Bone and Soft Tissue

5

Lisa A. Teot

5.1 Introduction

A wide variety of bone and soft tissue lesions are seen in children and adolescents, including benign and malignant neoplasms, as well non-neoplastic processes. Evaluation of these lesions traditionally has included open biopsy to establish a diagnosis prior to definitive treatment. With the development of increasingly sophisticated imaging techniques that allow accurate localization and sampling of these lesions, fine needle aspiration (FNA) and small biopsies are assuming an increasingly important role in the diagnosis of pediatric musculoskeletal lesions [1–6]. This is particularly true in light of the trend toward less invasive and more cost-effective diagnostic procedures. Although limitations and pitfalls exist, FNA is a valuable tool for the diagnosis of pediatric bone and soft tissue lesions, and can often provide information on which to base further diagnostic and therapeutic decisions [1–6]. In many cases, FNA allows accurate diagnosis of primary or metastatic lesions of bone and soft tissue, thereby obviating the need for a more invasive and significantly more expensive diagnostic biopsy. In other cases, although a definite diagnosis is not possible, FNA is useful for ruling out specific processes or for narrowing the diagnostic considerations, and in the appropriate clinical setting, this information may be sufficient for initiation of therapy. When a definitive cytologic diagnosis cannot be rendered and/or additional information is needed prior to therapy, material should be obtained for histologic evaluation. In such cases, rapid on site evaluation of an FNA can help to confirm that viable, diagnostic tissue is being sampled and guide triage of concurrent core biopsies.

It is important to note that FNA is not an appropriate tool for the evaluation of certain pediatric bone and soft tissue lesions. Some bone tumors have highly characteristic features on imaging studies that, when present, are virtually diagnostic and obviate the need for a pathologic diagnosis prior to definitive treatment. In addition, with some exceptions, benign bone lesions typically have intact overlying cortical bone and are not easily sampled by FNA or small biopsy. As treatment for many of these lesions is curettage with or without bone grafting or cementation, intraoperative frozen section or touch preparation is often the preferred method for confirming benignity and/or establishing a diagnosis, as well as guiding surgical management. Similarly, despite having a broad differential diagnosis, many benign-appearing soft tissue masses are treated by simple excision irrespective of the specific diagnosis, thereby making preoperative pathologic diagnosis unnecessary.

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Accurate interpretation of FNAs of bone and soft tissue lesions is best accomplished using an integrated approach in which the cytologic findings are correlated with the clinical data and imaging studies prior to rendering a final diagnosis. Integrated assessment of the clinical presentation, radiographic features, presence or absence of matrix production, and cytologic features usually allows the cytopathologist to generate a limited differential diagnosis, and in many instances, a specific diagnosis. In some cases, additional studies, such as histochemical and immunoperoxidase stains, flow cytometry, molecular studies, electron microscopy, or cultures, are needed for a definitive diagnosis. In other cases, the differential diagnosis can be resolved based on further correlation with clinical and radiographic data. In such cases, the final cytologic diagnosis is phrased to reflect this fact, e.g., "Atypical cartilaginous proliferation, consistent with the clinical and radiographic impression of digital enchondroma." This chapter describes the cytologic features of various common and uncommon neoplastic and non-neoplastic lesions of bone and soft tissue that are encountered in the pediatric population, as well as key clinical and radiologic features of these entities and differential diagnostic considerations.

5.2 Bone Lesions

Primary bone tumors, whether benign or malignant, are more common in the pediatric population than in adults. In children under 10 years of age, approximately 75% of bone tumors are benign, whereas malignant neoplasms comprise close to 50% of bone tumors in older children and adolescents. Some genetic disorders are also associated with increased risk of developing certain bone tumors; for example, patients with germline mutations in *TP53* or *RB1* are predisposed to the development of osteosarcoma.

As already noted, correlation with imaging studies is essential when evaluating an FNA from a pediatric bone lesion. Particular types of tumors tend to occur at specific sites within long bones, and thus, the site of involvement (epiphyseal, metaphyseal or diaphyseal; cortical or medullary) narrows the differential diagnosis. The presence or absence of matrix and its appearance also provide important diagnostic clues. Benign osseous lesions are characterized by orderly ossification, while malignant neoplasms have ill-defined cloud-like calcifications. Chondroid matrix appears as stippled or flocculent densities. The pattern of growth is also important and as a general rule is indicative of biological potential and behavior. The hallmark of a benign process is containment of the lesion by a rim of reactive host bone. In a slowly growing lesion, the rim of reactive bone often becomes thickened or sclerotic. Lesions with this pattern of growth are well circumscribed and have pushing rather than infiltrative margins. A periosteal reaction is usually absent, and if present, has a solid appearance. In contrast, infiltration of the surrounding bone is typical of an aggressive or malignant lesion that has the potential for local recurrence and/or distant metastasis. Permeation and destruction of the bone by a rapidly growing lesion result in ill-defined or "moth-eaten" borders. In addition, rapid erosion and significant weakening of the cortical bone induces a periosteal reaction, which appears as a complex pattern of either layering parallel to the cortical surface ("onion skin") or spiculation perpendicular to the cortical surface ("sunburst" or "hair on end"). Another radiographic hallmark of aggressive lesions is Codman's triangle, an incomplete triangle formed by periosteum at the interface between a growing tumor and the normal host bone. A comparison of the key radiographic features of benign and malignant skeletal lesions is listed in Table 5.1.

A microscopically useful and clinically relevant way of classifying lesions of bone is based on evidence of matrix production. In general, destructive processes in the skeleton can be divided into those that show evidence of matrix production, both radiographically and microscopically, and those that do not. The former are further subdivided based on the type of matrix produced, i.e., osteoid, chondroid, chondromyxoid, or myxoid matrix, or fibrous stroma. Matrix producing lesions of bone and soft tissue can be non-neoplastic or neoplastic, and benign or malignant.

Table 5.1 Radiographic features of benign versus malignant lesions of bone

Feature	Benign lesions	Malignant lesions
Pattern of growth	Pushing	Infiltrative
	No extension or penetration into surrounding bone	Permeation and destruction of surrounding bone
Borders of lesion	Well circumscribed	Ill-defined, moth-eaten
	Sclerotic rim or "rind" separates lesion from adjacent bone	Infiltration of adjacent host bone
Periosteal reaction	Absent or solid	Complex ("onion skin" or "hair on end")
		Codman's triangle

Table 5.2 Osteoid producing lesions of bone

Benign lesions	Malignant lesions
Osteoblastoma	Osteosarcoma
Osteoid osteoma	Conventional
Fracture callus	Surface (parosteal, periosteal, high grade)
	Telangiectatic
Aneurysmal bone cyst with reactive bone formation	Small cell
	Low grade central

In cytologic specimens, matrix is best appreciated in air-dried, modified Giemsa-stained preparations, and is often readily apparent at scanning power. Osteoid appears as irregular fragments of opaque, intensely metachromatic stroma, often arrayed in branched or interlacing cords or strands. The edges of the fragments may be sharply defined or have a frayed, fibrillar appearance. Variable numbers of benign or malignant osteoblasts are present within and/or at the periphery of the fragments. Fibrous matrix is also metachromatic, and varies from dense and opaque to pale and finely fibrillar or wispy. Fragments can be large or small, and have well-defined, smooth edges or be frayed and irregular. The fragments may be acellular or have variable numbers of benign or malignant spindle cells of fibroblastic or myofibroblastic origin embedded within the stroma. Due to biochemical and staining similarities, acellular or relatively hypocellular fragments of dense collagen may be difficult or impossible to distinguish from osteoid. Chondroid, chondromyxoid, and myxoid matrices, like osteoid, are intensely metachromatic, but in contrast to osteoid, often occur in large, sheet-like fragments or clumps. The matrix can appear opaque, or have a fibrillar or filmy quality, and the borders are often relatively well defined. The fragments can be acellular, or have variable numbers of benign or malignant cells embedded in the stroma. Because these matrices are essentially identical, the principal feature that distinguishes the various chondroid, chondromyxoid, and myxoid lesions from each other is the type(s) of benign or malignant mesenchymal cells associated with the matrix.

5.2.1 Osteoid Producing Lesions

A number of lesions of bone produce osteoid and its mineralized end product, woven bone. Production of lamellar bone, which is the mature, highly organized matrix of the skeleton, is seen only in osteoma and enostosis (bone islands). Osteoid is the unmineralized, protein matrix produced by osteoblasts. This matrix consists of type I collagen (approximately 90%) and a number of non-collagenous proteins, including osteocalcin, osteopontin, osteonectin, and various growth factors. The morphologic separation of osteoid from fibroblastic collagen is often qualitative; however, this distinction is important diagnostically. Fibroblastic collagen is laid down by flattened or spindle shaped fibroblasts and has a distinctly fibrillar, longitudinal arrangement. In contrast, osteoid forms irregular, amorphous masses that have a hard, waxy quality. Osteoid appears bright magenta in air-dried, modified Giemsa-stained smears, and green-blue in wet-fixed, Papanicolaou-stained preparations. Osteoblasts, that may be benign or malignant, become entrapped in the matrix, creating a lacy, interwoven pattern. The major osteoid producing lesions of bone that are encountered in the pediatric population are listed in Table 5.2.

5.2.1.1 Osteoblastoma

Clinical Features

Osteoblastoma (OB) is a rare benign neoplasm, accounting for approximately 1 % of primary bone tumors. Most patients are less than 30 years old, with a peak incidence in the second decade of life. Patients typically present with local pain.

Location

OB may arise in any portion of the skeleton, but has a distinct predilection for the axial skeleton, particularly the spine.

Radiographic Appearance

OB is typically intramedullary, although occasional intracortical examples occur. In long bones, OB arises in the metaphysis, whereas vertebral OB is usually located in the posterior elements. OB produces a uniform, sharply circumscribed, expansile lesion that is usually radiolucent. Periosteal reaction is generally absent. Calcification of the matrix may be present or absent radiographically.

Cytological Features

FNA yields moderately cellular smears composed of a polymorphous population of benign mesenchymal cells, and irregular fragments of osteoid and woven bone [7, 8]. Osteoblasts, osteoclasts, and fibrovascular stroma comprise the mesenchymal elements. Osteoblasts are plump, round, or polygonal cells with well-defined cellular borders, abundant cytoplasm, and eccentric, round nuclei with evenly dispersed chromatin and a single, round, often prominent nucleolus. The osteoblasts occur as individually dispersed cells or in rows "rimming" the fragments of osteoid. Individually dispersed, true osteoclasts are also present, and characteristically exhibit variation in size, shape, and number of benign nuclei. Benign spindle cells of fibroblastic and endothelial origin are arrayed within irregular fragments of fibrous stroma, and also occur singly. The background is usually bloody, reflecting the richly vascular nature of OB.

Differential Diagnosis

Differential diagnostic considerations include osteoid osteoma, fracture callus, and osteosarcoma. Usually, these entities can be distinguished from each other based on imaging characteristics. Moreover, neither osteoid osteoma nor fracture callus is likely to undergo FNA. Occasionally OB has an aggressive appearance on imaging studies, raising concern for osteosarcoma. However, the cytologically benign appearance of the cells in OB helps to distinguish this entity from osteosarcoma.

Pearls

Occasional OBs have atypical cytological features that may lead to misdiagnosis as osteosarcoma, particularly when combined with an aggressive radiologic appearance. Because osteosarcoma is the most common primary bone tumor in the second decade of life and is far more common than OB irrespective of the patient's age, histologic evaluation of tumors with atypical features is imperative to avoid misdiagnosis and guide appropriate treatment.

