Musculoskeletal System (Bone, Cartilage, Muscle, Soft Tissue) and Skin

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Adipose Tissue

Normal white adipose tissue is abundantly present subcutaneously and in surrounding organs. Fatty infiltration, lipomatosis, or lipomatous hypertrophy can also occur within certain organs (e.g., heart, pancreas, muscle, lymph nodes). Normal adipose tissue is present as sheets of cells with abundant, univacuolar cytoplasm with occasional interspersed thin blood vessels (Fig. 12.1). When sampled at the time of fine needle aspiration (FNA), fatty tissue tends to be hypocellular and present in cytology preparations as small cohesive clusters of large adipocytes [1–3]. Single cells are rare or absent. Benign adipocytes have abundant and univacuolated cytoplasm due to a large lipid vacuole, and small eccentrically located dark nuclei (Fig. 12.2). When viewed en face, the nucleus of an adipocyte is oval-shaped, but when seen from the side it may appear crescent-shaped. Intranuclear inclusions may be observed (Lochkern nucleus). Small capillaries are often visible traversing the clusters of adipocytes on smear cytology. If adipose tissue is aggressively aspirated and manipulated when preparing cytology slides, the adipocytes may be damaged, resulting in oily droplets in certain fixatives and on smeared slides. Remnant cell membranes can form lipid micelles that appear as clear round "holes" surrounded by proteinaceous material and blood on stained slides.

Differentiating normal adipose tissue from sampling of a circumscribed lipoma usually requires clinical and/or radiographic correlation, as mature adipose tissue and benign lipomas have very similar morphology [2, 3]. Single adipocytic cells and multivacuolated cytoplasm have been more commonly described in lipoma, but differentiating cytomorphologic factors are not well-established. Adipocytes demonstrate S100 immunoreactivity.

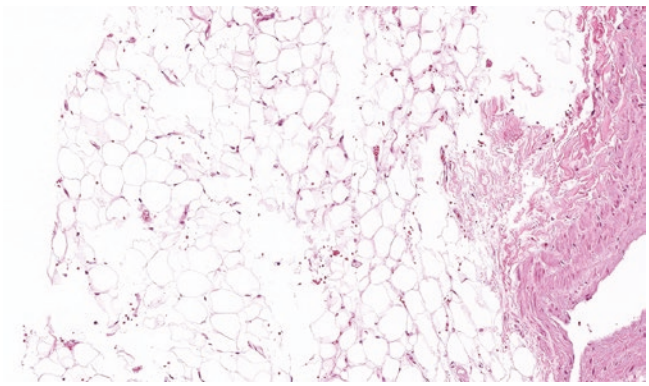

Fig. 12.1 Normal cohesive group of adipocytes with abundant univacuolar cytoplasm. Fibroadipose tissue, hematoxylin & eosin, 20× magnification

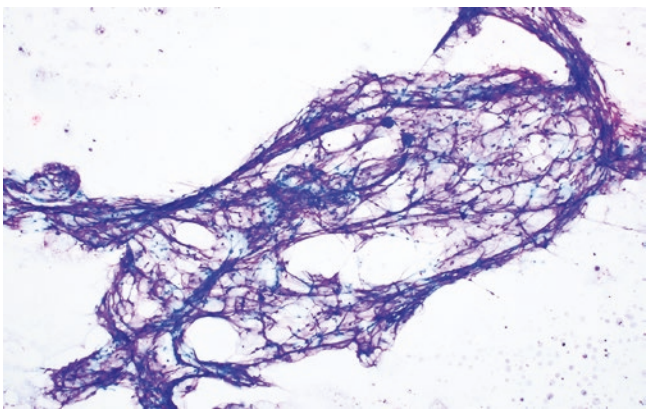

Fig. 12.2 Large cluster of normal adipocytes, exhibiting abundant pale, univacuolar cytoplasm, with traversing slender capillaries. Soft tissue, air-dried smear preparation, Diff-Quik, 10× magnification

Adipose tissue can undergo reactive and degenerative change in response to trauma, infection, prior biopsy, or previous surgical procedure [2–4]. In such situations, increased

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vascularity and proliferation of fibroblasts may be seen. Histiocytic inflammation, including multinucleated giant cells, can be present. Fat necrosis, which can occur following trauma, can present as a palpable mass in the breast or other fatty locations. Degenerative changes associated with fat necrosis include adipocytes that are smaller and have fine, multivacuolated cytoplasm present in an oily and granular background with foamy macrophages, inflammatory cells, and giant cells (Fig. 12.3).

Abdominal fat pad FNA is often performed in the workup of suspected systemic amyloidosis [5]. With special histochemical stains such as Congo red or fluorescent stains, amyloid material when present can be identified most prominently around the walls of intervening blood vessels, but also between adipocytes. Special stains for amyloid protein can be performed directly on air-dried smears or cell block material (Fig. 12.4).

Brown fat is distinctive adipose tissue involved in thermoregulation. When it forms a mass lesion, it is referred to as a hibernoma. Brown fat is often present in the mediastinum and retroperitoneum, as well as the soft tissue of the posterior neck and shoulders. The adipocytes of brown fat are smaller than those of white fat. The cytoplasm is multivacuolated rather than univacuolated, and eosinophilic mitochondrial granules are prominent and impart its characteristic red-brown color on hematoxylin and eosin stain (Fig. 12.5). Traversing capillaries

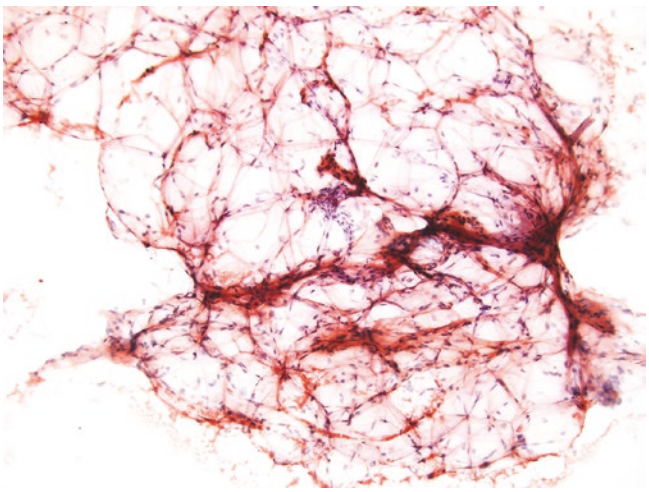

Fig. 12.4 Benign adipose tissue from an abdominal fat pad and is negative for amyloid protein on this Congo red stain. Abdominal fat pad, air-dried smear preparation, Congo red stain, 10× magnification

