasizing adipocytic neoplasm occurring predominantly in the retroperitoneum or mediastinum. When the same tumor arises at surgically curable sites such as the lower extremities, the term "atypical lipomatous tumor" (ALT) is preferred [1]. Cytologic findings in these tumors include the mixture of ordinary lipoma-like fragments and atypical stromal cells with enlarged, irregular hyperchromatic nuclei (see Fig. 14.22). Atypical lipoblasts with cytoplasmic vacuoles and scalloped nuclei may be present but are not necessary for the diagnosis. Dedifferentiated liposarcoma is diagnosed when a well-differentiated liposarcoma also displays nonlipogenic sarcomatous areas (see Fig. 14.22e). The presence of heterologous osteosarcomatous or rhabdomyosarcomatous differentiation in dedifferentiated liposarcoma is not uncommon, posing a huge diagnostic challenge in small biopsy samples. Well-differentiated liposarcoma/ALT is characterized by supernumerary ring and giant marker chromosomes, resulting in MDM2 and CDK4 amplification. These genetic abnormalities can be detected by FISH showing MDM2 amplification and/or by immunohistochemistry showing MDM2 and/or CDK4 nuclear reactivities (see Fig. 14.22f and Table 14.2) [46, 47].

Cytologic features:
- Clusters or sheets of lipogenic cells
- Large atypical stromal cells with irregular, hyperchromatic nuclei
- Rare, multivacuolated atypical lipoblasts
- Occasional floret cells
- Non-lipogenic elements suggestive of dedifferentiation

Differential diagnosis of well-differentiated liposarcoma/ALT:
- Variants of benign lipomatous tumor:
- Hibernoma, pleomorphic lipoma, and chondroid lipoma
- Fat necrosis with lipophages
- Any other mesenchymal tumor with nuclear atypia and a fat component

Differential diagnosis of dedifferentiated liposarcoma:
- Undifferentiated pleomorphic sarcoma
- Myxofibrosarcoma
- Myogenic sarcoma
- Extraskeletal osteosarcoma
- Rhabdomyosarcoma
- Other fibroblastic/myofibroblastic tumor

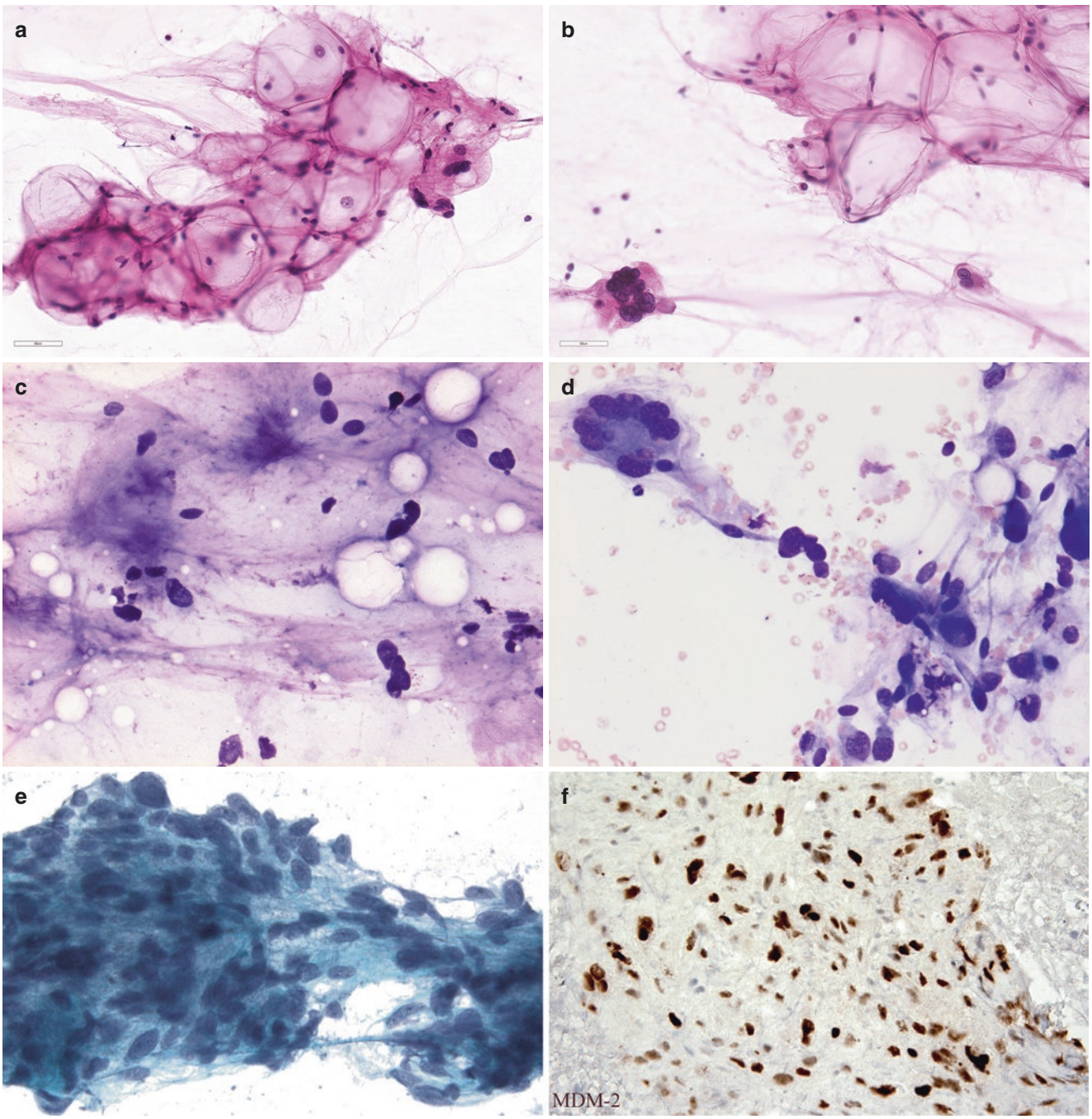

Fig. 14.22 Atypical lipomatous tumor/well-differentiated liposarcoma. (**a**–**d**) Mixture of ordinary lipoma-like fragments and atypical stromal cells and floret cells with enlarged, irregular hyperchromatic nuclei (H&E; MGG). (**c**) Occasional myxoid background in smears. (**e**) Dedifferentiated liposarcoma with non-lipogenic pleomorphic/spindle cells (Pap stain). Immunoreactivity with MDM2 (**f**) and CDK4, indicative of MDM2/CDK amplification, is characteristic for ALT/well-differentiated liposarcoma and dedifferentiated liposarcoma

Myxoid Liposarcoma

Myxoid liposarcoma accounts for 15–20% of liposarcomas. It occurs in young adults, and the most common site of involvement is in the deep soft tissue of the thigh. Myxoid liposarcoma is graded as low, intermediate, or high grade, based on the degree of cellularity. High-grade myxoid liposarcoma often demonstrates a round cell appearance, which accounted for the previous designation of "round cell liposarcoma." Myxoid liposarcoma, regardless of the grade, harbors the same genetic abnormalities *t(12;16)(q13;p11) or t(12;22)(q13;q12)* involving the *DDIT3* gene, which can be detected by FISH.

Myxoid Liposarcoma

Cytologic features:

- Tissue fragments with myxoid matrix and a branching capillary network
- Monotonous appearance with minimal pleomorphism
- Uni- or multivacuolated lipoblasts, some with signet-ring features
- Round to ovoid non-lipogenic primitive mesenchymal cells
- No mitoses
- Few dispersed tumor cells

Differential diagnosis and problem in diagnosis:

- Spindle-cell lipoma with abundant myxoid matrix
- Intramuscular myxoma, cellular type
- Low-grade myxofibrosarcoma

The diagnostic features of myxoid liposarcoma are the triad of abundant myxoid background matrix, fragments of tumor tissue with a branching network of thin capillaries, and slightly atypical lipoblasts as well as round to ovoid primitive cells, often associated with the capillaries in tissue fragments (see Figs. 14.23 and 14.24).

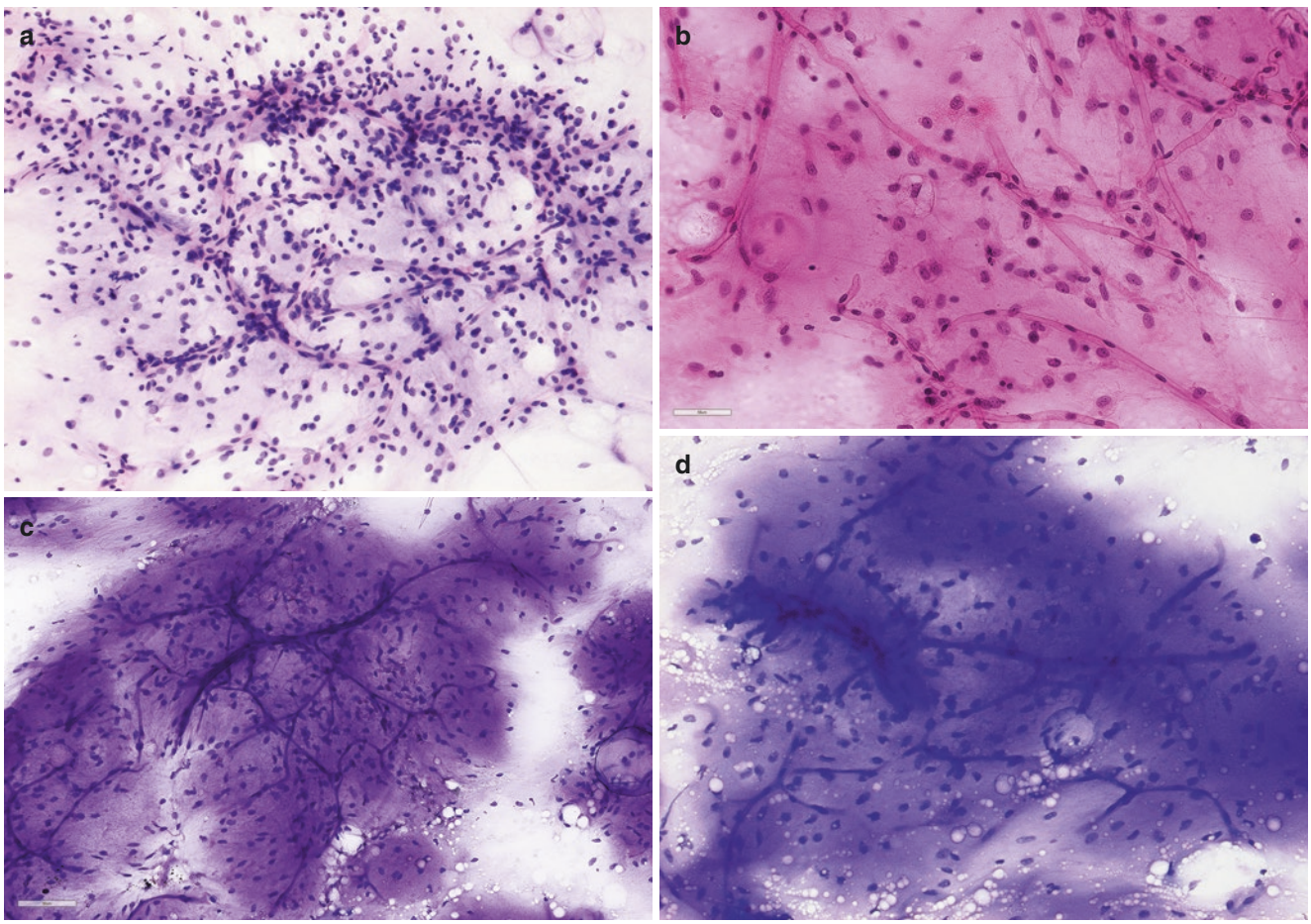

Fig. 14.23 Myxoid liposarcoma. Tissue fragments with round to ovoid primitive mesenchymal cells, myxoid matrix, and branching capillary network (**a**–**c**) (H&E); (**d**) (MGG)

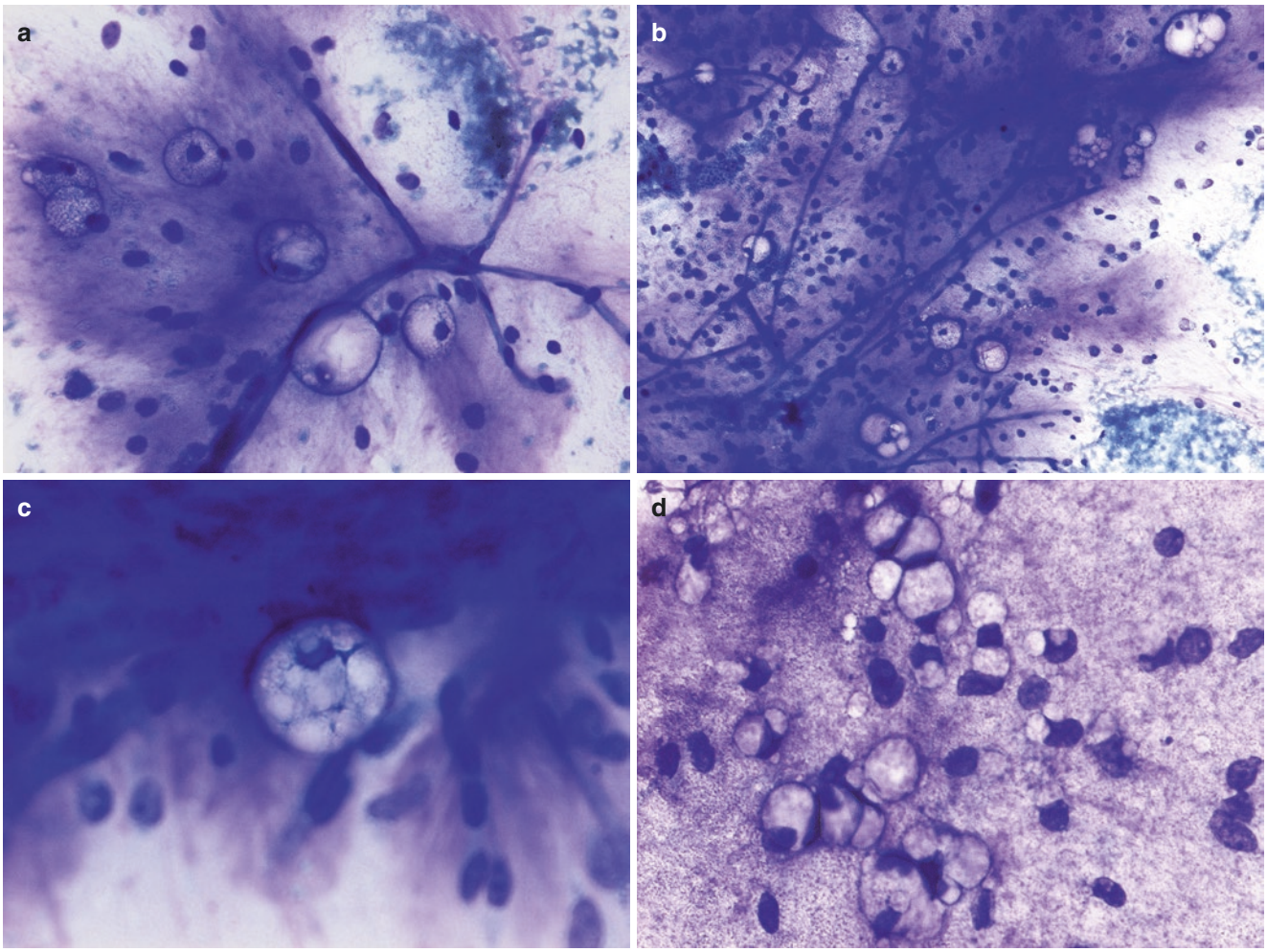

Fig. 14.24 Lipoblasts in myxoid liposarcoma. (**a**–**d**) Uni- or multivacuolated lipoblasts, some with signet-ring features, often associated with the capillary network (MGG)

Myxoid Liposarcoma, High Grade

A subset of myxoid liposarcomas have hypercellular areas containing numerous round to ovoid cells with scant cytoplasm, mixed with few to none lipoblasts. The myxoid matrix is scanty and the capillary network less prominent, often obscured by clusters of tumor cells (see Fig. 14.25) [48, 49].

Cytologic features:

- Rich yield of clusters and clumps of round or ovoid tumor cells embedded in matrix.
- Tumor cells with a high nuclear/cytoplasmic (N/C) ratio and round nuclei with vesicular chromatin.
- Less conspicuous myxoid matrix and capillaries compared to myxoid liposarcoma.
- Few to none lipoblasts.

Differential diagnosis and problems in diagnosis:

- Other types of round cell sarcoma infiltrating adipose tissue
- Soft tissue metastasis of renal cell carcinoma

Most myxoid/round cell liposarcoma is characterized by the recurrent translocation t(12;16)(q13;p11) with fusion of the *DDIT3* gene on chromosome 12 and the *FUS* gene on chromosome 16. In a small subset case, an *EWSR1-DDIT3* fusion resulting from the translocation t(12;22)(q13;q12) is present. The genetic abnormality can be detected by FISH for *DDIT3* rearrangement, which is very helpful in difficult cases, especially the round cell variant. Immunocytochemistry is usually neither necessary nor helpful to establish the diagnosis (Table 14.2) [50].

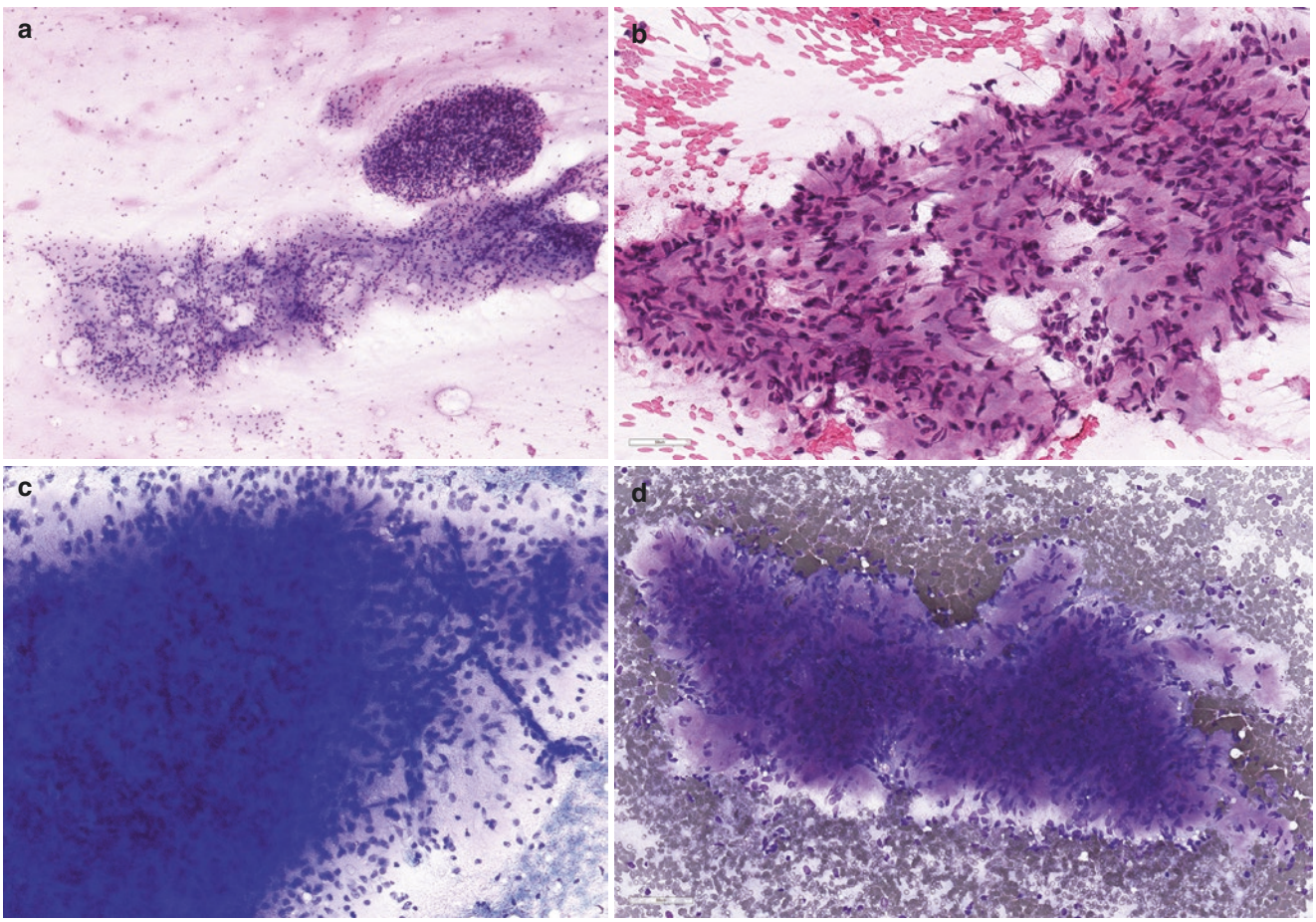

Fig. 14.25 Myxoid liposarcoma, high grade. (**a**–**d**) Capillary network less prominent, often obscured by clusters of tumor cells (H&E; MGG)

Pleomorphic Liposarcoma

Pleomorphic liposarcoma is a rare, high-grade liposarcoma containing markedly atypical, bizarre, and giant multinucleated tumor cells with adipocytic differentiation (see Fig. 14.26). Most cases occur in the extremities in elderly patients. The most important clue to the diagnosis is the presence of highly atypical uni- or multinucleated lipoblasts, which can be easily missed in needle biopsy samples, therefore leading to erroneous interpretation. Mitoses and necrosis are common [46, 49, 51].

Cytologic features:
- Dispersed cells and cell clusters
- Pleomorphic tumor cells including multinucleated giant tumor cells
- Variable presence of highly atypical, uni- or multinucleated lipoblasts
- Cells with hyaline cytoplasmic droplets occasionally present
- Necrosis

Differential diagnosis and problem in diagnosis:
- Pleomorphic high-grade sarcoma of another lineage
- Undifferentiated pleomorphic sarcoma
- Dedifferentiated liposarcoma
- Poorly differentiated carcinoma

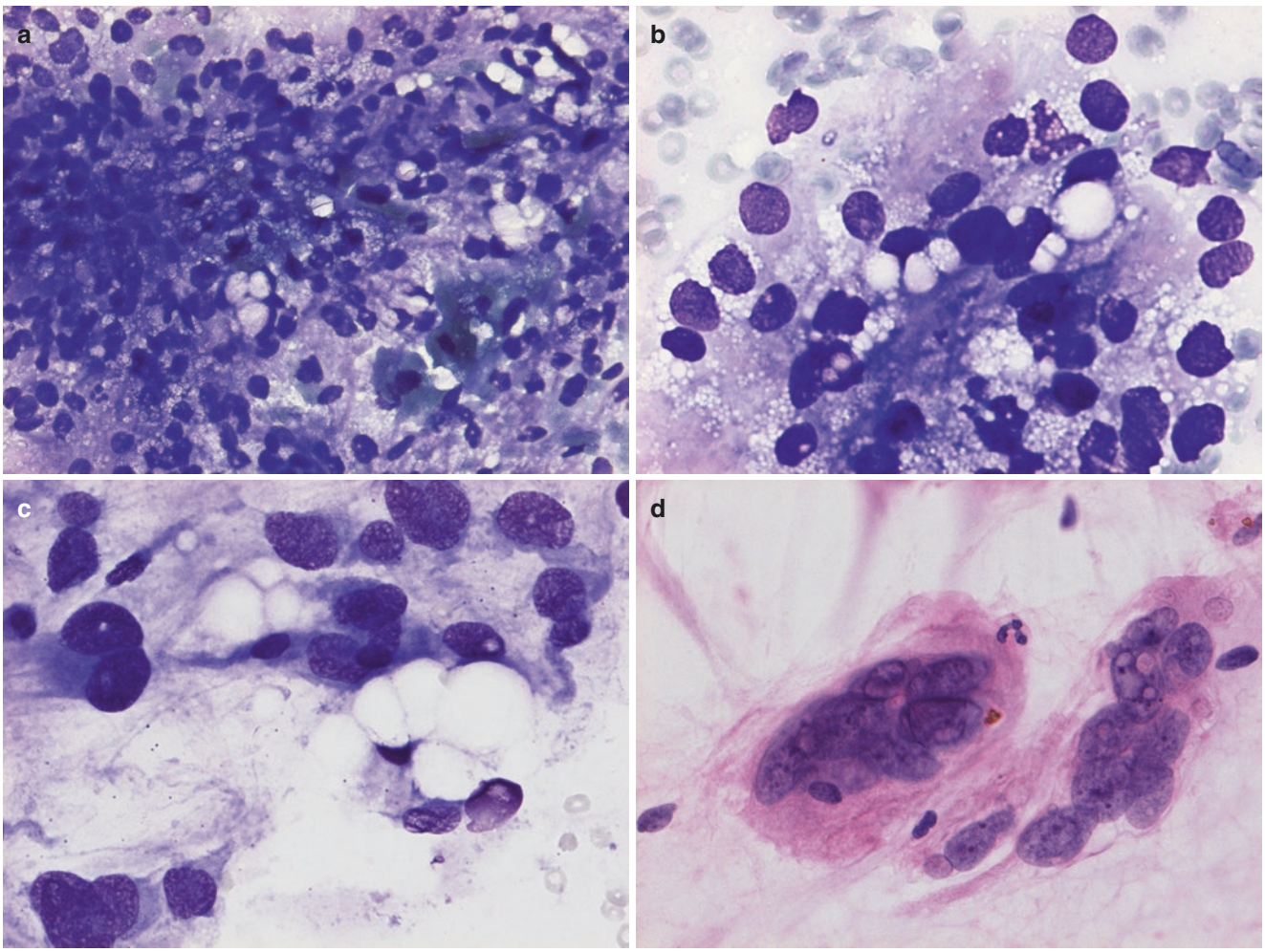

Fig. 14.26 Pleomorphic liposarcoma. (**a**–**c**) Smears are similar to non-lipogenic high-grade sarcomas but with admixed atypical lipoblasts (MGG). (**d**) Markedly atypical, bizarre, and giant multinucleated tumor cells (H&E)

Fibroblastic/Myofibroblastic Tumors

Desmoid Fibromatosis

Fibromatoses represent a broad spectrum of locally aggressive fibroblastic/myofibroblastic proliferations showing abundant extracellular collagenous matrix and infiltrative growth pattern. Their clinical course is connected to significant rate of recurrences, but fibromatoses lack metastatic potential. Extra-abdominal deep desmoid fibromatosis arises usually in the proximal parts of extremities, in the pelvic girdle and shoulder region, commonly in young adults and teenagers. However, fibromatoses occur in a wide age range, predominantly in young and middle-aged adults, although plantar and occasionally palmar fibromatoses can occur in children. Fibromatoses are categorized as superficial fibromatoses (palmar, plantar, knuckle pads and penile) and deep desmoid-type fibromatoses arising in deep soft tissues of proximal extremities and shoulder and pelvic girdles or in the abdominal wall. Fibromatosis is composed of fascicles of fibroblasts/myofibroblasts embedded in a collagenous stroma. Because of abundant collagenous stroma, it is often difficult to obtain sufficient material from the lesion, and therefore, vigorous aspiration using larger needles and/or core needle biopsy is often necessary [52, 53]. The mixture of uniform, occasional slightly atypical spindle cells and fragments of paucicellular collagenous stroma in aspirates from a deep-seated, firm, soft tissue tumor is the hallmark of desmoid fibromatosis. Bland spindle cells arranged in long fascicles is an additional important cytologic feature suggestive of desmoid (see Fig. 14.27) [52]. Smears from desmoids may contain myxoid matrix, evoking the differential diagnosis of low-grade myxoid spindle-cell lesions, such as nodular fasciitis or low-grade fibromyxoid sarcoma. Smears of superficial fibromatoses (see Fig. 14.27g) display sparse to moderate cellularity with predominantly dispersed uniform or slightly enlarged fibroblasts with cytoplasmic processes containing spindle-shaped bland nuclei with admixture of naked spindle-shaped nuclei.

The lesional cells of deep fibromatoses express SMA, MSA, focal desmin, and in approximately 70–80% of cases nuclear β-catenin. Demonstration of aberrant nuclear expression of β-catenin is helpful to confirm the diagnosis. Tumor cells are negative for CD34, caldesmon, S-100, and CD117. Hyaline material of juvenile hyaline fibromatosis stains with alcian blue and with diastase-resistant PAS.

Cytogenetic changes in fibromatoses include trisomies for chromosomes 8 and/or 20 in the tumor cells. Sporadic desmoid fibromatoses harbor mutations in β-catenin CTNNB1 gene and cases associated with Gardner syndrome in APC, 2, 3 both resulting in the intranuclear accumulation of protein. Cytogenetics, FISH, SNP array, and NGS can be used for evaluation on fresh or fixed material.

Cytologic features:

- Variable yield.
- Clusters of or dispersed fibroblasts.
- Bland or slightly atypical spindle cells in collagenous stroma arranged in long fascicles.
- Fibroblasts with elongated fusiform nuclei, insignificant nucleoli, and slight anisokaryosis.
- Cytoplasmic processes are seen in preserved cells, but stripped nuclei are a common finding.
- Fragments of paucicellular collagenous stroma.
- Occasional regenerating striated muscle fibers (muscle giant cells).

Differential diagnosis and problems in diagnosis:

- Nodular fasciitis
- Low-grade fibromyxoid sarcoma
- Deep-seated leiomyoma
- Low-grade malignant peripheral nerve sheath tumor (MPNST)
- Monophasic synovial sarcoma
- Fibrosarcoma
- Radiation-associated sarcoma

Mesenteric subtype of fibromatosis may be sporadic or occur in patients with Gardner-type familiar adenomatous polyposis. Juvenile hyaline fibromatosis, a milder form of hyaline fibromatosis syndrome, is a rare hereditary (autosomal recessive) disease caused by defects in collagen production and synthesis of glucosaminoglycans as a result of mutations in the ANTXR2 gene on chromosome 4q21. The disease presents congenitally or in early childhood with variable severity and is characterized by extracellular hyaline material deposition in skin, soft tissue (see Fig. 14.27h), and bone resulting of papulonodular skin lesions, soft tissue masses, joint contractures, gingival hypertrophy, stunted growth, and osteolytic bone lesions.