5.2.1.2 Osteoid Osteoma

Clinical Features

The majority of cases of osteoid osteoma (OO) occur in the second decade of life. OO is usually associated with marked pain that is worse at night and relieved with aspirin.

Location

OO may arise in any portion of the skeleton, and almost always involves cortical bone. Occasional subchondral and intramedullary lesions occur.

Radiographic Appearance

The characteristic radiographic appearance of intracortical OO is that of a well-circumscribed, lytic lesion surrounded by excessive sclerosis and reactive bone formation. The central lytic region, termed the nidus, is almost always less than 1 cm in diameter and by definition, less than 2 cm. Although periosteal new bone formation is characteristic, a true periosteal reaction is absent.

Cytological Features

To our knowledge, cytologic diagnosis of OO by FNA has not been reported. The diagnosis is usually apparent from the clinical history and radiographic findings, and this, combined with the characteristic intracortical location and extensive peripheral sclerosis, makes aspiration of OO highly unlikely.

5.2.1.3 Conventional Osteosarcoma

Clinical Features

Osteosarcoma (OS) is the most common primary malignant tumor of bone and more than 60 % of patients present in the second decade of life. While most osteosarcomas are sporadic, there is an increased incidence of this tumor in patients with hereditary retinoblastoma, Li–Fraumeni syndrome, and Rothmund–Thomson syndrome. Secondary or post-irradiation osteosarcoma may also occur in childhood. Primary conventional osteosarcoma is 1.5 times more frequent in males than females. The usual presenting symptom is pain with or without swelling that can be present for weeks or months. Pathologic fractures are present in 5–10 % of patients.

Location

OS has a predilection for the metaphyseal portion of long bones, particularly the distal femur, proximal tibia, and proximal humerus.

Radiographic Appearance

OS characteristically appears as a large, poorly defined, infiltrative, metaphyseal lesion arising in the medullary bone and extending through the cortex to form a large soft tissue mass. A periosteal reaction, usually of the hair on end, sunburst or onion skin type, and Codman's triangle are present. Lesions are usually mixed lytic and blastic, the latter feature reflecting matrix production. Occasionally, OS is purely lytic.

Cytological Features

OS has a spectrum of cytologic appearances, reflecting the histologic variability of these neoplasms [7, 9–11]. FNA of conventional OS yields variably cellular smears, depending on the amount of matrix within the area sampled. Aspirates are composed of varying proportions of malignant osteoblasts, spindle cells and bizarre, multinucleated tumor giant cells (Fig. 5.1a). In addition, scattered osteoclast-like giant cells are often present.

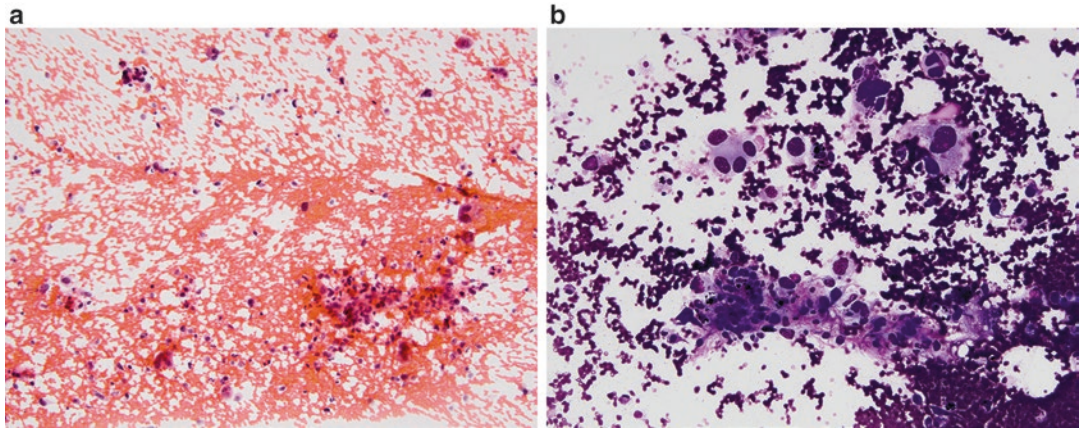

Fig. 5.1 Conventional osteosarcoma, osteoblastic subtype (**a**. Papanicolaou stain, medium power; **b**. Diff-Quik stain, medium power). Osteosarcoma is composed of obviously malignant osteoblasts and spindle cells, with occasional bizarre multinucleated giant cells and osteoclastic giant cells. The cells occur singly and in loosely cohesive clusters (**a**). Marked anisocytosis and nuclear pleomorphism are evident in this example of osteosarcoma. Magenta-colored matrix is present between and around some of the tumor cells in the cluster (**b**).

The malignant cells show considerable anisocytosis, nuclear pleomorphism, and increased nuclear to cytoplasmic ratios. Nuclei are characterized by absolute enlargement, irregular contours, coarsely clumped chromatin, and prominent, irregular nucleoli. The malignant cells occur as individually dispersed elements, in irregular aggregates, and in association with osteoid or other matrix (Fig. 5.1b).

The amount of osteoid varies considerably, and may dominate the smears or be exceedingly scant and focal. Osteoid can be distinguished from dense collagen in the air-dried, modified Giemsa-stained smears by its amorphous, lace-like quality in combination with the presence of entrapped or individually dispersed malignant cells reminiscent of osteoblasts. In cases lacking these features, osteoid may be difficult or impossible to distinguish from dense collagen. In addition to osteoid, chondroid and fibrous matrices may be present in aspirates from chondroblastic [12] and fibroblastic OS, respectively (Fig. 5.2).

Differential Diagnosis

The overtly malignant nature of these tumors is usually apparent thereby limiting differential diagnostic considerations, particularly when osteoid is evident. In the absence of convincing osteoid, cytologic distinction from chondrosarcoma and fibrosarcoma may be difficult or impossible [12].

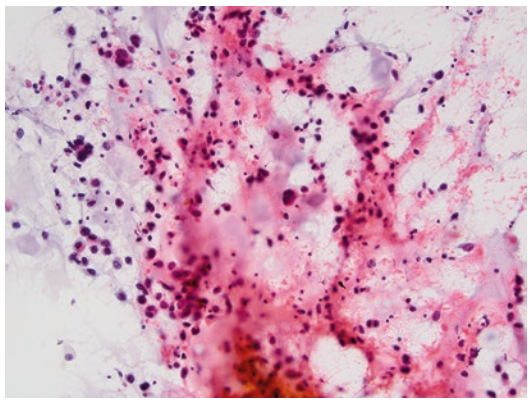

Fig. 5.2 Conventional osteosarcoma, chondroblastic subtype (Papanicolaou stain, medium power). Irregular fragments of chondroid matrix are present in this smear comprised of highly pleomorphic, overtly malignant cells.

Pearls

Preparation of a cell block can be helpful for identifying osteoid matrix (Fig. 5.3). In osteoid poor tumors, an immunoperoxidase stain for SATB2 can help to confirm the osteoblastic origin of the neoplasm; however, other immunoperoxidase stains are not helpful as OS can be positive for a variety of mesenchymal, as well as epithelial markers. Cytogenetics reveals a numerically and structurally complex karyotype and may help to distinguish OS from tumors characterized by recurrent translocations.

5.2.1.4 Other Variants of Osteosarcoma

Although a detailed discussion of the different variants of OS is beyond the scope of this chapter, cytopathologists should be aware of these entities.

Small Cell Osteosarcoma

This variant of OS comprises less than 2 % of OS and, as the name implies, is composed of small round cells. Osteoid matrix can be exceedingly scant, and rare examples may also have focal chondroid matrix. The cytologic features of small cell OS are considerably different from those of other types. Aspirates are composed of small round or ovoid cells with scant cytoplasm, oval to elongate nuclei with finely dispersed or clumped

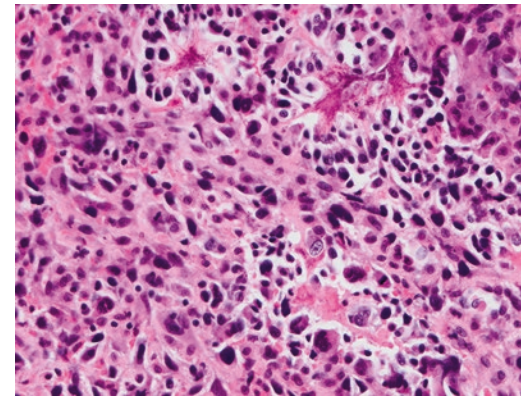

Fig. 5.3 Conventional osteosarcoma (Cell block, H&E stain, high power). Cell block preparations can help to confirm the presence of osteoid, which may be inconspicuous in smears. Delicate osteoid with focal evidence of calcification is evident between and around cells in this fragment of tissue from an osteosarcoma.

chromatin, and very high nuclear to cytoplasmic ratios. Nuclear pleomorphism is present, but may not be marked. Cells occur singly and in cohesive fragments. When osteoid is scant or absent in aspirate smears, small cell OS may be mistaken for Ewing sarcoma or metastasis from a pediatric small round cell tumor. Immunoperoxidase stains and fluorescent in situ hybridization for *EWSR1, FOXO1,* and *SS18(SYT)* can be helpful for excluding these entities.

Telangiectatic Osteosarcoma

This variant, which comprises less than 4% of OS, is a high grade intramedullary tumor with prominent intralesional blood-filled spaces and scant evidence of osteoid formation. Radiographically, these lesions are purely lytic with extensive destruction of bone and often, soft tissue extension. Aspirates are usually bloody and may have a paucity of diagnostic malignant cells, thereby mimicking aneurysmal bone cyst or a vascular lesion.

Low Grade Central Osteosarcoma

This rare variant, which comprises 1–2% of OS, lacks the marked nuclear pleomorphism that characterizes conventional OS. Tumors are composed of hypocellular fibrous tissue with variable amounts of osteoid and woven, or occasionally lamellar, bone, and due to the bland appearance of the malignant cells, may be confused with fibrous dysplasia. This variant typically progresses more slowly than conventional OS and has a better prognosis. Low-grade central osteosarcomas have also been shown to have *MDM2* amplifications, which can help to distinguish it from benign mimics.

Juxtacortical Osteosarcomas (Parosteal, Periosteal, and High Grade Surface)

These tumors originate from the periosteal surface of the bone and typically grow outward as well as into the cortex, with minimal or no involvement of the underlying medullary bone. High grade surface OS accounts for less than 1% of OS and is morphologically and biologically indistinguishable from conventional OS. In contrast, parosteal and periosteal OS are characterized by slow growth and have a better prognosis than conventional OS. Parosteal OS accounts for approximately 4% of OS and is characterized by a proliferation of spindle cells within a predominantly fibrous stroma with well-formed bony trabeculae in parallel array. The spindle cells tend to show minimal cytologic atypia. Periosteal OS comprises less than 2% of OS and usually appears as a lytic lesion with scalloping of the outer cortex. This variant of demonstrates abundant cartilaginous matrix. The cytologic features are those of an intermediate grade malignant neoplasm.

5.2.1.5 Fracture Callus

On occasion, an early or incipient fracture can mimic a sarcoma both clinically and pathologically. In addition, benign as well as malignant lesions of bone can lead to pathologic fracture, and the presence of fracture callus can make interpretation of the FNA or small biopsy difficult. For these reasons and to avoid false positive diagnoses, it is important that one be familiar with the pathology of fracture callus.