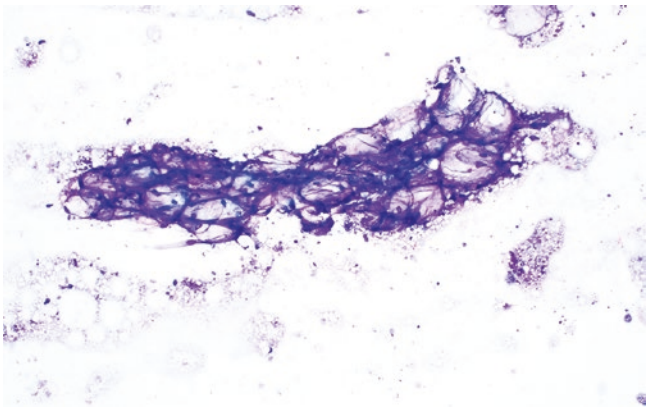

Fig. 12.3 Fat necrosis. A cluster of adipocytes is shown with degenerated, multivacuolated cytoplasm. Note that the background shows scant inflammatory cells and lipid deposits from ruptured adipocytes. Soft tissue nodule, air-dried smear preparation, Diff-Quik, 10× magnification

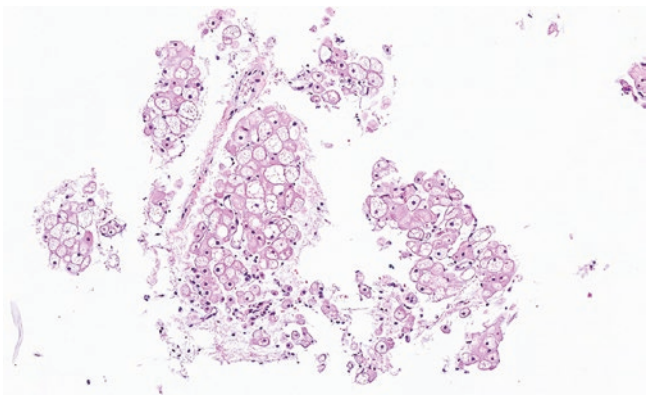

Fig. 12.5 In contrast to white fat, brown fat adipocytes are smaller with distinct cell borders, multivacuolated cytoplasm, and prominent eosinophilic mitochondrial granules. Peri-adrenal gland, cell block, hematoxylin & eosin, 20× magnification

are more prominent than in white fat. Brown fat demonstrates both S100 and CD31 immunoreactivity [6].

Striated Muscle

Skeletal muscles are composed of fascicles of parallel muscle fibers that insert onto bones via tendons (Fig. 12.6). In cytology samples, skeletal muscle presents as dense striated fibers with multiple small, dark, flat myocyte nuclei typically aligned along the subsarcolemmal periphery [2, 3]. These fibers stain strongly eosinophilic on hematoxylin and eosin (H&E), are amphophilic on Papanicolaou stain, and appear deep blue on modified Giemsa stains including Diff-Quik (DQ) (Fig. 12.7a, b). Striations may not always be seen. Fiber typing (dark type 1 and pale type 2 fibers) requires histochemical stains. Regenerating or degenerated skeletal muscle fibers can take on a multinucleated appearance ("bag of nuclei"). Regenerative skeletal muscle nuclei can also show reactive changes, including moderate nuclear enlargement and prominent nucleoli.

Cardiac muscle is also striated, but these muscle fibers are shorter, do not run as tightly parallel as skeletal muscle fibers, and exhibit branching [2, 3, 7] (Fig. 12.8a, b). Intercalated discs can sometimes be seen between cardiac myocytes, which appear as clear spaces. Cardiac myocytes have small, slightly eccentric nuclei, morphologically similar to those seen in skeletal muscle, that may be more centrally placed. One may find perinuclear lipofuscin pigment.

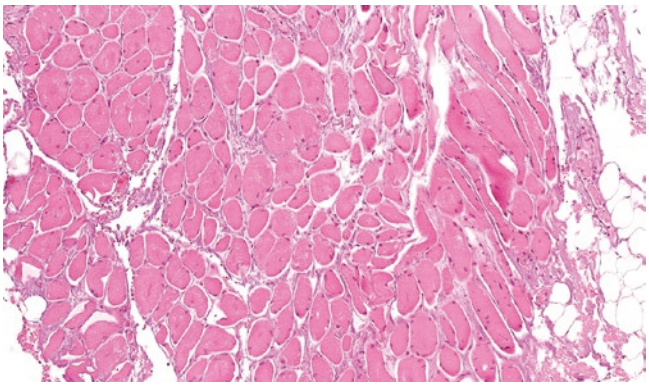

Fig. 12.6 Striated skeletal muscle fibers, seen in cross section, with peripherally located nuclei. Skeletal muscle, hematoxylin & eosin, 20× magnification

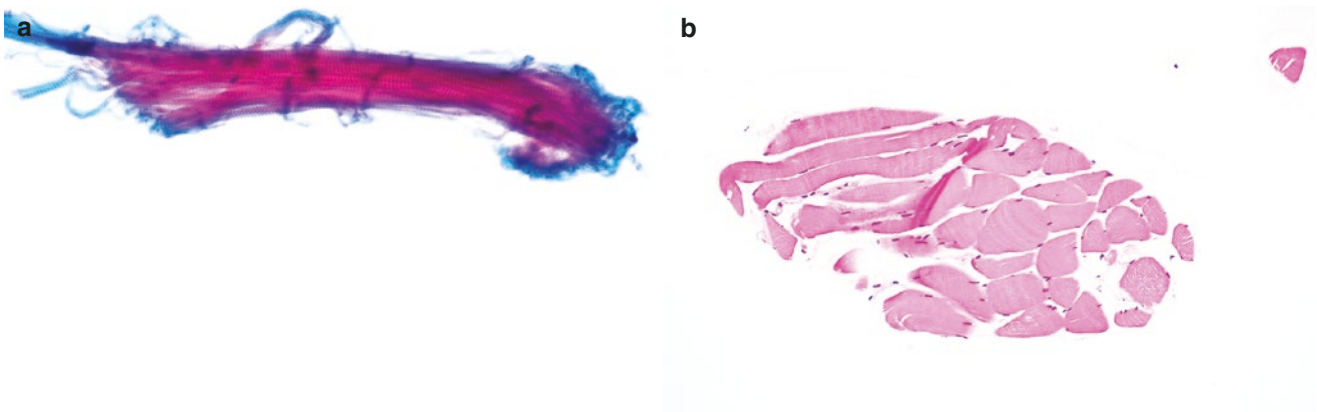

Fig. 12.7 (**a**) Nonbranching fragment of skeletal muscle fibers containing parallel cross striations, and myocytes with spindled nuclei and indistinct cell borders. (**b**) On cell block preparation, cross sections of muscle fibers reveal central eosinophilic fibers and peripheral small nuclei. Soft tissue, alcohol-fixed smear preparation, Papanicolaou stain, 60× magnification (**a**). Soft tissue, cell block, hematoxylin & eosin, 20× magnification (**b**)