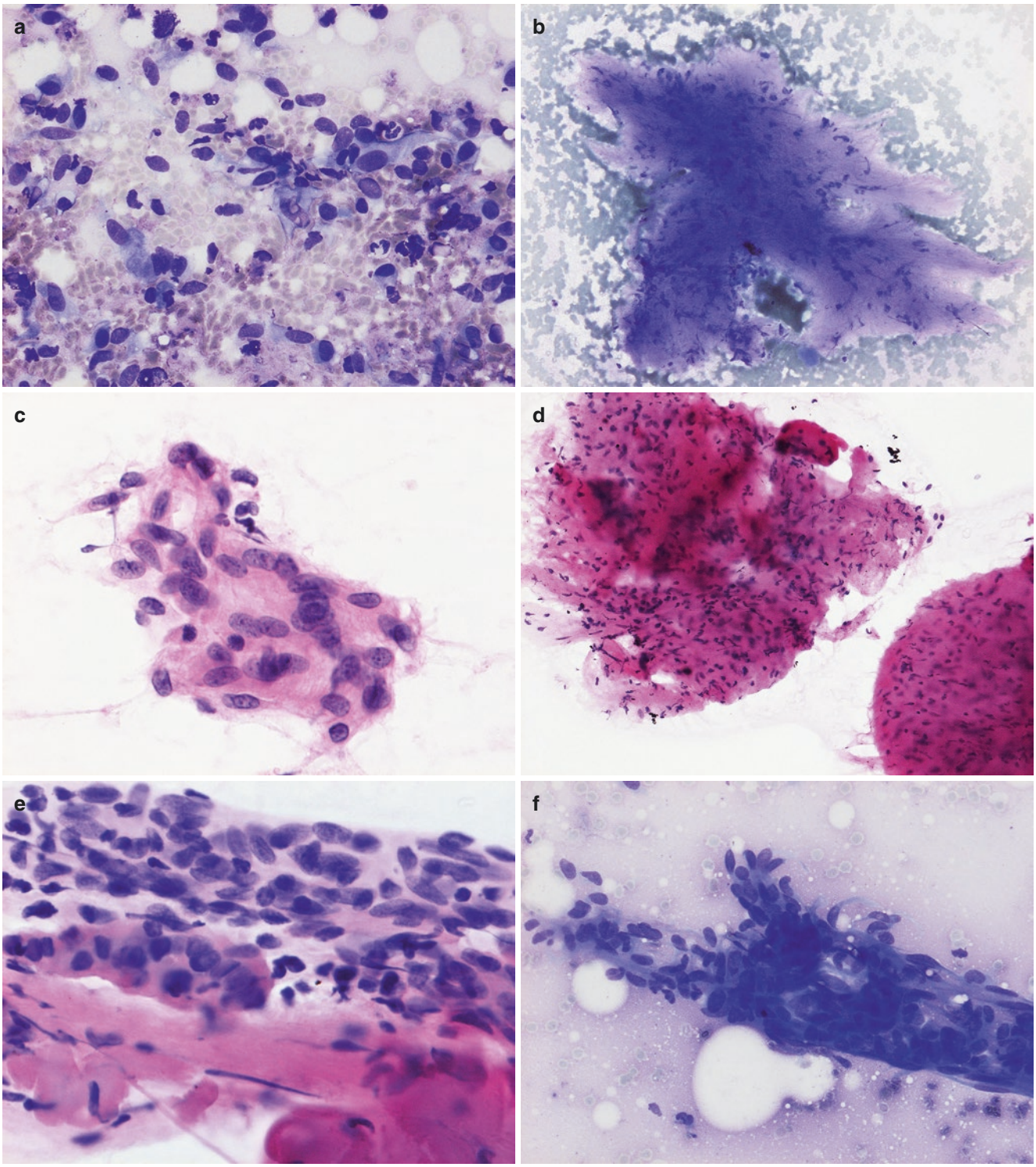

Fig. 14.27 Desmoid fibromatosis. (**a**–**d**) The mixture of cohesive or loosely cohesive clusters and dispersed uniform or slightly atypical spindle cells and fragments of paucicellular collagenous stroma (MGG; H&E). (**e**, **f**) Bland spindle cells in long fascicles, a useful clue suggestive of fibromatosis (H&E; MGG). Superficial fibromatosis. (**g**) Dispersed uniform or slightly enlarged fibroblasts with cytoplasmic processes and admixture of naked spindle-shaped bland nuclei (MGG). Juvenile hyaline fibromatosis. (**h**) Fragments of amorphous, paucicellular, eosinophilic hyaline material containing uniform fibroblasts and small capillaries (H&E)

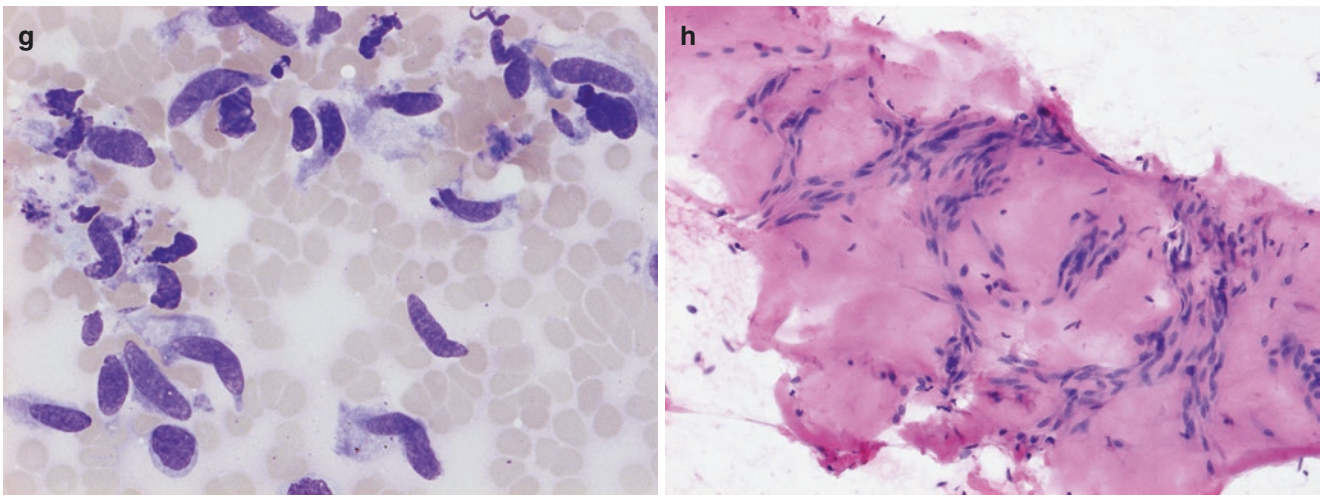

Fig. 14.27 (continued)

Elastofibroma Dorsi

Elastofibroma dorsi (EFD) is a relatively rare, soft tissue mass, probably of reactive nature. The lesion is typically slowly growing, located near the inferior margin of the scapula or between the inferior part of scapula and the chest wall in elderly women. Elastofibroma is composed of (myo)fibroblasts, abundant hypocellular collagenous stroma, and fat. The main diagnostic feature is the presence of elastic fibers with serrated borders, corresponding to faulty elastin fibrillogeneses [54]. FNA smears show small sheets or clusters of uniform spindle cells, mature adipocytes, fragments of acellular collagen bundles and fibers, and the degenerated elastic fibers presented as linear ("braid-like"), globular, and stellate structures with serrated edges (see Fig. 14.28). Diagnostic difficulties arise when the material is poor, fat cells are dominant, and the typical serrated elastic fibers are missing.

Cytologic features:
- Variably cellular smears
- Fat tissue intermingled with collagen fragments/collagen fibers and/or uniform spindle cells
- Spindle cells in loosely cohesive groups or dispersed
- Elastic fibers present as linear ("braid-like"), globular bodies with shell-like and stellate appearances, and the characteristic serrated "moth-eaten" borders

Differential diagnosis and problems in diagnosis:
- Extra-abdominal desmoids

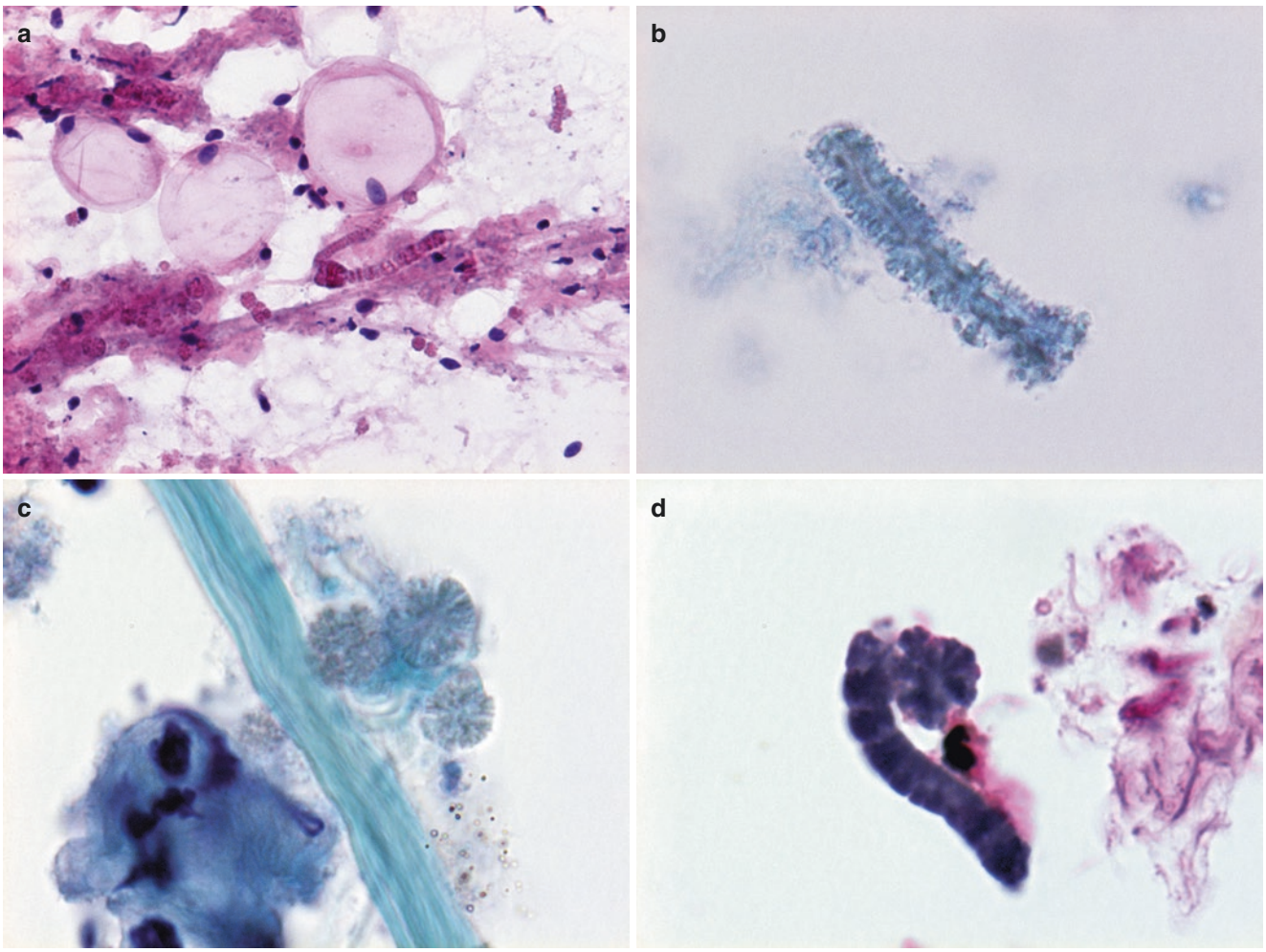

Fig. 14.28 Elastofibroma dorsi. (**a**) Smears show small clusters of and dispersed uniform spindle cells, mature adipocytes, and fragments of acellular collagen with admixture of degenerated elastic fibers. (**b**–**d**) Elastic fibers presented as linear ("braid-like"), distinct globular and stellate structures with serrated edges in high-magnification image (ThinPrep, Pap stain; cell block; Cellient; elastin stain; Hologic; Bedford, MA, USA)

Solitary Fibrous Tumor

Solitary fibrous tumor (SFT) is a mostly benign fibroblastic tumor, which can occur practically at any location in the body besides the pleura. The common sites of involvement include deep soft tissue of the lower extremities, head and neck region, mediastinum, and retroperitoneum. Many SFTs were previously termed hemangiopericytomas, and the rare, fat-forming variant was called lipomatous hemangiopericytoma [1]. Both malignant and dedifferentiated forms have been described [55, 56].

The aspirate yields variably cellular smears containing bland spindle cells, either dispersed or in tight clusters. The tumor cells are fibroblast-like with spindle or ovoid nuclei and scanty cytoplasm. Naked nuclei, ropy collagen fibers, and mast cells are common (see Fig. 14.29). The prominent "staghorn" vascular pattern seen in histology is rarely appreciated in FNA smears but can be seen in cell-block sections (see Fig. 14.29d). The smears from the fat-forming variant SFT show three-dimensional clusters of uniform spindle cells admixed with mature adipose tissue. A correct diagnosis of SFT is difficult based on cytomorphology alone [57, 58]. Immunocytochemistry is often diagnostically helpful as the spindle cells of SFT display characteristic reactivities for CD34 and STAT6 (nuclear positivity), and a considerable number of cases show positivity for CD99 and Bcl-2 and limited reactivities for EMA and keratins; the profile distinguishes it from synovial sarcoma. Positivity for CD34 may be decreased or lost in malignant variant. Majority SFTs display an inversion at the 12q13 which results in a fusion gene *NAB2-STAT6*. Nuclear overexpression of STAT6 detected by immunocytochemistry is a sensitive and specific marker for SFT [59].

Cytologic features:

- Variable cellularity
- A mixture of dispersed cells and tight, fascicle-like clusters
- Uniform population of bland spindle cells with inconspicuous nucleoli
- Ropy collagen fibers
- Stripped nuclei
- Mast cells
- Three-dimensional clusters of uniform spindle cells mixed with mature fat in the fat-forming variant

Differential diagnosis and problems in diagnosis:

- Monophasic synovial sarcoma
- Fibromatosis
- Low-grade fibromyxoid sarcoma
- Low-grade malignant peripheral nerve sheath tumor (MPNST)
- Benign or malignant lipomatous tumors versus fat-forming variant SFT

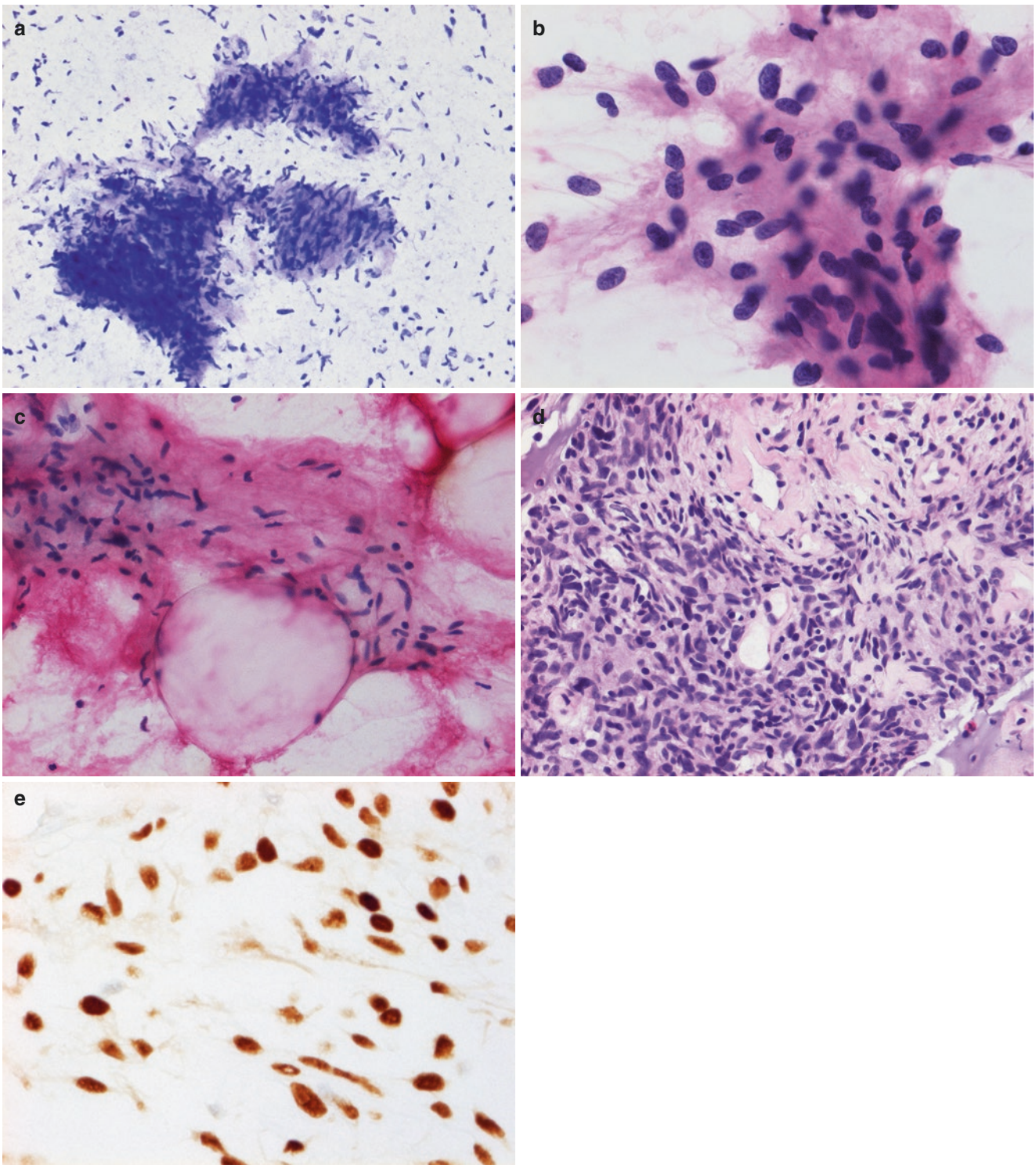

Fig. 14.29 Solitary fibrous tumor. (**a**, **b**) A mixture of dispersed cells and fascicle-like clusters of uniform population of bland spindle cells with inconspicuous nucleoli (MGG; H&E). (**c**) Clusters of spindle cells mixed with mature fat in the fat-forming variant (MGG). (**d**) Classic architecture of SFT with HPC-like vessels better appreciated in the cell block sections (H&E). (**e**) Nuclear STAT6 staining is a useful diagnostic marker for solitary fibrous tumor (cell block)

Fibromatosis Colli (Torticollis)

Fibromatosis colli is a very firm tumor-like lesion in the sternocleidomastoid muscle in newborn infants. A diffuse proliferation of fibroblasts is present within the muscle tissue. The involved muscle fibers are atrophic and contain regenerating muscle giant cells. The FNA smears of fibromatosis colli include a double population of bland spindle cells and muscle giant cells with nuclei showing prominent nucleoli (see Fig. 14.30). There is a risk to misinterpret muscle giant cells as malignant cells. It is important to remember that many tumors regress spontaneously; the primary therapy is expectancy and clinical symptom control.

Cytologic features:
- Bland fibroblasts and myofibroblasts dispersed or clustered
- Muscle giant cells and tadpole cells
- Occasionally small tufts of myxoid matrix
- Stripped nuclei

Differential diagnosis and problems in diagnosis:
- Pleomorphic sarcoma

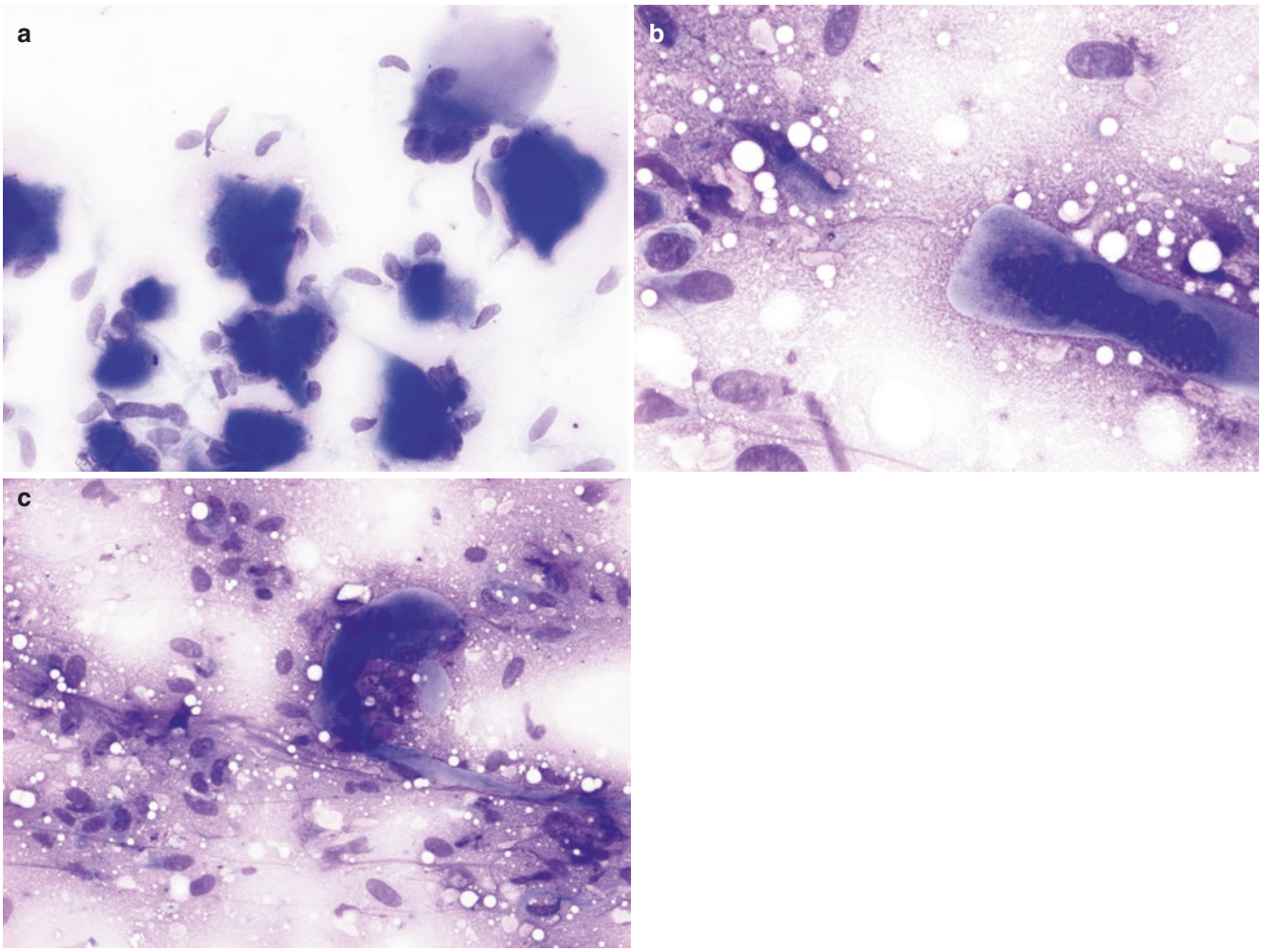

Fig. 14.30 Fibromatosis colli (torticollis). (**a**–**c**) Hypocellular smears with bland spindle cells and muscle giant cell with prominent nuclei (MGG)

Fibrous Hamartoma of Infancy

Fibrous hamartoma of infancy is a rare subcutaneous mass composed of a mixture of myxoid areas with small round primitive cells, septa or bands of fibrous tissue, and mature adipose tissue. Typical sites are the upper arms, shoulders, and axillary regions. In our limited experience of FNA of this entity, the spindle cells in fibrous hamartoma of infancy (see Fig. 14.31) resemble those in infantile fibrosarcoma. Most infantile fibrosarcomas arise in the extremities and yield hypercellular smears compared to poor cellularity of spindle-cell component seen in fibrous hamartoma of infancy.

Cytologic features:

- A mixture of normal fatty tissue and bland spindle cells in sheets and clusters
- Variable amounts of myxoid matrix

Differential diagnosis and problems of diagnosis:

- Infantile fibrosarcoma

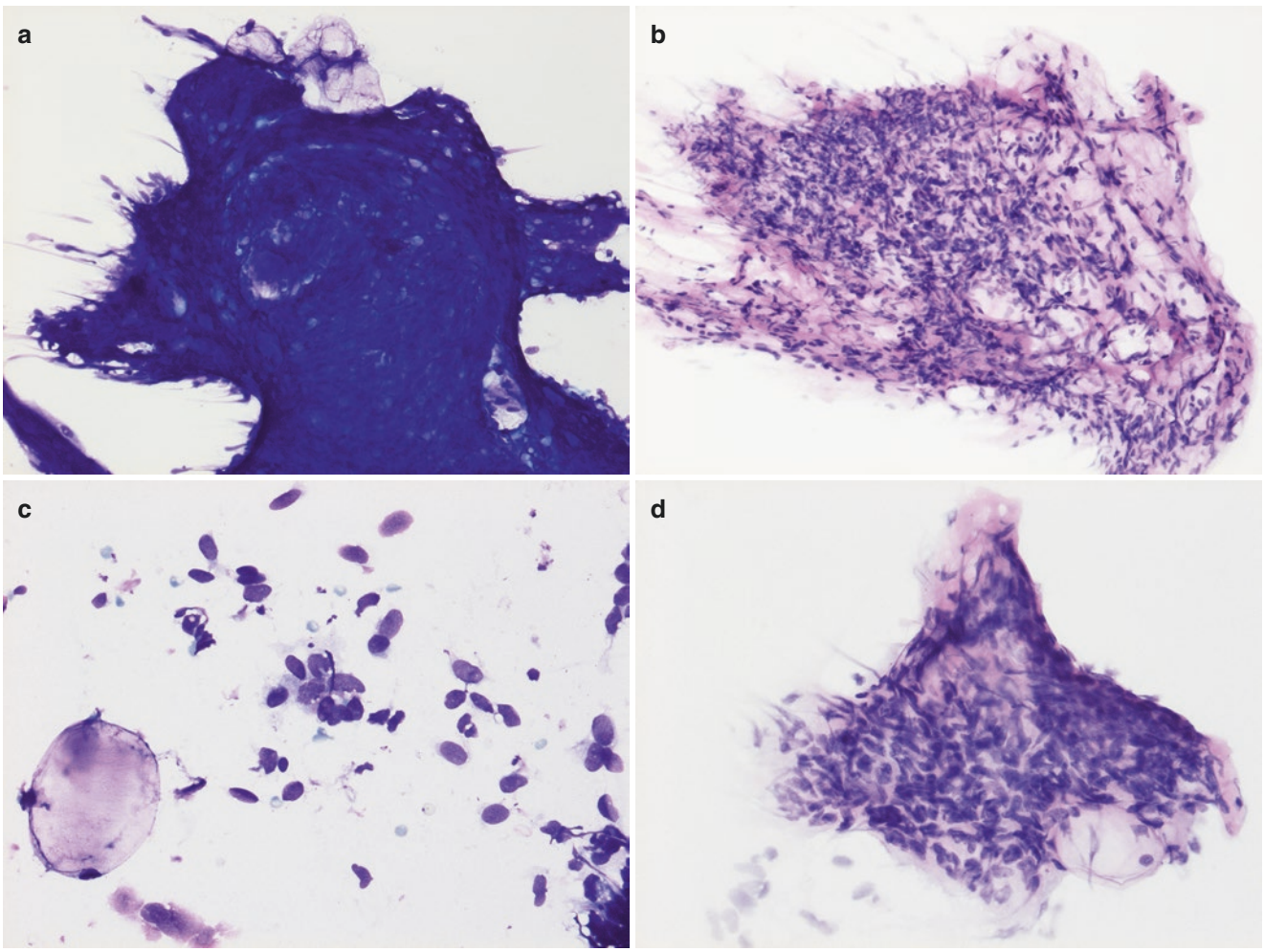

Fig. 14.31 Fibrous hamartoma of infancy. (**a**–**c**) Mixture of normal fatty tissue and bland spindle cells in sheets and clusters (MGG); (H&E). (**d**) Variable amounts of dispersed spindle cells or bare nuclei (MGG)

Low-Grade Fibromyxoid Sarcoma

Low-grade fibromyxoid sarcoma (LGFMS) is an uncommon, slowly growing, malignant fibroblastic neoplasm. It arises in the deep soft tissues of the extremities and trunk in young adults but may also occur in other age groups and locations. In histologic sections, LGFMS displays bland spindle cells arranged in a whorled pattern in a variable myxoid and collagenous stroma. In the myxoid areas, curvilinear vessels are a typical finding. The bland appearance may lead to the misperception of a benign spindle-cell or a myxoid lesion. Some tumors display rosette-like structures with a central hyalinized core surrounded by fibroblast-like cells. It is very difficult to render a diagnosis of LGFMS based on FNAC alone due to the morphologic overlapping with other spindle-cell and myxoid lesions. FNA smears usually show a mixture of uniform spindle to polygonal/rounded cells, embedded in a collagenous and myxoid matrix, and scattered single cells or bare nuclei with a mild anisokaryosis (see Fig. 14.32). The cytologic features of LGFMS have been described in case reports and in one series of eight cases [60–62]. LGFMS is characterized by a *FUS-CREB3L2* or a *FUS-CREB3L1* gene fusion, which can be detected by FISH, a very helpful ancillary test for difficult myxoid tumors [15, 40]. Recently, MUC4 has been shown to be a sensitive and specific marker to distinguish LGFMS from its benign mimics [63].

Cytologic features:

- Dispersed cells and cellular fascicles/clusters
- Fibroblast-like spindle cells with slightly atypical nuclei
- Monotonous appearance with mild anisokaryosis
- Stripped nuclei common
- Often abundant myxoid matrix
- Fragments of collagen tissue in the background
- Occasional fragments of curvilinear vessel in the myxoid areas

Differential diagnosis and problems in diagnosis:

- Intramuscular myxoma, cellular type
- Schwannoma
- Desmoid fibromatosis
- Low-grade myxofibrosarcoma
- Soft tissue perineurioma
- Dermatofibrosarcoma protuberans (myxoid variant)

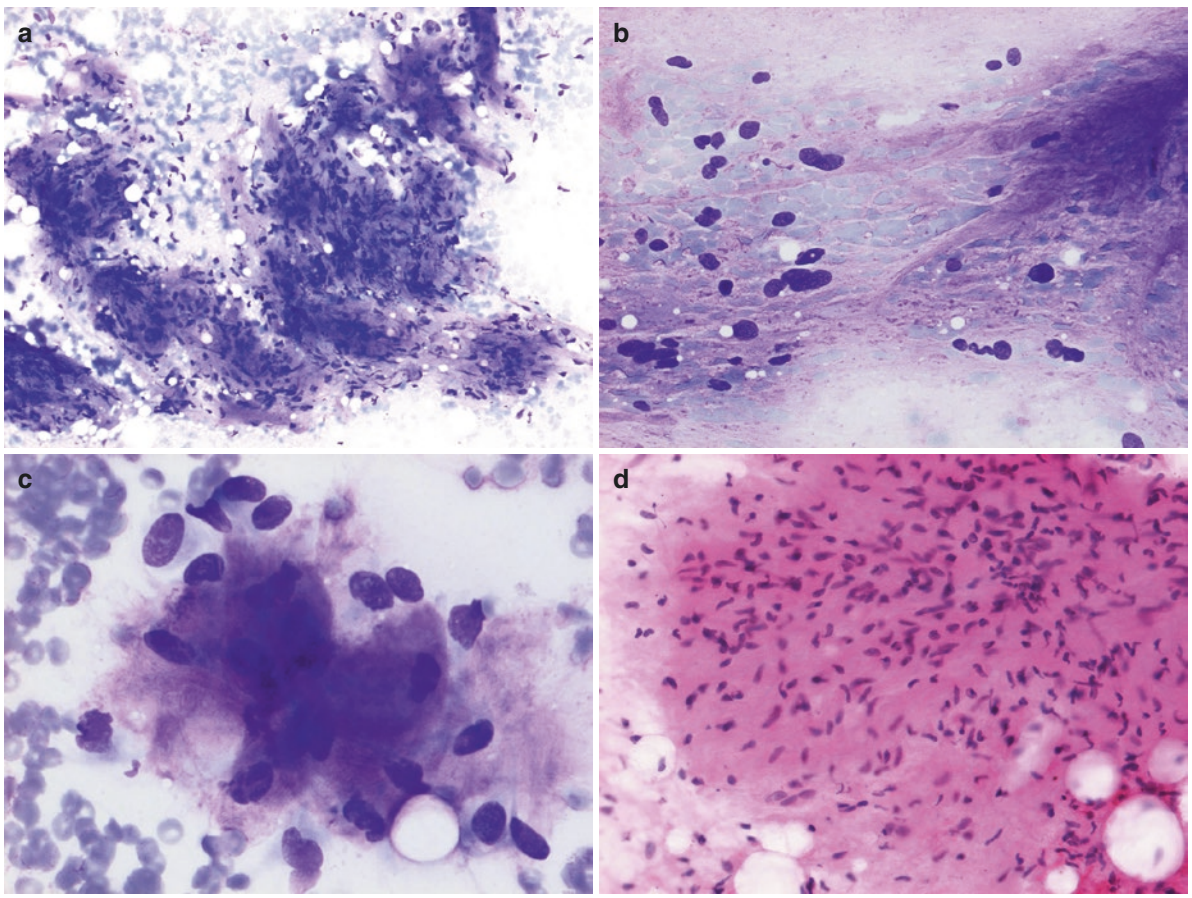

Fig. 14.32 Low-grade fibromyxoid sarcoma. (**a**–**c**) Mixture of uniform or slightly pleomorphic spindle and polygonal/rounded cells, embedded in a collagenous and myxoid matrix and scattered single cells or bare nuclei with mild to moderate anisokaryosis (MGG). (**d**) Occasionally large cohesive clusters of bland spindle cells embedded in collagenous/myxoid matrix (H&E)

Myxofibrosarcoma

Myxofibrosarcoma (MFS) is defined as a fibroblastic malignancy with variably myxoid stroma, cellular pleomorphism, and a prominent curvilinear vascularity. It was previously called "myxoid MFH." MFS commonly arises in the subcutaneous tissue in the extremities of elderly patients but may also arise in deep soft tissue. Low-grade MFS is characterized by slightly and moderately atypical spindle cells, whereas high-grade MFS presents marked cellular and nuclear pleomorphism including multinucleated bizarre tumor cells. From the clinical management point of view, it is most important to distinguish low-grade MFS from benign myxoid lesions such as intramuscular myxoma and nodular fasciitis. The presence of moderate nuclear pleomorphism and fragments of curved capillaries in the myxoid matrix are the most important clues to the diagnosis of MFS (see Fig. 14.33) [64–66].