In an acute fracture, there are hemorrhage, variable tissue damage, and necrosis of adjacent bone and marrow. The hematoma and necrosis stimulate rapid proliferation of mitotically active, spindled mesenchymal cells that appear atypical. After approximately 1 week, primitive osteoid and chondroid matrices are produced by the cells of the callus. This early osteoid and chondroid is disorganized and at this stage, is most likely to be confused with an OS. By the second week, the osteoblasts begin to appear in single rows along the periphery of osteoid, a phenomenon known as "osteoblastic rimming." The osteoblasts are plump and uniform, and appear to be at the same maturational stage. The islands of cartilaginous matrix show gradual transition to osteoid at their periphery (chondro-osseous bone). The orderly arrangement of osteoblasts in rows, the uniformity of the cells, and the gradual transition from one matrix type to another without a change in the appearance of the cells distinguish this process from sarcoma.

As evident from the previous discussion, the features of fracture callus in FNA vary with age of the fracture. Aspirates from acute fractures

may contain old blood, spicules of necrotic lamellar bone, fragments of necrotic tissue, and highly atypical spindled mesenchymal cells occurring singly and in irregular fragments. In maturing fractures, fragments of osteoid, chondroid, and eventually chondro-osseous bone are also present, while the number of primitive spindled mesenchymal cells decreases. Preparation of a cell block can help to distinguish fragments of fracture callus from more ominous lesions.

5.2.2 Chondroid Producing Lesions

Cartilaginous tumors of the skeleton are a major source of diagnostic difficulty, in both cytologic and histologic specimens. This is due, in part, to the tremendous amount of overlap in the morphologic spectrum of these lesions [13]. But in addition, considerable histologic variation often exists within a single tumor. In lesions that are deemed malignant, grading is sometimes difficult and is more subjective than in other neoplasms. Fortunately, differentiating low grade lesions with minimal risk of metastasis from high grade lesions is usually not a problem, and clinically, is the most relevant distinction.

It is critically important to include the clinical data, particularly the presence or absence of pain, and the radiographic findings in the evaluation of cartilaginous tumors. The plain films provide crucial information regarding the bone involved and the pattern of growth, both of which are important predictors of benign or malignant behavior. Tumors of the pelvis, axial skeleton and proximal ends of long bones are more likely to behave in a malignant fashion than lesions in the distal extremities and tubular bones of the hands and feet. When different patterns of growth are evident, the radiographic studies also guide the selection of the most appropriate area of the lesion to sample. Heavily calcified areas are more likely to be benign or low grade, whereas purely lytic areas usually represent a higher grade malignancy. The major chondroid producing lesions of bone are listed in Table 5.3.

Table 5.3 Chondroid producing lesions of bone

Benign lesions	Malignant lesions
Enchondroma	Chondrosarcoma Grade I, II, & III De-differentiated Mesenchymal
Osteochondroma	Secondary low grade chondrosarcoma arising within osteochondroma
Periosteal chondroma (Juxtacortical chondroma)	Periosteal osteosarcoma
	Periosteal chondrosarcoma
Chondromyxoid fibroma	Myxoid chondrosarcoma
Chondroblastoma	Clear cell chondrosarcoma
Synovial chondromatosis	
Fracture callus	

5.2.2.1 Enchondroma

Clinical Features

Enchondroma (EC) is a common benign bone tumor that occurs over a broad age range. Most solitary lesions in the pediatric population present in the second decade of life, whereas those associated with enchondromatosis syndromes manifest in infancy or early childhood. Most of the solitary tumors are asymptomatic and are incidental findings, or present after pathologic fracture. In contrast, enchondromatosis syndromes (Ollier disease, Maffucci syndrome) are characterized by multiple enchondromas involving multiple sites. The resulting skeletal deformities and symptoms vary depending on the sites involvement. Enchondromatosis is also associated with increased risk of malignant degeneration of EC.

Location

The most common location of EC is in the tubular bones of the hands. EC is also seen in the proximal humerus, proximal femur, distal femur and other locations, particularly in enchondromatosis.

Radiographic Appearance

EC arises in the medullary space, usually in the metaphysis. Most solitary lesions are small, lytic, and expansile, with well-demarcated borders.

Calcifications, that are described as rings, flocculent, fluffy, or popcorn-like, are characteristic and often, abundant. Cortical destruction or a soft tissue mass is unusual, and should raise the possibility of malignancy.

Cytological Features

FNA of enchondroma yields paucicellular smears dominated by mature cartilaginous matrix (Fig. 5.4). The benign chondroid has a filmy or granular quality, appears bright magenta to purple in air-dried, modified Giemsa-stained and blue-green to blue-gray in Papanicolaou-stained preparations. Fragments of matrix occasionally have a lobulated appearance that recapitulates the histologic pattern. Embedded in the matrix are variable numbers of uniform, round or ovoid cells, usually within lacunar spaces. Cells have small, round, dark nuclei without nucleoli. Nuclear detail is typically difficult to discern. Binucleated cells are rare. Multinucleated forms and mitotic figures are absent. Cells occur singly, as doublets, or occasionally as clusters within the lacunae. Individually dispersed cells may also be identified. Foci of calcification within the matrix are often, but not always, evident. In contrast to EC arising in other sites, digital EC often shows hypercellularity and cytologic atypia.

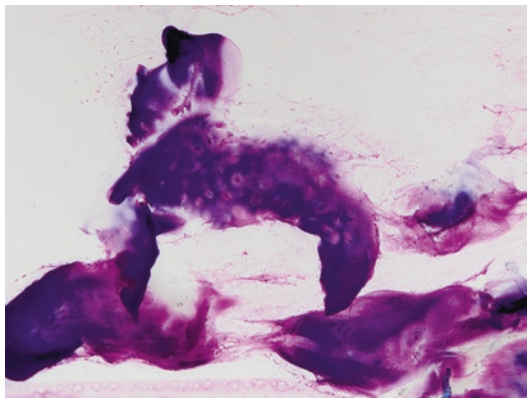

Fig. 5.4 Enchondroma (Diff-Quik stain, medium power). Irregular fragments of hyaline-type cartilage are present in this aspirate from a digital enchondroma. Although the cellularity is mildly increased, cytologic atypia is absent.

Differential Diagnosis

The major differential diagnostic consideration is low grade chondrosarcoma. Because hypercellularity and mild cytologic atypia are characteristic of digital EC, it is important not to overinterpret these findings as indicative of malignancy in lesions arising in the fingers and toes. Regardless of site, both significant myxoid degeneration and necrosis should be absent, and if present, should arouse suspicion of malignant transformation. Table 5.4 summarizes the features that help to distinguish enchondroma from low grade chondrosarcoma.

Table 5.4 Useful features for distinguishing enchondroma from low grade chondrosarcoma

Feature	Enchondroma	Low grade chondrosarcoma
Binucleated cells	Occasional (EC < LCS)	Occasional to frequent (LCS > EC)
Cellular morphology	Small, bland cells	Larger, "plump" cells
	Don't fill lacunar space	Tend to fill lacunae
	Atypia absent or minimal except in digital EC	Mild atypia
Nuclear morphology	Small, round nuclei	Larger, round nuclei
	Dark, pyknotic-appearing nuclei, chromatin detail absent	± evenly dispersed open chromatin
		± small nucleoli
Pattern of growth	Well circumscribed	Infiltrative
	Usually surrounded by a rim of trabecular bone	Invades/surrounds host bone
	Lobulated architecture	Erodes and destroys cortex
		Architecture is less organized
Skeletal location	Small bones hand and feet, long bones especially femur and humerus	Pelvis, axial skeleton, proximal long bones
Clinical history	Painless, usually asymptomatic	Usually painful (± night or rest pain)
	Most often discovered incidentally or after pathologic fracture	

Pearl

The radiographic appearance of EC is often diagnostic and treatment is curettage; thus, these lesions are rarely sampled by FNA.

5.2.2.2 Chondromyxoid Fibroma

Clinical Features

Chondromyxoid fibroma (CMF) is a very rare benign bone tumor. The vast majority of patients are between 5 and 30 years of age at presentation. CMF is usually asymptomatic, but may present with long standing, intermittent pain. When lesions occur in the small bones of the hand or feet, local swelling may be noted.

Location

CMF most often arises in the lower extremities, particularly the proximal tibia.

Radiographic Appearance

CMF is an eccentric, metaphyseal, lytic lesion with sharply circumscribed, sclerotic margins. The borders typically have a scalloped appearance. Cortical thinning is typical and may be marked. If present, cortical expansion is usually minimal. Periosteal reaction is absent.

Cytological Features

FNA of CMF yields mildly to moderately cellular smears composed of fragments of chondromyxoid matrix admixed with stellate, spindled, and round cells [14]. The stellate and spindled cells may be mildly pleomorphic, with variably shaped nuclei and finely clumped to dark chromatin. Binucleated and multinucleated forms may be identified. The stellate and spindled cells appear to float in the chondromyxoid matrix, and also occur as individually dispersed elements. Variable numbers of uniform, small, round to ovoid cells that are morphologically similar or identical to chondroblasts are also present, either singly or in small clusters. These cells have dense, well-defined cytoplasm and relatively uniform, round to ovoid nuclei with pale, finely dispersed chromatin. Nuclear grooves or convolutions may be seen. Mitotic figures are absent. The chondromyxoid matrix has a watery or filmy quality, and appears magenta or pale purple in air-dried modified Giemsa-stained smears and pale blue-green or gray-blue in Papanicolaou-stained preparations.

Differential Diagnosis

Differential diagnostic considerations include chondromyxoid fibroma-like conventional osteosarcoma and a chondrosarcoma. In contrast to CMF, these entities have aggressive radiographic appearances and are characterized by a greater degree of cytologic atypia.

5.2.2.3 Chondroblastoma

Clinical Features

Although chondroblastoma occurs over a wide age range, approximately 75 % of patients present in the second decade of life. CB is rare in patients less than 10 years old. Patients typically present with gradually increasing pain of long duration. Swelling and decreased range of motion may occur, but are usually late symptoms.

Location

CB is most often located in the proximal humerus, distal femur, or proximal tibia.

Radiographic Appearance

CB is located within the epiphysis or apophysis. Lesions are small, lytic defects with sharply circumscribed, sclerotic borders. Speckled calcifications may be present.