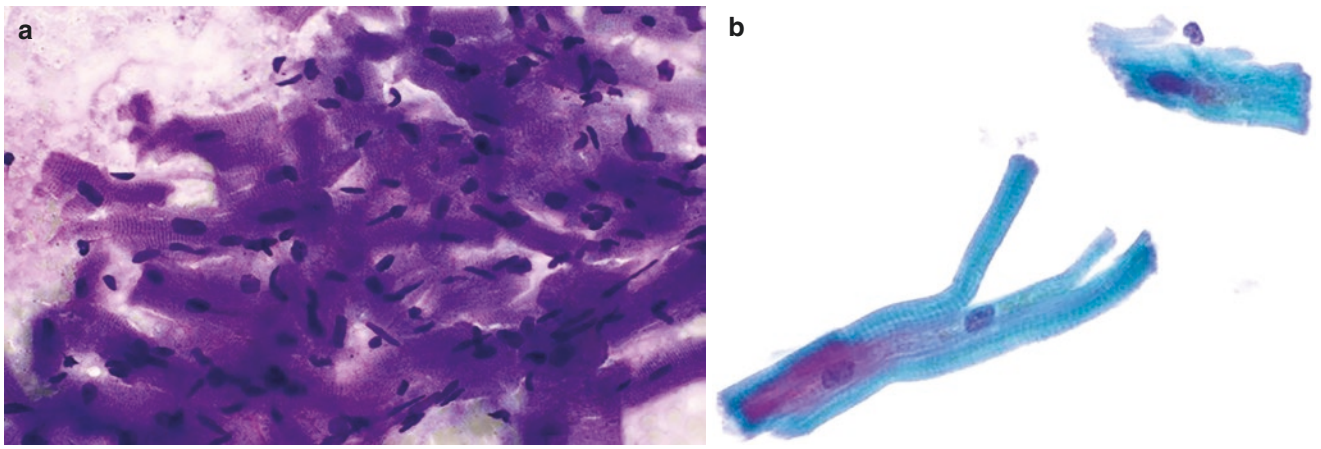

Fig. 12.8 (**a**) Cardiac muscle, exhibiting rectangular branching of fibers. Intercalated discs create greater separation between myocytes compared to those seen in skeletal muscle. (**b**) Branching of cardiac myocytes can be appreciated. Heart, air-dried smear preparation, Diff-Quik, 50× magnification (**a**). Heart, alcohol-fixed smear preparation, Papanicolaou stain, 50× magnification (**b**)

Fibrous Connective Tissue

Mesenchymal stroma and fascia are fibrous tissues composed of fibroblasts and extracellular matrix material, including collagen and ground substance. Dense fibrous connective tissue contains abundant collagen and elastin, and it makes up the strong connective tissue of the tendons, ligaments, and fascia (Figs. 12.9 and 12.10). Loose fibrous connective tissue contains little collagen and looser, pale-staining ground substance. It is found surrounding and supporting organs and blood vessels [7].

Fibroblasts are the principal cell of connective tissue, and they can be sampled from essentially any body site [2, 3, 7]. They produce the matrix materials of connective tissue, including collagen and ground substance, and are found embedded within the connective tissue they produce. Fibroblasts range in shape and appearance. They are present more abundantly in dense connective tissue, where they take on a spindled appearance embedded between collagen fibers (Fig. 12.11). In loose connective tissue, fibroblasts are less abundant, and they take on a polygonal or stellate shape. In both types of connective tissue, these cells have delicate cytoplasm and the nuclei of fibroblasts have bland even chromatin and absent or inconspicuous nucleoli. Naked fibroblast nuclei can sometimes be found in vigorous fine needle aspiration smears.

Myxoid change is a common degenerative process of connective tissue, in which the matrix material takes on an amorphous, granular amphophilic to mucoid appearance. It is associated with degenerative changes in mesenchymal elements of nonneoplastic, benign, and malignant entities.

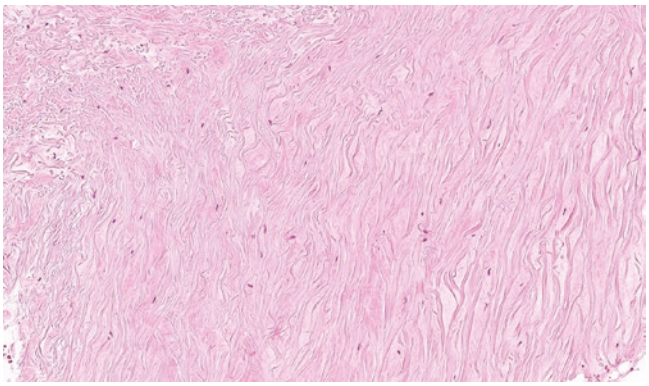

Fig. 12.9 Dense collagenous stroma of fascia with scattered fibroblastic cells. Fascia, hematoxylin & eosin, 20× magnification

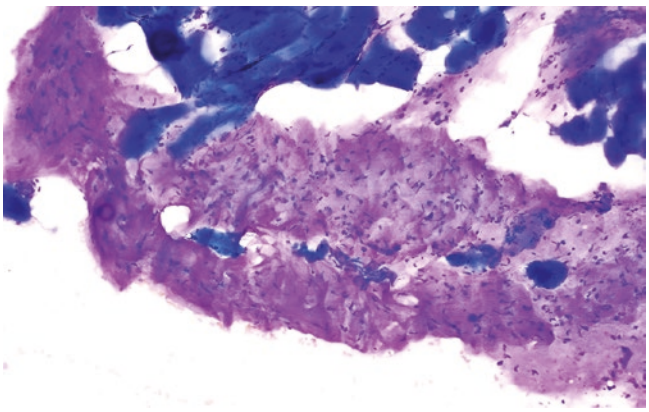

Fig. 12.10 Pink collagenous stroma containing embedded fibroblasts in soft tissue associated with blue-staining skeletal muscle. Fascia, air-dried smear preparation, Diff-Quik, 10× magnification

Reactive cellular changes in connective tissue are common following an injury or procedural intervention. In such circumstances, reactive (versus resting) fibroblasts show variation in size and shape, from spindled to polygonal to stellate, often with angulated cytoplasmic extensions [4, 8]. Variation in nuclear size and shape is common, as are reactive-type nucleoli (Fig. 12.12). Reactive fibroblasts may be binucleated. Loose but cohesive clusters of reactive fibroblasts without obvious associated stroma can be seen, which can mimic neoplastic processes.

Myofibroblasts are cells of uncertain origin with features of both normal fibroblasts and smooth muscle cells [9]. In reactive soft tissue conditions, they likely represent modified fibroblasts, and are not always readily distinguishable from reactive fibroblasts. Myofibroblasts are most often spindle shaped, have ill-defined eosinophilic cytoplasm that is paler than smooth muscle cells, and contain wavy or plump, rounded nuclei with small nucleoli. In contrast to fibroblasts, myofibroblasts express markers of smooth muscle differentiation, such as alpha-smooth muscle actin.