Cytologic features:

- Dispersed cells and cell clusters
- Abundant myxoid background
- Fragments of curved vessels embedded in the myxoid matrix
- Slight to moderate atypical spindle cells in low-grade neoplasm
- Marked cellular and nuclear pleomorphism in high-grade neoplasm
- Occasional pseudolipoblasts

Differential diagnosis and problems in diagnosis:

- Intramuscular myxoma, cellular type
- Myxoid liposarcoma
- Nodular fasciitis
- Low-grade fibromyxoid sarcoma
- Spindle-cell lipoma
- Dedifferentiated liposarcoma

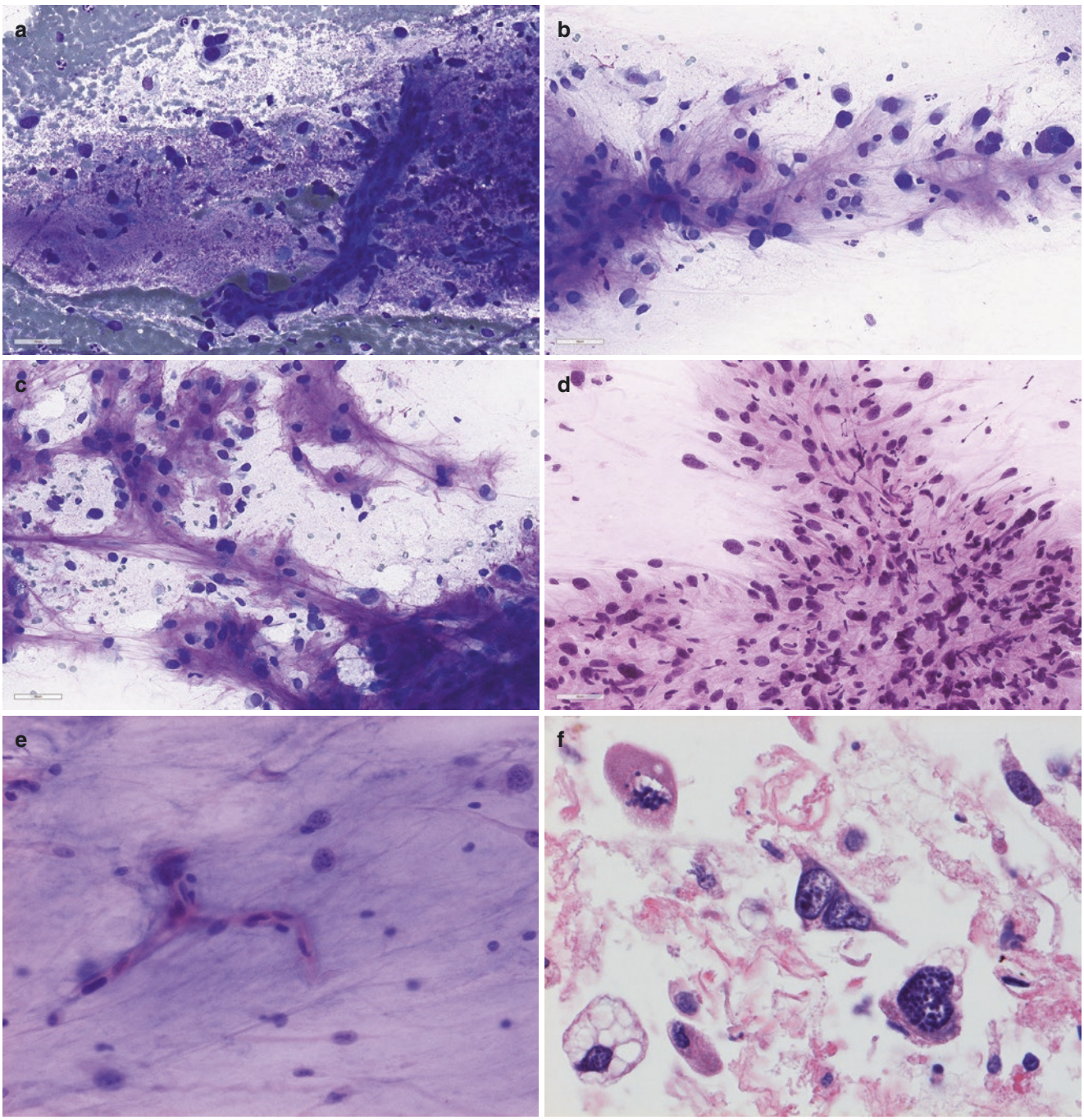

Fig. 14.33 Myxofibrosarcoma. (**a**–**d**) Loosely cohesive cell clusters of moderately to markedly pleomorphic spindle end epithelioid cells and dispersed atypical single cells in a myxoid background. Note fragments of curved vessels (MGG; H&E). (**e**) Low-grade myxofibrosarcoma is sometimes indistinguishable from benign cellular myxoid neoplasms, such as cellular intramuscular myxoma (H&E). (**f**) Pseudolipoblasts are common (cell block, H&E)

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a low-grade, locally aggressive fibroblastic neoplasm involving both the dermis and subcutis. Occasionally, higher-grade fibrosarcomatous progression occurs. FNA smears from DFSP are characterized by compact, often three-dimensional clusters of spindle cells. These spindle cells have poorly defined cytoplasmic borders and relatively uniform, spindle-shaped, or oval nuclei with finely dispersed chromatin (see Fig. 14.34). Collagen matrix with embedded spindle cells may show myxoid changes. Numerous dissociated spindle cells or naked nuclei are also commonly seen [67–69]. The FNA cytomorphology alone is not sufficiently characteristic to permit a confident diagnosis of DFSP. A definitive diagnosis requires the confirmatory CD34 positivity by immunocytochemistry [69].

Cytologic features:

- Variable yield
- Tight clusters or fascicles of spindle cells embedded in a collagen matrix
- Dispersed spindle cells and stripped nuclei
- Slight to moderate cellular and nuclear atypia but bland nuclear chromatin and inconspicuous nucleoli
- Pale and poorly defined cytoplasm, better-preserved cells with bipolar cytoplasmic extensions
- Occasionally fat fragments with admixture of spindle cells

Differential diagnosis and problems in diagnosis:

- Cellular benign fibrous histiocytoma
- Neurofibroma
- Schwannoma
- Nodular fasciitis
- Solitary fibrous tumor
- Other spindle-cell sarcoma arising in cutis–subcutis

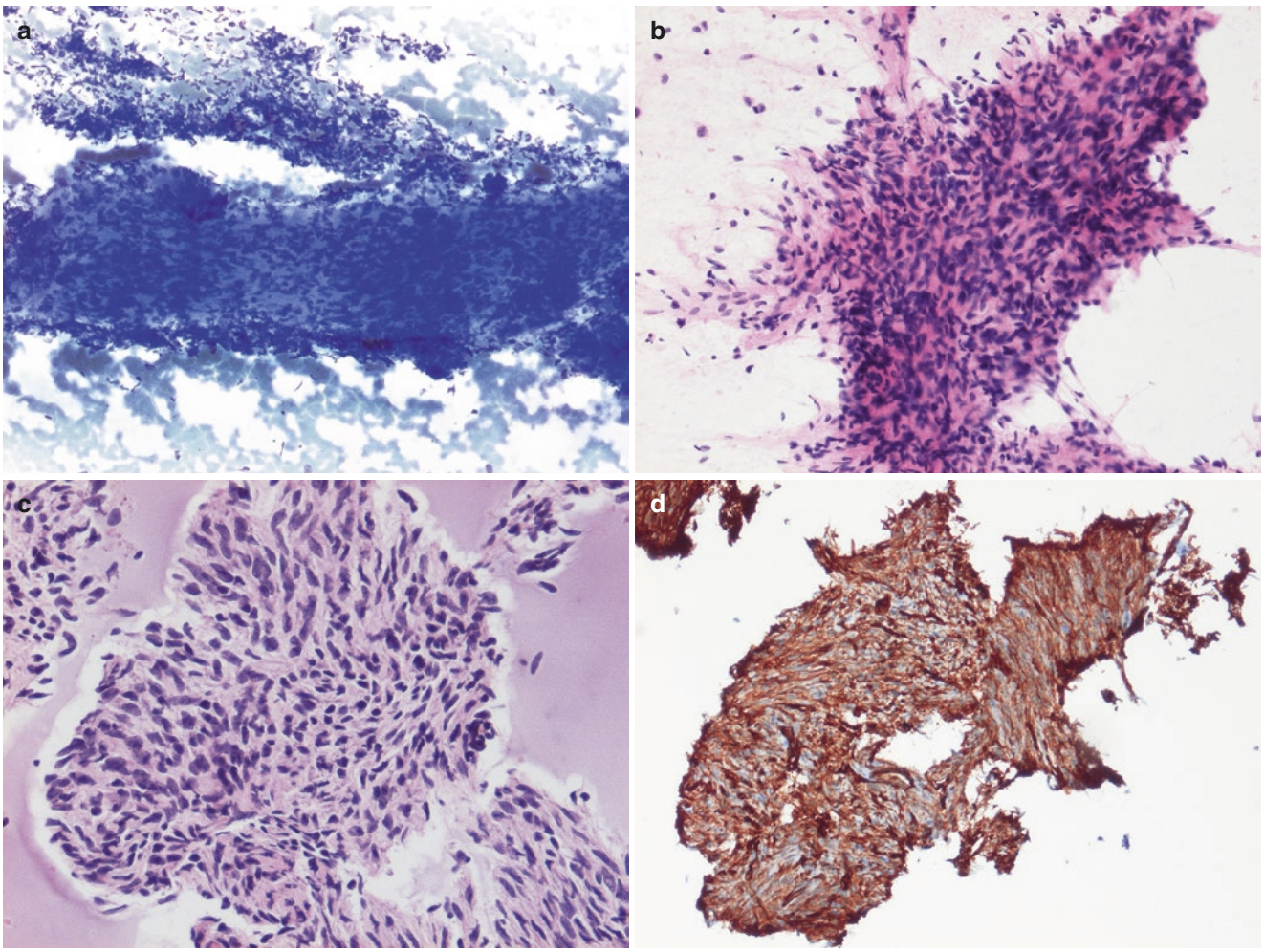

Fig. 14.34 Dermatofibrosarcoma protuberans (DFSP). (**a**, **b**) Compact, often three-dimensional clusters of spindle cells with poorly defined cytoplasmic borders (MGG; H&E). (**c**, **d**) Cell block sections show a storiform pattern and positive CD34 staining by immunohistochemistry (cell block; Shandon kit; H&E; CD34+). (Image courtesy of Elwira Bakuła-Zalewska, MD, PhD, Institute of Oncology, Warsaw, Poland)

Adult Fibrosarcoma

Adult fibrosarcoma was once considered the most common sarcoma in adults and is now a diagnosis of exclusion. It arises commonly in the deep soft tissue of the extremities, trunk, and head and neck region. Before the era of ancillary techniques, many cases of monophasic synovial sarcoma and malignant peripheral nerve sheath tumor were labeled as fibrosarcoma. The neoplastic cells resemble fibroblasts with no more than a moderate degree of pleomorphism, often arranged in fascicles or a herringbone-like pattern on histology. Dedifferentiated sarcoma and fibrosarcomatous progression from DFSP should be excluded. Adult fibrosarcoma is often diagnosed as a low- or high-grade spindle-cell sarcoma not otherwise specified (NOS) in FNA.

Cytologic features:

- Spindle cells arranged in thigh clusters, fascicles, or as dispersed cells.
- Variable cellular and nuclear atypia.
- Stripped nuclei are common findings.

Differential diagnosis and problems in diagnosis:

- Desmoid fibromatosis
- Solitary fibrous tumor
- Synovial sarcoma
- Malignant peripheral nerve sheath tumor
- Nodular fasciitis
- Dedifferentiated liposarcoma

Infantile Fibrosarcoma

Infantile fibrosarcoma is commonly seen before the age of 2 years; it occurs as a congenital neoplasm as well. Most tumors arise in the extremities as a large, fast-growing, nontender mass. The main histologic features are fibroblast-like cells with moderate atypia and often numerous mitoses arranged in tight fascicles. Foci of myxoid stroma, areas of round cells, and a hemangiopericytoma-like vascular pattern may be seen. FNA smears show tight clusters and fascicles of slight to moderate pleomorphic spindle cells (see Fig. 14.35). Spindle-cell population in smears from infantile fibrosarcoma and from fibrous hamartoma of infancy may show similar features. In addition, the mixture of spindle and round cells in aspirate may give a false impression of embryonal rhabdomyosarcoma. It has a distinctive *ETV6-NTRK3* gene fusion and is related to cellular congenital mesoblastic nephroma [70].

Cytologic features:
- Cellular aspirate
- Tight clusters and fascicles of slight to moderate pleomorphic spindle cells
- Spindle cells with bland nuclei
- Numerous mitoses

Differential diagnosis and problems in diagnosis:
- Fibrous hamartoma of infancy
- Childhood fibromatoses
- Embryonal rhabdomyosarcoma

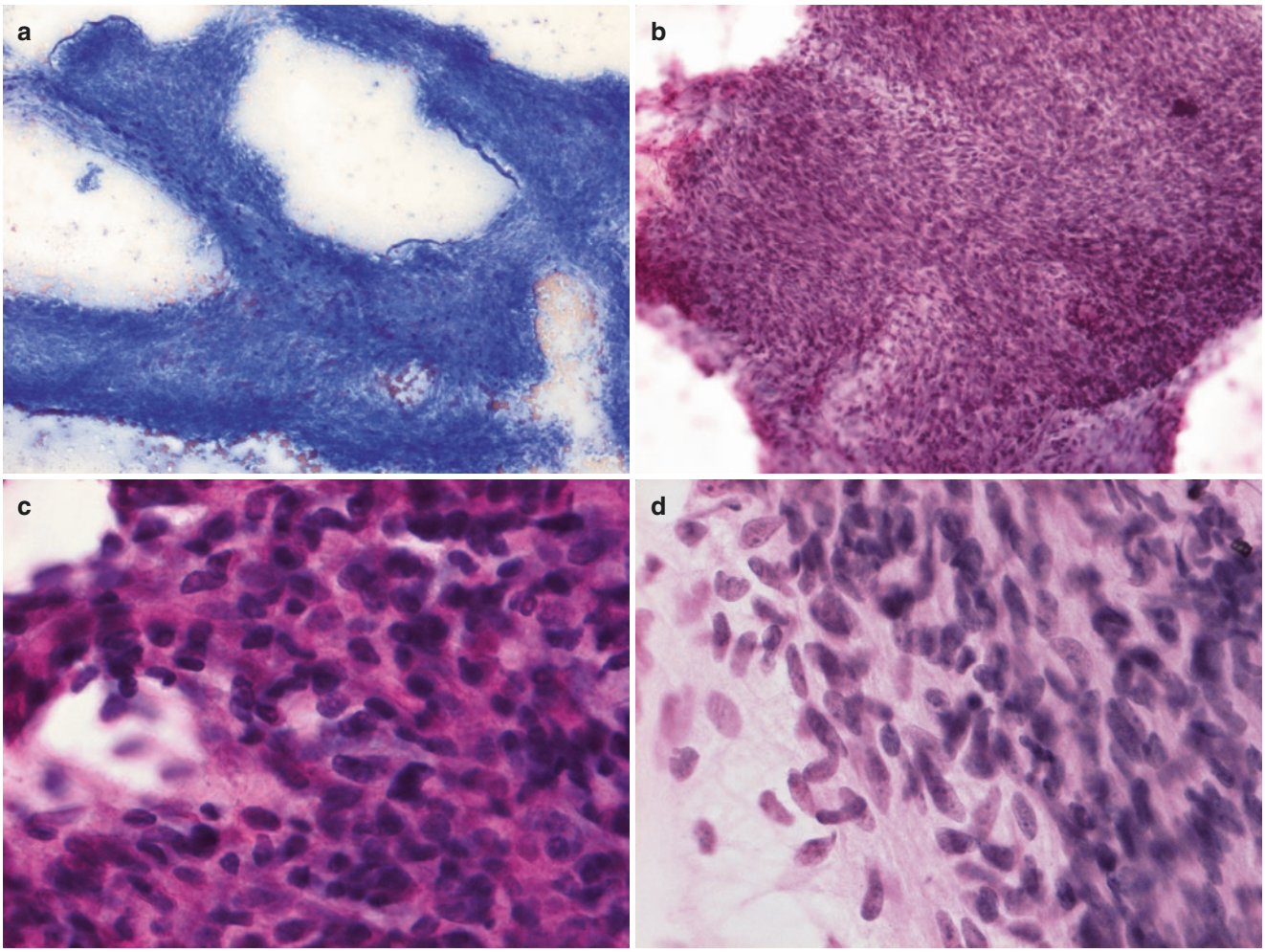

Fig. 14.35 Infantile fibrosarcoma. (**a**–**d**) Cellular aspirate with tightly clusters and fascicles of mildly to moderately pleomorphic spindle cells (MGG; H&E)

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) was once regarded as a reactive process, which was fallen in the spectrum of lesions termed "inflammatory pseudotumor." Over the past two decades, IMT has been recognized as a rare low-grade neoplasm with distinctive clinical, pathological, and molecular features. IMT shows a predilection for the visceral soft tissue of children and adolescents. The FNA cytologic features of IMT are somewhat nonspecific and variable and usually impose a benign, reactive impression. Typically, the smears show a mixture of plump myofibroblasts, inflammatory cells (mainly plasma cells and lymphocytes), and occasional large ganglion-like cells (see Fig. 14.36a) [71, 72]. Approximately 50% of IMTs show chromosomal translocations involving *ALK* gene rearrangements resulting in ALK protein overexpression (see Fig. 14.36b), especially in young patients [73].

Cytologic features:
- Hypercellular smears
- Plump myofibroblasts arranged in thigh clusters or dispersed cells
- Inflammatory infiltrate including plasma cells, lymphocytes, and histiocytes
- Occasional ganglion-like cells

Differential diagnosis and problems in diagnosis:
- Reactive myofibroblastic proliferation
- Angiomatoid fibrous histiocytoma
- Follicular dendritic cell sarcoma
- Langerhans cell histiocytosis

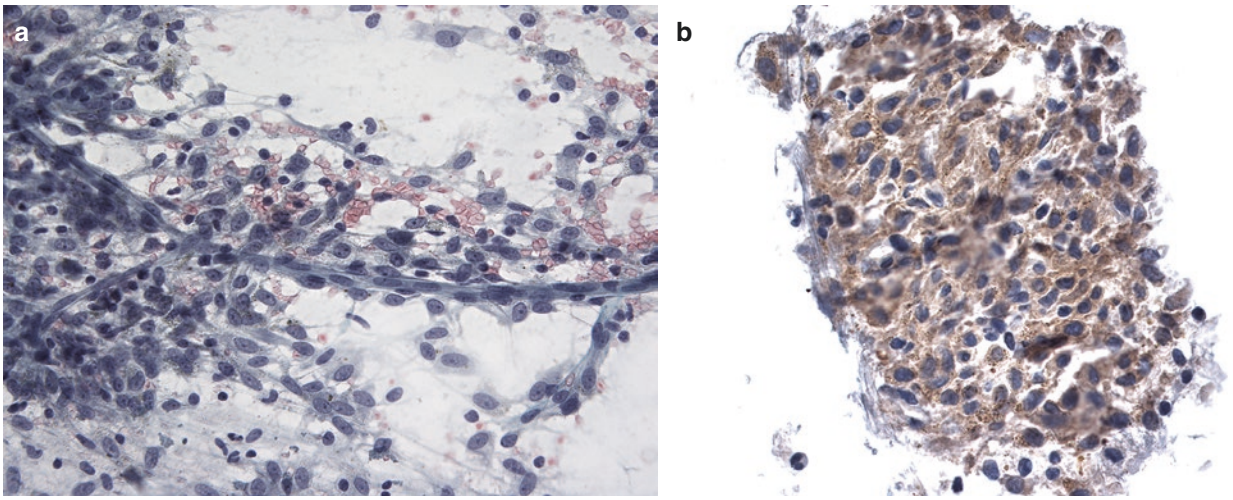

Fig. 14.36 Inflammatory myofibroblastic tumor. (**a**) Nodular fasciitis-like smears containing clusters of plump myofibroblasts and admixed lymphoplasmacytic infiltrate (Pap stain). ALK protein expression (**b**) is seen in about 50% of cases (cell block)

So-Called Fibrohistiocytic Tumors

Tenosynovial Giant Cell Tumor (Localized and Diffuse Types)

Tenosynovial giant cell tumors are among the most targeted benign neoplasms by FNAC. The localized and diffuse types of tenosynovial giant cell tumor share a common pathogenesis and a similar morphology but differ in their growth patterns, clinical features, and biological behaviors. Both can be intra- or extra-articular. The localized type (giant cell tumor of tendon sheath) is a relatively common neoplasm of the digits with a female predominance. It is a painless, slowly growing, well-circumscribed tumor, usually smaller than 4 cm in size. The diffuse type (pigmented villonodular tenosynovitis) is a locally aggressive neoplasm affecting mainly the knee and hip in younger patients. It presents as an ill-defined, periarticular mass, often larger than 5 cm. Both neoplasms are composed of mononuclear cells with round to oval nuclei, admixed with osteoclast-like giant cells, xanthoma cells, and siderophages, embedded in a collagenous, occasionally hyalinized matrix. All these components can be seen in the FNA smears (see Fig. 14.37) [74–77].

Cytologic features:

- Variable yield, hypocellular smears in tumors with hyalinized stroma
- Dispersed and clusters of mononuclear cells with round to oval nuclei (sometimes plasma cell-like)
- Mild to moderate cellular and nuclear pleomorphism
- Osteoclast-like giant cells
- Xanthomatous histiocytes and siderophages
- Mitoses may be found

Differential diagnosis and problems in diagnosis:

- Deep benign fibrous histiocytoma
- Reactive synovial hyperplasia
- Giant cell-rich sarcoma

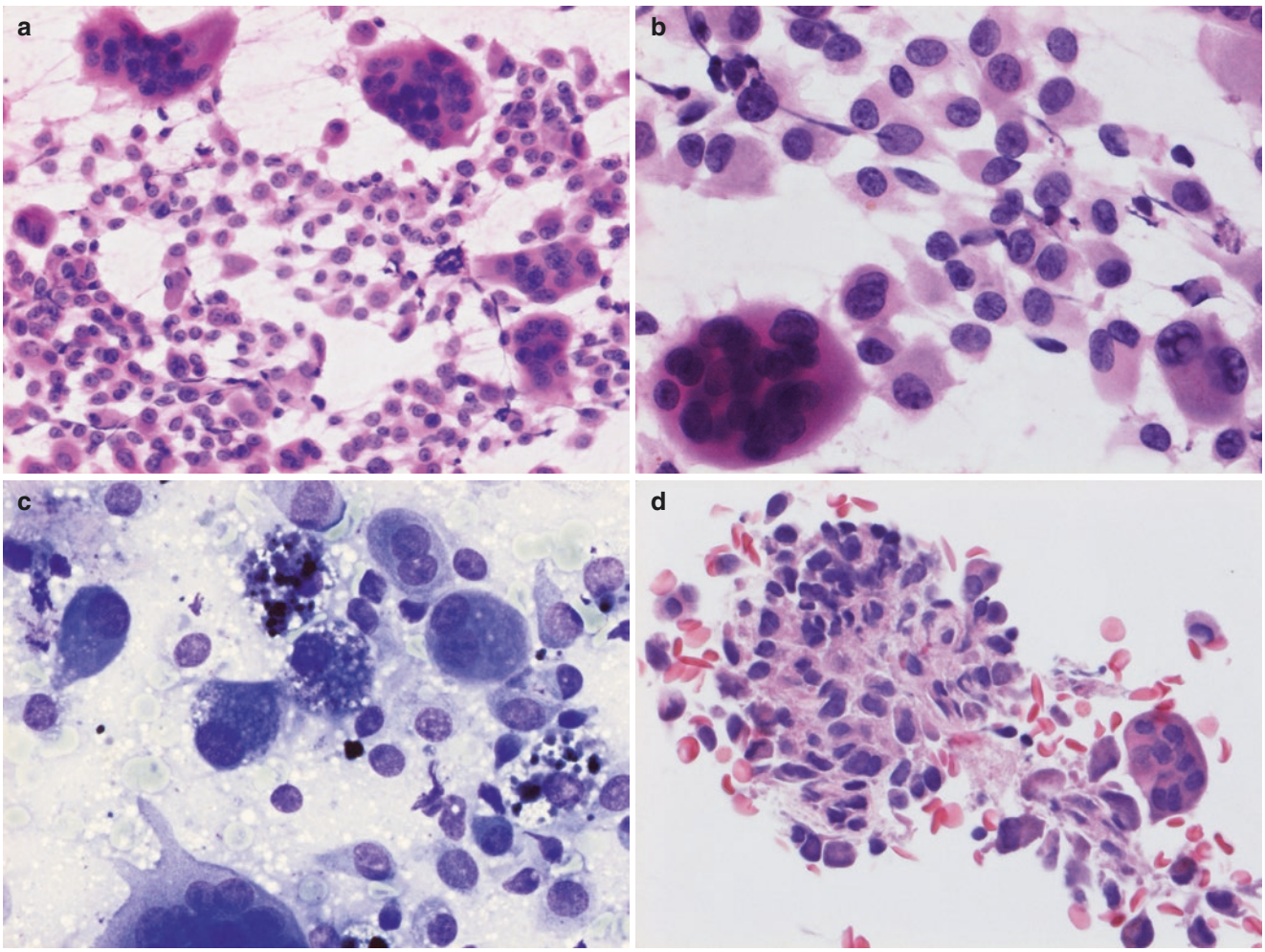

Fig. 14.37 Tenosynovial giant cell tumor (localized and diffuse types). (**a**–**c**) Dispersed and small clusters of mononuclear cells with round to oval nuclei and mild to moderate cellular and nuclear pleomorphism with admixture of osteoclast-like giant cells, xanthomatous histiocytes, and siderophages (H&E; MGG). (**d**) Similar morphology in cell block sections (H&E)

Benign Fibrous Histiocytoma

Benign fibrous histiocytoma, a common neoplasm, typically arises in the skin or subcutaneous tissue, occasionally extends to deep soft tissue. The cytologic features are described in section "Dermatofibroma (Benign Fibrous Histiocytoma)" in Chap. 15.

Smooth Muscle Tumors

Benign smooth muscle neoplasms such as cutaneous leiomyoma, angioleiomyoma, and uncommon deep leiomyoma of soft tissue are rare targets for FNA. Leiomyosarcoma of soft tissue, one of the most common soft tissue sarcomas, is relatively frequently examined by FNA cytology.

Leiomyoma of Deep Soft Tissue

Leiomyoma of deep soft tissue is a rare, slowly growing, well-circumscribed benign neoplasm, commonly arising in the retroperitoneum and different parts of the abdominal cavity in women. The cells have the morphology reminiscence of normal smooth muscle cells (see Fig. 14.38).

Low-grade leiomyosarcoma, an important diagnostic pitfall, displays more nuclear pleomorphism and coarser chromatin than leiomyoma [78].

Cytologic features:

- A mixture of clusters and dispersed, bland spindle cells
- Elongated, blunt-ended, cigar-shaped, occasionally truncated nuclei with insignificant nucleoli
- Collagenous matrix stains bluish-red (MGG) and often in the cell clusters
- Occasional mild to moderate cellular pleomorphism
- Some cells display gray or blue-gray cytoplasm with cytoplasmic extensions
- No mitotic figures

Differential diagnosis and problems in diagnosis:

- Extra-abdominal desmoid fibromatosis
- Low-grade leiomyosarcoma
- Gastrointestinal stromal tumor, spindle-cell type
- Schwannoma
- Low-grade malignant peripheral nerve sheath tumor (MPNST)
- Monophasic synovial sarcoma

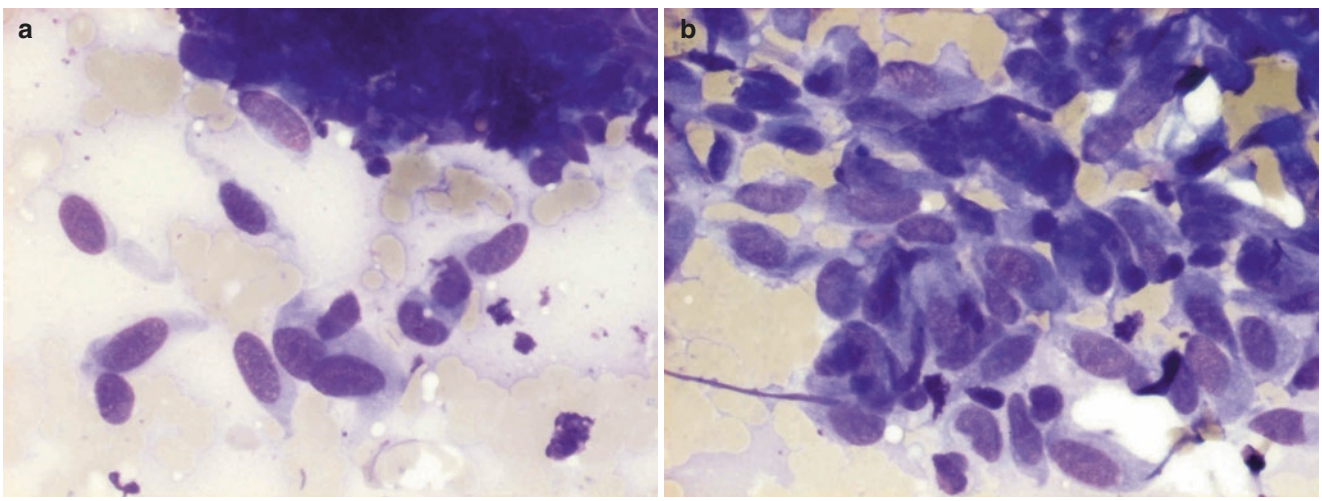

Fig. 14.38 Leiomyoma of deep soft tissue. (**a**, **b**) Mixture of clusters and dispersed bland spindle cells with elongated, blunt-ended, cigar-shaped nuclei (MGG)

Angioleiomyoma

Angioleiomyoma (ALM) is a benign neoplasm that usually presents as a tender or painful nodule in the skin or subcutaneous tissue in adults, commonly located in the lower extremities, but it can be widely distributed over the body. Clinically, ALM can be easily confused with glomus tumor, cutaneous cylindroma, and schwannoma. Morphologically, it may overlap with myopericytoma. One series of FNA of ALM has been published to date [79]. The most common findings are variable proportions of benign smooth muscle cells and benign uniform spindle cells, either dissociated or arranged in fascicles. Small fragments of collagenous matrix are also present (see Fig. 14.39).

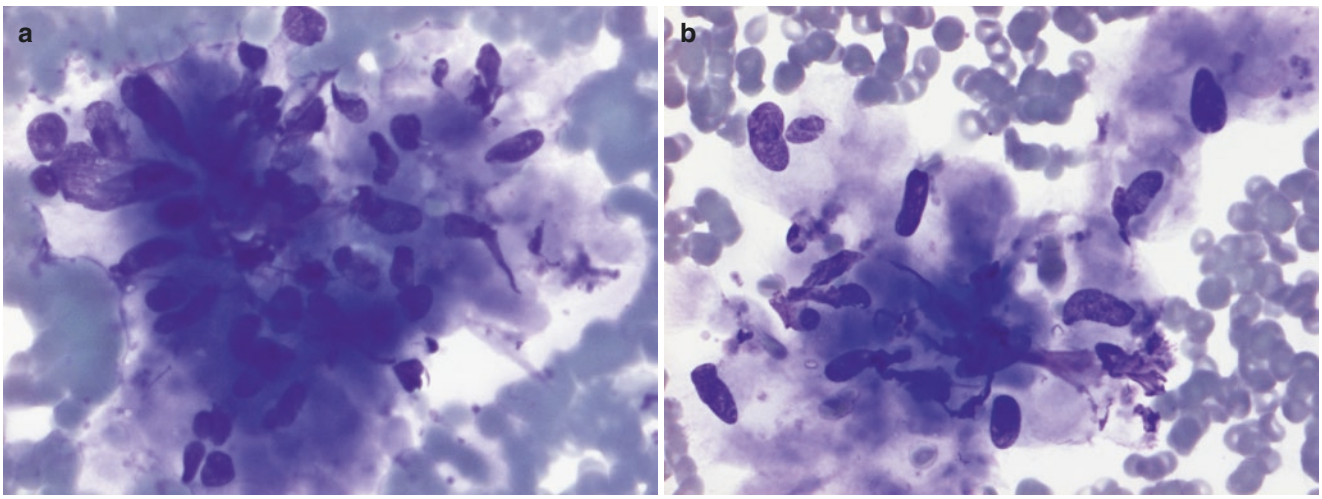

Fig. 14.39 Angioleiomyoma. (**a**, **b**) Fascicles of smooth muscle cells and uniform spindle cells in a collagenous matrix (MGG)

Leiomyosarcoma

Leiomyosarcoma (LMS) accounts for 10–15% of all primary soft tissue sarcomas [5]. Soft tissue LMS occurs most often in the retroperitoneum and limbs but also in other locations such as visceral organs and bones. Superficial LMS most often shows an indolent clinical course, whereas deeply seated soft tissue or retroperitoneal LMS shows an aggressive behavior with a high risk of metastasis. The morphology of LMS is similar in both settings. Typical tumor cells have elongated, cigar-shaped nuclei, sometimes segmented "in tandem" position (see Figs. 14.40 and 14.41). In most cases, a characteristic fascicular/pleomorphic pattern is recognizable at low-power examination. A pure spindle-cell or epithelioid pattern is less common (see Fig. 14.42). In high-grade LMS, marked cellular atypia, pleomorphism, necrosis, and multinucleated giant cells (some osteoclast-like giant cells) are common [80, 81].