Cytological Features

FNA of CB yields variably cellular smears dominated by small, mononuclear cells occurring singly and in small clusters, admixed with osteoclast-like giant cells and fragments of chondroid matrix (Fig. 5.5) [15, 16]. The mononuclear cells have dense cytoplasm, sharp cytoplasmic borders, and eccentric, round to oval nuclei with finely dispersed chromatin, and absent or inconspicuous nucleoli. Nuclei often have longitudinal grooves or convolutions. The fragments of chondroid matrix are typically small, have an amorphous or fibrillar quality, and may be calcified. Cellular aggregates in which matrix surrounds individual mononuclear

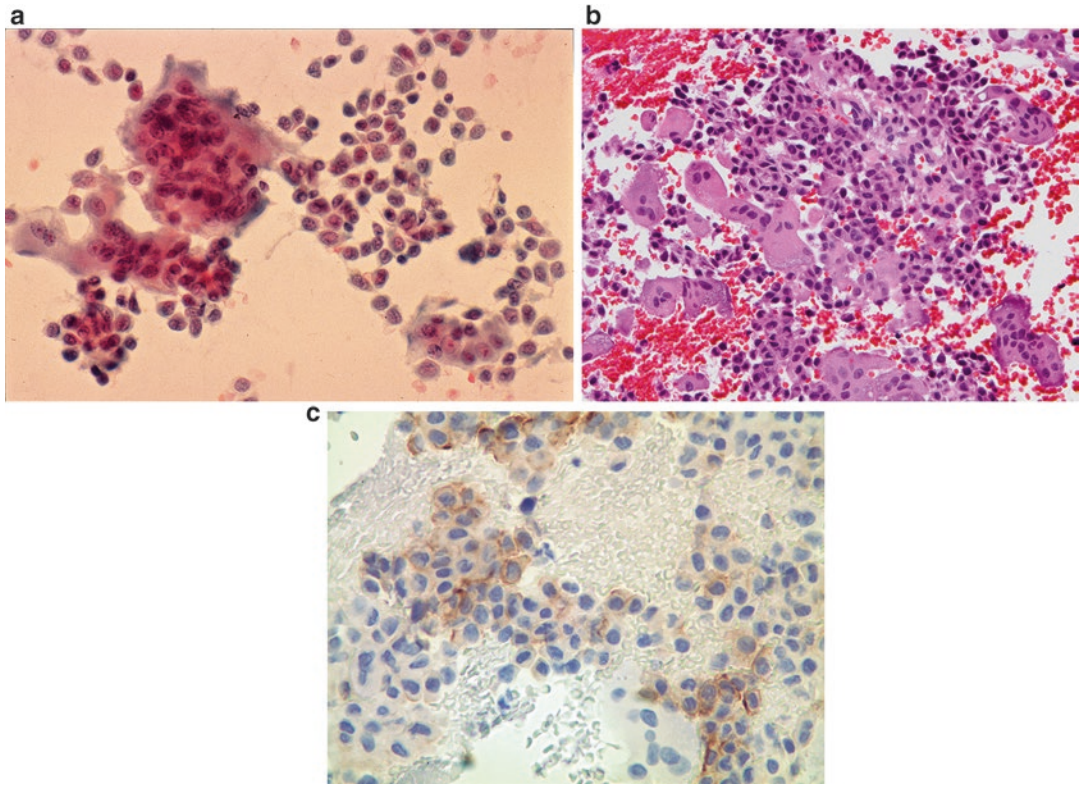

Fig. 5.5 Chondroblastoma (**a**. Papanicolaou stain, high power; **b**. Cell block, H&E stain, high power; **c**. Cell block, DOG1 immunoperoxidase stain, high power). Chondroblastoma is comprised of mononuclear cells admixed with multinucleated giant cells. The cells occur singly and in small loosely cohesive aggregates. Nuclei in the mononuclear cells are ovoid with finely dispersed chromatin, small nucleoli, and nuclear grooves (**a**). The cell block shows mononuclear cells with nuclear grooves interspersed with multinucleated giant cells (**b**). An immunoperoxidase stain for DOG1 is positive in a subset of the mononuclear cells in this cell block preparation (**c**). (Image of DOG1 immunoperoxidase stain courtesy of Dr. Jeffrey Goldstein).

cells in a "chicken-wire" pattern, with or without calcification, may be present and are virtually diagnostic of this entity.

Differential Diagnosis

The main differential diagnostic consideration is giant cell tumor of bone (GCT). Although GCT can occur in the pediatric population, it is more common in skeletally mature individuals. In contrast to CB, mononuclear cells of GCT lack nuclear grooves and their nuclei resemble those of the multinucleated giant cells. In addition, the giant cells in GCT typically have many more nuclei (sometimes greater than 50) than those of CB. The mononuclear cells in CB are positive for DOG1, a feature that can help to confirm the diagnosis (Fig. 5.5).

Pearl

Cell block preparations can help to demonstrate the characteristic chicken-wire calcifications.

5.2.2.4 Chondrosarcoma

Clinical Features

Chondrosarcoma (CS) usually occurs in patients older than 40 years of age, and is rare in persons under 20 years of age. Usually, there is a history of pain that may be of long duration. Rest pain or night pain is not uncommon. CS may be primary, or arise in a previously benign lesion, such as osteochondroma or enchondroma. Patients with osteochondromatosis or enchondromatosis are at increased risk for secondary CS. Mesenchymal chondrosarcoma (MCS) is a rare variant of CS,

comprising 3–10% of tumors, and has a uniformly dismal prognosis. MCS tends to occur at a younger age than conventional CS, with a peak incidence in the second and third decades of life.

Location

More than three quarters of primary chondrosarcomas are located in the axial skeleton (especially the pelvis), and the proximal femur and humerus. The most common sites of involvement by intraosseous MCS are the craniofacial bones, ribs, ilium, and vertebrae. MCS may also develop extraskeletally in the soft tissues of the head, neck, and lower extremities, and occasionally in the meninges.

Radiographic Appearance

CS appears as a poorly demarcated, lytic lesion that erodes or destroys the cortex. In large lesions, extension into soft tissue is common. A periosteal reaction is usually absent in low grade CS, but present in high grade tumors. Speckled calcification may be present, but is less than seen in the typical EC and decreases in amount with increasing grade of tumor. MCS tends to be less heavily mineralized than conventional CS.

Cytological Features

The cytological appearance varies with the grade of the tumor. FNA of low grade CS yields variably cellular smears in which malignant chondrocytes occur singly, in small clusters, and embedded within chondroid matrix (Fig. 5.6) [13]. Individually dispersed cells are round, oval, or polygonal with abundant vacuolated or granular cytoplasm. Nuclei are relatively uniform, round to oval, and have fine to coarse, evenly dispersed chromatin. Nucleoli may be absent, and when present, are small, round, and regular. Binucleated forms may occur. Within the matrix, cells occur singly, as doublets or in small clusters within lacunar spaces. Cells are plump, and tend to fill lacunar spaces. The chondroid matrix is dense or opaque, and has an amorphous quality. Foci of myxoid degeneration may be present, and impart a fibrillar or stringy quality to the matrix.

In contrast, FNA of high grade CS typically yields moderately to highly cellular smears in which cellular and nuclear pleomorphism are readily apparent. Nuclei are enlarged and hyperchromatic, with irregular contours and prominent, often irregular nucleoli. Variable numbers of anaplastic cells are present and can be the predominant cell type. Mitotic figures, including abnormal forms, are present and may be abundant. Myxoid degeneration and/or necrosis may be evident. The amount of chondroid matrix may be scant in high grade lesions.

Aspirates from MCS yield highly cellular smears dominated by small, round cells that occur singly and in loosely cohesive aggregates (Fig. 5.7). These cells have scant or moderate amounts of granular cytoplasm, distinct cellular borders, and central, round to oval nuclei with coarsely granular chromatin and small nucleoli. The nuclear

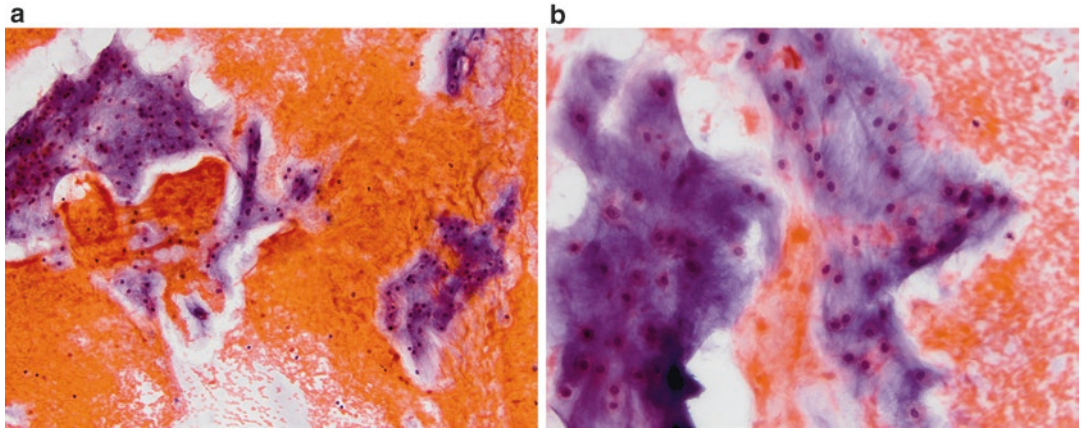

Fig. 5.6 Chondrosarcoma, grade 2 (**a**. Papanicolaou stain, medium power; **b**. Papanicolaou stain, high power). Irregular fragments of hypercellular cartilaginous matrix, as well as scattered single cells, are present in this smear from a low grade chondrosarcoma (**a**). At high magnification, mild cytologic atypia is evident. Overt anaplasia is absent (**b**).

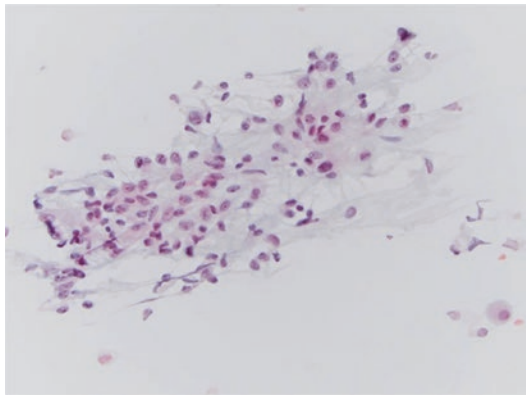

Fig. 5.7 Mesenchymal chondrosarcoma (Papanicolaou stain, high power). Chondroid matrix is usually present in mesenchymal chondrosarcoma but can scanty and focal. In this field the tumor cells are embedded in pale chondroid matrix that has a frayed, stringy appearance.

membranes are smooth and thickened, and longitudinal nuclear grooves may be present. A chondroid component indistinguishable from usual CS is usually present, but may be extremely scant or absent, making distinction from other small round cell tumors difficult. Necrosis may be present.

Differential Diagnosis

In low grade CS, the primary differential diagnostic consideration is enchondroma. Features that help to distinguish these lesions are summarized in Table 5.4. In high grade CS, conventional osteosarcoma is the main consideration. The presence or absence of osteoid distinguishes these lesions from each other. MCS must be distinguished from Ewing sarcoma and metastatic small cell tumors. The presence of matrix helps to distinguish MCS from other small round cell tumors, but when matrix is absent immunoperoxidase stains can be used to confirm the diagnosis. Cells in the chondroid component are positive for S100, while those in the small cell component are positive for SOX9 and negative for FLI-1.

Pearls

The distinction between low grade CS and EC may be difficult or impossible on cytologic preparations. Radiographic correlation is essential; however, when imaging studies are equivocal a core or open biopsy should be considered. In practice, a cytologic diagnosis of "low grade cartilaginous neoplasm" may suffice, as treatment for both EC and low grade CS is complete curettage. The distinction between high grade CS and chondroblastic OS is more problematic, as high grade CS is treated by surgical resection, whereas treatment for OS is neoadjuvant chemotherapy followed by surgical resection. In the absence of convincing osteoid in an FNA, a core or open biopsy is needed to resolve the differential diagnosis.