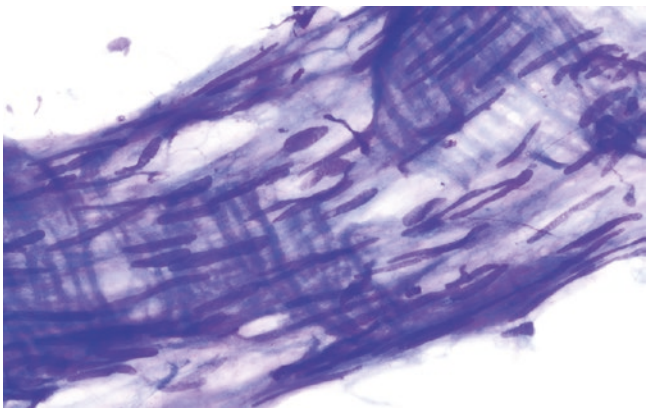

Fig. 12.11 Densely cellular connective tissue from fascia, with spindle-shaped fibroblast nuclei running in parallel rows. Fascia, air-dried smear preparation, Diff-Quik, 60× magnification

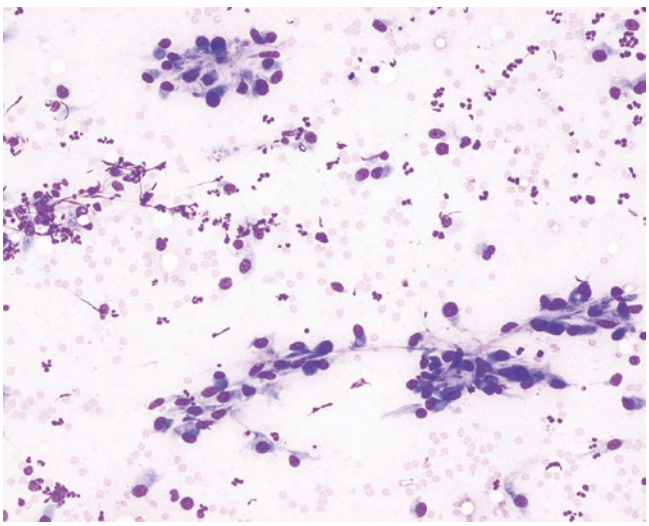

Fig. 12.12 Reactive fibroblasts are present as single cells and in small groups, with round nuclei, occasional nucleoli, and angulated cytoplasmic borders. The background also contains scattered neutrophils. Post-surgical site, air-dried smear preparation, Diff-Quik, 20× magnification

Bone

Bones vary in shape and include tubular and flat bones. Tubular bones are anatomically subdivided into epiphysis (articular edge), metaphysis, and diaphysis (shaft). Bone tissue is composed of ossified (mineralized) organic matrix (e.g., collagen), inorganic minerals (calcium hydroxyapatite), and cellular elements including osteoblasts, osteoclasts, and marrow elements. Lamellar bone is mature, highly organized, and ossified bone that makes up the dense compact (cortical) outer structural bone and spongy cancellous (trabecular) bone of the marrow cavity (Fig. 12.13). Woven bone is immature bone found in fetal development and bone healing, which is the foundation on which lamellar bone forms. It is weaker and more flexible, with disorganized collagen and less mineralization than lamellar bone. In lamellar bone, the collagen is deposited with a parallel pattern. The outer surface of bone is lined by thin fibrous periosteum and the inner medullary surface is lined by endosteum. Bone formation and remodeling (e.g., endochondral or intramembranous ossification) is best appreciated in histopathology sections [2, 3].

Bone material may be present in a number of cytology specimens, especially for primary and secondary bone lesions that are targeted for computed tomography (CT)-guided FNA. In addition, contaminating fragments of bone can be obtained during aspiration of lesions adjacent to bone and in cerebrospinal fluid specimens (Fig. 12.14a, b). They often appear as acellular fragments of amorphous calcified

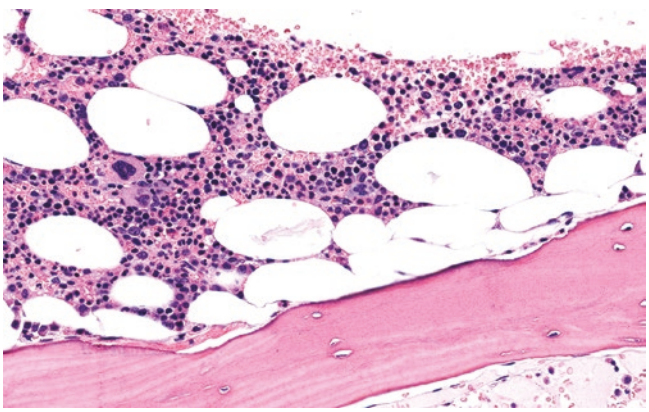

Fig. 12.13 Trilineage bone marrow elements and bony trabeculae of normal spongy bone. Bone, hematoxylin & eosin, 40× magnification

material. These bone fragments often cause air bubbles to form under glass slide coverslips. Decalcification of bone specimens can impair cellular preservation.

Normal cellular elements of bone encountered in cytology samples must not be misinterpreted as atypical or malignant [10]. Osteoblasts are uniform, round to polygonal cells with abundant cytoplasm and typically have eccentric nuclei which may show perinuclear hofs due to their Golgi apparatus (Fig. 12.15a). They can thus mimic plasma cells. They are usually found as single cells. However, when they present in sheets and clusters, they can resemble epithelium. However, osteoblast nuclei are ovoid and regular, have open chromatin with distinct nucleoli, and they lack the three dimensionality of metastatic carcinoma. Osteoblasts that become embedded within bone matrix become osteocytes and are located within a lacunar space. These are infrequently seen in FNA samples because they are hard to reach with aspiration. Osteoclasts are cells of histiocytic origin involved in bone reabsorption. They typically appear as single, large (40–100 uM in diameter), multinucleated giant cells similar to those seen in foreign body giant cell reactions (Fig. 12.15b). Their nuclei (often 4–20 in number, but can reach up to 100) are scattered throughout the cytoplasm, which is abundant and often granular or vacuolated. These nuclei are ovoid with regular nuclear membranes and euchromatin. Nucleoli may range from being indistinct to prominent.

Bone marrow cellular elements can also be encountered in cytology specimens, including all three lines of blood cell precursors: erythropoietic, myelopoietic, and megakaryocytic [10] (Fig. 12.16a, b). Megakaryocytes are large cells