Cytologic features:

- Hypercellular smears (hypocellular in tumors with hyalinized matrix)
- Three major cellular patterns in low power: mixed fascicular/pleomorphic, predominantly fascicular, and predominantly pleomorphic
- Minor component of dispersed, well-preserved cells with dense cytoplasm
- Stripped atypical, degenerate nuclei, with blue- or magenta-colored background in fascicles or clusters (MGG)
- Nuclei with elongated, blunted ends, cigar-shaped, occasionally segmented "in tandem" position
- Epithelioid tumor cells in epithelioid variant
- Pleomorphic, occasionally bizarre, multinucleated cells
- Mitoses and necrosis
- Osteoclasts

Differential diagnosis and problems in diagnosis:

- Soft tissue leiomyoma
- Nodular fasciitis
- Schwannoma
- Desmoid fibromatosis
- Malignant peripheral nerve sheath tumor (MPNST)
- Myofibroblastic sarcomas
- Undifferentiated pleomorphic/spindle-cell sarcoma
- Dedifferentiated sarcoma
- Metastatic sarcomatoid carcinoma
- Metastatic melanoma

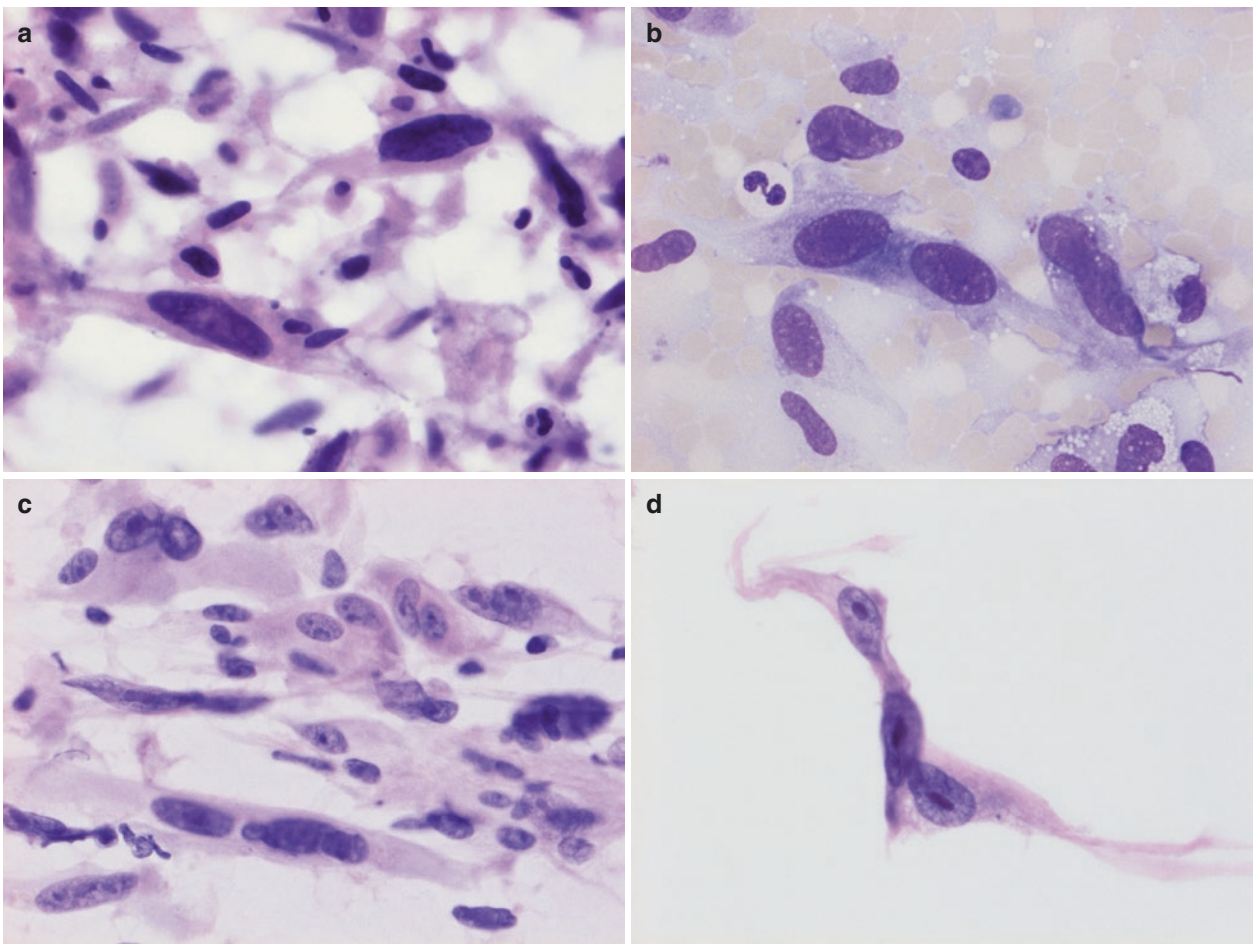

Fig. 14.40 Leiomyosarcoma. (**a**–**d**) Small clusters and dissociated tumor cells with elongated, cigar-shaped, occasionally truncated or "in tandem" position nuclei (H&E; MGG)

Epithelioid variant leiomyosarcoma may be misdiagnosed as undifferentiated carcinoma. In LMS, at least few cells with cigar-shaped or blunt-ended nuclei are present. Immunocytochemical examinations are helpful in doubtful cases (see Fig. 14.42). Leiomyosarcoma stains for smooth muscle actin (SMA), desmin, and caldesmon, although sometimes only focally. Focal cytokeratin positivity has been reported in leiomyosarcoma. The cytomorphology of leiomyosarcoma has been thoroughly evaluated in a few large series [80, 81].

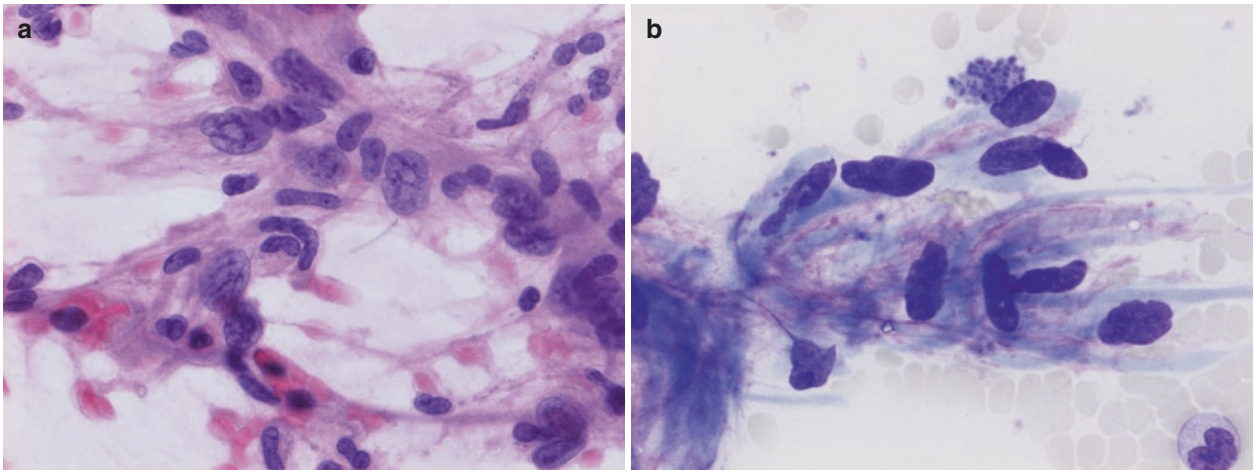

Fig. 14.41 Leiomyosarcoma. (**a**, **b**) Loosely cohesive clusters with a mixed fascicular/pleomorphic pattern (H&E; MGG)

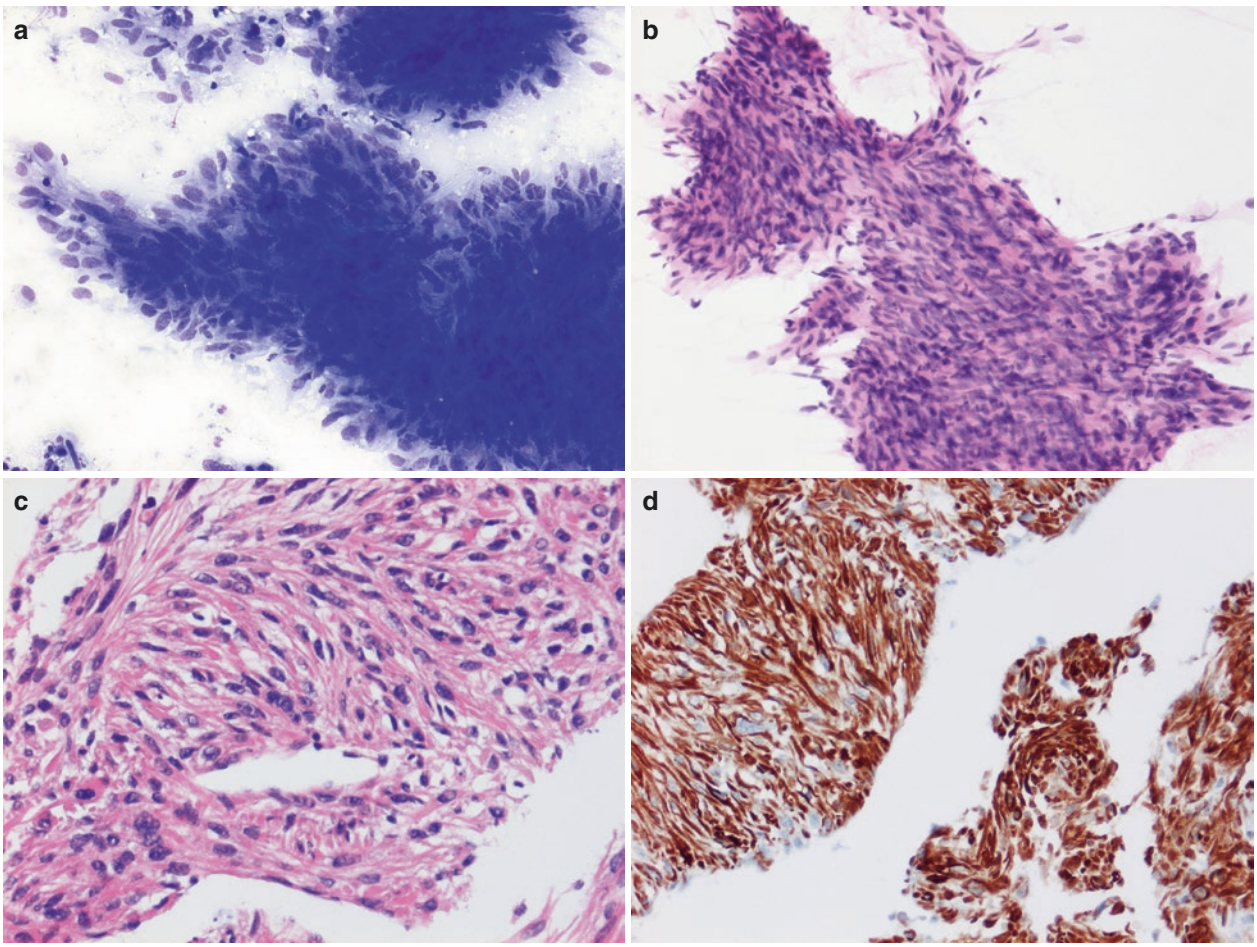

Fig. 14.42 Leiomyosarcoma. (**a**, **b**) Cohesive fascicles of atypical spindle cells (MGG; H&E). (**c**) Similar pattern is obvious in the cell-block section. (**d**) Strong desmin positivity supports diagnosis (H&E; desmin; cell block)

Striated Muscle Tumors

Benign and malignant striated muscle tumors are rare in adults in general. Embryonal and alveolar subtypes of rhabdomyosarcoma (RMS) are among the most common sarcomas of childhood, whereas pleomorphic RMS and spindle cell/sclerosing RMS occurs exclusively in adults.

Adult Rhabdomyoma

Adult rhabdomyoma is a rare benign neoplasm showing mature skeletal muscle differentiation. Most arise in the head and neck region, especially the tongue and floor of mouth. Smears display dispersed cells or cohesive clusters of large, round to polygonal, or elongated cells with abundant eosinophilic granular cytoplasm, often peripherally, located, uniform round nuclei with large nucleoli (see Fig. 14.43). Cytoplasm may be vacuolated due to dissolved glycogen.

Cytologic features:

- Large rounded, polygonal, or elongated cells, dispersed or arranged in cohesive clusters
- Abundant eosinophilic (H&E) granular cytoplasm
- Small, peripherally located nuclei with prominent nucleoli
- Occasional stripped nuclei
- Rarely visible cross-striation

Differential diagnosis and problems in diagnosis:

- Granular cell tumor
- Hibernoma

FNAC evaluation of rhabdomyoma may be difficult due to the similarity of the tumor cells to normal striated muscle and to other tumors with cells containing abundant granular cytoplasm [82, 83]. Hibernoma cells have also granular and/or vacuolated cytoplasm in smears, but the cells are generally smaller than those in rhabdomyoma. Granular cell tumors have no cytoplasmic vacuoles and diffusely stain with S-100 protein, whereas desmin and myoglobin expression is typical for rhabdomyoma.

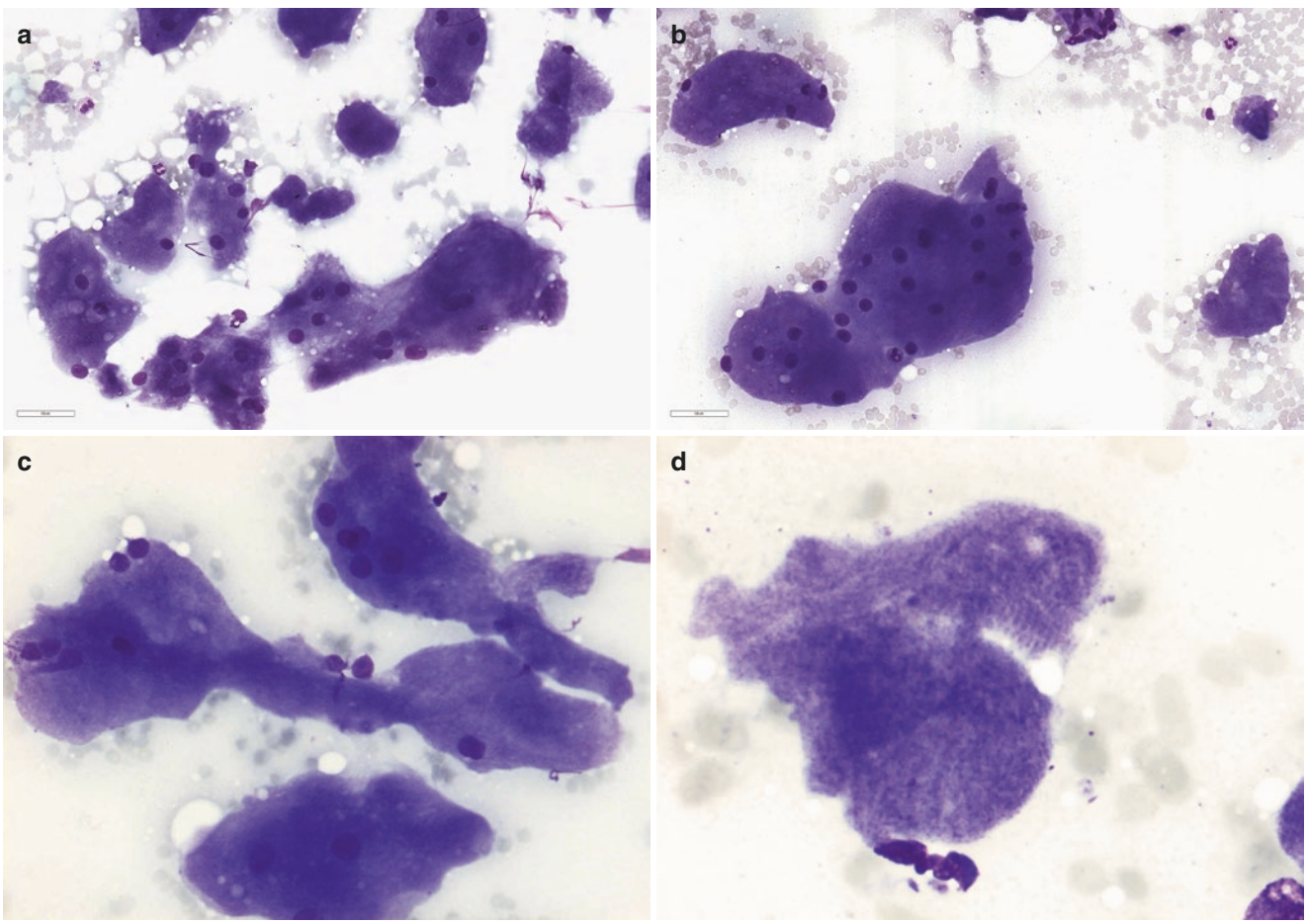

Fig. 14.43 Adult rhabdomyoma. (**a**–**c**) Syncytial sheets of dispersed large, rounded, polygonal, or elongated cells with small round to oval nuclei, fine chromatin, and abundant granular cytoplasm. (**d**) Rarely visible cross-striation (MGG)

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and accounts for approximately 50% of diagnosed rhabdomyosarcomas. Common locations include the head and neck region, genitourinary tract, and retroperitoneum. Typically, the smears are variably cellular, with marked cellular pleomorphism. Primitive spindle cells and rhabdomyoblast-like cells of various morphologies (triangular, rounded, and tadpole- or strap-shaped) are commonly seen (see Fig. 14.44) [84, 85]. Tumor cells express desmin, myogenin, and MyoD1. Embryonal RMS has a better prognosis than alveolar RMS.

Cytologic features:
- Mixture of loosely cohesive clusters and dispersed cells.
- Spindle cells or round cells are most common.
- Cellular and nuclear pleomorphism.
- Nucleoli may be prominent.
- Rhabdomyoblast-like tumor cells (triangular, rounded, and tadpole- or strap-shaped) variably present.
- Rhabdomyoblasts with eosinophilic (H&E) or gray-blue (MGG) dense cytoplasm.
- Areas of myxoid matrix variably present.

Differential diagnosis and problems in diagnosis:
- Alveolar rhabdomyosarcoma
- Infantile fibrosarcoma
- Leiomyosarcoma (LMS)

LMS is extremely rare in children and does not express myogenin or MyoD1. Spindle-cell neoplasm such as infantile fibrosarcoma is excluded when tumor cells are positive for desmin, myogenin, or MyoD1.

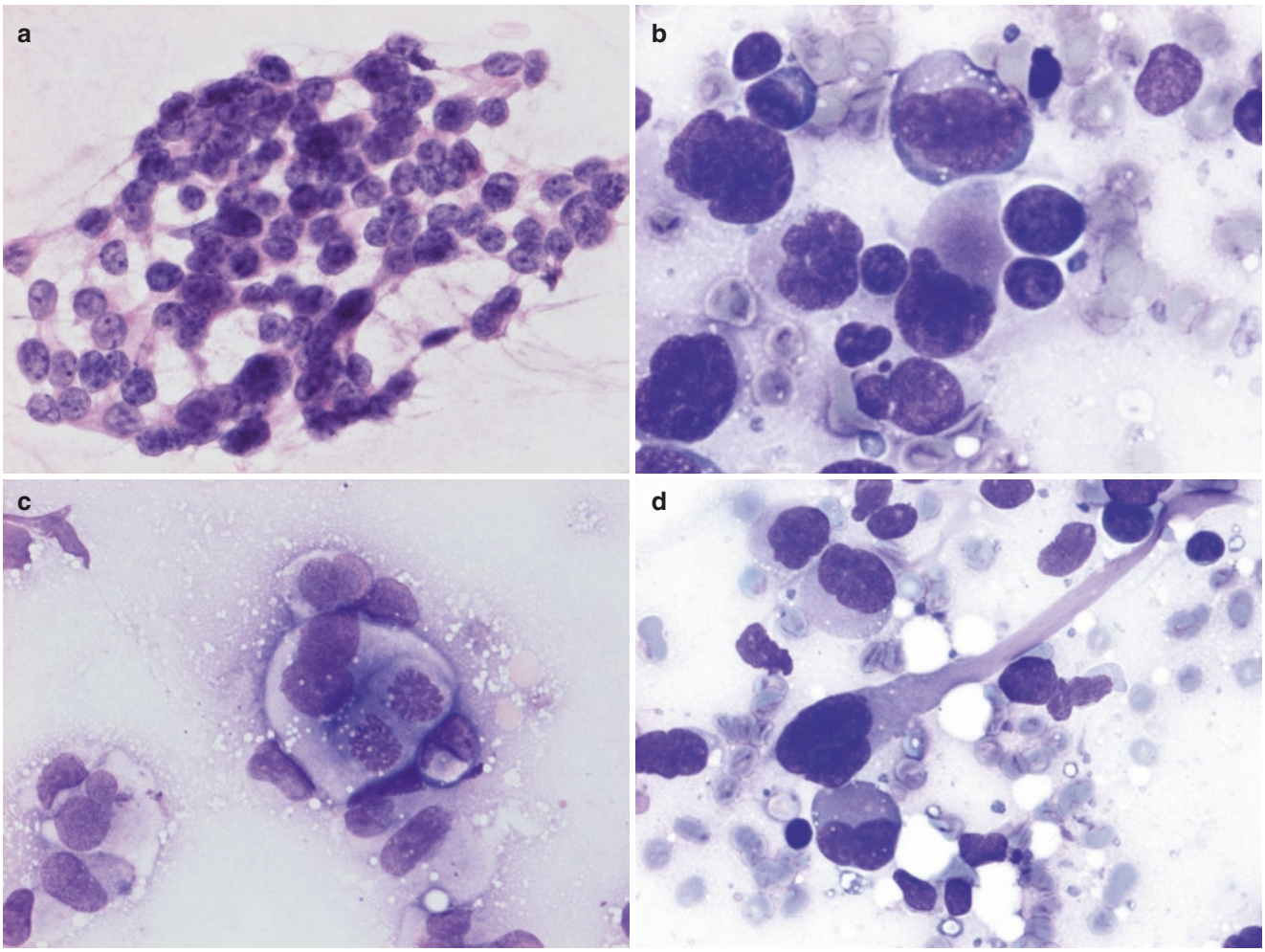

Fig. 14.44 Embryonal rhabdomyosarcoma. (**a**–**d**) Hypercellular smears with loosely cohesive clusters and dispersed single cells of various morphologies (triangular, rounded, tadpole- or strap-shaped) (H&E; MGG). Mitoses and multinucleation are common

Alveolar Rhabdomyosarcoma

Alveolar RMS (ARMS) accounts for about 20% of all pediatric RMSs and occurs in older children and adolescents. In contrast to embryonal RMS, the cellular composition of smears is more uniform with predominantly small- to medium-sized round or ovoid cells with round- or pear-shaped hyperchromatic nuclei, often with large nucleoli (see Fig. 14.45). Multinucleated tumor giant cells with small nuclei are common [85]. Similar to the embryonal subtype, tumor cells are immunoreactive with desmin, myogenin, and MyoD1. Aberrant expression of keratins, CD99, S-100 protein, lymphoid markers, and NSE poses

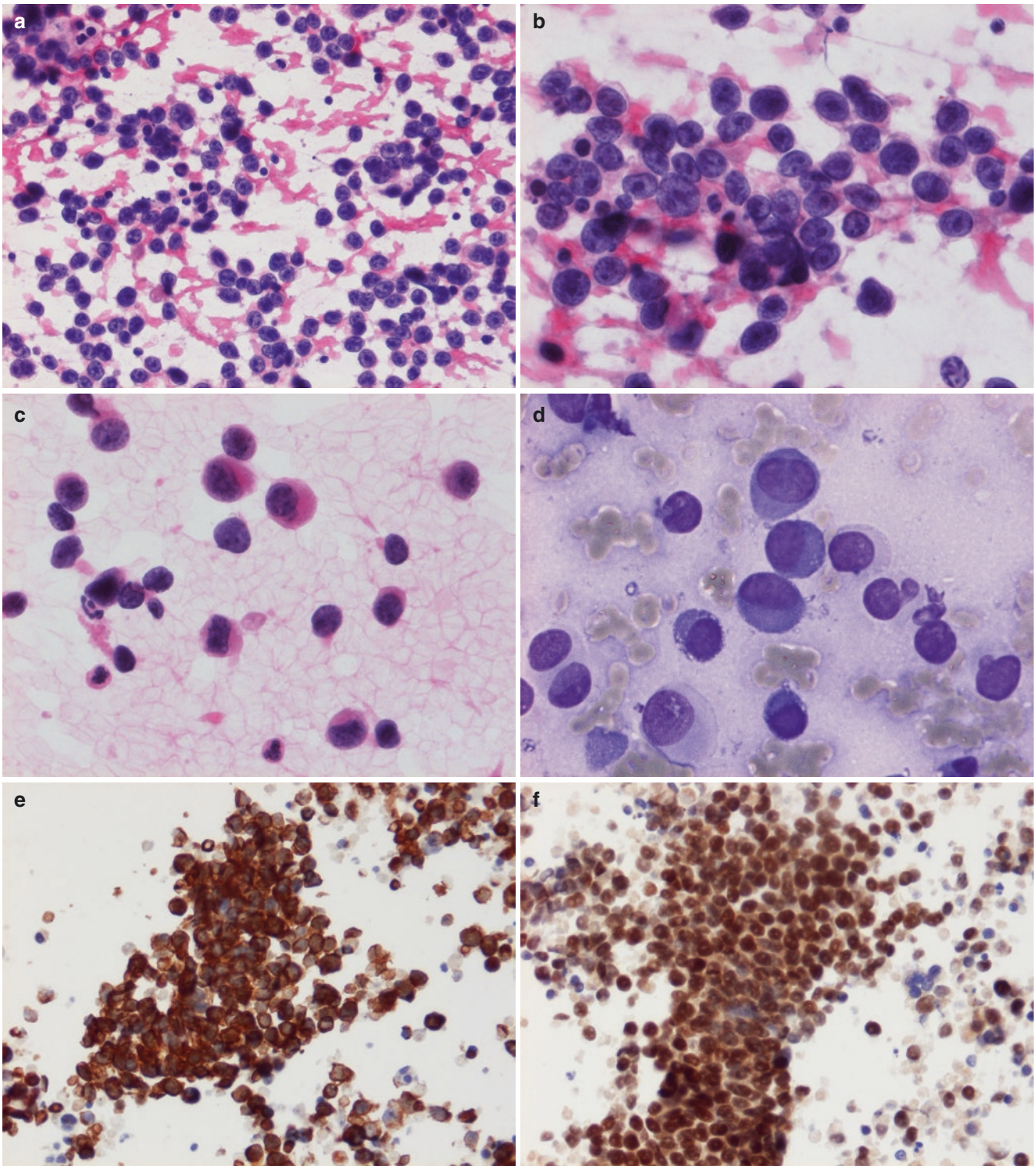

Fig. 14.45 Alveolar rhabdomyosarcoma. (**a**, **b**) Loosely cohesive clusters and dispersed, single, small- and medium-sized cells with hyperchromatic nuclei and prominent nucleoli (H&E). (**c**, **d**) Rhabdomyoblastic morphology (H&E; MGG). (**e**, **f**) Diffuse and strong desmin and myogenin positivities support with diagnosis (cell block; desmin; myogenin)

significant diagnostic challenges and confusion with other small round blue cell tumors. Most ARMS have either *PAX3-FOXO1* or *PAX7-FOXO1* gene fusion, which can be detected by FISH [19]. Identification of ARMS is clinically important as it has unfavorable prognosis and is treated more aggressively.

Cytologic features:
- Hypercellular smears
- Cell clusters mixed with dispersed cells
- Stripped nuclei commonly mixed with gray-blue blebs of cytoplasm
- Small- or medium-sized, round to polygonal, and ovoid or pear-shaped cells
- Scanty cytoplasm, coarse nuclear chromatin, and often large nucleoli
- Cytoplasmic vacuolization
- Mitoses
- Binucleated and multinucleated tumor cells

Differential diagnosis and problems in diagnosis:
- Ewing sarcoma
- Poorly differentiated synovial sarcoma
- Precursor lymphoblastic lymphoma
- Desmoplastic small round cell tumor (both are keratin and desmin positive)
- Poorly differentiated neuroendocrine carcinoma

Alveolar RMS belongs to a group of round cell malignant neoplasms, and distinguishing ARMS from other small round cell tumors can be difficult in routinely stained smears. The final diagnosis should be confirmed with ancillary tests such as immunocytochemical and molecular genetic studies (Tables 14.1 and 14.2).

Pleomorphic Rhabdomyosarcoma

Pleomorphic RMS is an uncommon sarcoma of adults older than 50 years of age. Common sites are the limbs. This is a high-grade sarcoma with marked cellular and nuclear pleomorphism. The FNA smears are hypercellular, containing highly atypical spindle or polygonal cells and large rhabdoid cells with abundant eosinophilic cytoplasm (H&E) and eccentrically located nuclei (see Fig. 14.46) [86, 87]. These rhabdoid cells are similar to those seen as a heterologous component in other sarcomas such as MPNST. Tumor cells stain for desmin and myogenin.

Cytologic features:
- Cell clusters and dispersed cells
- Marked cellular and nuclear pleomorphism
- Mixture of atypical spindle cells, rhabdoid cells, and multinucleated tumor cells

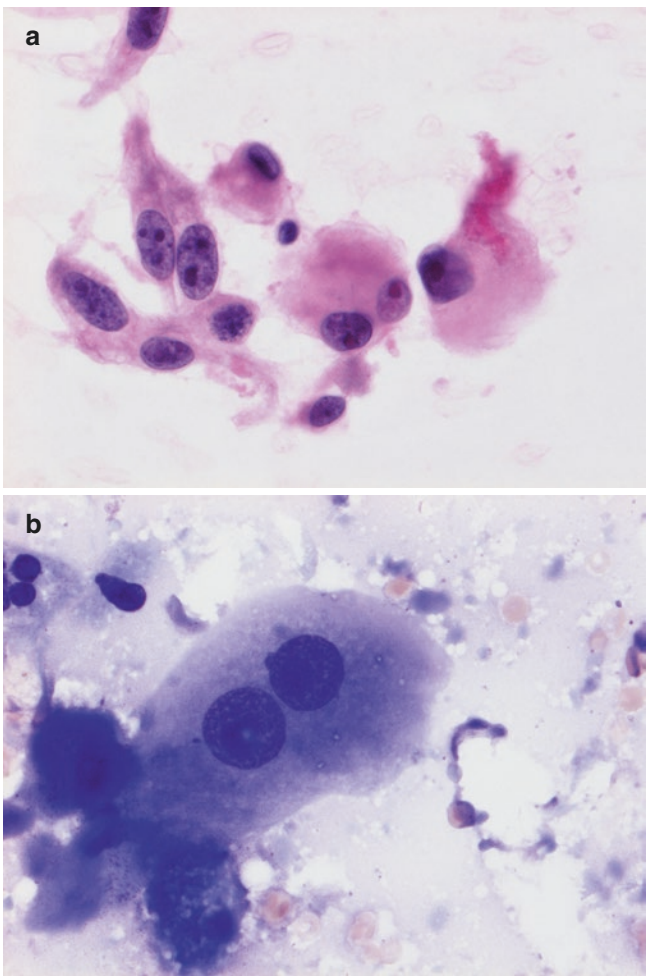

Fig. 14.46 Pleomorphic rhabdomyosarcoma. (**a**) Highly pleomorphic, spindle, or polygonal cells of variable size with round to oval nuclei, with prominent nucleoli, and often with abundant eosinophilic cytoplasm (H&E). (**b**) Tumor cells with rhabdomyoblastic morphology (MGG)

Differential diagnosis and problems in diagnosis:
- Pleomorphic variant of other sarcomas
- Malignant peripheral nerve sheath tumor with heterologous rhabdoid differentiation
- Dedifferentiated liposarcoma with heterologous rhabdoid differentiation

Tumors of Peripheral Nerves

Benign Nerve Sheath Tumors

Schwannoma (Neurilemmoma)

Schwannoma occurs in all age groups but most frequently in adults between 40 and 60 years old but may be seen in all age groups. Most schwannomas are deep seated, arising in the limbs, head and neck region, retroperitoneum, and posterior mediastinum.