Table 5.5 Fibrous lesions without associated bone formation

Benign lesions	Malignant lesions
Desmoplastic fibroma of bone (desmoid tumor of bone)	Fibrosarcoma
Non-ossifying fibroma/benign fibrous histiocytoma of bone	Adamantinoma
Giant cell reparative granuloma	
Brown tumor of hyperparathyroidism	

5.2.3 Fibrous and Fibrohistiocytic Lesions Without Associated Bone Formation

A number of fibrous and fibrohistiocytic lesions of bone without associated bone formation occur in the pediatric population as summarized in Table 5.5. However, FNA is rarely used for the evaluation of these lesions. Non-ossifying fibroma, giant cell reparative granuloma, and adamantinoma each has a characteristic radiographic appearance that obviates the need for pathologic diagnosis prior to definitive treatment in most cases. Similarly, brown tumor of hyperparathyroidism can be suspected based on clinical history and in the absence of unusual radiographic features is unlikely to undergo FNA or small biopsy. Desmoplastic fibroma is a locally aggressive tumor that is most common in adolescents and young adults, but is vanishingly rare (less than 0.1 % of bone tumors). Fibrosarcoma of bone is a rare and controversial entity, the hallmark of which is absence of differentiation other than fibroblastic. Most previously reported examples of this tumor likely represent other

Table 5.6 Fibro-osseous lesions of bone

Benign lesions	Malignant lesions
Fibrous dysplasia	Parosteal osteosarcoma
Osteofibrous dysplasia (ossifying fibroma)	Adamantinoma
Resolving (healing) osteomyelitis	

Table 5.7 Giant cell lesions of bone

Benign/inflammatory lesions	Malignant lesions
Giant cell tumor of bone	Giant cell rich fibroblastic subtype of conventional osteosarcoma
Brown tumor of hyperparathyroidism	
Chondroblastoma	
Giant cell reparative granuloma	
Langerhans cell histiocytosis	
Aneurysmal bone cyst	
Non-ossifying fibroma	

entities. The diagnosis is one of exclusion. Given the rarity of these tumors and/or the very low likelihood of encountering these entities in cytological specimens, further discussion of these tumors is beyond the scope of this chapter.

5.2.4 Fibrous Lesions with Associated Bone Formation (Fibro-Osseous Lesions)

Fibro-osseous lesions of bone are uncommon overall. The most common fibro-osseous lesions encountered in the pediatric population are listed in Table 5.6. These lesions either have a characteristic radiographic appearance or are difficult to access by FNA and thus, are rarely encountered in cytologic specimens.

5.2.5 Lesions with a Prominent Giant Cell Component

Giant cells are a ubiquitous feature of osseous tumors, but in a small number of benign and malignant lesions, are prominent and diagnostically important. Table 5.7 lists the major giant cell lesions of bone seen in the pediatric population.

5.2.5.1 Giant Cell Tumor of Bone

Clinical Features

Although giant cell tumor of bone (GCT) generally presents in young adults, with the peak incidence in the third decade, approximately 10% occur in the second decade of life. Lesions are almost always painful, and swelling is present in about 75% of cases. Pathologic fracture may also occur.

Location

More than 75% of GCT are located near the articular end of a tubular bone. Approximately 50% occur in the region of the knee. Other sites include the distal radius, proximal femur, proximal humerus, and distal tibia.

Radiographic Appearance

GCT of long bones invariably involves the epiphysis, usually with metaphyseal extension. The vast majority of lesions arise eccentrically, and many abut the articular cartilage. Lesions are lytic, with well-defined borders, and typically have fine to moderately coarse trabeculations. GCT is usually confined within the normal bony contour, but may occasionally erode and expand the cortex. Lesions that extend into the surrounding soft tissues are usually covered by a thin layer of periosteal new bone. True periosteal reaction is rare.

Cytological Features

FNA yields moderately or highly cellular smears composed of a biphasic population of multinucleated osteoclast-like giant cells and mononuclear stromal cells occurring in large, cohesive sheets, in clusters, and singly. Within cellular aggregates, giant cells are fairly evenly distributed and intimately admixed with the mononuclear stromal cells. The latter are plump, spindled cells with scant to moderate amounts of cytoplasm and nuclei with granular chromatin and regular, round to oval nucleoli. Mitotic figures are rare.

The osteoclast-like giant cells contain few to greater than 50 nuclei that are randomly distributed throughout the cytoplasm and are morphologically identical to those in the mononuclear stromal cells. The latter feature is a hallmark of GCT, and helps to distinguish it from other lesions with a prominent giant cell component.

Differential Diagnosis

In the context of the clinical and radiographic features, the principal differential diagnostic consideration is chondroblastoma, which was discussed in Sect. 5.2.2.3. The often high number of nuclei in the giant cells and their morphologic similarity to those of the mononuclear cells are hallmarks of GCT, and help to distinguish it from CB and other lesions with a prominent giant cell component. In some cases, GCT has an aggressive radiographic appearance that raises the possibility of malignancy. However, the cells in GCT lack the overtly malignant features seen in osteosarcoma.

5.2.6 Cystic Lesions of Bone

Cystic lesions of bone that are encountered in the pediatric population are listed in Table 5.8. The benign, cystic nature of simple, unicameral and ganglion cysts of bone is readily apparent on imaging studies and therefore, these lesions rarely undergo FNA or small biopsy prior to definitive treatment with curettage and bone packing. Aspirated fluid obtained at the time of surgery may be submitted for cytological evaluation. Specimens are typically paucicellular and comprised of bland spindle cells admixed with histiocytes. Rarely, small fragments of characteristic cementum-like matrix are present in intraoperative aspirates from unicameral bone cysts. In contrast to other benign cystic lesions, aneurysmal bone cyst has a more complex radiographic appearance that can raise the possibility of either aneurysmal bone cyst arising in an underlying neoplasm or telangiectatic osteosarcoma. It is these lesions with solid areas and/or aggressive features that are most likely to undergo FNA or small biopsy.

Table 5.8 Cystic lesions of bone

Benign lesions	Malignant lesions
Aneurysmal bone cyst Primary or secondary	Telangiectatic osteosarcoma
Simple cyst (uncommitted cyst)	
Unicameral bone cyst	
Ganglion cyst of bone	

5.2.6.1 Aneurysmal Bone Cyst

Clinical Features

Aneurysmal bone cyst (ABC) is most common in children and adolescents with 75% of lesions occurring in patients under 20 years of age, and has a peak incidence in the second decade of life. Pain and swelling in the area of the involved bone are the main symptoms.

Location

ABC may occur in any part of any bone, but has a predilection for long bones and the vertebral column.

Radiographic Appearance

ABC appears as a well-demarcated, lytic lesion with a sclerotic rim and fluid–fluid levels. Although ABC can occur in any part of any bone, in long bones it most often involves the metaphysis. In rapidly growing lesions, sclerosis is usually absent and marked cortical thinning and a periosteal reaction are often present, raising concern for malignancy.

Cytological Features

FNA characteristically yields bloody, paucicellular smears [17]. Cellular elements include variable numbers of osteoclast-like giant cells, hemosiderin-laden macrophages, and benign spindle cells consistent with fibroblasts and myofibroblasts. In some cases, osteoblasts and osteoid are also noted. Mitotic figures may present in the spindle cells, particularly in rapidly growing lesions, but abnormal forms are absent.

Differential Diagnosis

The main differential diagnostic considerations include secondary ABC arising in an underlying benign or malignant tumor, and telangiectatic osteosarcoma. Cytologic evidence of other bone tumors should be carefully sought to exclude an underlying neoplasm with secondary ABC. The absence of overtly malignant cells helps to exclude telangiectatic osteosarcoma. *USP6* gene rearrangements are found in approximately 70% of primary ABC but not in secondary ABC. Identification of a *USP6* rearrangement by FISH can help to confirm the diagnosis and exclude other possibilities.

Pearl

When aggressive radiographic features are present, it is important to exclude telangiectatic osteosarcoma. Because aspirates from telangiectatic osteosarcoma are usually bloody, the diagnostic overtly malignant cells can be sparse and may be overlooked. This pitfall should be borne in mind when evaluating an FNA from a clinically suspected ABC with atypical or aggressive features.

5.2.7 Small Round Blue Cell Tumors and Inflammatory Infiltrates of the Marrow Space

A distinctive group of highly malignant neoplasms of bone are the so-called small round blue cell tumors (SRBCT). These include Ewing sarcoma/primitive neuroectodermal tumor (PNET), primary malignant lymphoma, mesenchymal chondrosarcoma (see Sect. 5.2.2.4), and small cell osteosarcoma (see section "Small Cell Osteosarcoma"). A number of metastatic lesions should also be considered in the differential diagnosis of SRBCT, including neuroblastoma, lymphoma, and rhabdomyosarcoma.

As SRBCTs usually consist of a monomorphous population of small, round cells with scant cytoplasm and hyperchromatic nuclei, distinction between these neoplasms may be difficult or impossible without ancillary studies. Notable exceptions include small cell osteosarcoma and mesenchymal chondrosarcoma, in which the presence of osteoid and chondroid material, respectively, allows accurate diagnosis. Unfortunately, these matrices may be scant or absent in aspirates from these lesions. Ancillary studies, including histochemical and/or immunoperoxidase stains, flow cytometry, molecular studies and electron microscopy, usually allow definitive diagnosis of a SRBCT. Of note, electron microscopy has largely been replaced by immunoperoxidase stains and is rarely used. The importance of rapid on site evaluation of aspirates from SRBCTs cannot be overstated, as it allows collection of additional material for appropriate ancillary studies, and often obviates the need for a more invasive diagnostic biopsy.

Table 5.9 lists the common neoplastic and inflammatory small cell lesions of bone seen in the pediatric population. Features that help to distinguish some of the more common SRBCT of bone are summarized in Table 5.10.

5.2.7.1 Ewing Sarcoma/Primitive Neuroectodermal Tumor (ES/PNET)

Clinical Features

Ewing sarcoma/PNET is the second most common primary malignant neoplasm of bone, and 80% of cases occur within the first two decades of life. Localized pain and swelling are the most common symptoms. Occasional patients present with systemic illness, which is usually indicative of a worse prognosis.

Table 5.9 Small cell lesions of bone: neoplastic and inflammatory

Benign/inflammatory lesions	Malignant neoplasms
Acute osteomyelitis	Ewing sarcoma/PNET
Chronic osteomyelitis	Malignant lymphoma
Plasma cell osteomyelitis	Small cell osteosarcoma
Langerhans cell histiocytosis	Mesenchymal chondrosarcoma
	Metastatic lesions
	Neuroblastoma
	Lymphoma
	Rhabdomyosarcoma

Table 5.10 Useful features for distinguishing between various SRBCT of bone

Features	ES/PNET	Lymphoma	Small cell OS	MCS
Cytoplasm	ES: scant, indistinct borders; PNET: ± wispy extensions	Scant to moderate	Scant to moderate	Scant, distinct borders
Cytoplasmic glycogen (PAS + diastase digestible)	Usually prominent	Absent	Absent	Rare
Nuclear features	Oval to round, evenly dispersed fine chromatin to coarse, clumped chromatin, ± small nucleoli	Irregular contours; coarse or vesicular chromatin; nucleoli usually prominent	Round, oval or irregular; fine to clumped chromatin; pleomorphism may be present	Oval to spindled shaped; fine to coarse chromatin; ± nucleoli
Matrix	Absent	Absent	Focal osteoid, rarely chondroid	Focal chondroid (may be scant)
Immunoperoxidase stains	+ CD99, FLI-1; ± synaptophysin, chromogranin; (−) LCA	+ LCA; B-cell: + CD20, others; T-Cell: + CD3, others	± SATB2	+ S100 in chondroid component, + SOX9 in small cell component
Molecular studies	*EWSR1* rearrangements	T-cell receptor rearrangements in T-cell lymphomas	Not helpful	Not helpful
Pattern	Single cells, loose clusters and pseudorosettes	Single cells; lymphoglandular bodies	Single cells	Single cells
Age range	Broad with peak in the second decade of life	Broad, rare in the pediatric population	Broad with peak in the second decade of life	Broad
Extraosseous mass	Usually prominent	Usually prominent	Usually prominent	Common

Location

ES/PNET has a predilection for the diaphysis of long tubular bones, although any portion of any bone may be affected.

Radiographic Appearance

ES/PNET typically appears as a large, poorly defined, lytic lesion with a moth-eaten appearance. A thin rim of cortex may persist, and an "onion skin" or "sunburst" periosteal reaction is often present. Extension into the soft tissue with formation of a large extraosseous mass is characteristic. Matrix production is absent.