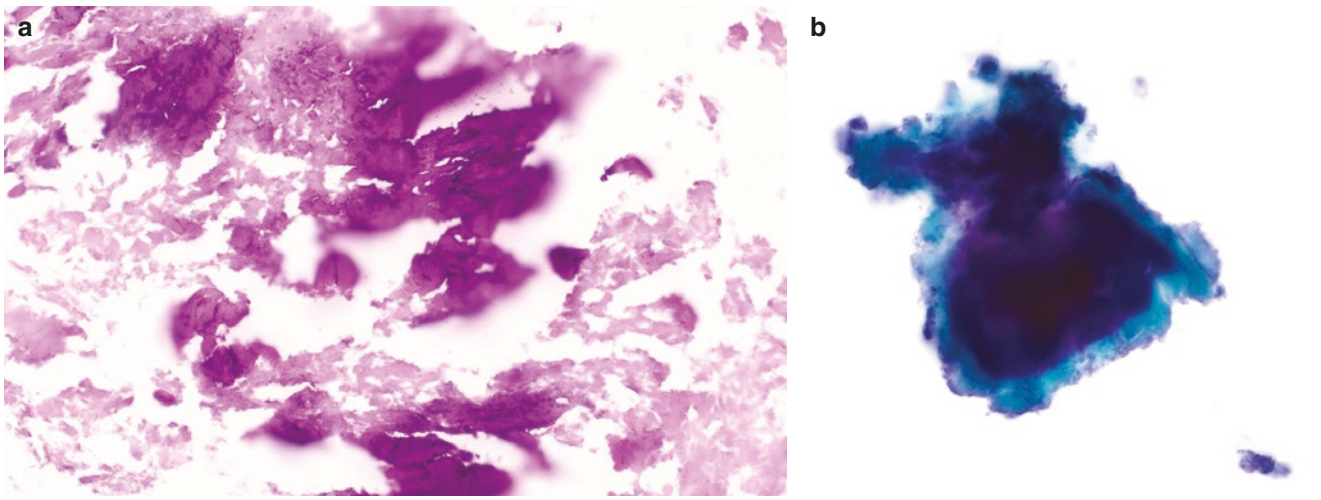

Fig. 12.14 Amorphous, calcified bone matrix material. Bone, air-dried smear preparation, Diff-Quik, 40× magnification (**a**). Bone, alcohol-fixed smear preparation, Papanicolaou stain, 60× magnification (**b**)

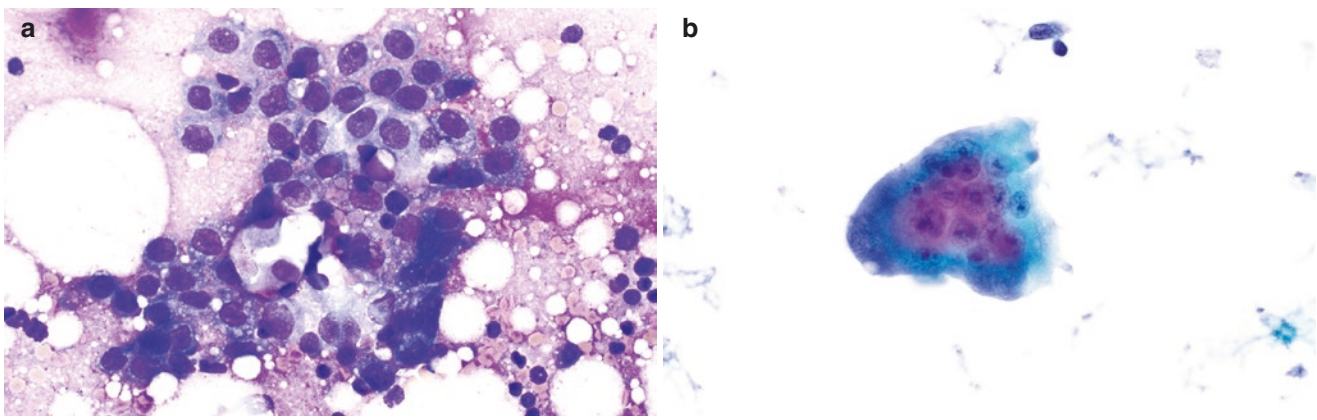

Fig. 12.15 (**a**) Osteoblasts forming epithelioid clustering. The cells are polygonal with uniform round nuclei, round central nucleoli, and smooth nuclear membranes. (**b**) An osteoclast is shown which appears as a multinucleated giant cell containing many ovoid, bland nuclei. Bone, air-dried smear preparation, Diff-Quik, 60× magnification (**a**). Bone, alcohol-fixed smear preparation, Papanicolaou stain, 60× magnification (**b**)

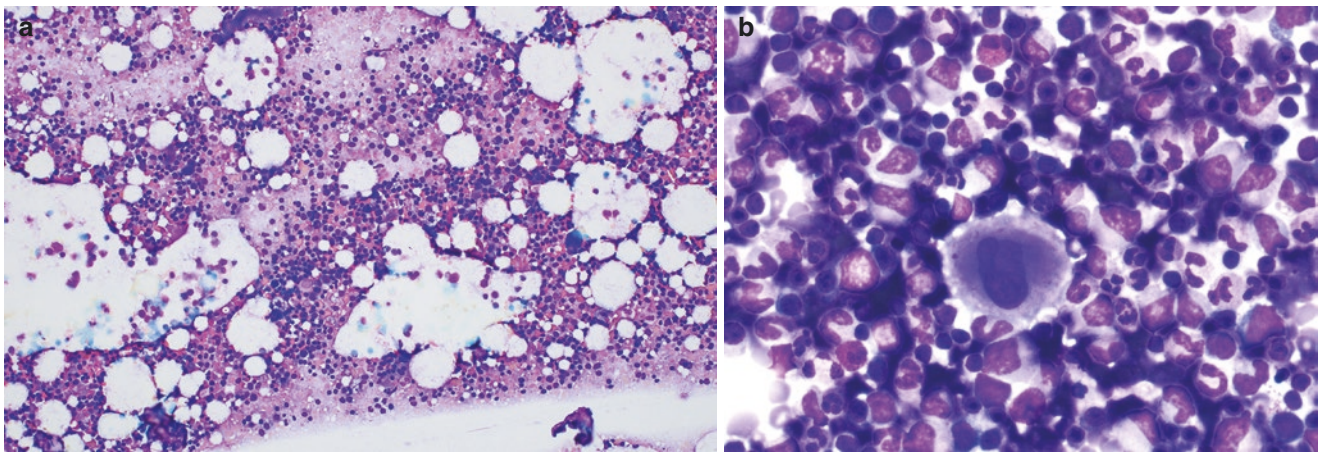

Fig. 12.16 Bone marrow elements. (**a**) Adipocytes are shown admixed with hematopoietic bone marrow elements. (**b**) Normal trilineage elements are present including a central megakaryocyte with a large lobated nucleus, and numerous erythroid and myeloid elements. Bone marrow, air-dried smear preparation, Diff-Quik, 20× (**a**) and 60× (**b**) magnification

with abundant amphophilic, granular cytoplasm, and multilobated nuclei. Their chromatin is dense and nucleoli are usually absent. The multilobation and dark staining of the nuclei can be mistaken for the nuclear changes of malignant cells such as metastatic carcinoma. However, normal megakaryocytes are always present singly in the background of other marrow elements while carcinoma cells often present in crowded clusters. Erythroid precursors appear as small, lymphocyte-sized cells with round eccentric nuclei and condensed to pyknotic chromatin. Myeloid precursors have a range of appearances, from larger cells with unilobed, pale nuclei to smaller cells with band-like or lobated nuclei.

Cartilage

Cartilage is composed of its primary cellular elements (chondrocytes) embedded within an acellular matrix (Fig. 12.17). Chondrocytes appear as large polygonal cells, often with angular edges (Fig. 12.18). Their cytoplasm is lightly basophilic, and their nuclei are typically pyknotic and degenerated [2, 3, 10].

There are three types of cartilage: hyaline, elastic, and fibrocartilage. Hyaline cartilage is the most abundant form in the body, and it is the most commonly encountered form seen in cytology preparations. Hyaline cartilage is found at the tip of the nose, around the trachea, and at joints. So named because of its glassy appearance, hyaline cartilage is predominantly made of collagen fibers. The collagen matrix appears as homogenously dense but amphophilic matrix material with embedded chondrocytes (Fig. 12.19). Hyaline cartilage can be encountered by needle contamination in transbronchial FNA and cerebrospinal fluid samples, as well as sampling of bone and soft tissue lesions.