Schwannoma is a neoplasm commonly examined by FNAC. Needling the lesion itself may produce a sharp pain radiating along the nerve, a valuable clue to the diagnosis; however, it is not entirely specific and can occur in any soft tissue lesion seated close to a nerve. Smears are variably but often hypercellular and contain irregular tissue fragments—"pieces of jigsaw puzzle" of spindle cells embedded in a fibrillary stroma. It is often possible to identify both the highly cellular Antoni A and the poorly cellular myxoid Antoni B components. Most spindle cells exhibit neurogenic differentiation including elongated, wavy nuclei that are often pointed or folded and sometimes show a fishhook-like appearance. Many aspirates also contain variable amounts of small- or medium-sized epithelioid cells with round, bland-looking nuclei (see Fig. 14.47). Many schwannomas show cystic changes resulting in poor cellularity or nondiagnostic yield [88, 89].

Cytologic features of Antoni A-type schwannoma:
- Cohesive tissue fragments of different sizes, often with irregular borders ("of a jigsaw puzzle pieces").
- Rare dispersed cells.
- In the fragments, cells have indistinct cytoplasm and elongated, slender nuclei with pointed ends and boomerang-shaped or comma-like nuclei embedded in a fibrillary stroma.
- Occasional nuclear palisading and Verocay bodies.
- Occasionally small round nuclei.
- Occasionally slight to moderate nuclear pleomorphism.

Cytologic features of Antoni B-type schwannoma:
- Poor cellular smears with variable areas of myxoid matrix
- Dispersed cells more common than in smears from Antoni A areas
- Cystic degeneration with presence of histiocytes and inflammatory cells

Differential diagnosis and problems in diagnosis:
- Spindle-cell lipoma
- Solitary fibrous tumor
- Low-grade MPNST
- Low-grade LMS
- Meningioma
- Myxoid soft tissue tumors (Antoni B-type neurilemmomas with large foci of myxoid matrix)
- Pleomorphic sarcomas (smears from ancient schwannomas)

A common problem is to distinguish sarcomas from ancient schwannomas, which often exhibit nuclear pleomorphism with marked anisokaryosis and hyperchromasia. Many of those large nuclei, however, show evenly distributed chromatin and typical large intranuclear vacuoles ("Kern-loche") (see Fig. 14.48). It is usually possible to find other components of a schwannoma in addition to the scattered atypical cells [90]. Another diagnostic pitfall is misinterpreting cellular schwannoma as a low-grade spindle-cell sarcoma [91]. Demonstration of diffuse and strong positivity for S-100 protein by immunocytochemistry is very helpful to confirm the diagnosis of schwannoma.

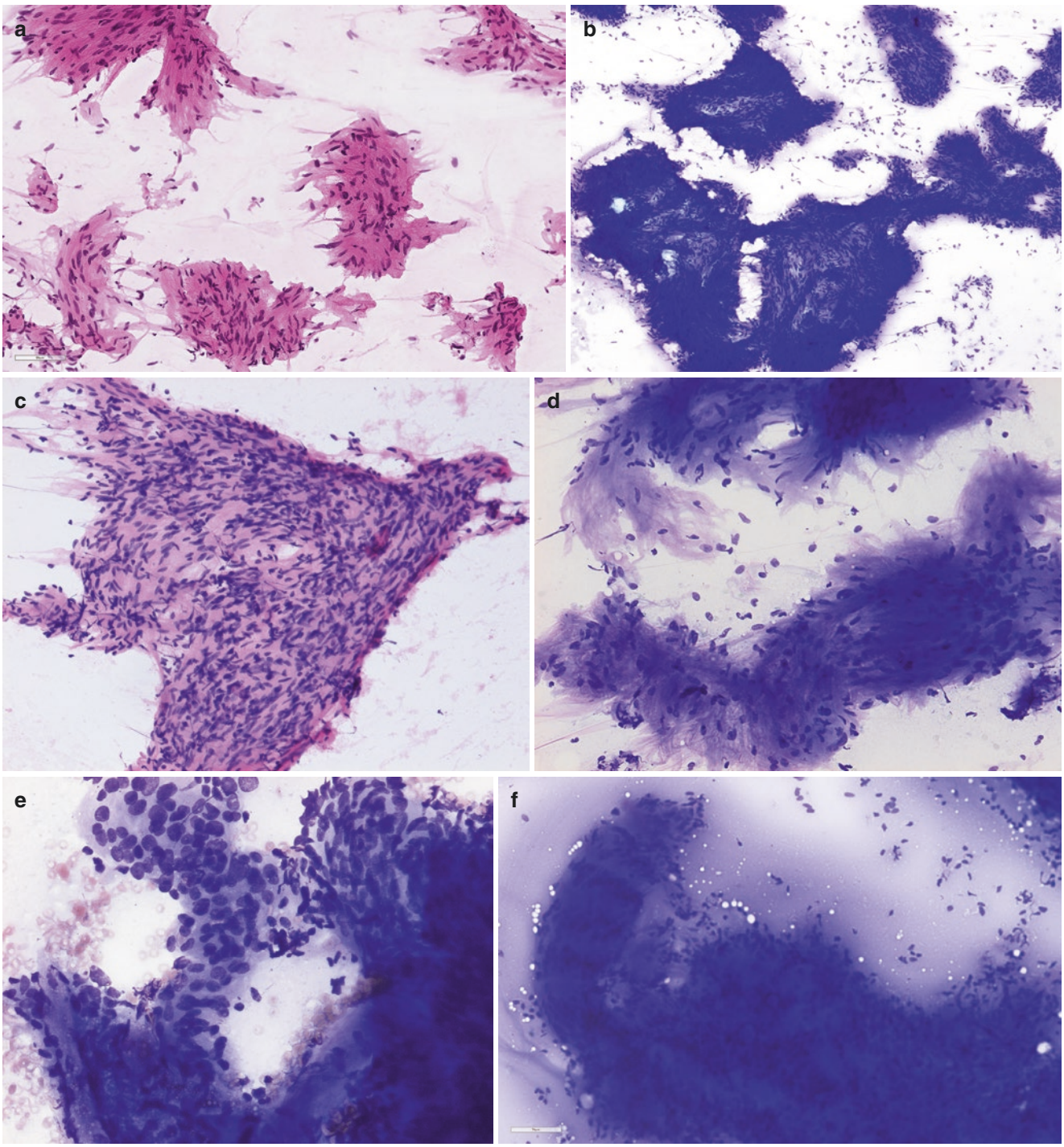

Fig. 14.47 Schwannoma. (**a**–**b**) Cohesive tissue fragments of variable size and shape with irregular borders—"pieces of jigsaw puzzle" (H&E; MGG). (**c**) Cohesive clusters of spindle cells showing pointed ends embedded in a fibrillary stroma Antoni A and poorly cellular myxoid Antoni B component (**d**) (H&E; MGG). Occasional round cell component (**e**) and nuclear palisading creating Verocay bodies (**f**, **g**) (MGG; H&E) Verocay body better appreciated in the cell block section (**h**) (H&E)

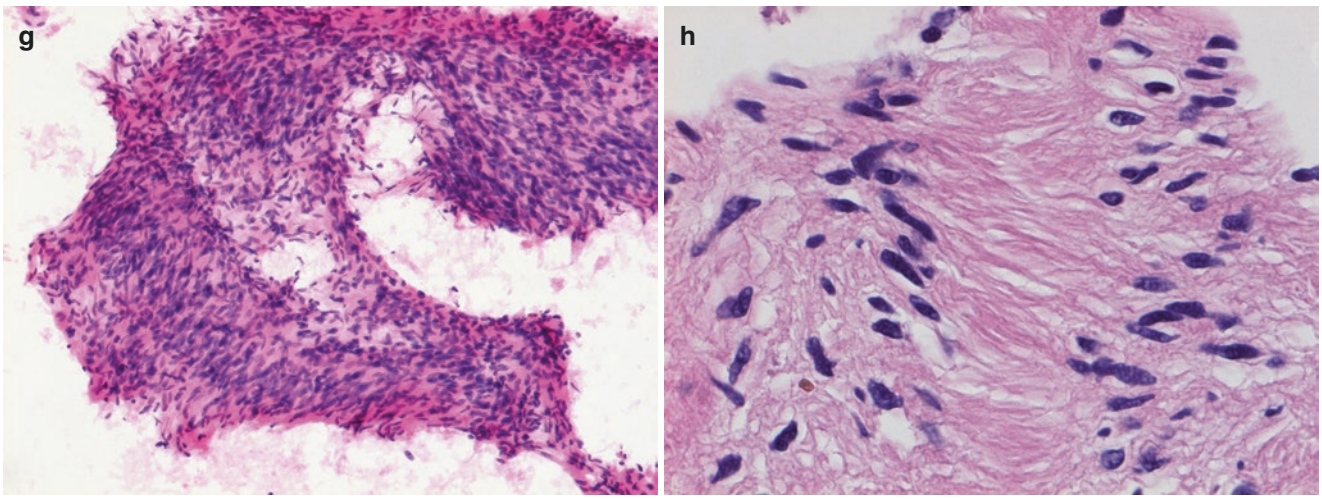

Fig. 14.47 (continued)

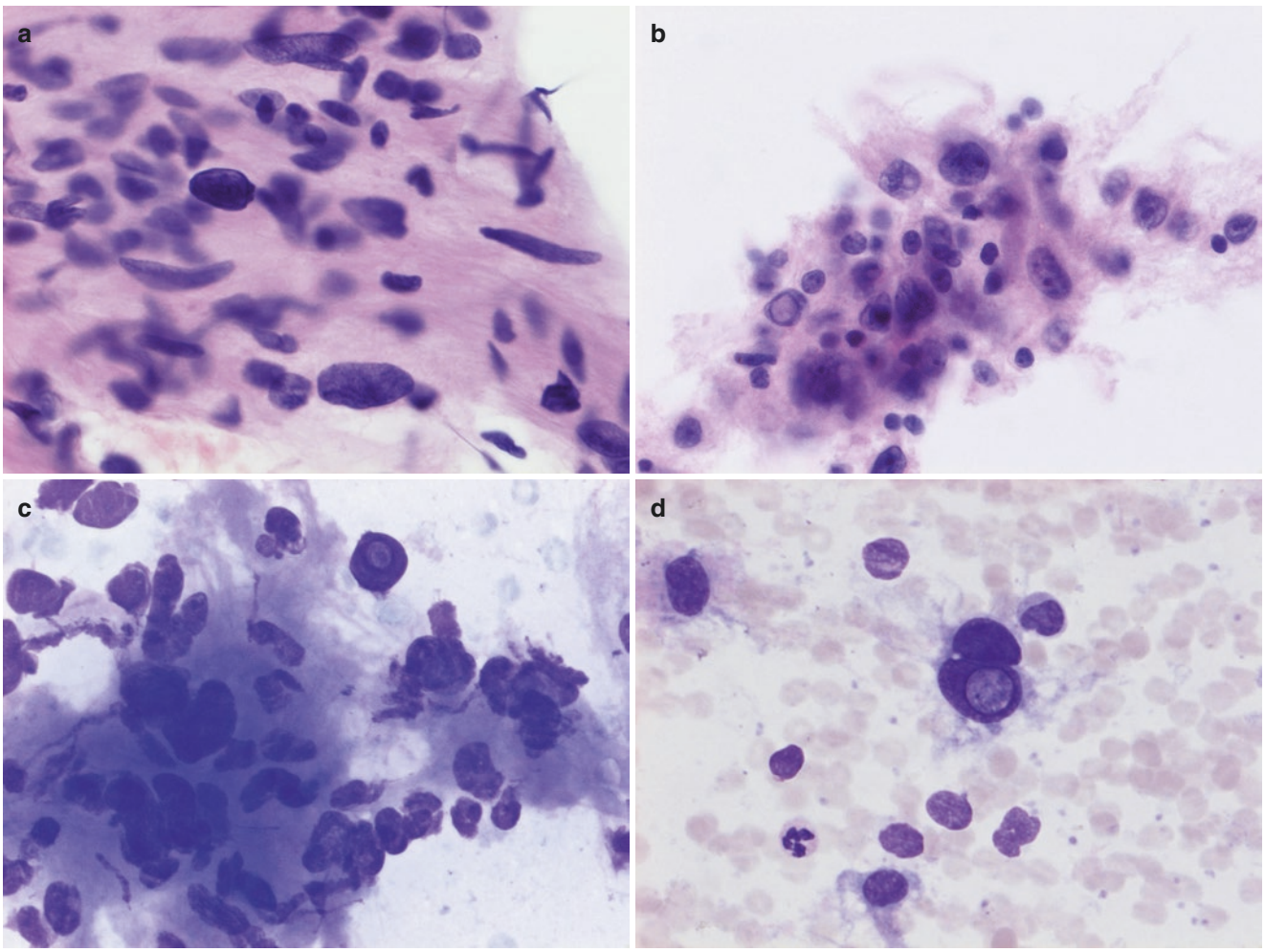

Fig. 14.48 Ancient schwannoma. (**a**–**d**) Irregular clusters and some dispersed single cells with marked anisokaryosis and hyperchromasia. Note typical intranuclear inclusions ("Kern-loche") (H&E; MGG)

Neurofibroma

Neurofibromas, especially large neurofibromas in patients with von Recklinghausen's disease, are occasionally referred for FNA when there is a question of malignant transformation. Neurofibroma is composed of a mixture of Schwann cells, perineural-like cells, fibroblasts, mast cells, and scattered axons all embedded in a stroma. Because the stroma is typically fibromyxoid, at times collagenous or hyalinized, FNA of these stroma-rich areas can result in poor or hypocellular smears. The aspirated cells are similar to those in smears from schwannoma: cohesive spindle cells with slender and often comma-like, bent, or wavy nuclei (see Fig. 14.49). Different cell types in neurofibroma are indistinguishable in smears. A specific diagnosis of neurofibroma based on FNA alone can be difficult. Immunocytochemical studies are often necessary.

Cytologic features:

- Variable cellularity
- Occasionally myxoid matrix
- Small, poorly cohesive cell clusters and dispersed cells
- Bland fibroblast-like spindle cells and spindle cells reminiscent of those in schwannoma
- Stripped nuclei

Differential diagnosis and problems in diagnosis:

- Antoni B-type schwannoma
- Intramuscular myxoma
- Solitary fibrous tumor
- Spindle-cell lipoma
- Low-grade malignant peripheral nerve sheath tumor

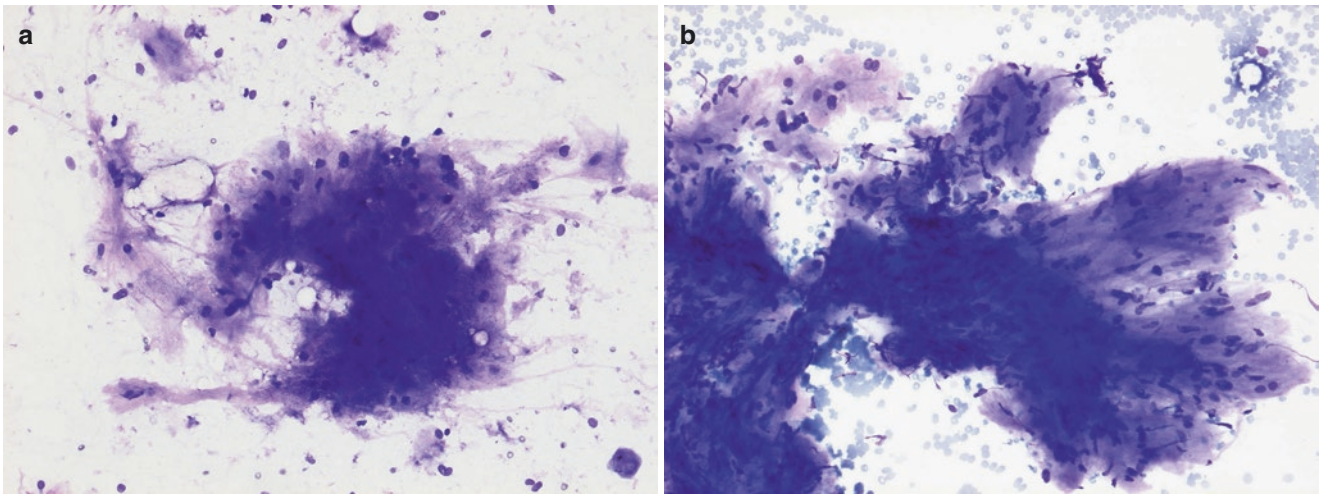

Fig. 14.49 Neurofibroma. (**a**) A loosely cohesive cluster of uniform and some slightly variable in size cells with bland, round to ovoid nuclei and fibrillary/myxoid background matrix. (**b**) Sheet of spindle cells with both schwannian cells and fibroblasts characteristic in a fibrillary/myxoid background matrix (MGG)

Granular Cell Tumor (See Section "Granular Cell Tumor" in Chap. 15)

Granular cell tumor is an uncommon benign neoplasm commonly arising in the tongue, skin and subcutaneous tissue, gastrointestinal tract, mediastinum, breast, and other sites in the middle-aged adults.

The tumor cells have round to oval nuclei, inconspicuous nucleoli, and abundant granular cytoplasm. Because of the fragility of tumor cells, smears often contain stripped nuclei in a background of finely granular material (see Figs. 15.37 and 15.38). Nuclei are small and dark but occasionally with mild to moderate atypia. The tumor cells stain for S-100 protein (see Fig. 15.38), NSE, CD68, and inhibin contain PAS-positive diastase-resistant cytoplasmic granules representing the phagolysosomes. Malignant granular cell tumors are very rare, and smears show morphologic criteria of malignancy such as predominance of pleomorphic spindle cells with large nucleoli, mitoses, and necrosis [92].

Cytologic features:
- Dispersed cells and poorly cohesive clusters.
- Intact polygonal cells with abundant granular cytoplasm.
- Stripped nuclei in a granular background.
- Rounded, small nuclei with insignificant nucleoli.
- Cells with large nuclei with coarse chromatin and macronucleoli may be present.

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

Perineurioma

Soft tissue perineurioma is a rare benign peripheral nerve sheath neoplasm composed of cells resembling the normal perineural cells. A specific diagnosis is most likely not feasible based on cytomorphology alone because the FNA smears share a similar appearance with other low-grade spindle-cell and myxoid neoplasms, such as cellular intramuscular myxoma. Nevertheless, the presence of elongated spindle cells with bland oval nuclei and characteristic long, thin, bipolar cytoplasmic processes in a myxoid stroma is a typical finding (see Fig. 14.50) [63, 93, 94]. The perineurioma cells are positive for CD34, epithelial membrane antigen (EMA), and claudin-1 (as normal perineural cells) and negative for S-100 protein.

Cytologic features:
- Variable cellularity
- Often myxoid background
- Elongated cells with oval nuclei and long, thin, bipolar cytoplasmic processes
- Few vessel fragments

Differential diagnosis and problems in diagnosis:
- Cellular intramuscular myxoma
- Schwannoma with prominent Antoni B area
- Neurofibroma
- Myxofibrosarcoma, low grade
- Low-grade fibromyxoid sarcoma

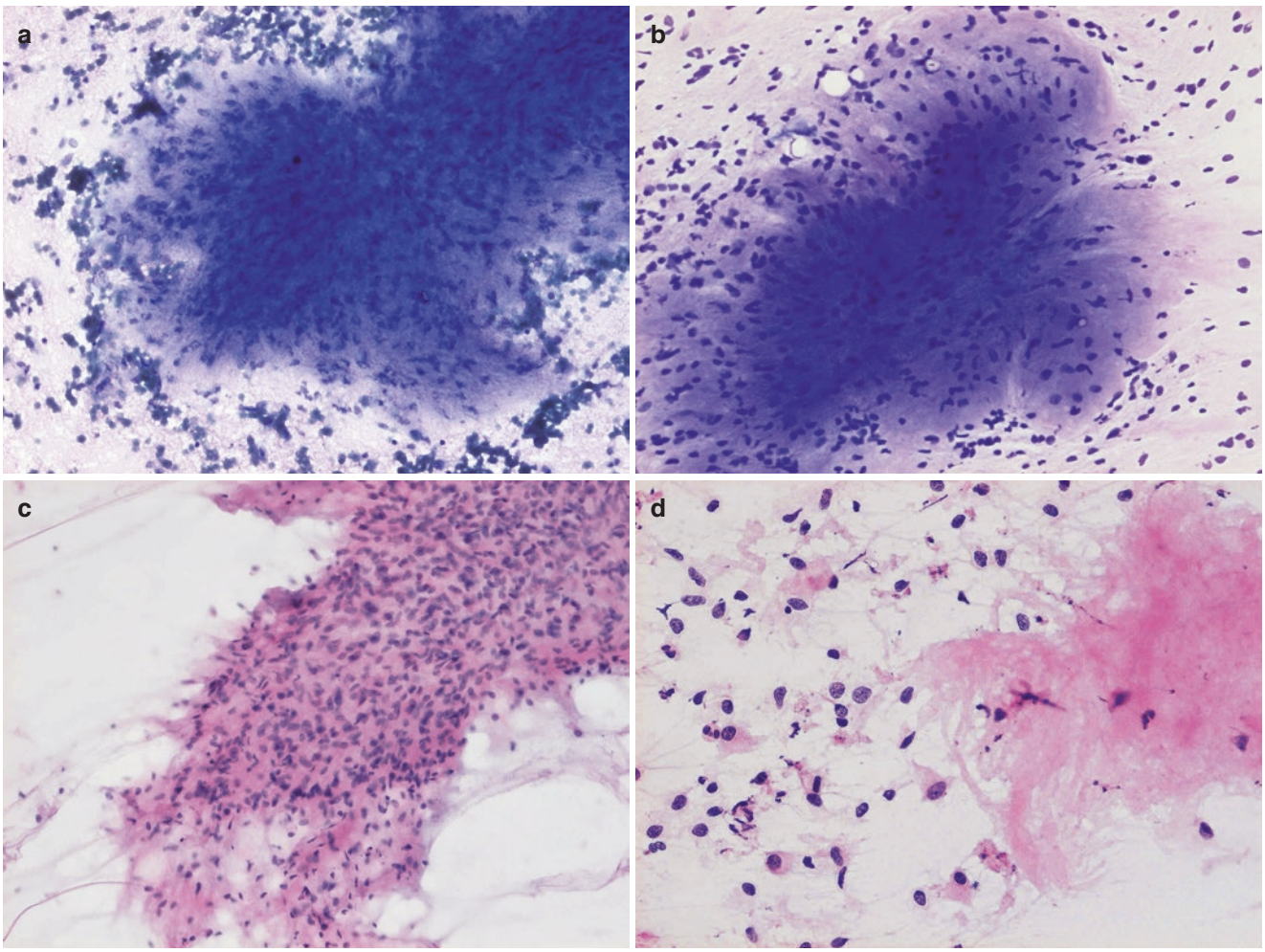

Fig. 14.50 Perineurioma. (**a**–**c**) Poorly preserved, elongated spindle cells with bland nuclei in the myxoid background. (**d**) Scattered slightly pleomorphic cells and fragments of collagenous tissue (MGG; H&E)

Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumor (MPNST) is a sarcoma arising from a peripheral nerve or as a malignant transformation of neurofibromas in patients with von Recklinghausen's disease (NF1). Common sites of involvement include large- and medium-sized nerves of the upper arm, buttock, brachial plexus, and paraspinal nerves. The cytomorphologic features, reflecting very diverse histologic appearances, are extremely variable and nonspecific. The most commonly described tumor cells are elongated with fusiform, often comma-shaped, wavy, or buckled nuclei, but other forms of neoplastic cells are also present. Pleomorphic and multinucleated tumor cells are found in high-grade tumors. Polygonal or rounded cells may predominate in epithelioid MPNST. Common helpful histologic features such as whorled perivascular arrangement of cells, fascicles, or a storiform pattern (see Figs. 14.51 and 14.52) and alternative cellular and hypocellular areas are not perceptible in FNA smears. Heterologous components (cartilage, bone, epithelial glands, or rhabdoid cells) present focally in approximately 10–15% of MPNST, which are rarely sampled by FNA [95–97]. Although focal S-100 protein and/or GFAP positivity is helpful, a panel of antibodies (e.g., CD34, cytokeratins, EMA, desmin, MDM2) should be used to exclude its many morphologic mimics. Recently, complete loss of trimethylation of lysine 27of histon3 (H3K27me3) expression was observed in more than half of the MPNST cases, especially in high-grade MPNST cases [98]. Epithelioid MPNST is a rare variant of MPNST (<5% of cases), and not associated with NF1. The neoplastic cells are epithelioid and usually embedded in a myxoid stroma. In contrast to conventional MPNST, in which S-100 protein staining is only focal, epithelioid MPNST is strongly and diffusely positive for S-100 protein. INI-1 loss of expression is observed in epithelioid MPNST, but not in conventional MPNST.

Cytologic features:

- Hypercellular smears
- Mixture of cell clusters, fascicles, and dispersed cells
- A fibrillar background may be found in clusters or fascicles
- Predominantly spindle-shaped cells often with bipolar cytoplasmic processes and fusiform, wavy, or comma-like nuclei
- Often hyperchromatic nuclei with large nucleoli
- Variable presence of pleomorphic and/or multinucleated tumor cells
- Infrequent heterologous components
- Rounded or polygonal cells predominate smears of epithelioid MPNST
- Mitotic figures

Differential diagnosis and problems in diagnosis:

- Ancient schwannoma
- Cellular schwannoma
- Leiomyosarcoma
- Synovial sarcoma
- Sarcomatoid carcinoma
- Spindle-cell melanoma
- Malignant solitary fibrous tumor
- Dedifferentiated liposarcoma
- Myoepithelial carcinoma (epithelioid MPNST)
- Malignant melanoma

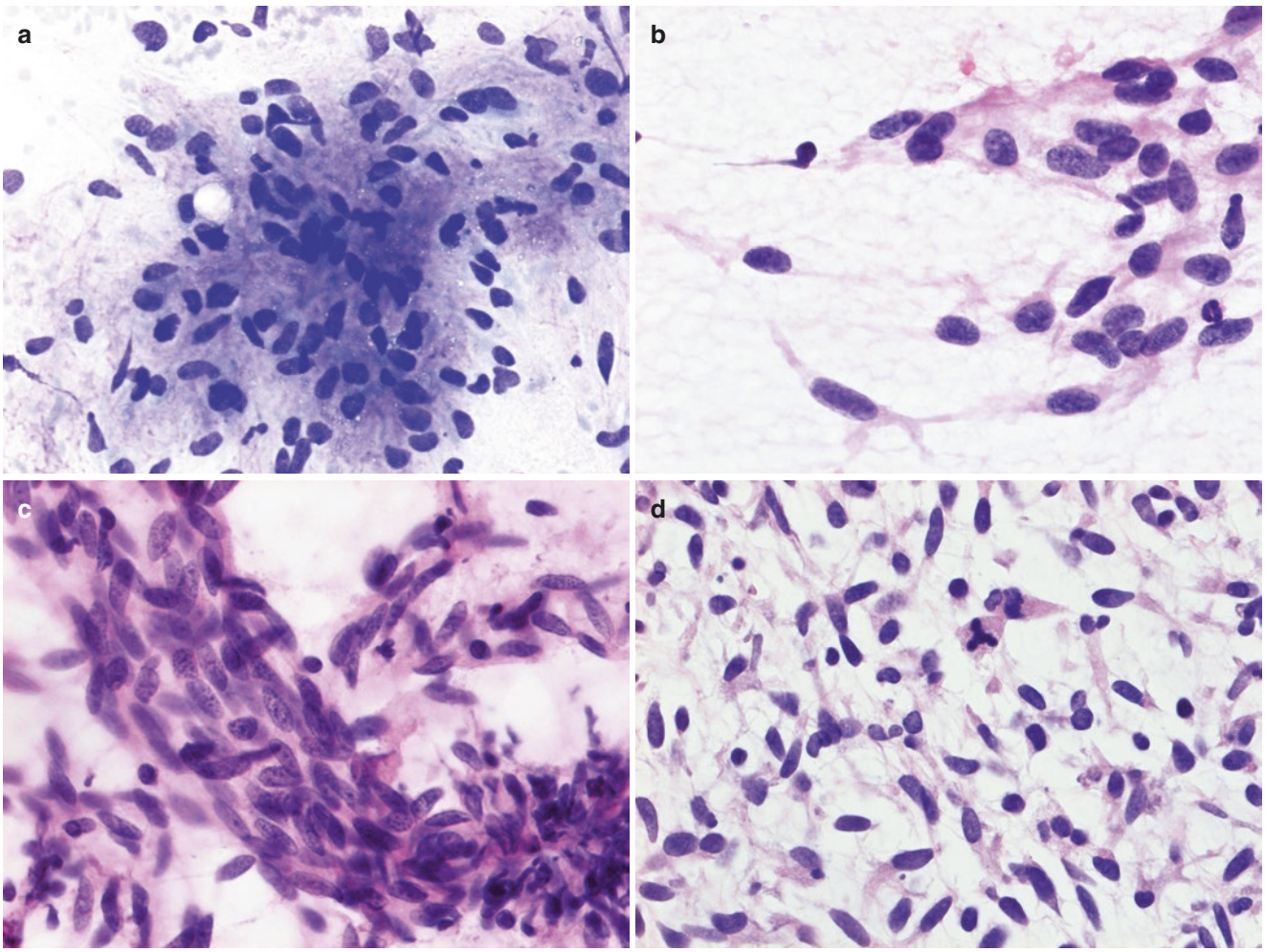

Fig. 14.51 Malignant peripheral nerve sheath tumor. (**a**–**c**) Smears of low-grade MPNST: loosely fascicles of slightly or moderately atypical spindle cells with fusiform, wavy, or comma-like nuclei and occasional cytoplasmic processes in the fibrillary background matrix may be difficult to distinguish from benign nerve sheath tumors (MGG; H&E). (**d**) Corresponding cell block section with slightly pleomorphic spindle cells but atypical mitosis (cell block; H&E)

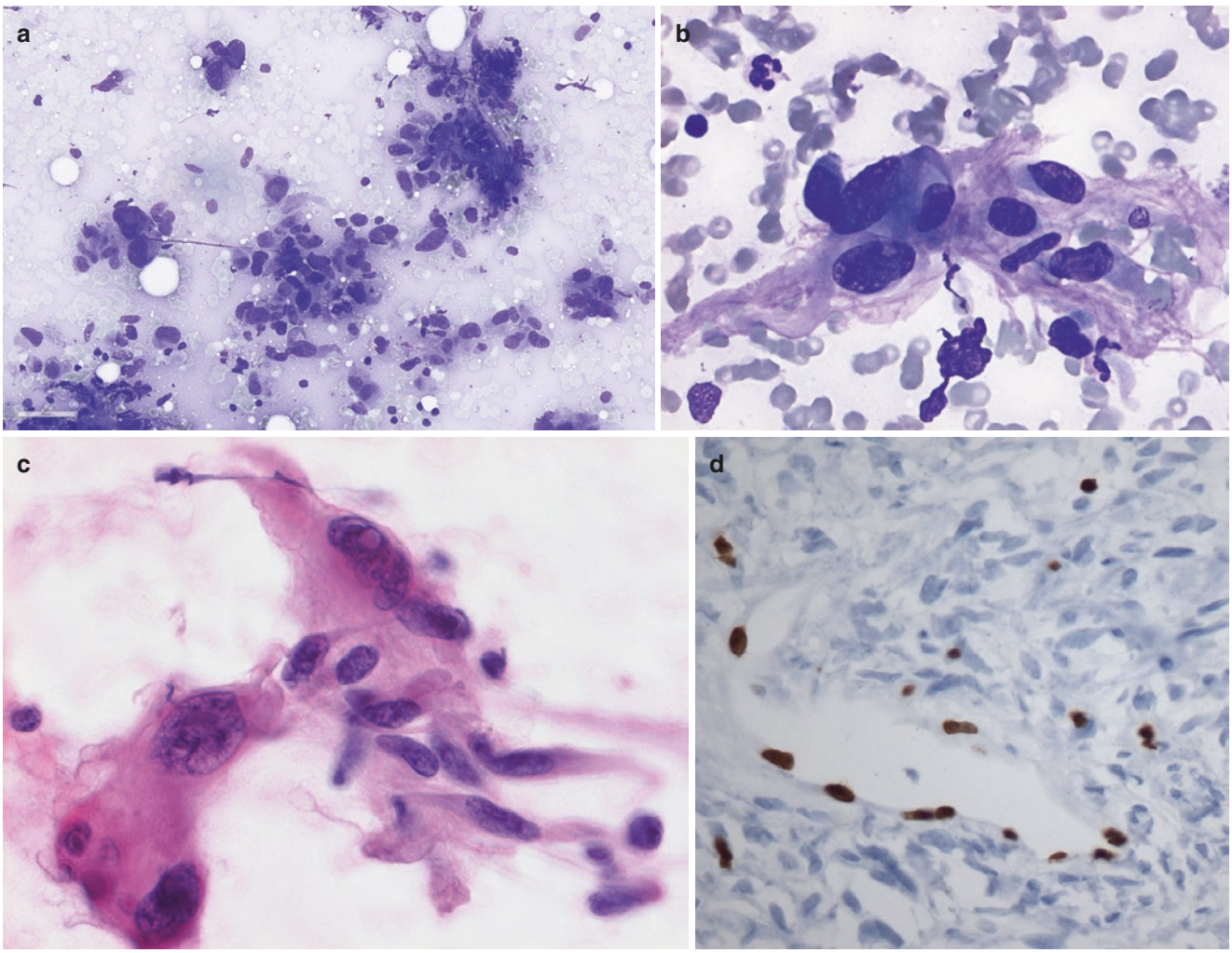

Fig. 14.52 Smears of high-grade malignant peripheral nerve sheath tumor. (**a**–**c**) Pleomorphic epithelioid and spindle cells with hyperchromatic nuclei in loosely clusters and dispersed tumor cells. Without knowledge of clinical history and ancillary immunostains, correct diagnosis of MPNST is difficult to render based on cytomorphology alone (MGG; H&E). (**d**) Loss of H3K27me3 expression is seen in high-grade MPNST

Vascular Neoplasm

Vascular neoplasms comprise a wide spectrum of entities, including varieties of benign hemangioma, low-grade/intermediate vascular neoplasms such as Kaposi sarcoma and pseudomyogenic hemangioendothelioma (PMH), and malignant vascular neoplasm such as epithelioid hemangioendothelioma (EHE) and angiosarcoma. Benign entities such as subcutaneous and intramuscular hemangioma are those most often referred for FNA. Cytologic features of benign vascular tumors are usually nonspecific, and FNAC diagnosis must be supplemented by clinical and radiographic findings. Cytological findings in smears from angiosarcoma and epithelioid hemangioepithelioma are more specific, especially in conjunction with ancillary techniques, and have been reported in some series and case reports [99–103].