Cytological Features

FNA of ES/PNET yields highly cellular smears in which cells are individually dispersed and arrayed in loosely cohesive clusters (Fig. 5.8) [18, 19]. Cells are relatively uniform, small and round to ovoid with scant cytoplasm and indistinct cellular borders. The cytoplasm is often vacuolated due to abundant glycogen and disruption of the cytoplasm may impart a tigroid appearance to the background that is best seen in air-dried, modified Giemsa-stained smears. Cytoplasmic projections may be evident in some cells and variable numbers of pseudorosettes may also be present. Nuclei are round to ovoid with finely granular, evenly distributed chromatin and inconspicuous nucleoli. In some tumors nuclei are more irregular with clumped chromatin and small nucleoli. Naked nuclei and DNA streaks (crush artifact) are common. Mitotic figures are typically present, but few in number. Necrosis is usually present and may be prominent.

Differential Diagnosis

Differential diagnostic considerations include primary and metastatic small round blue cell tumors arising in the pediatric population, including

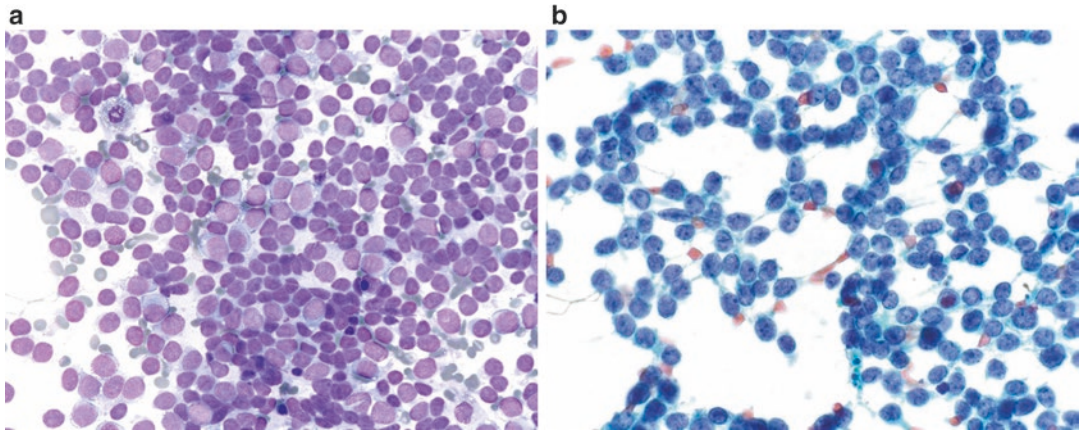

Fig. 5.8 Ewing sarcoma (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). This hypercellular smear is composed of a relatively monotonous population of round to oval cells with scant cytoplasm and fine chromatin. Note the "light and dark" appearance of the cells in this smear (**a**). The evenly dispersed, fine chromatin and inconspicuous nucleoli are better seen in the Papanicolaou-stained preparation. Some cells have delicate cytoplasmic extensions (**b**).

lymphoma, small cell OS, MCS neuroblastoma, and rhabdomyosarcoma. Features that help to distinguish ES/PNET from other primary bone tumors are summarized in Table 5.10. Metastatic lesions can usually be distinguished from primary ES/PNET of bone on the basis of clinical history with or without confirmatory immunoperoxidase stains. Recurrent translocations, the most common of which (>95 %) involve *EWSR1*, are also characteristic of ES/PNET and can be identified using FISH or other molecular studies. Recently, Ewing-like tumors with translocations involving *DUX4* or *BCOR* have also been described.

Pearls

- Immunoperoxidase stains and FISH are usually required for definitive diagnosis of ES/PNET, thus it is essential to submit material for cell block and when possible, prepare extra smears for FISH. *EWSR1* rearrangements are seen in a variety of tumors other than ES/PNET, and rare ES/PNETs lack *EWSR1* rearrangements, both of which can lead to misdiagnosis.
- In addition, there are now a group of Ewings-like tumors, referred to as round cell sarcomas, that have more atypical cytologic features, lack the diffuse membranous CD99 immunostaining, and are more likely to show diffuse nuclear WT1 positivity.

5.2.7.2 Malignant Lymphoma of Bone

Clinical Features

Primary lymphomas of bone may occur at any age, but are much more frequent after the second decade of life and are rare in young children. In the pediatric population, secondary involvement of bone, particularly by lymphoblastic lymphoma, is far more common than primary lymphoma of bone. Bone pain is the most common presenting symptom of both primary and secondary bony involvement.

Location

Malignant lymphoma can occur in any part of any bone.

Radiographic Appearance

These lesions almost always appear malignant radiographically. However, the appearances are quite variable and characteristic features that suggest the diagnosis of lymphoma are lacking.

Cytological Features

The cytologic features vary considerably, depending on the type of lymphoma and are discussed in more detail in Chap. 3. In general, FNA of lymphoma yields highly cellular smears in which cells occur singly or in loosely cohesive pseudoepithelial clusters. Due to cytoplasmic fragility,

the background contains numerous lymphoglandular bodies that are best appreciated in air-dried, modified Giemsa-stained smears. Intact cells are generally round to ovoid, with scant to moderate amounts of cytoplasm and indistinct borders. Mild cellular and nuclear pleomorphism is usually evident. Nuclei are round to ovoid, with irregular nuclear membranes, fine to coarsely clumped chromatin, and one or more, often irregular nucleoli. Mitotic figures, including abnormal forms, may be scarce or abundant. DNA streaks are usually evident. Necrosis is variably present. Nuclear molding is absent.

Differential Diagnosis

Differential diagnostic considerations include other primary and metastatic small round blue cell tumors. Features that help to distinguish lymphomas from other primary bone tumors are summarized in Table 5.10. Metastasis from other small round blue cell tumors can usually be distinguished from either primary or secondary lymphoma of bone on the basis of clinical history, with or without confirmatory immunoperoxidase stains. In many cases, the lymphoid origin of the malignant cells is readily apparent at the time of rapid on site evaluation. In such cases, additional passes should be performed for flow cytometry and immunoperoxidase stains. When the cell of origin is less certain, material should also be obtained for cytogenetics and molecular studies, whenever possible.

5.2.7.3 Osteomyelitis

Clinical Features

Not infrequently, the acute phase of an aggressive infection involving bone can mimic a malignancy both clinically and radiographically. Osteomyelitis can be bacterial, fungal or possibly, viral in origin, and can result from either hematogenous dissemination or direct surgical or traumatic introduction of microorganisms.

Location

Osteomyelitis can involve any part of any bone.

Radiographic Appearance

The radiographic findings in osteomyelitis depend on the stage and activity of the disease. Alterations that are detectable on plain radiographs are not present until the disease is well established and significant destruction of bone has occurred. At this stage, acute osteomyelitis appears as a lytic lesion in which the permeative destruction of trabecular and cortical bone often mimics malignancy.

Cytological Features

The cytological findings reflect the stage of the disease. In general, aspirates contain inflammatory cells admixed with necrotic tissue and osteoclasts. In early lesions, neutrophils and granular, necrotic debris often dominate the smears, while necrotic trabeculae and osteoclasts are less conspicuous. Aspirates from later lesions contain a mixed population of neutrophils, macrophages, lymphocytes, and eventually plasma cells, and both necrotic trabeculae with or without conspicuous resorption lacunae and osteoclasts are present in increased numbers. Rarely, microorganisms are identified in routinely stained preparations or with histochemical stains. In resolving acute osteomyelitis, smears may be paucicellular and dominated by irregular fragments of granulation tissue.

Differential Diagnosis

Differential diagnostic considerations include Langerhans cell histiocytosis, which is discussed in detail in Sect. 5.2.7.4, and necrotic tumor. The abundance of neutrophils and absence of malignant cells support a diagnosis of osteomyelitis, as does the demonstration of microorganisms on a smear or cell block. However, biopsy may be warranted to exclude malignancy in cases with less prominent neutrophilic inflammation and/or conspicuous reactive endothelial or myofibroblastic cells derived from granulation tissue. Whenever possible, material should be obtained for culture and sensitivity. Polymerase chain reaction (PCR) can help to identify the causative microorganism in some cases.

5.2.7.4 Langerhans Cell Histiocytosis

Clinical Features

Langerhans cell histiocytosis (LCH) involving bone generally presents in the first two decades of life, with a peak incidence between 5 and 10 years. LCH has a broad spectrum of clinical

presentations with highly variable prognoses. Older children typically present with single or multiple skeletal lesions that usually follow a benign course and either regress spontaneously or require minimal treatment. In contrast, infants and very young children may present with multifocal, multisystem disease, which can progress to organ failure and has an aggressive or sometimes fatal clinical course. Bone lesions usually manifest as a painful swelling.

Location

The most frequent sites of involvement are the skull, followed by long bones, flat bones, and vertebrae.

Radiographic Appearance

Three stages have been described in the evolution of LCH, including incipient, mid, and late phases. During the incipient or early phase, lesions tend to have an aggressive radiographic appearance that is characterized by a permeative pattern of growth, indistinct borders, and a lamellated periosteal reaction. This radiographic picture overlaps with that of aggressive osteomyelitis and malignancies such as Ewing sarcoma and lymphoma, and these entities are frequently considered in the radiographic differential diagnosis. Later in the course of the disease the lesions tend to develop well-demarcated borders that are often surrounded by a rim of sclerotic bone.

Cytological Features

FNA of LCH yields moderately to highly cellular smears composed of a polymorphous population of individually dispersed cells that include variable numbers of Langerhans cell histiocytes, eosinophils, osteoclast-like giant cells, lymphocytes, neutrophils, and plasma cells (Fig. 5.9) [20]. Langerhans cell histiocytes are characterized by moderate to abundant cytoplasm and eccentric, oval to reniform nuclei with pale, evenly dispersed chromatin and inconspicuous nuclei. Nuclear folds or grooves are characteristic, and help to distinguish these cells from ordinary macrophages by light microscopy. Definitive diagnosis of LCH usually requires immunoperoxidase stains to confirm the identity of the lesional cells. In contrast to ordinary macrophages, Langerhans cell histiocytes are immunoreactive for S100, CD1a, langerin, and CD68. The cells are negative for lysozyme and alpha-1 antitrypsin. The diagnostic ultrastructural feature of Langerhans cell histiocytes is the presence of Birbeck granules within the cytoplasm, but these structures may be difficult to find.

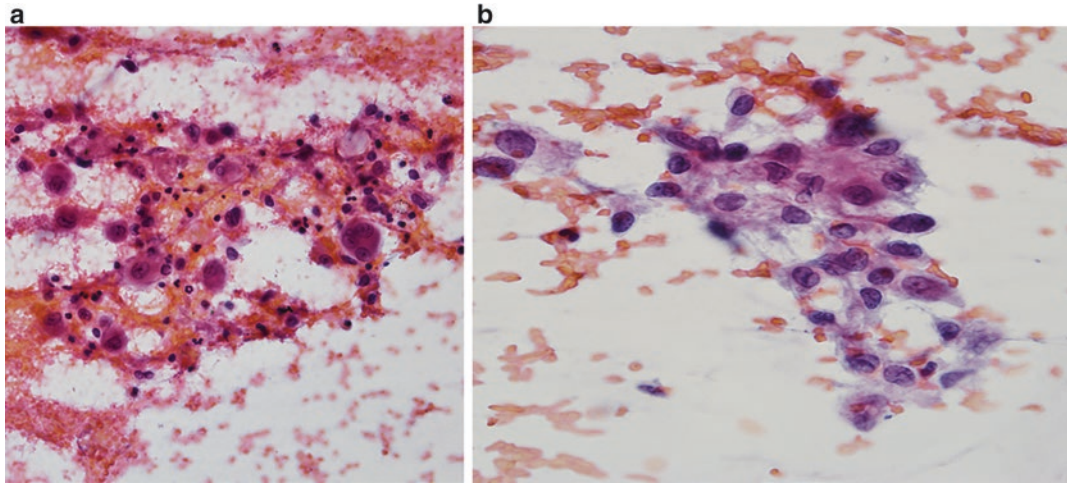

Fig. 5.9 Langerhans cell histiocytosis (**a**, **b**. Papanicolaou stain, medium and high power). Langerhans cell histiocytosis is comprised of Langerhans cell histiocytes admixed with variable numbers of eosinophils, neutrophils, lymphocytes, and plasma cells (**a**). Multinucleated Langerhans cells, as well as osteoclast-like giant cells are also present. As seen in this cluster of Langerhans cell histiocytes, the cells have moderate to abundant cytoplasm and ovoid to reniform, grooved or folded nuclei (**b**).