Elastic cartilage is less strong but more flexible than hyaline cartilage. Its matrix contains an abundance of elastin fibers and relatively less collagen than hyaline cartilage, but the histologic appearance is otherwise similar to hyaline cartilage. Elastic cartilage is found in the external ear and the larynx. Fibrocartilage is the strongest and most dense cartilage. It is found in the transition points between hyaline cartilage and tendons or ligaments, and its histologic features often resemble a transition between hyaline cartilage and dense fibrous connective tissue.

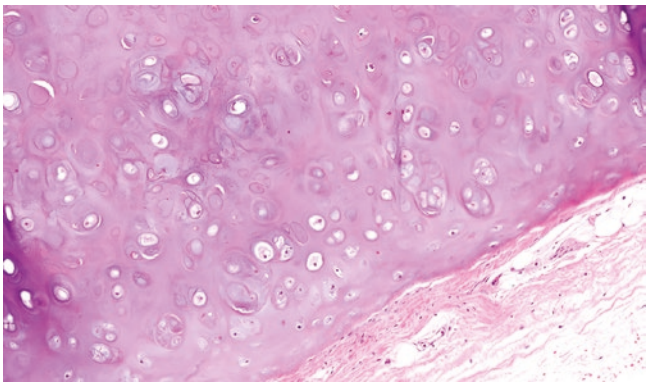

Fig. 12.17 Hyaline cartilage from the bronchial wall, composed of homogeneous amphophilic matrix material with embedded chondrocytes. Bronchus, hematoxylin & eosin, 40× magnification

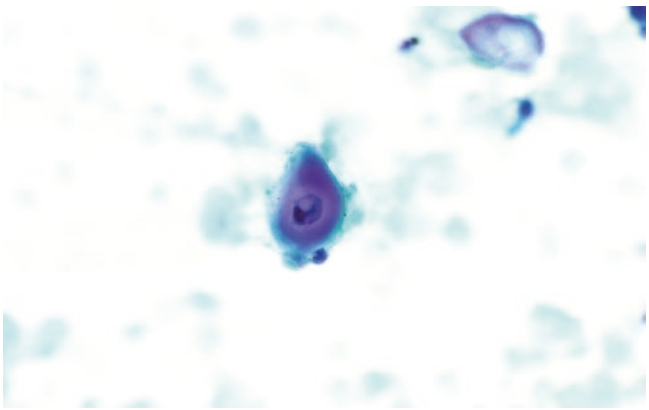

Fig. 12.18 A single benign chondrocyte is shown with moderate pale cytoplasm, pyknotic nucleus, and surrounding chondroid matrix material. Cerebrospinal fluid, ThinPrep preparation, 60× magnification

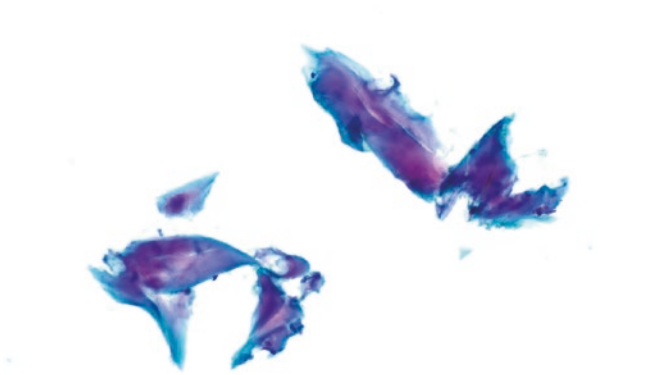

Fig. 12.19 Fragments of hyaline cartilage from the bronchial wall, collected during endobronchial fine needle aspiration of a lung nodule, containing scant embedded chondrocytes with small pyknotic nuclei. Endobronchial fine needle aspiration, alcohol-fixed smear preparation, Papanicolaou stain, 20× magnification

Synovium

The joints of the skeletal system typically include hyaline cartilage covering the articular surfaces of bones, ligaments formed mainly by collagen, and synovium. The temporomandibular, sternoclavicular, and intervertebral joints are instead covered by fibrocartilage. The joint capsule includes three layers: outer fibrous layer, subsynovium, and inner synovial lining [11, 12]. The synovial lining is composed of synoviocytes, which include type A cells (histiocyte-like) and type B cells (fibroblast-like) (Fig. 12.20). The type A cells have a phagocytic function while the type B cells produce hyaluronic acid. Synovial cells can be obtained during aspiration of lesions involving or adjacent to joints. On aspiration cytology, they present as clusters of bland, fibroblastic cells (Fig. 12.21). Macrophages and other inflammatory cells can also be obtained on sampling of joint fluid. The subsynovium is comprised of fibrovascular tissue with variable fat, nerves, and scattered histiocytes.

Arthrocentesis of joint fluid for cytology examination and synovial fluid analysis is often undertaken in patients with a joint effusion or inflammation. Normal synovial fluid is usually clear and viscous, and should not clot in a tube. It functions as a lubricant and supplies nutrients to the articular cartilage. The volume of this fluid is usually minimal in the normal state, even for large joints. When there is inflammation, this volume increases, along with the number of inflammatory cells. Normal synovial fluid contains very few cells. Polarized microscopic examination of normal synovial fluid should not identify crystal deposition, as occurs with crystal-induced arthropathy (e.g., gout and pseudogout).

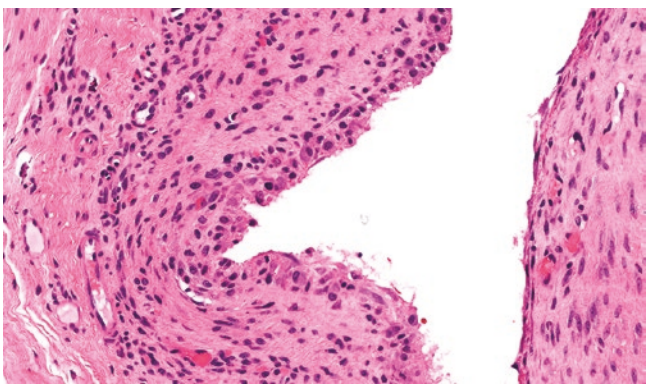

Fig. 12.20 Synovium composed of an inner lining of histiocyte-like and fibroblast-like cells within a fibrous wall. Synovium, hematoxylin & eosin, 40× magnification