Hemangioma (See Section "Vascular Neoplasm" in Chap. 15)

Cytologic features (Figs. 15.30, 15.31, and 15.32):
- Often, when a needle reaches the tumor, the syringe is filled with blood before aspiration.
- Cell poor, bloody smears.
- Small sheets and clusters of uniform spindle cells with thin cytoplasmic processes.
- Fusiform nuclei with pointed ends.
- Variable presence of fragments of small capillaries, occasionally with metachromatic matrix.
- Histiocytes in variable numbers, some with hemosiderin pigment
- Occasionally adipose tissue fragments, at times with fragments of vessels.

Differential diagnosis and problems in diagnosis:
- Benign spindle-cell neoplasms
- Angiomatoid fibrous histiocytoma
- Angiosarcoma
- Benign lipomatous tumors

A specific diagnosis of hemangioma may be made with confirmatory endothelial markers such as CD31 (see Fig. 15.32), factor VIII, and Fli-1.

Pseudomyogenic Hemangioendothelioma

Pseudomyogenic hemangioendothelioma is a distinctive, intermediate, rarely metastasizing vascular neoplasm, arising often in the superficial and deep soft tissues and bone of extremities, particularly the lower limbs. Approximately half of the cases of pseudomyogenic hemangioendothelioma are multicentric, involving different tissue planes in the extremities, trunk, abdomen, and head and neck. Most cases occur in the second and third decades of life with a striking male predominance. No case describing the FNA findings has been reported to date, but based on own experience, smears from pseudomyogenic hemangioendothelioma resemble those from nodular fasciitis, with loosely cohesive fascicles and clusters with admixture of dispersed variable pleomorphic spindle cells with abundant cytoplasm with cytoplasmic extensions. Tumor cells contain oval and occasionally rounded, irregular nuclei with relatively finely distributed chromatin and distinct nucleoli. Binuclear ganglion-like cells are easy to find, resembling smears of nodular fasciitis (see Fig. 14.53). Demonstration of positive staining for cytokeratin AE1/AE3, FLI-1, and ERG, retained nuclear INI-1 staining, and negative staining for CD34 is helpful to confirm diagnosis. CD31 are positive in approximately 50% of cases.

Cytologic features:
- Cellular aspirates.
- Occasionally a sparse myxoid background matrix.
- Dispersed spindle cells mixed with small- and medium-sized, loosely cohesive clusters and sheets of spindle cells.
- Spindle cells show often abundant cytoplasm and long cytoplasmic extensions.
- In some cell clusters a collagenous matrix and occasional capillary vessels.
- Variable anisocytosis and anisokaryosis and distinct nucleoli.
- Mono- and binucleated ganglion-like cells.

Differential diagnosis and problems in diagnosis:
- Nodular fasciitis
- Proliferative fasciitis

Chromosome banding and FISH analyses have shown a balanced t(7;19)(q22;q13) translocation as the sole aberration in several cases. The detected t(7;19)(q22;q13) translocation results in a *SERPINE1-FOSB* fusion gene that acts as a transcription factor. The high frequency of this specific fusion, which can be detected by FOSB immunostaining [104], makes it a useful diagnostic tool to distinguish pseudomyogenic hemangioendothelioma from morphological mimics.

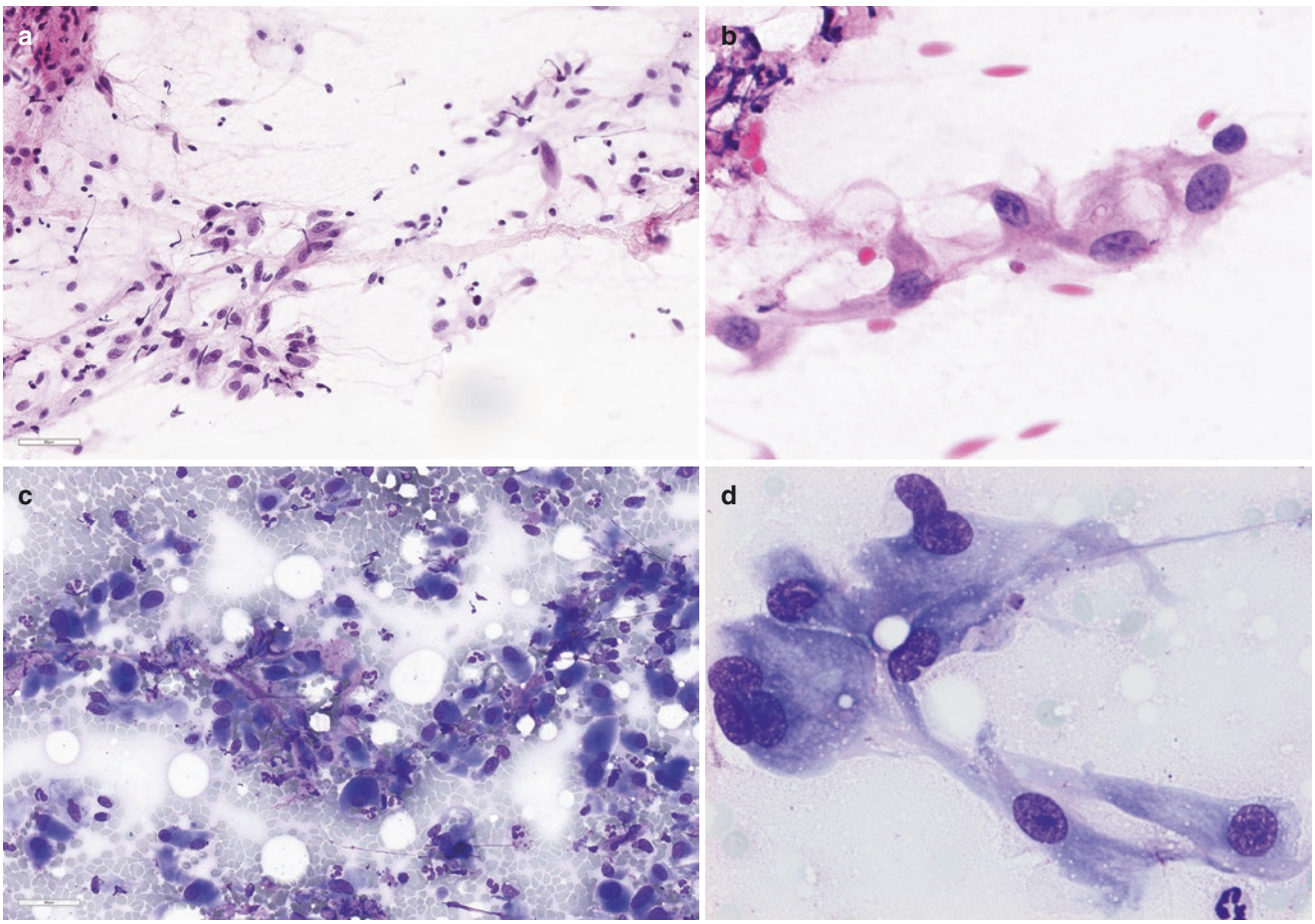

Fig. 14.53 Pseudomyogenic hemangioendothelioma. (**a**, **b**) Loosely cohesive sheets and dispersed atypical spindle cells with fusiform and ovoid nuclei and occasionally abundant cytoplasm with cytoplasmic processes resembling smears of nodular fasciitis (H&E). (**c**, **d**) Dispersed spindle and plump cells with abundant cytoplasm and fusiform, rounded to oval nuclei with slight anisonucleosis and tiny nucleoli. Some of binucleated tumor cells with abundant cytoplasm resembling "ganglion cells" of nodular/proliferative fasciitis (MGG stain)

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a malignant vascular neoplasm arising in middle-aged adults with a wide distribution in both soft tissues of the extremities, trunk and head and neck region, bone, and in visceral organs, particularly the lung and liver. About half of cases show clear angiocentricity involving medium-sized or larger vessels. Smears from epithelioid hemangioendothelioma show small clusters and dispersed epithelioid, polygonal, occasional spindle-shaped cells with variable nuclear pleomorphism, dense cytoplasm, and distinct cytoplasmic borders. Variable but often slight to moderate anisokaryosis, nuclear grooves, pseudoinclusions, and occasional nucleoli are observed in some tumor cells (see Fig. 14.54). EHE usually express CD31, CD34, ERG, FLI-,1 and keratin (in 1/3 of cases).

Cytologic features:
- Variable yield
- Small clusters and dispersed epithelioid cells
- Occasional spindle cells
- Dense cytoplasm with distinct cell borders
- Round nuclei with nuclear grooves and small nucleoli
- Minimal pleomorphism
- Stromal fragments

Differential diagnosis and problems in diagnosis:
- Angiosarcoma
- Metastatic carcinoma (in liver or lung)
- Epithelioid sarcoma
- Epithelioid hemangioma

Recurrent fusion genes have been recently identified in EHE. *WWTR1-CAMTA1,* resulting from a t(1;3)(p36.3;q25) translocation, is the most common fusion gene in EHE. Demonstration of positive nuclear staining for CAMTA1 is helpful to confirm the diagnosis [105].

Angiosarcoma (See Section "Malignant Vascular Tumors" in Chap. 15)

The vast majority of angiosarcomas are cutaneous tumors, and approximately 20% arise in the soft tissue. Smears of angiosarcomas are most often diagnosed as malignant. A correct diagnosis of angiosarcoma is difficult to reach in routinely stained smears. Immunocytochemical studies with endothelial markers are necessary to establish the diagnosis (see Fig. 15.35). An exception is for those cases in which vasoformative structures such as small acinar-like formations with central erythrocytes or vacuolated cells with single erythrocytes are present.

Cytologic features:
- Variable yield
- Often hemorrhagic aspirates
- Mixture of dispersed cells, cells in clusters or groups
- Occasionally acinar structures and intracytoplasmic erythrocytes
- Variable cellular and nuclear pleomorphism
- Variable presence pleomorphic/polygonal cells and spindle cells
- Signet-ring-like cells often with single erythrocytes within cytoplasmic vacuoles
- Epithelial-like cells in epithelioid angiosarcoma

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

Tumor cells in epithelioid angiosarcoma express cytokeratins in approximately 50% of cases, which can lead to the misinterpretation of metastatic carcinoma.

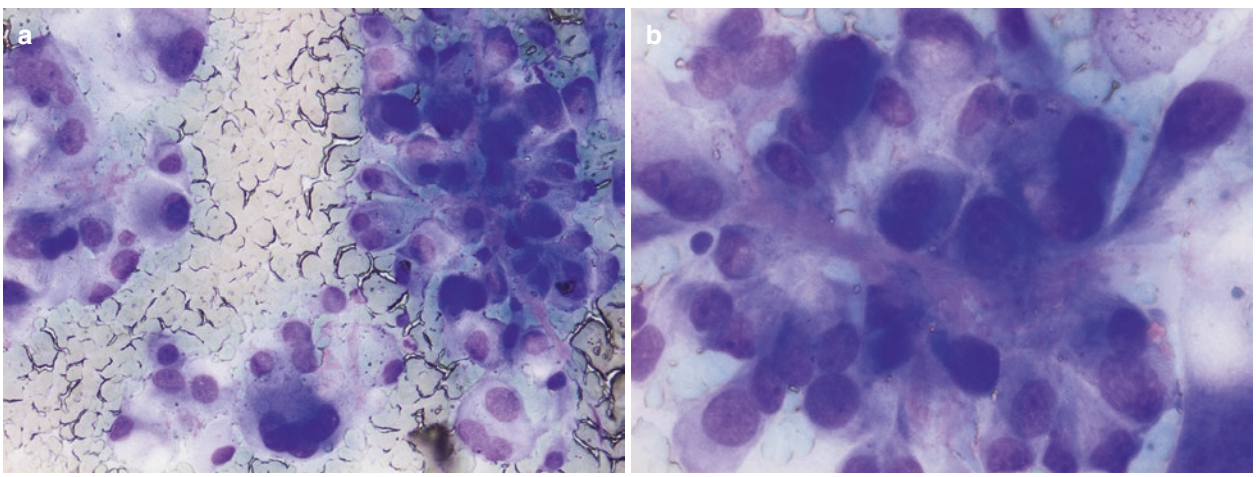

Fig. 14.54 Epithelioid hemangioendothelioma. (**a**, **b**) A poorly cohesive group of moderately pleomorphic, some binucleated, and occasional multinucleated cells showing round to oval nuclei with small nucleoli and abundant cytoplasm (MGG)

Neuroectodermal Tumors

Neuroblastoma (See Section "Retroperitoneal Tumors" in Chap. 17)

Neuroblastoma is the most common extracranial solid malignant tumor in children. Ninety percent of neuroblastomas are diagnosed before the age of 5 years. As neuroblastoma and ganglioneuroblastoma originate in sympathetic ganglia, neuroblastomas may arise in the adrenal medulla or from any sympathetic ganglia within the retroperitoneum, posterior mediastinum, neck, and sacral region.

Neuroblastomas are composed of clusters of small tumor cells with rounded or irregular nuclei showing finely granular chromatin and small nucleoli. Variable amount of intercellular fibrillary material from neuritic cell processes (neuropil) is present. A typical microscopic finding is the rosette-like structures with a central tangle of fibrillary material (Homer-Wright rosettes). In more mature tumors, large ganglion-like cells are present, and in undifferentiated neuroblastoma, there is no fibrillary matrix. Criteria for cytologic diagnosis are described in detail in section "Principles of Evaluation and Reporting of Breast FNAC" in Chap. 3 on pediatric tumors.

Ganglioneuroblastoma (See Section "Retroperitoneal Tumors" in Chap. 17)

Typical features in smears are large ganglion cell-like cells mixed with the small cell population.

Ganglioneuroma

In ganglioneuroma smears, both large ganglion cells and schwannoma-like tissue fragments are present (see Fig. 14.55) [106].

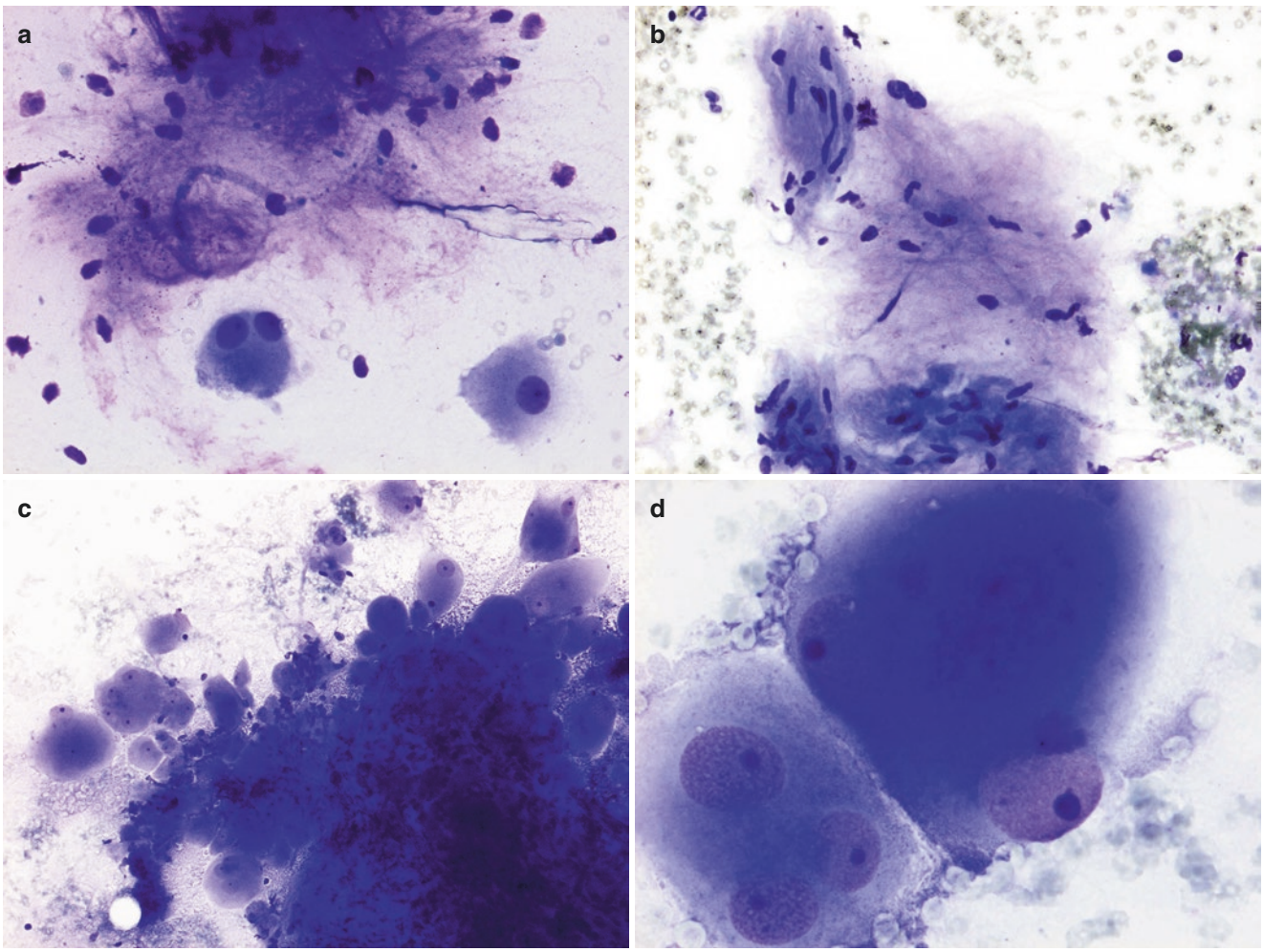

Fig. 14.55 Ganglioneuroma. (**a**) Double cell population of large ganglion cells and schwannoma-like tissue fragments and (**b**) schwannoma-like loose clusters of bland spindle cells in a fibrillary matrix. (**c**) A cluster rich in ganglion cells and (**d**) high-power view of ganglion cells (MGG)

Ewing Sarcoma

Extraosseous Ewing sarcoma (ES) is a primitive round cell sarcoma showing varying degrees of neuroectodermal differentiation. It mainly occurs in adolescents and young adults but affects elderly patients as well. It predominantly arises at extraskeletal sites such as deep soft tissue of chest wall (the so-called Askin tumor), subcutis, and extremities, but it can also occur in the lung, kidney, and genital organs. In our files, there is a patient with a tumor in the myocardium.

Cytologic features are similar to conventional ES in bone (see Chaps. 16 and 17) (Fig. 14.56).

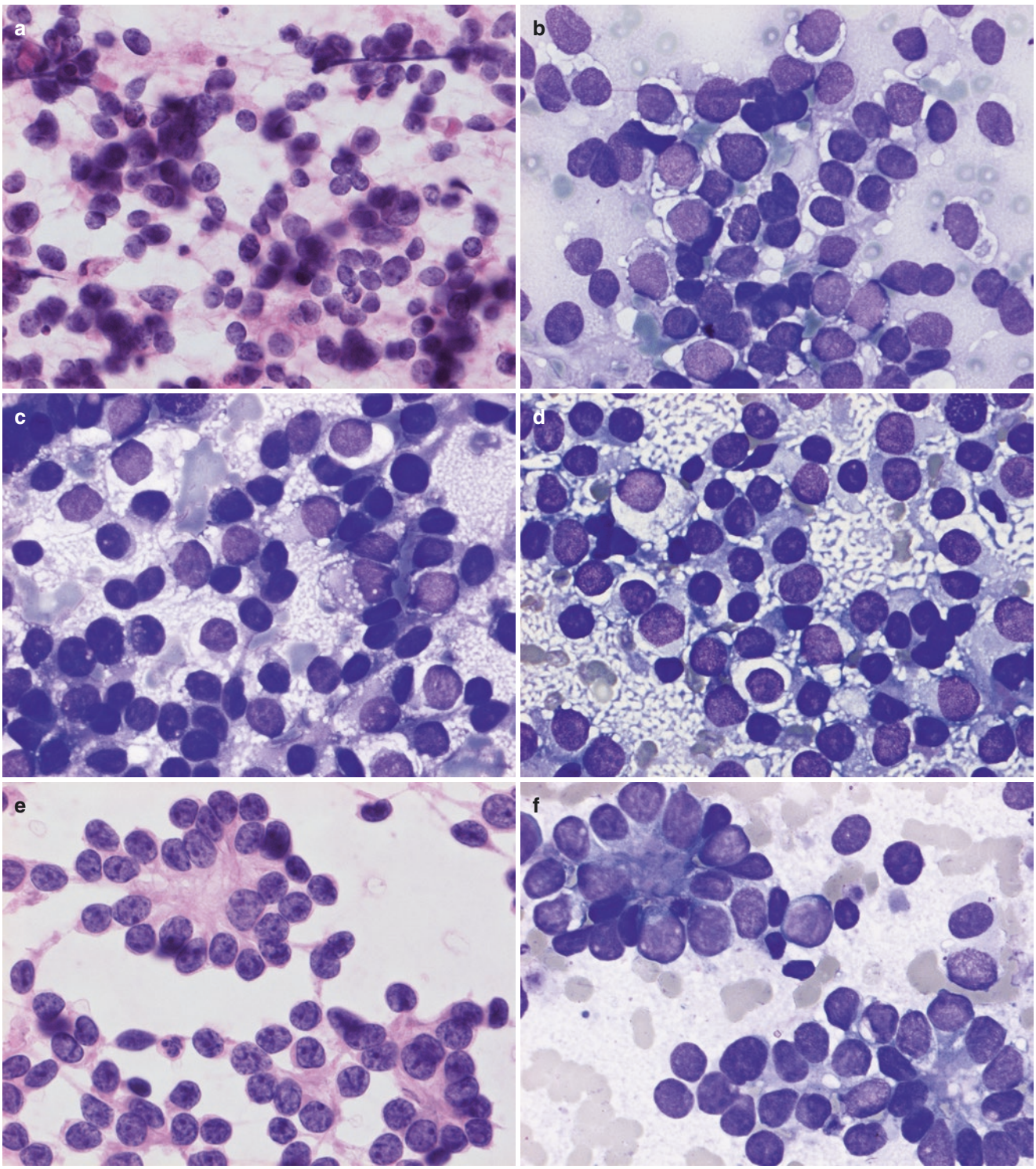

Fig. 14.56 Ewing sarcoma. (**a**) Wet-fixed smears with irregular cluster of loosely cohesive cells (H&E). Dual appearances: small dark and large light cells and tigroid background (**b–d**) obvious in air-dried smears (MGG). (**e**, **f**) Rosette formation is less common (H&E; MGG)

Tumors of Unknown, Uncertain, or Debated Histogenesis

Intramuscular Myxoma

Intramuscular myxoma is a benign tumor typically found in middle-aged or elderly patients. Predilection sites are thigh, buttock, and the shoulder region. As they are deep seated and rather firm at palpation, they might be perceived as malignant clinically. The smears are extremely hypocellular and contain abundant myxoid background and few bland, spindle to stellar cells with long cytoplasmic processes (see Fig. 14.57). Fragments of capillaries are rare or absent. Scattered macrophages with cytoplasmic vacuolation are often seen.

Cytologic features:
- Droplets of stringy, glue-like colorless fluid at aspiration
- Abundant myxoid matrix
- Dispersed cells more common than small tissue fragments
- Slender tumor cells with small, bland nuclei and (very) long, thin, uni- or bipolar cytoplasmic processes
- Scattered macrophage-like cells with vacuolated cytoplasm
- Infrequent small vessel fragments.

Differential diagnosis and problems in diagnosis:
- Schwannoma with foci of myxoid stroma
- Soft tissue perineurioma
- Ganglion
- Myxoid liposarcoma
- Low-grade myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Extraskeletal myxoid chondrosarcoma

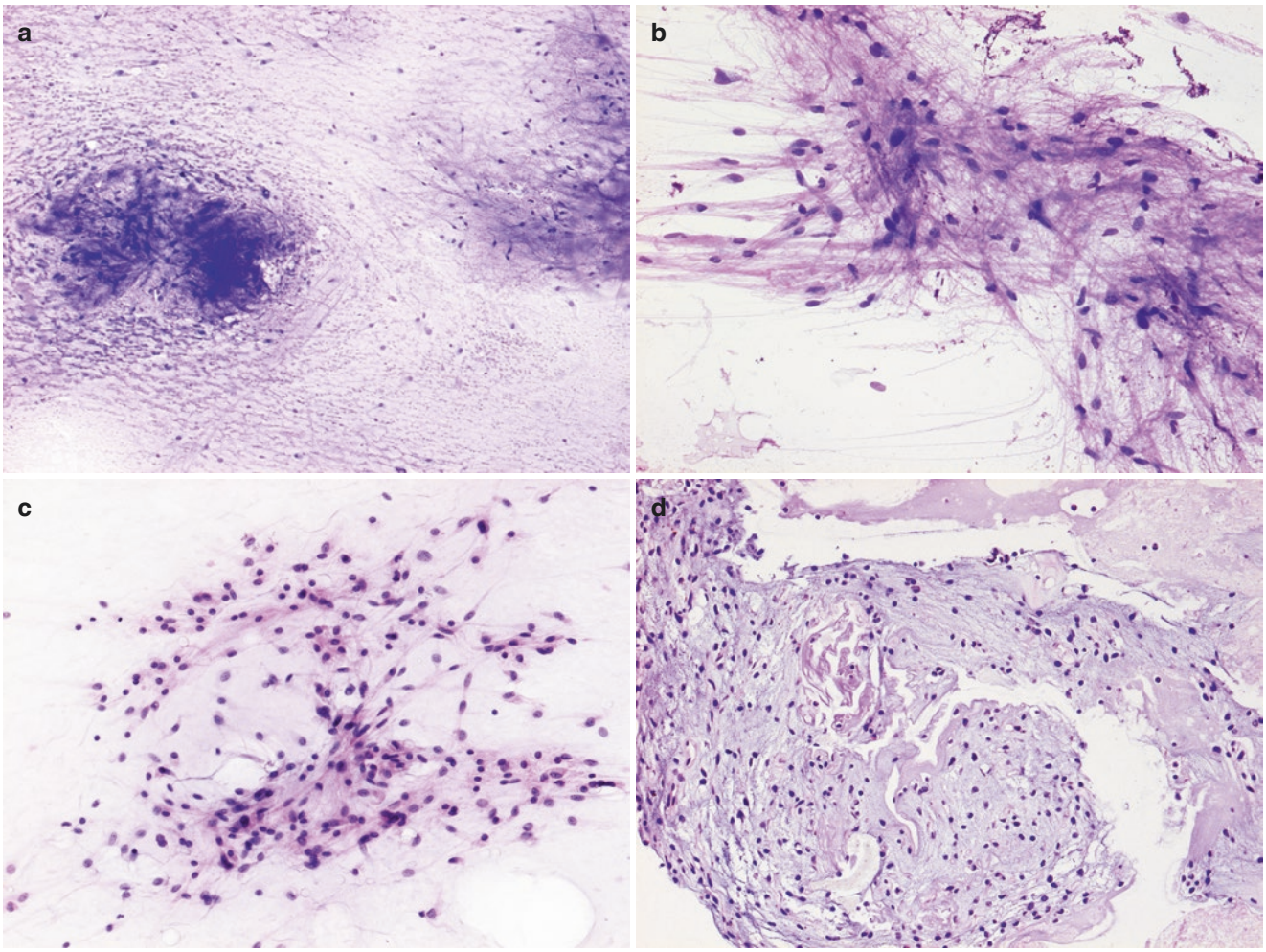

Fig. 14.57 Intramuscular myxoma. (**a**–**c**) Hypocellular smears with abundant myxoid background and small dyscohesive clusters of bland, spindle to stellar cells with long cytoplasmic processes (MGG; H&E). (**d**) Cell-block section showing similar morphology of bland spindle cells in a myxoid matrix (H&E)

Angiomatoid Fibrous Histiocytoma

Angiomatoid fibrous histiocytoma (AFH) is an indolent neoplasm commonly arising in the subcutaneous tissue of the extremities in children and young adults. AFH may present as a partly cystic mass with hemorrhage. FNA smears show variable cellularity and contain ovoid to spindled histiocytoid cells that may be isolated or in clusters. Some of these cells are atypical, and others contain hemosiderin. Large cellular clusters with a capillary structure and a whorled arrangement of tumor cells can be appreciated in some cases (see Fig. 14.58) [107]. FNA cytomorphology is nonspecific. Clinical correlation and ancillary studies are necessary to render the diagnosis. Tumor cells are positive for desmin and EMA in approximately 50% cases. Most of these tumors show an *EWSR1–CREB1* fusion gene, which can be detected by FISH studies (Table 14.2).