Differential Diagnosis

The main differential diagnostic consideration is osteomyelitis. The distinctive morphologic appearance of Langerhans cell histiocytes provides an important clue to the correct diagnosis which can be confirmed with immunoperoxidase stains.

5.3 Soft Tissue Tumors

A wide variety of benign and malignant neoplasms, as well as non-neoplastic lesions occur in the soft tissues of children and adolescents. Benign neoplasms and reactive processes are generally small and superficial. In contrast, most soft tissue sarcomas appear as bulky, deep-seated masses. Soft tissue tumors are classified based on the presumed mesenchymal cell of origin, as summarized in Table 5.11. However, a pattern-based approach, as summarized in Table 5.12, is often more practical for cytological evaluation of these lesions. Discussion of the myriad soft tissue lesions seen in the pediatric population, only some of which are included in Tables 5.11 and 5.12, is beyond the scope of this book; therefore, this chapter will focus on some of the more common soft tissue lesions seen in the children and adolescents.

5.3.1 Small Round Cell Tumors

Small round cell tumors are the most common primary malignant tumors of soft tissue in children and adolescents. Rhabdomyosarcoma, Ewing sarcoma/PNET, poorly differentiated (small cell) synovial sarcoma, and desmoplastic small round

Table 5.11 Classification of pediatric soft tissue tumors based on presumed mesenchymal tissue of origin

Origin	Benign	Locally aggressive	Malignant
Fat cells	Lipoma	Atypical lipomatous tumor	Liposarcoma
	Lipoblastoma		Myxoid
	Hibernoma		Round cell
			Pleomorphic
Fibroblasts/ myofibroblasts	Nodular fasciitis	Desmoid-type fibromatosis	Fibrosarcoma
	Fibrous hamartoma of infancy	Dermatofibrosarcoma protuberans (DFSP)	Infantile
	Digital fibroma		Adult type
	Myofibroma		
	Gardner fibroma		
	Hypertrophic scar		
So-called fibrohistiocytic tumors	Benign fibrous histiocytoma		
	Tenosynovial giant cell tumor, nodular or diffuse		
Peripheral nerve sheath elements	Neurofibroma		Malignant peripheral nerve sheath tumor
	Schwannoma		
	Granular cell tumor		
Endothelial cells	Hemangioma	Epithelioid hemangioendothelioma	Angiosarcoma
Skeletal muscle	Rhabdomyoma		Rhabdomyosarcoma
			Embryonal
			Alveolar
			Spindle cell/sclerosing
Smooth muscle	Leiomyoma		Leiomyosarcoma
Uncertain		Angiomatoid fibrous histiocytoma	Synovial Sarcoma
			Epithelioid Sarcoma
			Alveolar soft part sarcoma
			Desmoplastic small round cell tumor
			Extrarenal rhabdoid tumor

Table 5.12 Classification of pediatric soft tissue tumors based on pattern

Pattern	Benign	Locally aggressive	Malignant
Small round cell			Rhabdomyosarcoma Ewing sarcoma/PNET Desmoplastic small round cell tumor Poorly differentiated (small cell) synovial sarcoma Extrarenal rhabdoid tumor Metastatic neuroblastoma or other round cell tumor
Spindle cell	Nodular fasciitis Fibrous hamartoma of infancy Digital fibroma Myofibroma Gardner fibroma Hypertrophic scar Hemangioma Leiomyoma Neurofibroma Schwannoma Rhabdomyoma	Desmoid-type fibromatosis Dermatofibrosarcoma protuberans (DFSP) Angiomatoid fibrous histiocytoma	Fibrosarcoma Infantile Adult type Synovial sarcoma Spindle cell/sclerosing rhabdomyosarcoma Malignant peripheral nerve sheath tumor Low grade fibromyxoid sarcoma Angiosarcoma
Epithelioid	Granular cell tumor Rhabdomyoma	Epithelioid hemangioendothelioma Angiomatoid fibrous histiocytoma	Epithelioid malignant peripheral nerve sheath tumor Epithelioid sarcoma Angiosarcoma Alveolar soft part sarcoma
Myxoid	Myxoma	Aggressive myxoma	Myxoid liposarcoma Low grade fibromyxoid sarcoma
Pleomorphic			Pleomorphic liposarcoma Pleomorphic undifferentiated sarcoma
Clear cell	Lipoblastoma Lipoma Hibernoma	Atypical lipomatous tumor	Clear cell sarcoma of soft tissue

cell tumor account for the overwhelming majority of these neoplasms. Considerable overlap exists in cytomorphologic features of these tumors and in most cases, ancillary studies are needed to confirm the diagnosis and exclude other entities. In general, additional material should be collected for a cell block and air-dried unstained smears prepared and reserved for FISH.

5.3.1.1 Rhabdomyosarcoma

Clinical Features

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the pediatric population. The majority of patients (60–70 %) present in the first decade of life, most before 5 years of age. Embryonal rhabdomyosarcoma (ERMS) can be congenital, occurs the first year of life in up to 10 % of cases, and is uncommon in children older than 10 years of age. ERMS most often arises in the head and neck and genitourinary system, and is rare in the extremities. Alveolar rhabdomyosarcoma (ARMS) can occur at any age, but is more common in adolescents than ERMS and is rare in very young children. ARMS most often arises in the extremities. Other sites include the paraspinal and perineal regions and paranasal sinuses.

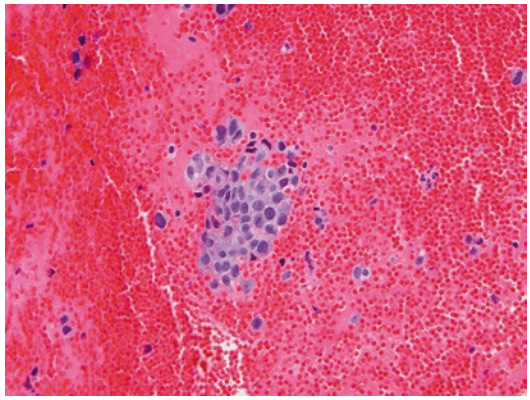

Fig. 5.10 Alveolar rhabdomyosarcoma (Cell block, H&E stain, high power). Alveolar rhabdomyosarcoma is characterized by a relatively monotonous population of round cells with round nuclei and one or more conspicuous nucleoli.

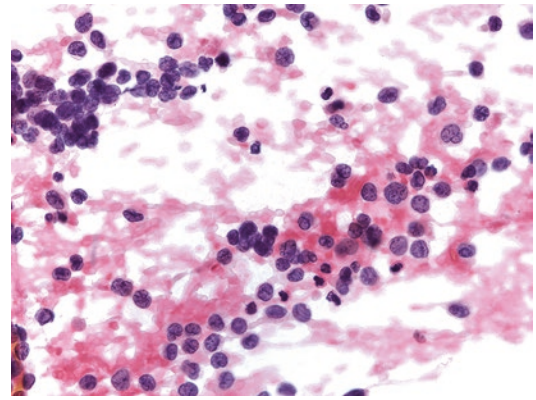

Fig. 5.11 Embryonal rhabdomyosarcoma (Papanicolaou stain, high power). Embryonal rhabdomyosarcoma is characterized by round cells with scant cytoplasm and round to irregular nuclei with fine chromatin and inconspicuous nucleoli. The cells occur singly and in small loosely cohesive clusters.

Cytological Features

Aspirates from RMS are usually highly cellular and are composed of relatively monotonous cells occurring singly and in small, loosely cohesive clusters. In ARMS the cells are round and have round nuclei with coarse chromatin and one or more nucleoli (Fig. 5.10). Cells with eccentric cytoplasm and multinucleated cells are present in variable numbers, and when present, are an important clue to the diagnosis. However, cells with cross striations are rare. The cells in ERMS are typically smaller than those in ARMS and have round to ovoid or irregular nuclei with fine chromatin and inconspicuous nucleoli (Fig. 5.11). Elongate or strap-like cells with cross-striations can be present and are occasionally prominent. Anaplastic cells with enlarged, hyperchromatic nuclei are present in a minority of cases. Fragments of myxoid stroma are sometimes seen in ERMS.

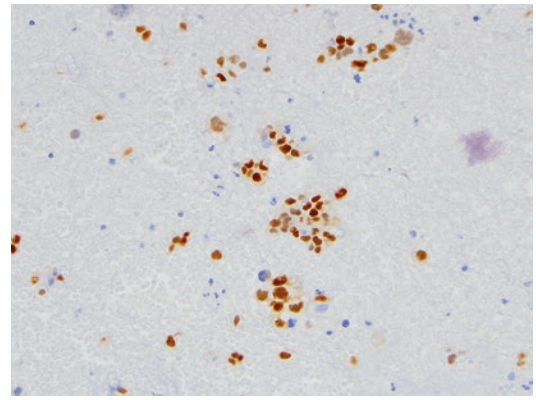

Fig. 5.12 Alveolar rhabdomyosarcoma (Cell block, myogenin immunoperoxidase stain, medium power). Alveolar rhabdomyosarcoma (ARMS) shows strong, diffuse nuclear staining for myogenin. This pattern of staining helps to distinguish alveolar from embryonal rhabdomyosarcoma, which typically shows patchy, variable staining for myogenin.

Differential Diagnosis

Differential diagnostic considerations include Ewing sarcoma/PNET, desmoplastic small round cell tumor, poorly differentiated (small cell) synovial sarcoma, lymphoma, neuroblastoma, and other pediatric small round cell tumors. Although the clinical history and site of involvement can help to narrow the differential diagnosis, ancillary studies are essential for confirming the diagnosis of RMS and excluding other entities. RMS shows nuclear staining for myogenin and MyoD1, which distinguishes it from other entities in the differential diagnosis, as well as cytoplasmic staining for desmin and muscle specific actin, and is usually negative for CD99, FLI-1, synaptophysin, chromogranin, epithelial membrane antigen, cytokeratin, TLE-1, and CD45. Nuclear staining for myogenin is typically strong and diffuse in ARMS (Fig. 5.12) and patchy and variable in ERMS, and

helps to distinguish these entities. Gene rearrangements involving *FOXO1* and either *PAX3* or *PAX7* are present in approximately 80 % of ARMS, but are absent in ERMS. The morphologic, immunophenotypic, and molecular genetic features of soft tissue and osseous Ewing sarcoma/PNET are identical and are discussed in Sect. 5.2.7.1. Synovial sarcoma and desmoplastic small round cell tumor are discussed below, while other entities in the differential diagnosis are discussed in detail elsewhere in this book.