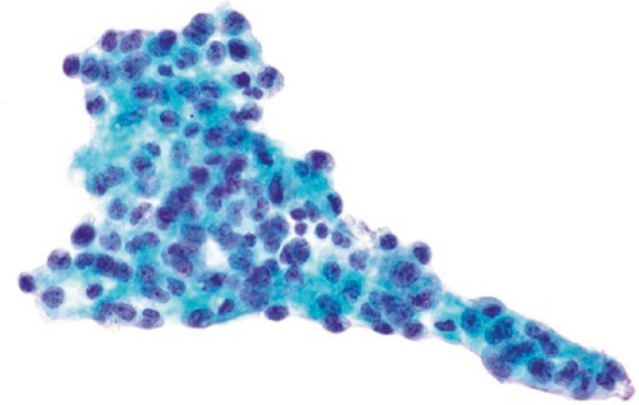

Fig. 12.21 Cluster of bland, fibroblastic synovial cells. Nuclei are ovoid and contain euchromatin. Joint fluid, alcohol-fixed smear preparation, Papanicolaou stain, 60× magnification

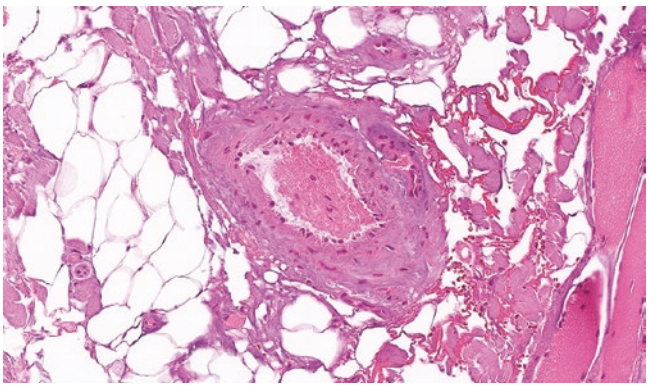

Fig. 12.22 Muscular artery lined by a low cuboidal layer of endothelium surrounded by smooth muscle. Soft tissue, hematoxylin & eosin, 20× magnification

Blood Vessels

Fragments of blood vessels and endothelial cells are frequently present in FNA samples at a variety of sites [2, 3, 7]. Small capillaries are commonly collected at aspiration, particularly in highly vascular sites such as the endocrine organs. Capillaries, arterioles, and venules present as thin, branching structures containing endothelial cells, the nuclei of which usually present in a "single file" appearance along the vascular structure. Larger arterial vessels are lined by inner endothelium surrounded by smooth muscle (Fig. 12.22).

Endothelial cells can show a range of appearances on aspiration cytology (Fig. 12.23). Nonreactive endothelium most commonly presents as clusters of small, elongated cells with flat nuclei. Reactive changes can occur, such as in the setting of inflammation and/or angiogenesis, resulting in nuclear enlargement, rounding of nuclei, and prominent nucleoli. Normal endothelium usually does not have mitotic figures. Endothelial cells are immunoreactive for CD34, CD31, and ERG.

Large and medium-sized arteries include both elastic and muscular types. Elastic arteries are the large arteries of the cardiopulmonary system (i.e., aorta and pulmonary arteries). These vessels have thin walls relative to the size of their lumen. The wall of elastic arteries contains abundant collagen and elastin fibers, and relatively scant smooth muscle myocytes, which are embedded within the fibrous stroma of the vessel wall. Elastic arteries may occasionally be sampled on aspiration of mediastinal and central lung lesions. Muscular arteries include the medium- and large-sized arteries which arise and draw blood from elastic arteries (Fig. 12.24a, b). They are of smaller caliber, and their wall is composed of a greater density of smooth muscle myocytes and relatively less fiber material. Veins are also lined by endothelial cells. They have thinner walls than arteries, with abundant collagen and few smooth muscle myocytes within their vessel wall.

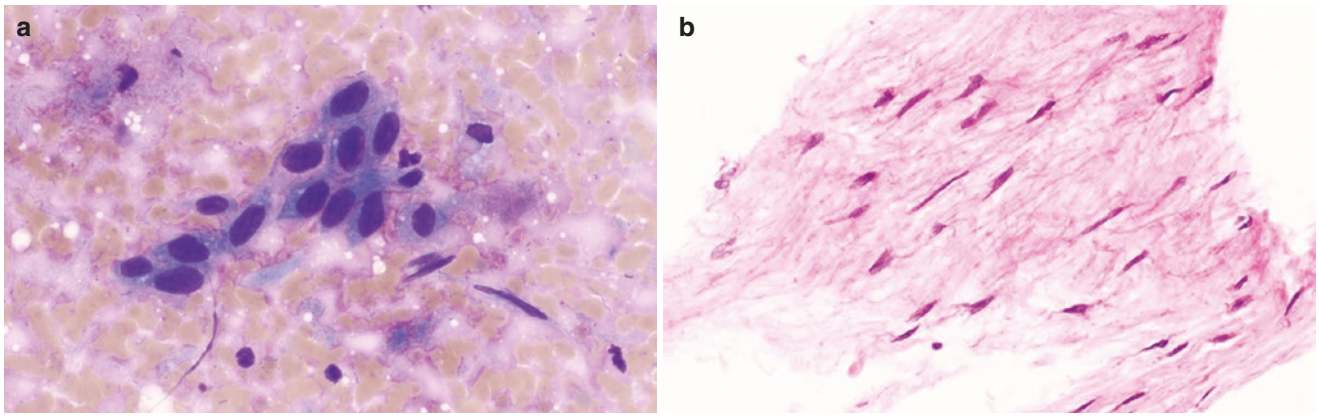

Fig. 12.23 Endothelial cells from the aortic lining. (**a**) Endothelial cells are ovoid to elongated, with bland, ovoid nuclei. (**b**) The wall of the aortic contains single smooth muscle myocytes embedded in collagen and elastin material. Aorta, air-dried smear preparation, Diff-Quik, 60× magnification (**a**). Aorta, cell block, hematoxylin & eosin, 40× magnification (**b**)

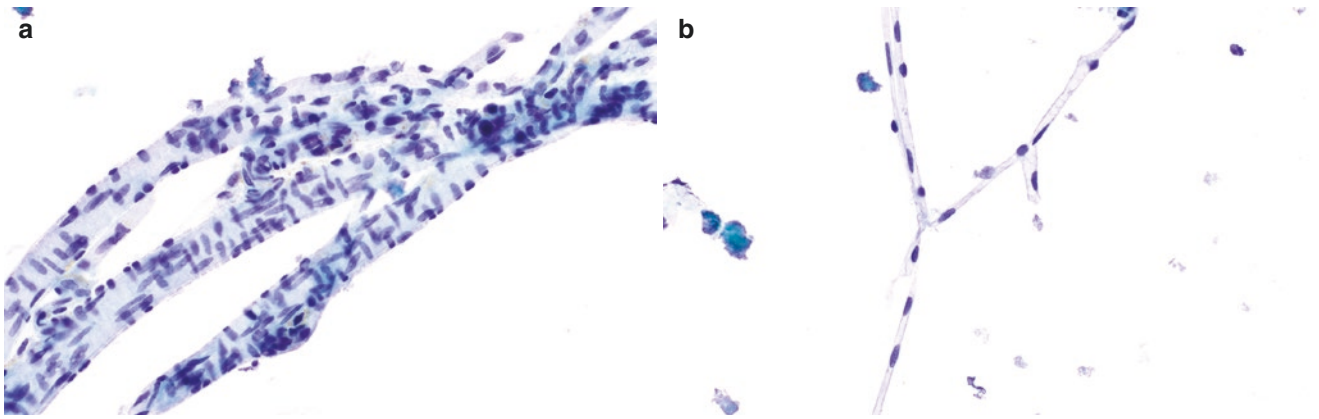

Fig. 12.24 (**a**) Medium-sized muscular arteries have a greater density of myocyte nuclei than elastic arteries, while (**b**) capillaries appear as thin, branching structures with single-file endothelial nuclei and no smooth muscle. Soft tissue, alcohol-fixed smear preparation, Papanicolaou stain, 40× (**a**) and 20× magnification (**b**)

Skin

The skin is composed of the outer epidermis and the underlying dermis, separated by a basement membrane [2, 13, 14] (Fig. 12.25). The epidermis contains a superficial layer of keratin, with a mid-portion composed of several layers of keratinocytes (squamous cells), and basal cells near the basement membrane admixed with fewer melanocytes and Langerhans cells.