Cytologic features:

- Variable cellularity
- Dispersed cells and cell clusters
- Ovoid to spindled histiocytoid cells
- Bloody background and hemosiderin
- Infrequent lymphoplasmacytic infiltrate
- Occasional whorled arrangement of tumor cells associated with vessels

Differential diagnosis and problems in diagnosis:

- Hemangioma
- Benign fibrous histiocytoma
- Nodular fasciitis
- Inflammatory myofibroblastic tumor
- Follicular dendritic sarcoma
- Metastatic carcinoma

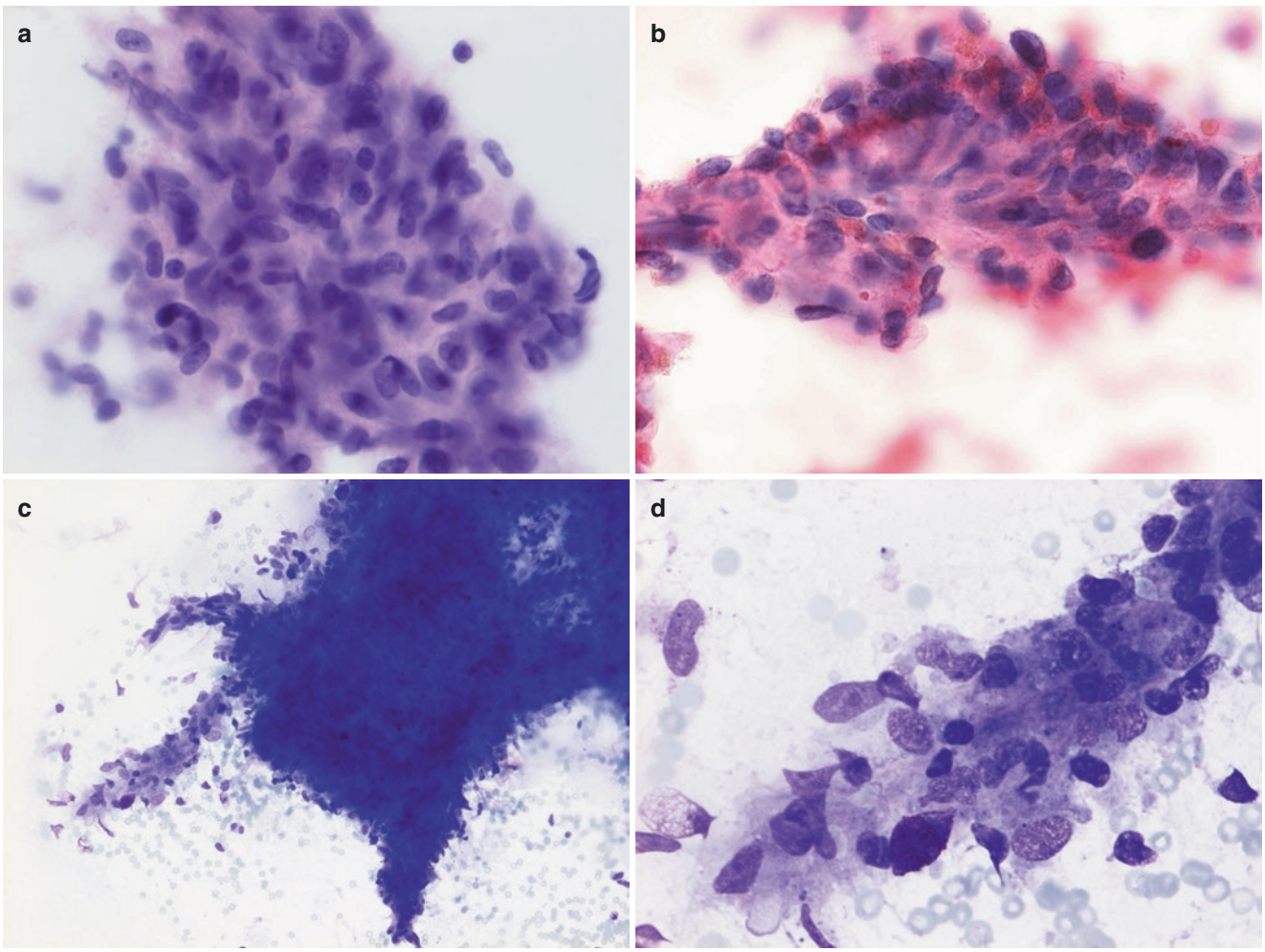

Fig. 14.58 Angiomatoid fibrous histiocytoma (AFH). (**a**–**d**) Cellular clusters of oval to spindled histiocytoid cells with ill-defined cell borders, ovoid to folded nuclei, finely dispersed chromatin, and inconspicuous nucleoli. In large cellular clusters, capillary structures with spindled endothelial cells are seen (**a**). Cytologic atypia and pleomorphism (**b**, **d**) may be present, without correlation of malignancy (H&E; MGG)

Ossifying Fibromyxoid Tumor

Ossifying fibromyxoid tumor (OFMT) is a rare subcutaneous tumor, predominantly in adults. Extremities are the most common sites, but OFMT in the trunk and head and neck region has been described. It is a lobulated, well-circumscribed lesion with fibrous capsule often containing a more or less complete shell of mature metaplastic bone. The uniform, oval to spindled neoplastic cells form cords or trabeculae that are situated in fibromyxoid stroma on histology and present as dispersed single cells, clusters of cells, and/or acinar-like structures on FNA smears (see Fig. 14.59) [108–110]. OFMT was considered as a benign neoplasm until 1995 when Kilpatrick et al. [111, 112] reported six cases of malignant OFMT.

Cytologic features:

- Variable cellularity (tumors with an extensive shell of bone difficult to aspirate)
- Dispersed cells, cell clusters, and acinar-like structures in a variable myxoid matrix
- Rounded (epithelioid-like) or ovoid nuclei with central nucleoli and slightly anisokaryosis
- Rather abundant cytoplasm

Differential diagnosis and problems in diagnosis:

- Epithelioid peripheral nerve sheath tumors
- Mixed tumor of soft tissue
- Epithelioid smooth muscle tumors
- Thyroid neoplasms (head and neck tumors)
- Extraskeletal myxoid chondrosarcoma
- Myxoid liposarcoma

The cytology of OFMT in FNA has not been sufficiently investigated, except for a few case reports [108–112]. When the FNA material is sufficient, IHC is of diagnostic value; positivity for S-100 protein (>90% cases) and desmin (40–50% cases) would be supportive for OFMT. Recently, *PHF1* gene rearrangement has been found in typical or atypical OFMT but only rarely in malignant ones [113].

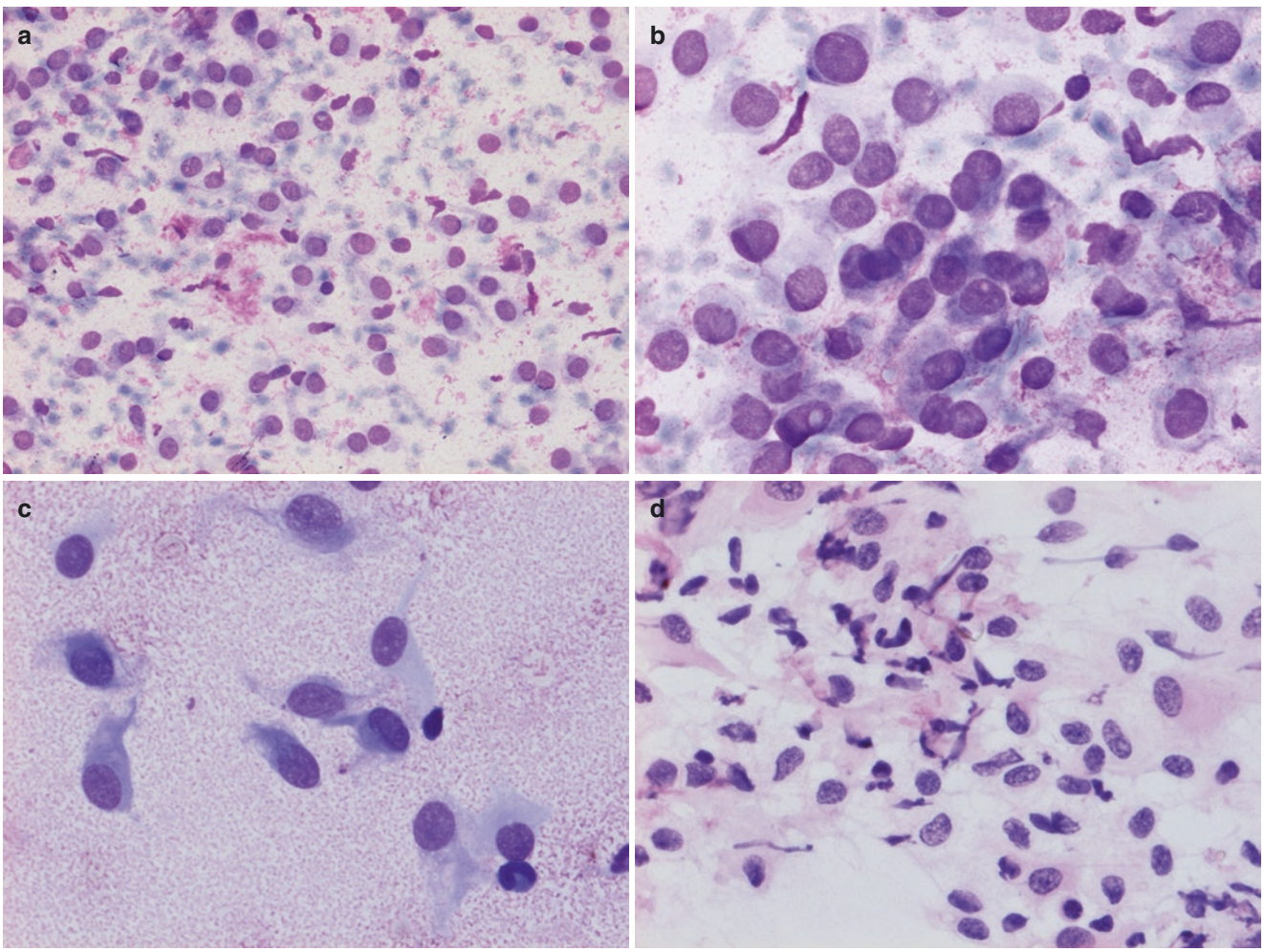

Fig. 14.59 Ossifying fibromyxoid tumor. (**a**–**d**) Dispersed, bland, round (epithelioid-like), or ovoid cells with mostly poorly preserved cytoplasm, associated with a variable myxoid matrix (MGG; H&E)

Myoepithelioma/Myoepithelial Carcinoma of Soft Tissue

Myoepithelial tumors and its morphologic variants, parachordoma and mixed tumor of soft tissue, are neoplasms composed of cells with myoepithelial phenotype, similar to their counterparts in salivary glands. These neoplasms are composed of epithelial- and myoepithelial-like cells in a chondromyxoid or hyalinized stroma. Myoepitheliomas arise commonly in the subcutaneous and deep soft tissue of limb, limb girdles, trunk, and head and neck area in adults, but approximately 20% of cases arise in children. They show benign clinical course in the majority of cases, which may recur in approximately 20% of cases but rarely metastasize. Myoepithelial carcinomas show diffuse moderate to severe nuclear atypia and large, epithelioid cell morphology with a high mitotic rate and necrosis, resembling poorly differentiated carcinomas. In FNA smears, cytomorphology of myoepitheliomas resembles that of pleomorphic adenoma of the salivary gland and chondroid syringoma [114, 115] (see Fig. 14.60). Most important, differential diagnosis is extraskeletal myxoid chondrosarcoma and chondroid syringoma. Myoepithelial carcinomas show undifferentiated, large, round cell morphology with a high mitotic rate and necrosis. Interestingly, myoepithelial tumors from different locations display rearrangement of the *EWSR1* gene in almost 50% of the cases [116]. Majority of cases express broad-spectrum keratins, S-100 protein, SOX10, calponin, and EMA, GFAP is expressed in about 50% of cases, and occasionally focal expression of SMA and p63 is observed.

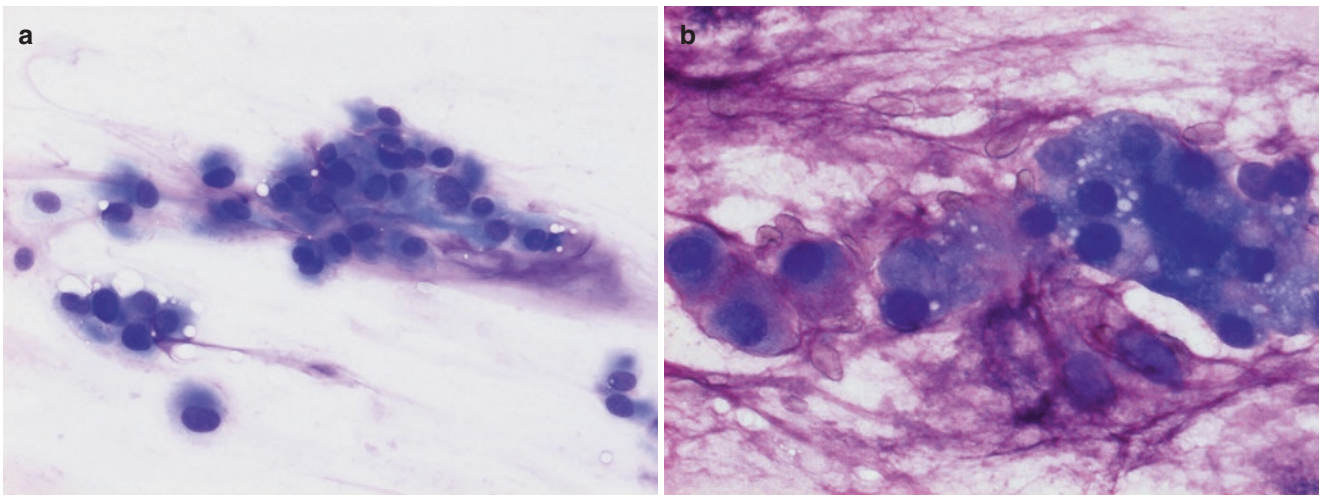

Fig. 14.60 Myoepithelioma of soft tissue. (**a**, **b**) Epithelial- and myoepithelial-like cells in a chondromyxoid stroma resembling pleomorphic adenoma of salivary gland (MGG)

Synovial Sarcoma

Synovial sarcoma (SS) accounts for 5–10% of soft tissue sarcomas. It may occur at any age, but more than half of the patients are between the ages of 10 and 35 years. Most SS are deep seated and arise in the extremities, trunk, and head and neck region, but they may arise elsewhere in the body. SS is monophasic (see Fig. 14.61), biphasic (see Fig. 14.62), or poorly differentiated. Three morphologic variants of the poorly differentiated SS have been described: the small cell variant resembling Ewing sarcoma (see Fig. 14.62), a spindle-cell variant resembling MPNST, and epithelioid variant with rhabdoid features [117–120]. The majority of SSs stain positively for EMA and cytokeratins 7 and 19. More than 50% stain positively for CD99 and Bcl-2. These stainings may appear focally, especially in the poorly differentiated areas. Strong and diffuse positive staining for TLE1 is characteristic for SS. A translocation t(X;18)(p11;q11) is present in most SSs, resulting in *SS18-SSX* gene fusion, which can be detected by FISH (Table 14.2).

Cytologic features:

- Often hypercellular yield
- Tissue fragments mixed with dispersed cells in almost equal proportions
- Stripped nuclei
- Branching capillary strands bordered by tumor cells
- Spindle cells with bland fusiform or ovoid nuclei end inconspicuous nucleoli
- Mitotic figures
- Small acinar-like and alveolar structures in biphasic tumors
- Often scattered mast cells

Differential diagnosis and problems in diagnosis:

- Solitary fibrous tumor (monophasic SS)
- Thymoma (biphasic SS)
- Carcinosarcoma (biphasic SS)
- MPNST (poorly differentiated or monophasic SS)
- Ewing sarcoma (poorly differentiated SS)

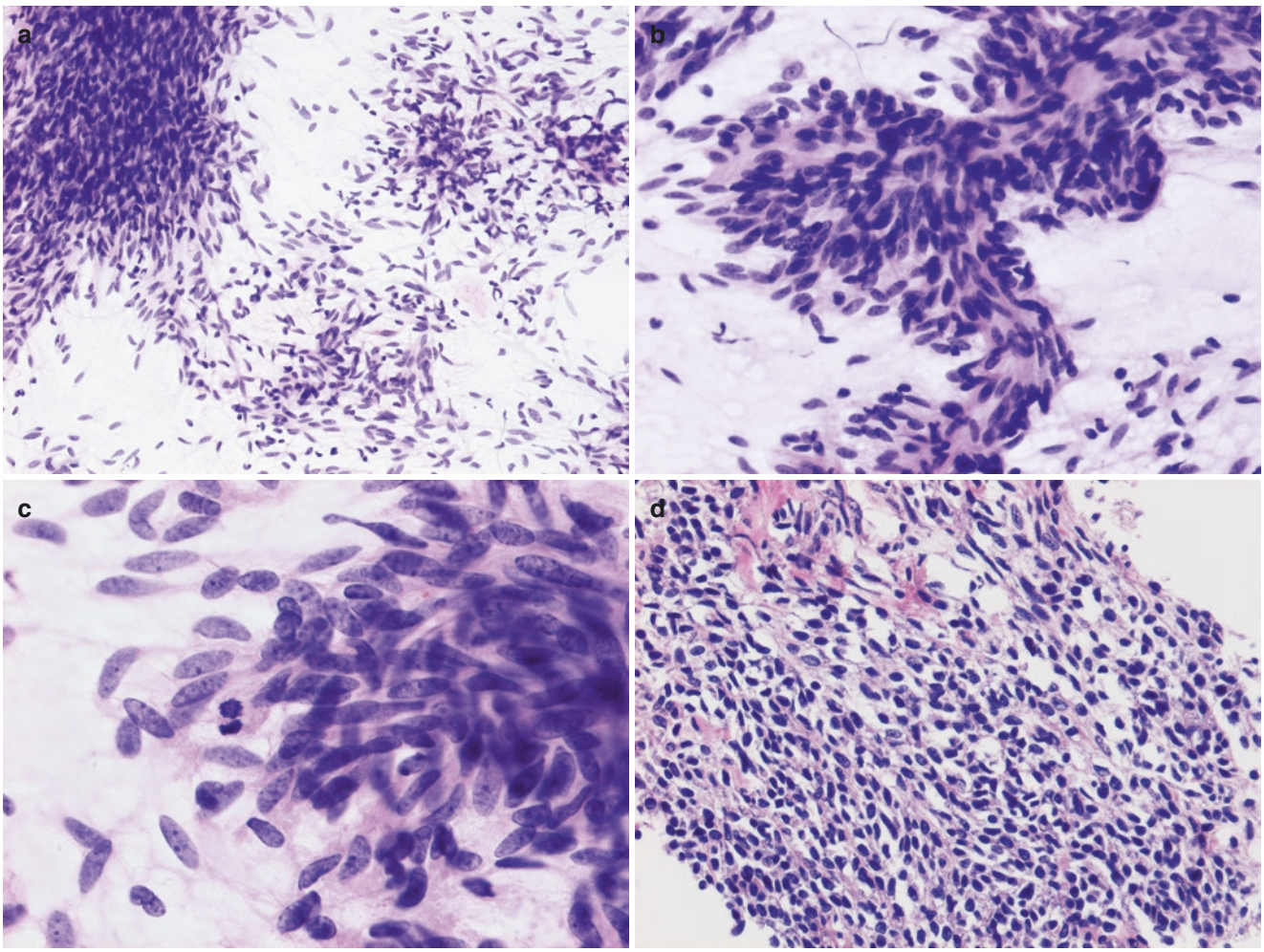

Fig. 14.61 Synovial sarcoma. (**a**–**c**) Tissue fragments mixed with dispersed uniform spindle cells in almost equal proportions. Note nuclear hyperchromasia and mitosis (H&E). (**d**) Cell block section with hyperchromatic spindle cells in a collagenous stroma (H&E)

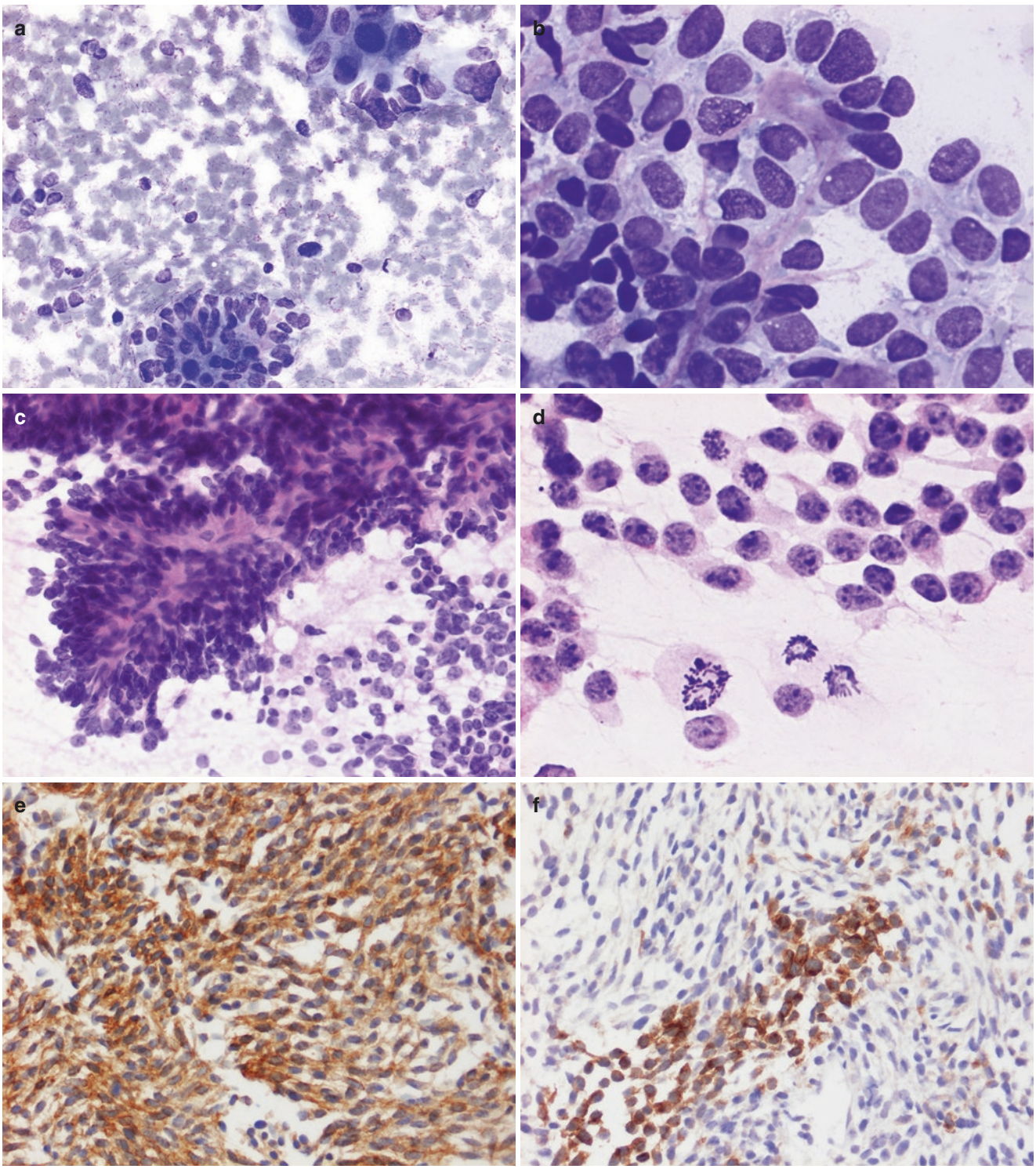

Fig. 14.62 Synovial sarcoma. (**a**, **b**) Biphasic subtype showing small acinar-like and alveolar structures (MGG). (**c**, **d**) Poorly differentiated synovial sarcoma resembling Ewing sarcoma (H&E). (**e, f**) immunoreactivity for CD99 and focal positivity for keratin confirms diagnosis (cell block; CD99; Ck 19)

A cellular aspirate containing bland spindle cells with mitotic figures and scattered mast cells from a deep-seated tumor in an adolescent or middle-aged adult is suggestive of monophasic fibrous synovial sarcoma. However, a definitive diagnosis of a synovial sarcoma should be confirmed by ancillary techniques such as immunocytochemical and molecular genetics examinations.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare soft tissue sarcoma accounting for less than 1% of all sarcomas and mainly seen in adolescents and young adults with a slight female predominance. Common sites are deep soft tissue of the lower limbs or limb girdles, and head and neck region. The cytomorphologic features of ASPS include large, dyshesive tumor cells with round nuclei and prominent centrally situated nucleoli. Tumor cells have abundant granular, fragile cytoplasm. Presence of stripped nuclei in a cytoplasmic granular background is a useful clue to the diagnosis (see Fig. 14.63). The typical alveolar architecture on histology is imperceptible on FNA smears [121, 122]. Intracytoplasmic glycogen may be seen in cell-block sections. The most characteristic rhomboid crystals containing actin filaments may be evident by ultrastructural examination (see Fig. 1.30). ASPS is characterized by an *ASPSCR1-TFE3* gene fusion and nuclear overexpression of TFE3 protein.

Cytologic features:
- Variable cellularity
- Large, dyshesive epithelioid cells with abundant granular cytoplasm
- Round nuclei with very prominent nucleoli
- Bare nuclei and granular cytoplasmic background

Differential diagnosis and problems in diagnosis:
- Granular cell tumor
- Metastatic renal cell carcinoma
- Adult rhabdomyoma
- Paraganglioma
- PEComa

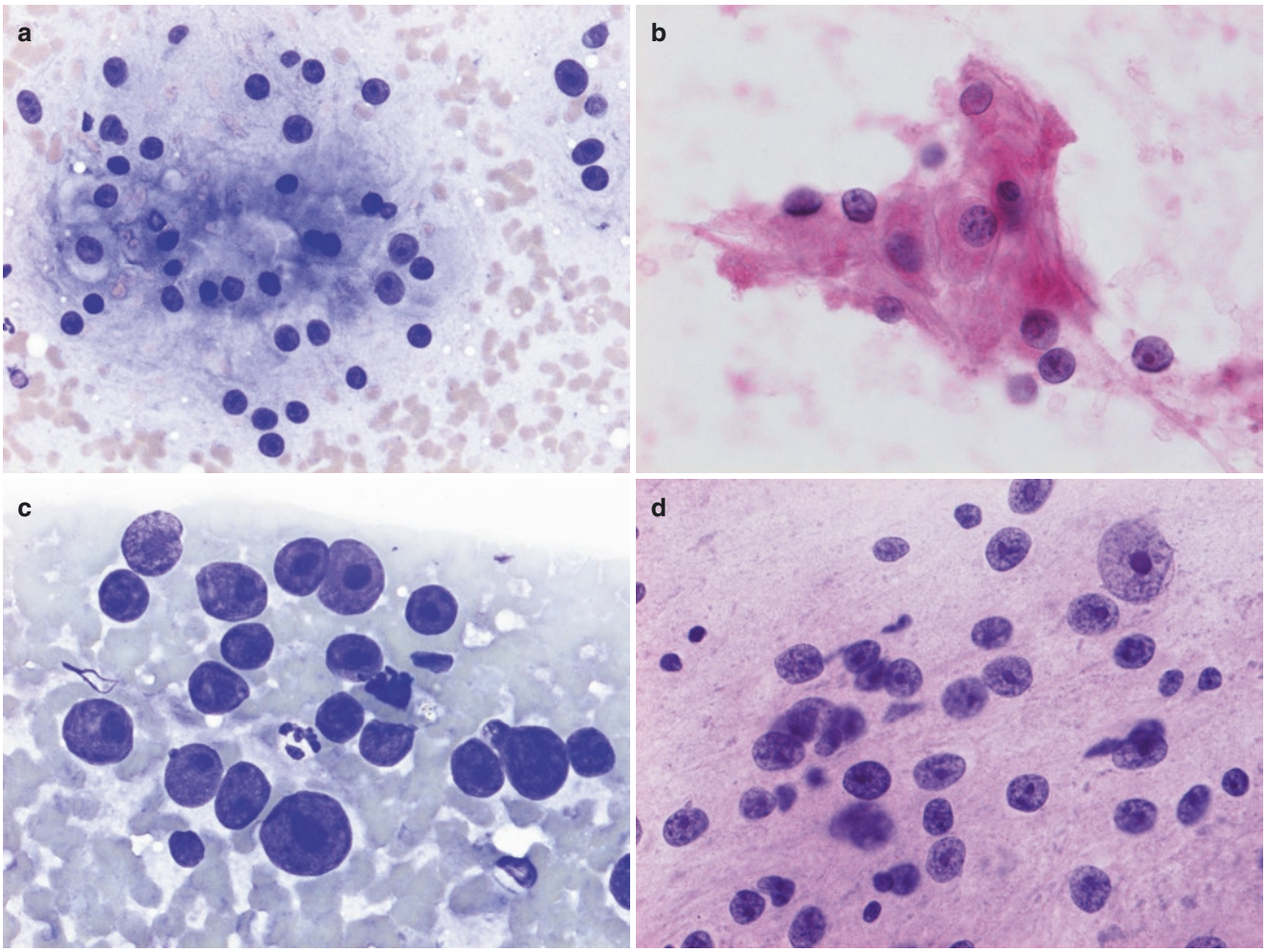

Fig. 14.63 Alveolar soft part sarcoma. (**a**, **b**) Large, dyshesive tumor cells with round nuclei and abundant granular, fragile cytoplasm (MGG; H&E). (**c**, **d**) Presence of stripped nuclei with prominent, centrally situated nucleoli in a cytoplasmic granular background is a useful clue to the diagnosis (MGG; H&E)

Epithelioid Sarcoma

Epithelioid sarcoma (ES) is a rare malignant mesenchymal neoplasm showing epithelioid morphology and phenotype. It arises in the skin and subcutaneous tissue or tendon aponeurosis of distal extremities, mainly hands and wrists of young adults and adolescents. There are two subtypes, the conventional/distal form and proximal type, which mainly occurs in proximal/truncal regions. FNA smears show a mixture of spindle cells and epithelioid cells, with eccentrically placed nuclei and eosinophilic to dense cytoplasm in the H&E-stained smears (see Fig. 14.64). It may be difficult to aspirate cellular material likely due to necrosis and/or hyalinization. ES tumor cells express cytokeratins, especially keratins 8 and 19 and/or EMA, and more than 50% of cases express CD34. Loss of nuclear expression of INI1 is characteristic for both types of ES (see Fig. 14.64b, c) [123–125].

Cytologic features:

- Variable cellularity
- Dyshesive and small clusters of spindled to epithelioid cells
- Round to oval nuclei with vesicular chromatin and prominent nuclei
- Dense to eosinophilic cytoplasm
- Necrotic background

Differential diagnosis and problems in diagnosis:

- Metastatic carcinoma
- Metastatic melanoma
- Epithelioid hemangioendothelioma
- Clear cell sarcoma
- Granulomatous inflammation

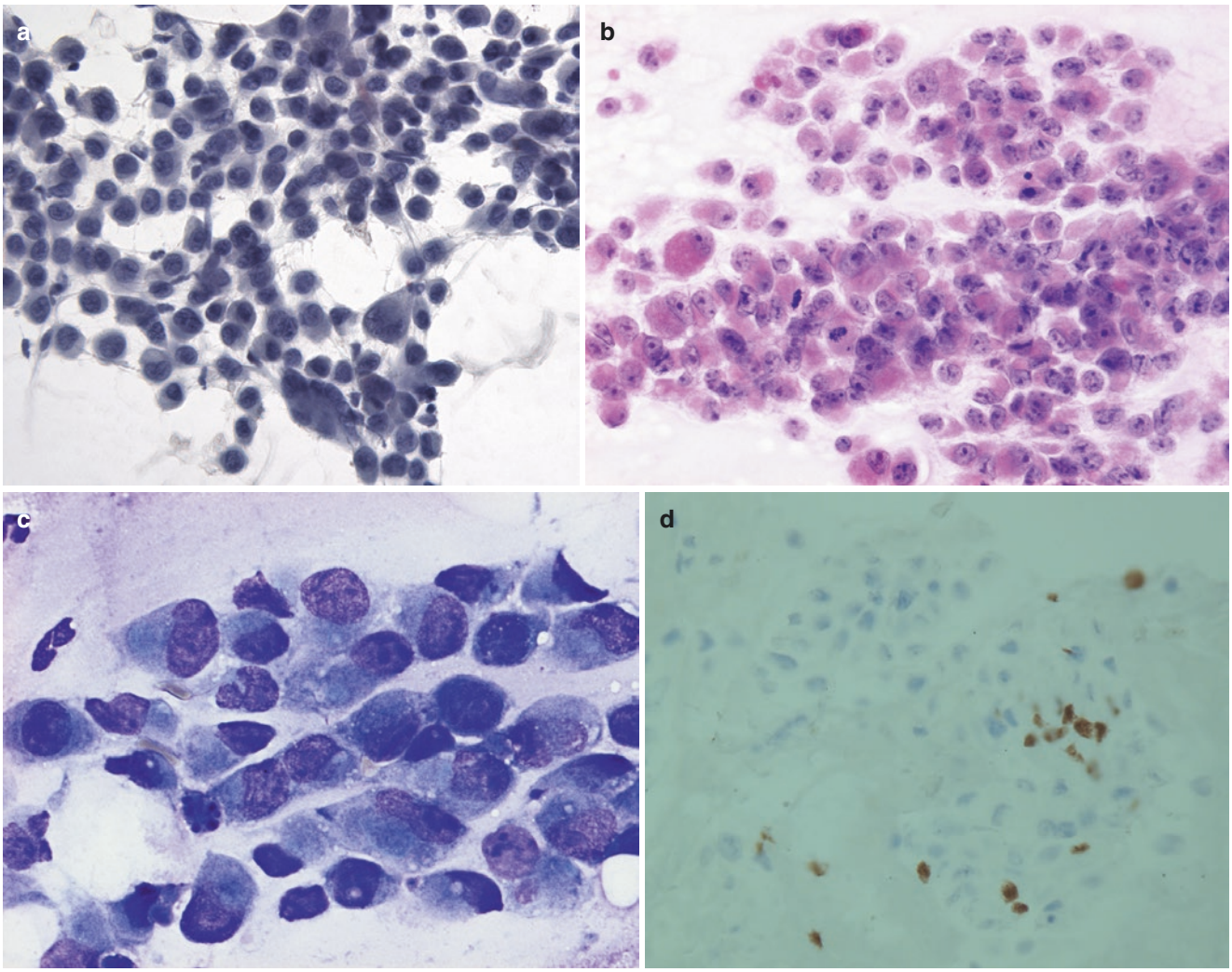

Fig. 14.64 Epithelioid sarcoma. (**a**) Dispersed, round, or polygonal cells with an eccentrically placed nucleus and dense cytoplasm (Pap stain). (**b, c**) Smears from proximal type epithelioid sarcoma display similar morphology to conventional type (H&E; MGG). (**d**) Loss of nuclear expression of INI-1 is seen in both conventional and proximal-type epithelioid sarcomas

Clear Cell Sarcoma (Malignant Melanoma of Soft Parts)

Clear cell sarcoma (CCS), first described by Enzinger in 1965, is a rare, distinct entity with melanocytic differentiation. It predominantly arises in the deep soft tissue of the extremities in young adults, and it is often found in close proximity to aponeurotic structures and tendons. FNA smears are at least moderately cellular, containing mostly dispersed cells. Small clusters of loosely cohesive cells can also be seen. Tumor cells are polygonal or spindly shaped with rather abundant clear or pale cytoplasm and large round or ovoid nuclei and prominent nucleoli (see Fig. 14.65). Intranuclear cytoplasmic pseudoinclusions, melanin, multinucleation, and tigroid background can also present [126, 127]. Similarly to malignant melanoma, CCS tumor cells are diffusely and strongly positive for S-100 protein and HMB-45. Metastatic malignant melanoma is the most important differential diagnosis. CCS harbors the characteristic translocation t(12;22)(q13;q12) with *EWSR1-ATF1* fusion, which is not present in malignant melanoma.