Pearl

Although the pattern of myogenin staining helps to support a diagnosis of either ARMS or ERMS, demonstration of a *FOXO1* translocation is required to reliably distinguish these entities in cytologic specimens.

5.3.1.2 Desmoplastic Small Round Cell Tumor

Clinical Features

Desmoplastic small round cell tumor (DSRCT) is a rare tumor that predominantly occurs in children and young adults and has a male predilection. DSRCT usually presents with widespread intra-abdominal disease, involving the serosa, mesentery, omentum, retroperitoneum, and/or pelvis. However, tumors occasionally arise in the thoracic cavity and paratesticular regions, and rarely in other sites. Patients present with abdominal pain, distention, ascites, a palpable mass, and/or intestinal obstruction. DSRCT is an aggressive tumor with a poor prognosis.

Cytological Features

Aspirates from DSRCT are variably cellular with small to intermediate-sized round cells arrayed singly and in loosely cohesive sheets and clusters. Fragments of hypocellular fibrous stroma are variably present. The tumor cells are uniform, round to oval, and have scant cytoplasm and hyperchromatic nuclei with finely granular chromatin and inconspicuous nucleoli (Fig. 5.13). Occasional tumors are composed of larger, more pleomorphic cells. Necrosis can also be present.

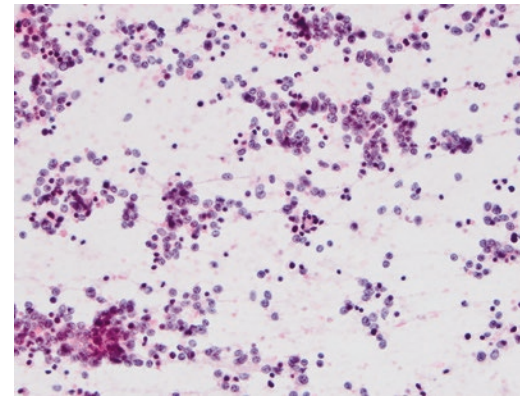

Fig. 5.13 Desmoplastic small round cell tumor (Papanicolaou stain, medium power). The tumor is composed of small round cells lying singly and in loosely cohesive clusters. The cells have scant cytoplasm with indistinct borders and round nuclei with fine chromatin and inconspicuous nucleoli. Numerous single necrotic cells are present in the background.

Differential Diagnosis

Differential diagnostic considerations include Ewing sarcoma/PNET, rhabdomyosarcoma, lymphoma, poorly differentiated (small cell) synovial sarcoma, and metastasis from other pediatric small round cell tumors. In contrast to other tumors in the differential diagnosis, DSRCT is a polyphenotypic tumor and stains positively for low molecular weight cytokeratins, epithelial membrane antigen, desmin (perinuclear dot-like pattern), neuroendocrine markers, and WT1 (C-terminus). The tumors are variably positive for CD99. DSRCT is characterized by a translocation involving *EWS* and *WT1*. Ewing sarcoma/PNET and rhabdomyosarcoma are discussed in Sects. 5.2.7.1 and 5.3.1.1, respectively, and other tumors in the differential diagnosis are discussed in greater detail elsewhere in this book.

Pearls

Because *EWSR1* gene rearrangements are present in both DSRCT and Ewing sarcoma/PNET and DSRCT can be positive for CD99, it is essential to perform a panel of immunoperoxidase stains to confirm the polyphenotypic nature of DSRCT and avoid misdiagnosis. Confirmation of the

translocation partner is also helpful but in the context of the appropriate immunophenotype is not critical.

5.3.2 Spindle Cell Pattern

Spindle cell morphology is characteristic of a wide variety of benign and malignant neoplasms and non-neoplastic proliferations involving soft tissues. Some of the more common spindle cell lesions seen in the pediatric population are listed in Table 5.12. Overall, non-neoplastic reactive processes and benign neoplasms account for the majority of spindle cell lesions in children and adolescents. These lesions are usually small, superficial, and well circumscribed and treatment, if any, consists of simple excision. Because FNA is rarely used for the evaluation of these benign lesions, this discussion will focus on selected pediatric spindle cell malignancies.

5.3.2.1 Synovial Sarcoma

Clinical Features

Synovial sarcoma can occur at any age but is most frequently seen in adolescents and young adults, with the peak incidence in the second and third decades of life. Tumors commonly involve the extremities, most often in a juxta-articular location, but can arise in virtually any anatomic site. Pain, either spontaneous or on palpation, is a frequent symptom. These tumors are typically indolent, and years may elapse between the first symptom and diagnosis. Irregular calcifications are detected in up to one-third of tumors on imaging studies.

Cytological Features

FNA yields moderately to highly cellular smears in which cells occur singly, and in irregular sheets and clusters (Fig. 5.14). The cytologic appearance varies with the subtype of the tumor, and may be biphasic or monophasic [21, 22]. Aspirates from biphasic lesions contain variable numbers spindle and epithelial cells, although the former usually predominate. The spindle cells are relatively uniform cells with scant, tapering cytoplasm and solitary, hyperchromatic, oval or elongate nuclei with inconspicuous nucleoli. Epithelial elements have scant to abundant cytoplasm and uniform, often eccentric, round to oval nuclei with pale, evenly distributed chromatin. Mitotic figures may be few to abundant. Monophasic tumors are comprised of either spindle or epithelial elements. Rarely, calcifications may be identified in the aspirates. When both spindle and epithelial elements are present,

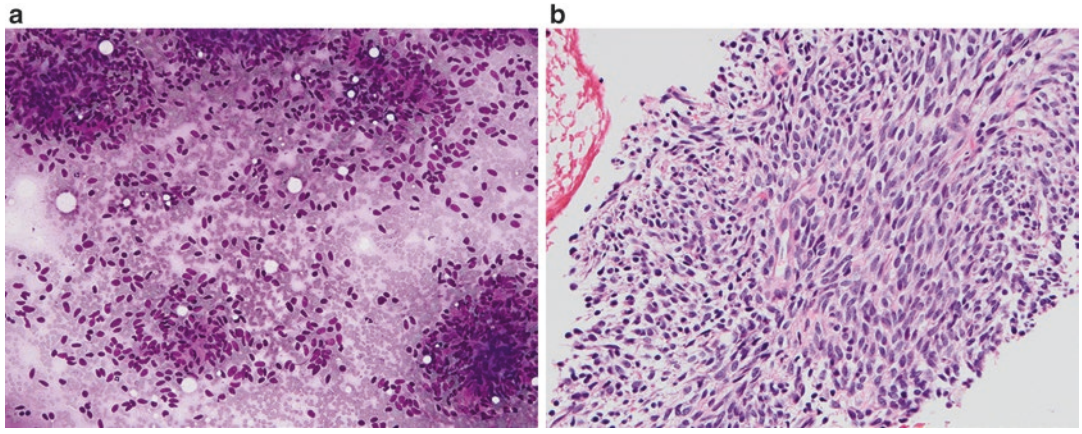

Fig. 5.14 Synovial sarcoma (**a**. Diff-Quik stain, medium power; **b**. Cell block, H&E stain, high power). The smear is highly cellular and shows tumor cells arranged in clusters and singly. The tumor cells are uniform with spindled nuclei and evenly dispersed chromatin Cytoplasm is scant and many stripped nuclei are present (**a**). This fragment of tissue in the cell block is composed of short, bland spindle cells arrayed in fascicles. The cells have uniform nuclei with evenly dispersed chromatin and inconspicuous nucleoli. Mitoses are not apparent (**b**).

the cytologic diagnosis is usually straightforward. In contract, monophasic lesions may be difficult to distinguish from fibrosarcoma or adenocarcinoma. Rarely tumors are composed of poorly differentiated small round cells reminiscent of those in other small round cell tumors. These cells have scant cytoplasm and uniform, round to ovoid, hyperchromatic nuclei with coarse chromatin.

Differential Diagnosis

Differential diagnostic considerations include malignant peripheral nerve sheath tumor, fibrosarcoma, solitary fibrous tumor, and leiomyosarcoma. With the exception of malignant peripheral nerve sheath tumor, these neoplasms are rare in the pediatric age group. Immunoperoxidase stains can help to resolve the differential diagnosis. Synovial sarcoma is usually positive for epithelial membrane antigen, CD99 and TLE-1 (nuclear), variably positive for keratins and S100, and negative for CD34. Poorly differentiated (small cell) synovial sarcoma, for which the differential diagnosis is other pediatric small round cell tumors, shows a similar pattern of staining. Rearrangements involving the *SS18 (SYT)* gene are seen in over 95 % of synovial sarcomas.

Pearls

Because both spindle cell and poorly differentiated (small cell) synovial sarcoma can mimic other malignancies morphologically and, in some cases, immunophenotypically, demonstration of an *SS18* rearrangement is important for confirming the diagnosis.

5.3.2.2 Malignant Peripheral Nerve Sheath Tumor

Clinical Features

Malignant peripheral nerve sheath tumor (MPNST) is a rare tumor that is most often seen in adults but can be seen in children and adolescents, particularly those with neurofibromatosis type 1 (NF-1). MPNST usually arises in a preexisting neurofibroma, with the extremities and trunk being common sites of involvement. Rapid growth of an existing lesion and pain are the typical presenting symptoms.

Cytological Features

Aspirates from MPNST are usually highly cellular with cells arranged singly and in irregular fragments [23]. Depending on the grade of the tumor, the individual cells vary from bland and virtually indistinguishable from those of benign spindle cell lesions to highly pleomorphic with obviously malignant features. Cells have scant cytoplasm and enlarged hyperchromatic nuclei with variably prominent nucleoli. Nuclei are often wavy or comma shaped. Bizarre tumor giant cells can also be present. Mitotic figures, including abnormal forms, are usually apparent. Necrosis can also be present.

Differential Diagnosis

Differential diagnostic considerations vary depending on the degree of differentiation of the tumor. Low grade MPNST should be distinguished from schwannoma, atypical neurofibroma, and other bland spindle lesions. In contrast the differential diagnosis of intermediate or high grade lesions includes synovial sarcoma, malignant solitary fibrous tumor, leiomyosarcoma, spindle cell melanoma, and other malignant spindle cell sarcomas. MPNST shows staining for S100 in less than 50 % of cases and for GFAP in 20–30 %; however, nuclear positivity for SOX10 can be a helpful finding in some cases. Staining is usually focal, in contrast to the diffuse staining seen in the majority of benign peripheral nerve sheath tumors. Because MPNST can mimic a variety of spindle cell neoplasms at both ends of the spectrum of differentiation, a panel of immunoperoxidase stains is needed to exclude other entities.

Pearl

Immunoperoxidase stains are helpful for excluding other tumors but, in the absence of S100 staining, do not confirm the diagnosis of MPNST. In such cases, the presence a preexisting lesion and a history of NF-1 are highly suggestive of MPNST.

5.4 Conclusion

FNA is a valuable tool for the primary diagnosis of pediatric bone and soft tissue lesions. When correlated with the clinical presentation and

findings on imaging studies, FNA combined with the judicious use of ancillary studies can often provide information on which to base further diagnostic or therapeutic decisions. In many cases, FNA allows accurate and specific diagnosis of primary or metastatic lesions of bone and soft tissue, thereby obviating the need for a more invasive and significantly more expensive diagnostic biopsy. In other cases, although a definite diagnosis is not possible, FNA is useful for ruling out specific processes or for narrowing the diagnostic considerations, and in the appropriate clinical setting, this information may be sufficient for initiation of therapy. Although limitations and pitfalls exist, FNA represents a highly accurate and cost-effective technique for the diagnosis of pediatric bone and soft tissue tumors.

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General Resource

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