Keratin, anucleated squamous cells, and occasional mature, nucleated superficial squamous cells are typically the most abundant elements seen on skin scraping specimens (Fig. 12.26). These outer epidermal elements are also commonly a minor contaminating component of percutaneous FNA at any site.

The dermis is composed of similar mesenchymal elements as seen elsewhere in the soft tissues of the body. As a connective tissue layer, the dermis is composed of fibroblasts and abundant collagen, as well as elastin fibers. Adipocytes, macrophages, mast cells, blood vessels, and nerves may also be present.

The dermis also contains skin appendages that connect to the surface skin and hair follicles [13, 14]. Eccrine sweat glands, found essentially on all body surfaces, are tortuous ductal structures lined by stratified, cuboidal epithelial cells with scant to moderate cytoplasm. Apocrine sweat glands, which are associated with hair follicles, are ductal structures

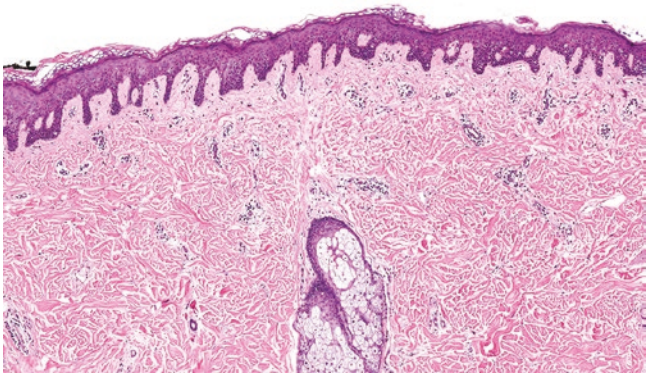

Fig. 12.25 Normal skin with a surface layer of keratinocytes and underlying dermis with embedded sebaceous gland. Skin, hematoxylin & eosin, 4× magnification

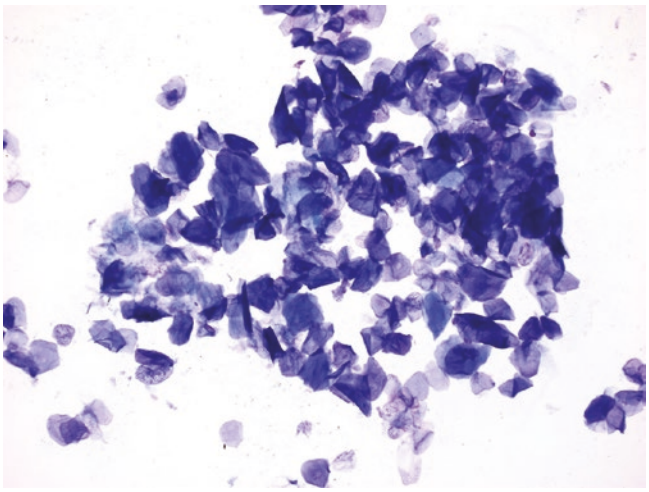

Fig. 12.26 When superficial skin is sampled, anucleated surface squamous cells predominate, with occasional mature nucleated squamous cells seen. Skin scraping, air-dried smear preparation, Diff-Quik, 20× magnification

lined by a single layer of apocrine-type epithelium, which is columnar epithelium marked by abundant eosinophilic cytoplasm and conspicuous nucleoli. Sebaceous glands (Fig. 12.25), which are found both at the skin surface and at hair follicles, are acinar glands filled with large, round sebaceous cells marked by abundant vacuolated cytoplasm (Fig. 12.27a, b).

Hair follicles may be occasionally sampled on superficial FNA, particularly from the scalp, axillary, or inguinal areas. They are tubular structures extending from the dermis and opening onto the skin surface. The hair follicle is composed of multiple layers of keratocytes surrounding a central hair shaft. Melanin pigment is frequently seen, particularly at the base of the hair bulb within the inner keratinocytes. Hair follicle material appears as tightly cohesive epithelial structures composed of keratinocytes with variable amounts of melanin pigment.

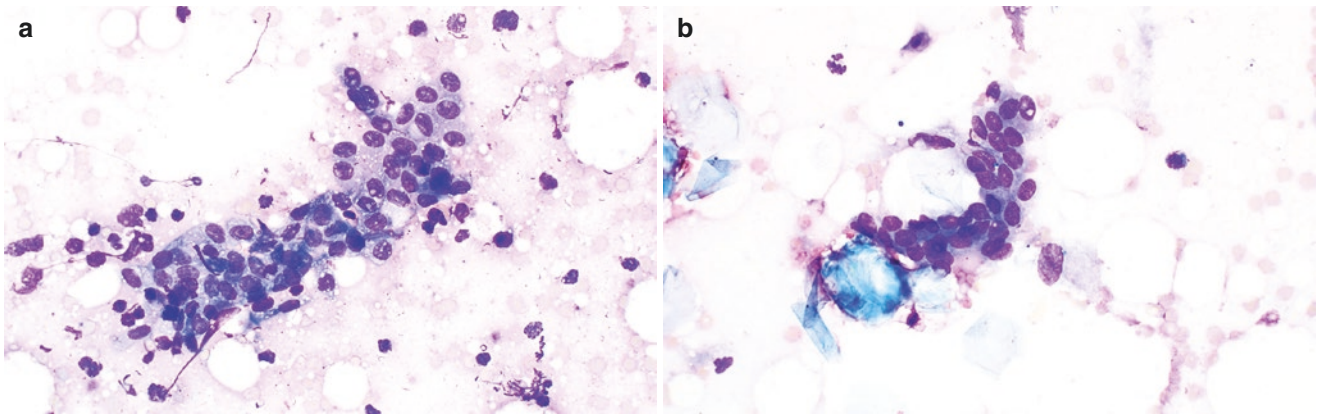

Fig. 12.27 Sebaceous glandular cells (**a**) exhibit abundant multivacuolated cytoplasm, ovoid nuclei, and distinct nucleoli, whereas eccrine sweat glands (**b**) are lined by basaloid, cuboidal cells with scant cytoplasm lacking vacuoles. Cutaneous fine needle aspiration, air-dried smear preparation, Diff-Quik, 50× magnification (**a**, **b**)

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