Cytologic features:

- Moderately cellular smears with tigroid background
- Dispersed cells and occasional loose clusters
- Polygonal or spindle cells with abundant clear to pale cytoplasm
- Round to ovoid nuclei with vesicular chromatin and macronucleoli

Differential diagnosis and problems in diagnosis:

- Metastasis melanoma
- Metastatic carcinoma with clear cell features
- Alveolar soft part sarcoma

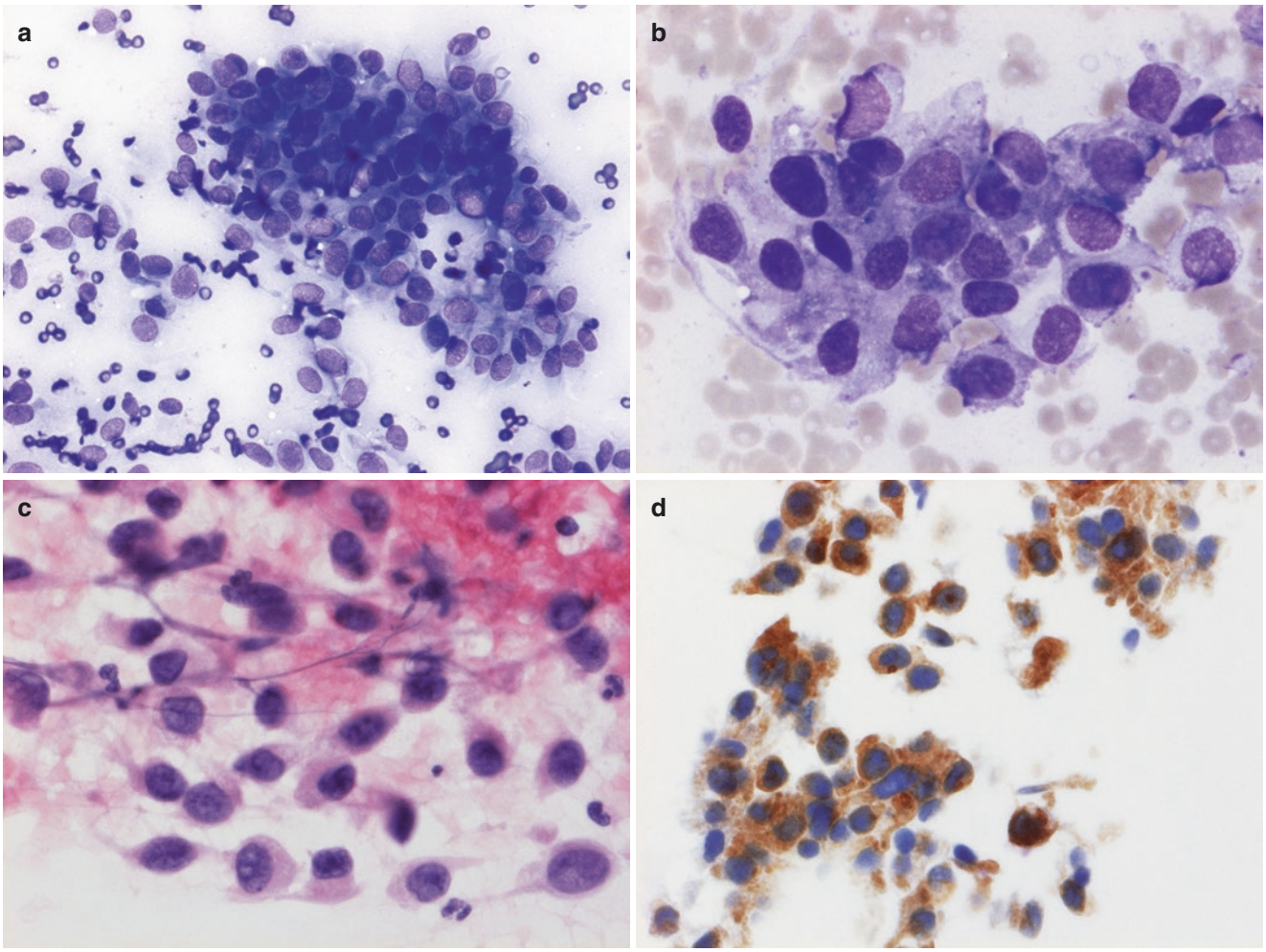

Fig. 14.65 Clear cell sarcoma (malignant melanoma of soft parts). (**a-c**) Polygonal or spindly shaped cells with rather abundant, clear cytoplasm, and large, round, or ovoid nuclei (MGG; H&E). (**d**) Immunoreactivity for melanoma markers confirms diagnosis (cell block; HMB45)

Extraskeletal Myxoid Chondrosarcoma

Extraskeletal myxoid chondrosarcoma (EMC) is a malignant mesenchymal tumor of unknown differentiation in adults, despite bearing "chondrosarcoma" in the name. Most EMCs arise in the deep soft tissue of the trunk and the limbs, with the thigh being the most common site. FNA smears show uniform, fusiform to spindle or round epithelioid tumor cells arranged as cords, strands, or balls in a myxoid and fibrillary matrix. Chondroblast-like lacunar structures mimicking real chondrosarcoma are common findings (see Fig. 14.66) [128]. The immunophenotype is not specific, up to 20% stain for S-100 protein and about 30% for CD117 (KIT) and occasionally for neuroendocrine markers. A characteristic translocation t(9;22)(q22/q3;q12), resulting in *EWSR1-NR4A3* fusion gene, is present in most cases. In about 25% cases, a translocation t(9;17)(q22;q11) is identified, which is probably connected with neuroendocrine differentiation [129].

Cytologic features:

- Myxoid background matrix
- Dispersed cells, branching cords, strands, and cell balls
- Spindly shaped, fusiform or round cells with ovoid or rounded nuclei
- Bland nuclear chromatin and small nucleoli
- Chondroblast-like lacunar structures
- Lack of significant vascularity

Differential diagnosis and problems in diagnosis:

- Low-grade myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Mixed tumor/myoepithelioma of soft tissue
- Myxoid liposarcoma, high grade
- Chondroid lipoma

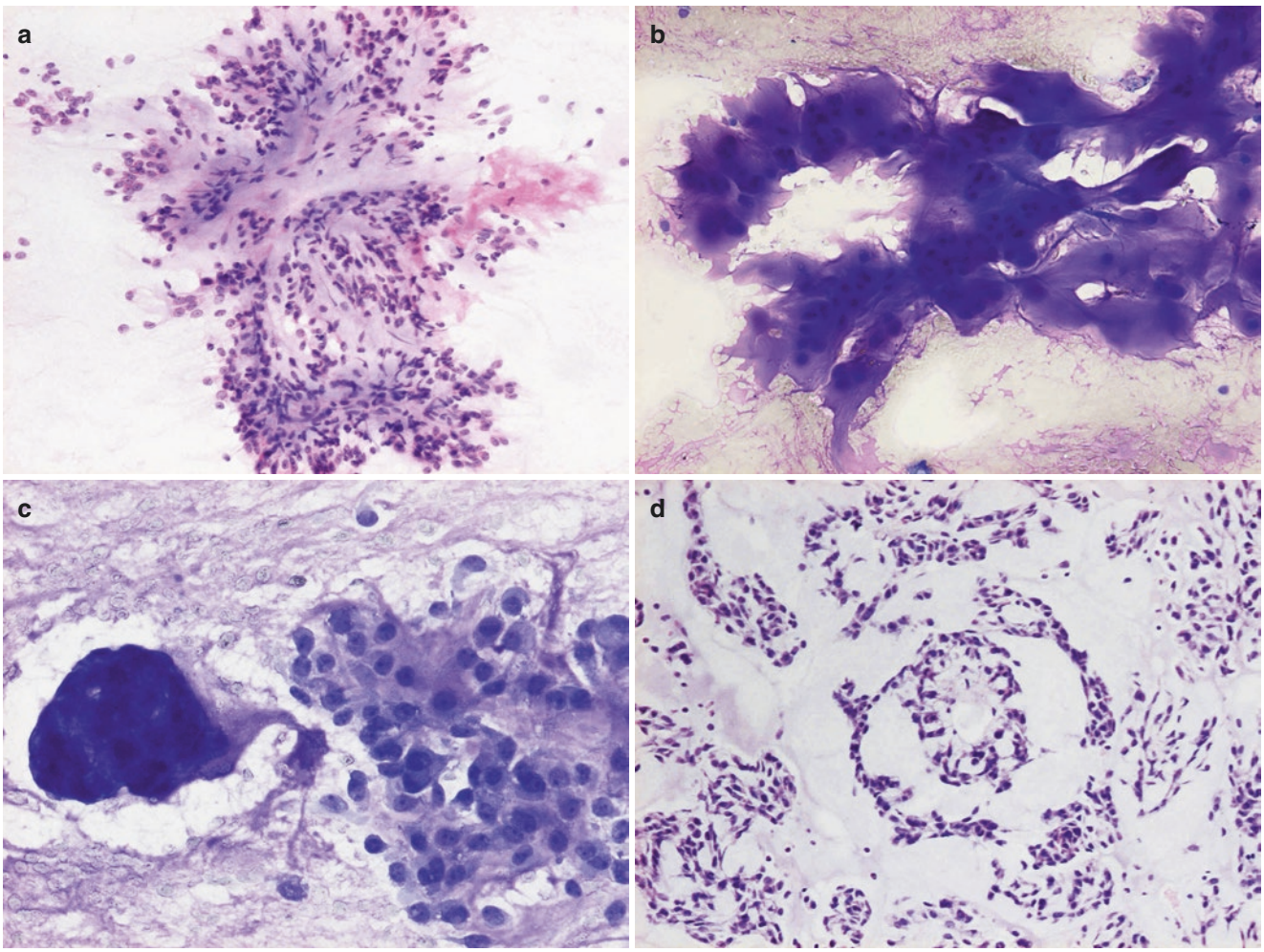

Fig. 14.66 Extraskeletal myxoid chondrosarcoma. (**a**–**c**) Dispersed cells, branching cords, strands, and cell balls of spindly shaped, fusiform, or round cells with ovoid or rounded nuclei in the myxoid background matrix (H&E; MGG). (**d**) The typical histologic appearance of branching cords and strands of bland spindle cells is best appreciated in cell-block sections (H&E; cell block; Shandon kit)

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is an aggressive malignant mesenchymal tumor of unknown histogenesis. It is predominantly found in the abdominal cavity in adolescents and young adults with a striking male predominance. The cytomorphology of DSRCT, though similar to other small round cell malignancies, displays some distinct features: relatively low cellularity, some cohesiveness retained, slightly angulated nuclei, and acinar-like structures (see Fig. 14.67). The characteristic finding of small nests of tumor cells associated with desmoplastic stroma is better appreciated in cell-block sections [130, 131]. DSRCT exhibits polyphenotypic differentiation, with immunoreactivity for cytokeratins, desmin, and neuroendocrine markers. DSRCT is characterized by a unique translocation t(11;22)(p13:q12) with *EWSRI-WT1* gene fusion, with can be detected by FISH studies (Table 14.2).

Cytologic features:

- Moderately cellular smears with loosely cohesive small clusters
- Tight clusters of cells with scant and poorly preserved cytoplasm
- Desmoplastic stroma fragments
- Uniform undifferentiated cells with slightly angulated nuclei and scant cytoplasm
- Nuclear molding and small acinar-like structures

Differential diagnosis and problems in diagnosis:

- Metastatic carcinoma (basaloid squamous cell carcinoma)
- Rhabdomyosarcoma
- Poorly differentiated synovial sarcoma
- Ewing sarcoma
- Neuroendocrine tumor

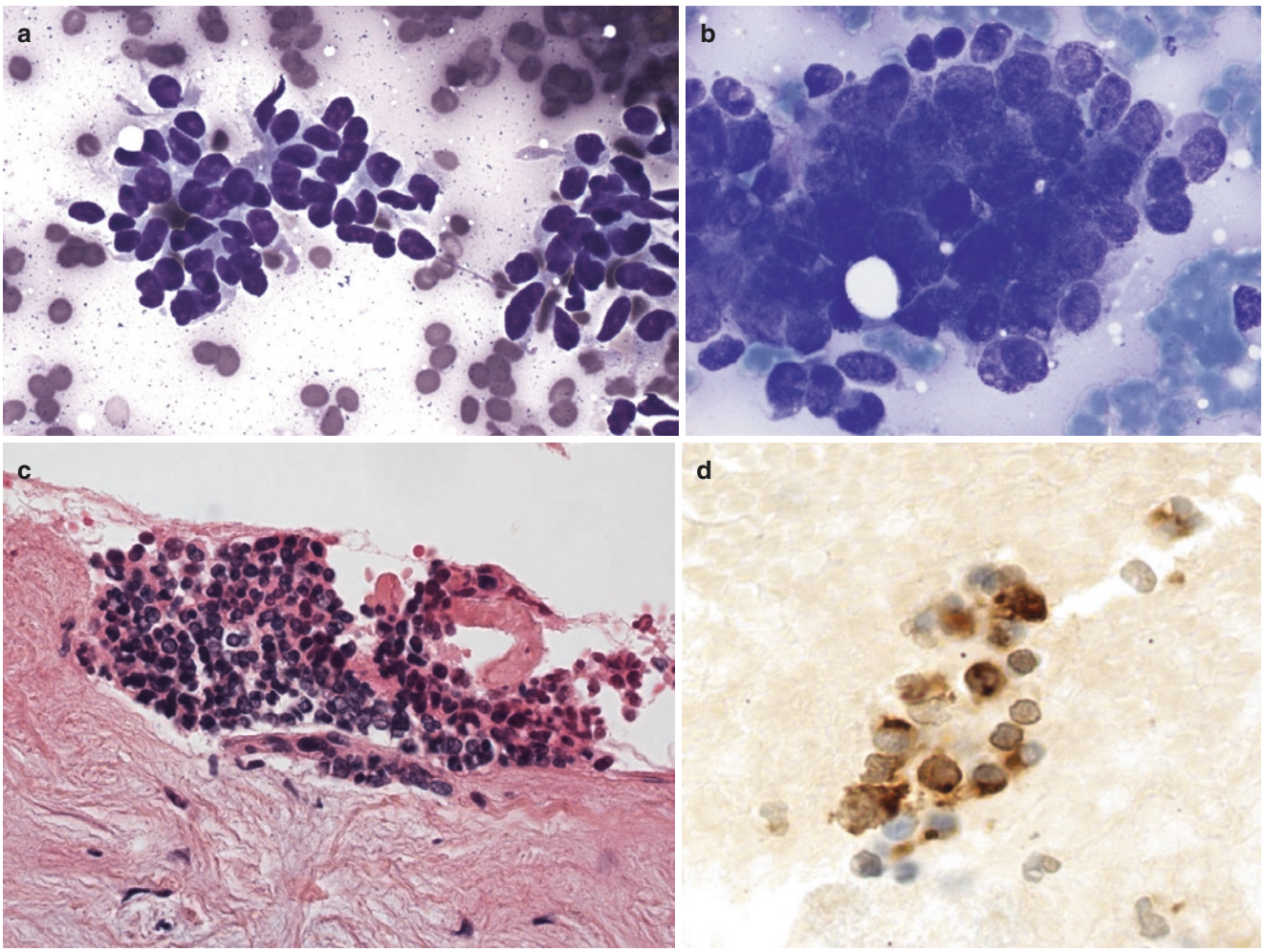

Fig. 14.67 Desmoplastic, small round cell tumor. (**a**) Loosely cohesive small clusters of ovoid undifferentiated cells with slightly irregular nuclear contours, finely granular chromatin, and scant cytoplasm (Pap stain). (**b**) Tight cluster of malignant cell with scant and poorly preserved cytoplasm, irregular hyperchromatic nuclei, and molding (MGG). (**c**) Small nests of tumor cells with associated desmoplastic stroma are characteristic (cell block; H&E). Demonstration of polyphenotypic differentiation with positive immunoreactivity for cytokeratins, EMA, desmin (**d**), and neuroendocrine markers is diagnostically helpful. Note the perinuclear dot-like staining pattern for desmin (cell block)

Extrarenal Rhabdoid Tumor of Soft Tissue

This rare, highly malignant tumor of soft tissue occurs in deep soft tissue of the neck and paraspinal region in infants and children. Congenital cases have been reported. This tumor also affects skin and visceral organs such as liver and retroperitoneum. The main cytologic feature is a mixture of dispersed cells and cell clusters of large rhabdoid cells and smaller round or polygonal or spindled cells. The rhabdoid cells have eccentrically placed large nuclei with macronucleoli and perinuclear cytoplasmic densities (see Fig. 14.68). Although a diagnosis of a malignancy is relatively easy to render from FNA smears, a correct specific diagnosis needs the demonstration of *SMARCB1* gene loss by cytogenetic techniques and/or INI1 protein loss by immunohistochemistry [132, 133].

Cytologic features:

- Variable cellularity with dispersed cells and clusters
- Large rhabdoid cells with eccentric nuclei, prominent nucleoli, and perinuclear density
- Smaller round, polygonal, and spindled cells
- Occasional binucleation and multinucleation
- Brisk mitoses and necrosis

Differential diagnosis and problems in diagnosis:

- Rhabdomyosarcoma
- Epithelioid sarcoma
- Other sarcomas with rhabdoid differentiation
- Poorly differentiated carcinoma with rhabdoid differentiation

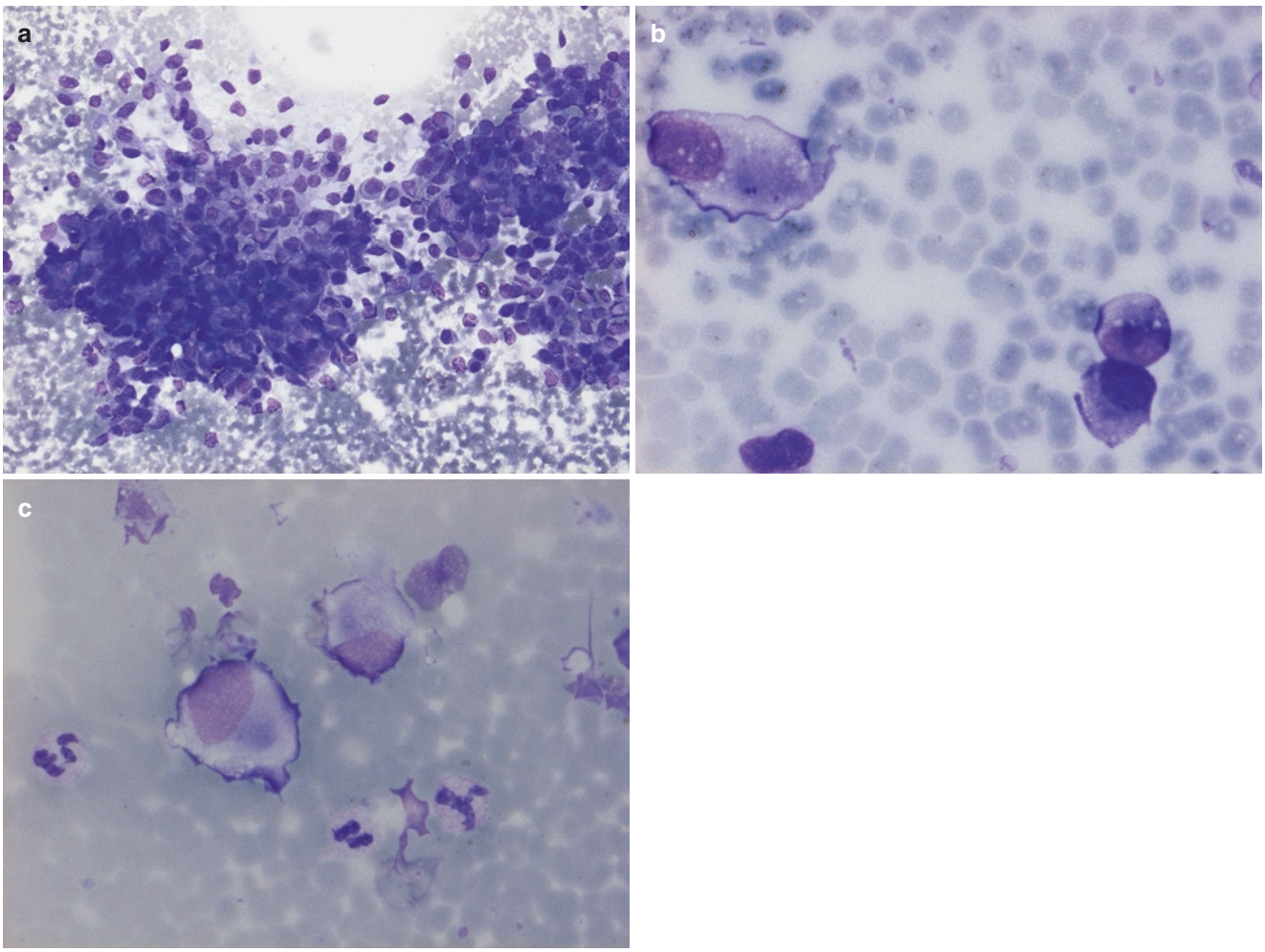

Fig. 14.68 Extrarenal rhabdoid tumor of soft tissue. (**a**) Smears containing both dispersed cells and cohesive cellular clusters composed of typical large rhabdoid cells and smaller round cells. (**b**, **c**) Rhabdoid cells with eccentrically placed large nuclei and abundant cytoplasm with perinuclear densities (MGG)

Perivascular Epithelioid Cell Tumor (PEComa)

PEComas are distinctive mesenchymal neoplasms arising from perivascular epithelioid cells with usually combined melanocytic and smooth muscle phenotype. The PEComa family includes neoplasms that arise in specific organs such as angiomyolipoma (kidney and liver), "sugar" tumor (lung), lymphangioleiomyomatosis (lung), and a variety of histologically and immunophenotypically related neoplasms arising almost in any site, most often in the retroperitoneum, abdomen, pelvis, uterus, and gastrointestinal tract. PEComa occurs in wide age range but most often in young and middle-aged adults with mean age of 45 and marked female predominance. Histologically PEComa shows variable morphology with nests, trabeculae, and sheets of epithelioid to spindled cells with variable eosinophilic to clear cytoplasm and round to oval nuclei with small nucleoli. In addition PEComas show unique morphologic features of specific subtypes (see Fig. 14.69). PEComa cells express HMB45, Melan-A, MITF, and often immunoreactivity for SMA and less common for desmin and h-caldesmon. About 10% of cases express S-100 positivity.

Cytologic features:
- Variable cellularity with dispersed cells and clusters
- Uniform or slightly pleomorphic cells with round to oval and spindled nuclei with small nucleoli
- Abundant granular cytoplasm with indistinct cytoplasmic borders
- Smaller round, polygonal, and spindled cells
- Unique morphologic features of specific subtypes

Differential diagnosis and problems in diagnosis:
- Adult rhabdomyoma
- Granular cell tumor
- Alveolar soft parts sarcoma

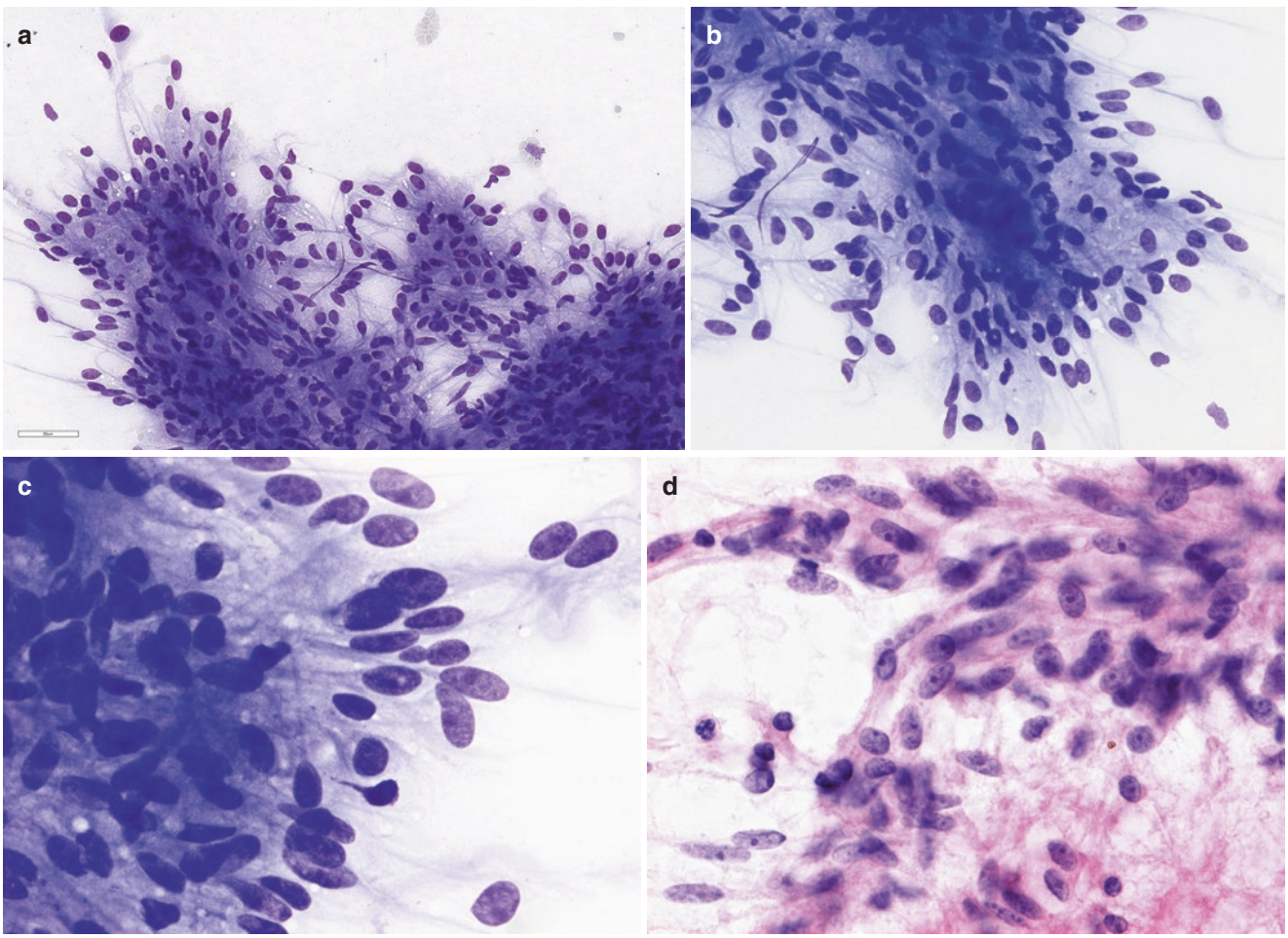

Fig. 14.69 PEComa. (**a–c**) Loosely clusters of uniform or slightly pleomorphic cells containing round to oval and spindled nuclei with small, occasionally somewhat larger nucleoli and abundant clear or granular cytoplasm with indistinct cytoplasmic borders (MGG). (**d**) Spindle cells with oval and fusiform nuclei, small nucleoli, and occasional spindle cells with cytoplasmic processes (H&E)

Undifferentiated/Unclassified Sarcoma

Undifferentiated sarcomas are defined as a heterogenous group of sarcomas without evidence of line of differentiation by presently available technology in the latest 2013 World Health Organization (WHO) classification [1]. Most of undifferentiated sarcomas with round cell morphology arise in young patients, while those of pleomorphic morphology (previously pleomorphic malignant fibrous histiocytoma—MFH) occur usually in elderly adults. Morphologically, they can be either spindle cell, epithelioid, round cell, or pleomorphic (formerly often known as pleomorphic malignant fibrous histiocytoma [MFH]) (see Fig. 14.70). MFH was, for many years, used to be considered a distinct entity. Several subtypes had been described, and the most common one was the pleomorphic type. Retrospective examinations of series of pleomorphic MFH have identified lipogenic, myogenic, and Schwann cell differentiation, as well as non-mesenchymal histogenesis in the majority of neoplasms diagnosed initially as MFH. Now, these groups of sarcomas are the diagnoses of exclusions. Because of limited sampling, undifferentiated sarcoma should only be made on FNAC if immunocytochemical studies are possible. In undifferentiated round cell and spindle-cell sarcomas, the EWSR1 gene is involved in fusions with genes such as POU5F1. Another recurrent mutation is the CIC-DUX4 fusion gene [134]. However, it is not yet fully understood if these changes represent specific entities.

Cytologic features:

- Hypercellular smears
- Necrosis and hemorrhage
- Mixture of dispersed cells, cell clusters, and small tissue fragments in variable proportions
- Variable cellular morphology, commonly spindle, polygonal, and epithelioid cells with marked cellular and nuclear pleomorphism, coarse chromatin, and large nucleoli
- Uni- and multinucleated giant cells
- Atypical mitoses
- Round cell morphology

Differential diagnosis and problems in diagnosis:

- Other pleomorphic sarcomas with a specific line of differentiation (pleomorphic liposarcoma, pleomorphic leiomyosarcoma, pleomorphic MPNST, and pleomorphic rhabdomyosarcoma)
- Dedifferentiated sarcomas
- Radiation-associated pleomorphic sarcoma
- Non-mesenchymal tumors (anaplastic large cell lymphoma, soft tissue metastases of anaplastic carcinoma, and sarcoma-like malignant melanoma)
- Sarcomatoid mesothelioma
- Round cell sarcomas of specific subtype

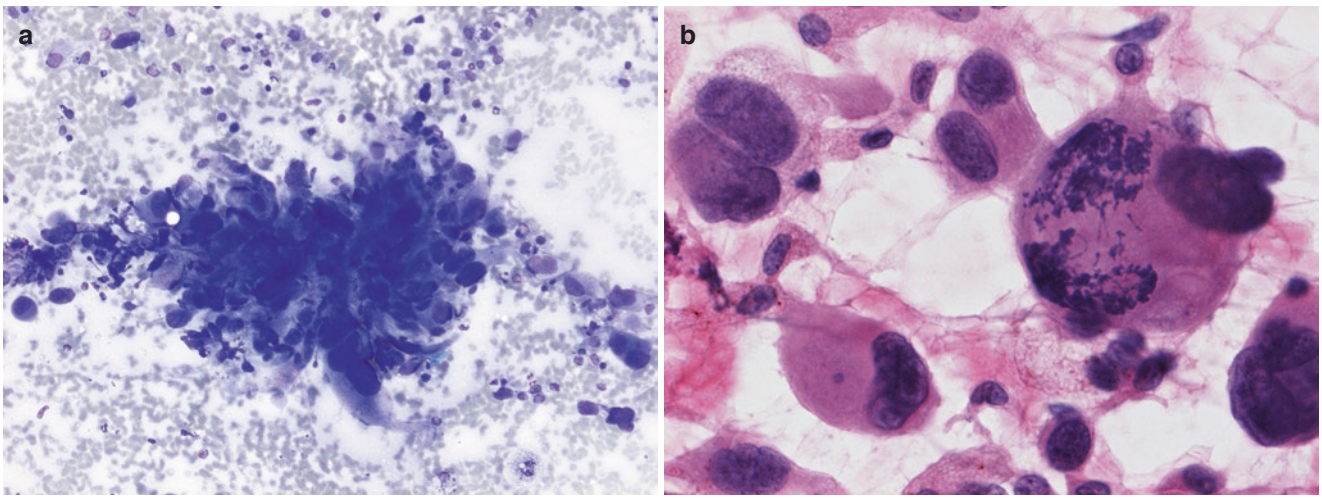

Fig. 14.70 Undifferentiated sarcoma. (**a**, **b**) Polygonal and epithelioid cells with marked cellular and nuclear pleomorphism (MGG; H&E)

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