# 28 Soft Tissue and Bone

Tumors of soft tissue are among the most challenging in surgical pathology. There are several reasons for this: they are rare, so you see few in training; they are overlapping in morphology; they do not always obey the principles that help you to identify malignant potential in carcinomas; and each entity has at least three names, four variants, and seven mimickers. However, we will cover some of the names you will hear most commonly. The tumors are broken down into lines of differentiation, with the caveats that there are some tumors that do not differentiate along any known lineage (grouped separately) and that many soft tissue tumors dedifferentiate into the same final common malignant pathway, the entity formerly known as *malignant fibrous histiocytoma* (MFH). In many instances, MFH is simply a generic dedifferentiated sarcoma, the high-grade form of any one of a number of precursor lesions. The good news is, once it is that high grade, the origin becomes sort of academic.

When diagnosing a soft tissue lesion, especially in its initial presentation, you must always walk yourself through the mental game of, *"what else could this be?"* It is a good habit for any organ system but especially in the field of sarcomas and spindle cell lesions. For lesions that do not look clearly malignant (by which we mean they lack nuclear atypia and necrosis), you must always consider that it might be a reactive lesion. For lesions with bizarre and huge nuclei, despite the malignant look, you must consider benign entities with degenerative atypia (such as an ancient schwannoma). For lesions in or near an organ, such as in visceral sites, you must always ask yourself if it could be a carcinoma masquerading as a sarcoma. For spindle cell lesions anywhere, you must ask yourself if it could be melanoma. Some of these questions require immunostains to answer, some just a skeptical eye.

The second question to ask, once you have ordered the cytokeratins and melanoma markers, is *"what family of soft tissue does it belong in?"* Table 28.1 lists some stereotypical features of different tumor families, seen best in low-grade (well-differentiated) lesions.

## High-Grade Sarcomas

As mentioned, once sarcomas turn high grade, they may take on any number of appearances, regardless of differentiation. Some classic visual patterns are shown in Figure 28.1 and described in Table 28.2.

In high-grade sarcomas, the subtype may be clarified through immunostains, history, or the low-grade remnants of the tumor found at the periphery. Identifying the line of differentiation can be helpful in determining prognosis. Solving this puzzle is one of the more interesting games pathologists can play and breaks up the monotony of routine biopsies. However, from a clinical perspective, the oncologist is more concerned about the grade than the type, and, fortunately for all of us, high-grade sarcomas are hard to miss.

**Table 28.1.** Characteristics of tumor families.

| | |
|---|---|
| Lipomatous ("lipo") | Fat cells intermixed with other elements; fat cells are identified by their crescent-shaped nuclei hugging large clear vacuoles |
| Fibrous ("fibro") | Fibroblasts and myofibroblasts are typically fusiform or stellate cells with pale nuclei in a collagenous (pink) matrix |
| Smooth muscle ("leiomyo") | Smooth muscle cells are elongated cells that run in parallel bundles, intersecting at right angles. The nuclei may be cigar or corkscrew shaped and often have paranuclear vacuoles |
| Skeletal muscle ("rhabdomyo") | Skeletal muscle may show either rhabdoid cells, which are plump round cells with eccentric nuclei and pink cytoplasm, or strap cells, like individual elongated myocytes with cytoplasmic cross-striations |
| Nerve sheath (neurofibroma, schwannoma) | Nerve sheath tumors may show delicate spindle cells with wavy nuclei in a myxoid background with thin curly tendrils of collagen, as in a neurofibroma. They may also show the dense nuclear palisading and fibrillar background of a schwannoma |
| Vascular ("hemangio," "angio") | Vascular tumors are characterized by a network of irregular vascular spaces, often with admixed blood. Malignant endothelial cells tend to protrude into the lumens with a hobnail appearance |

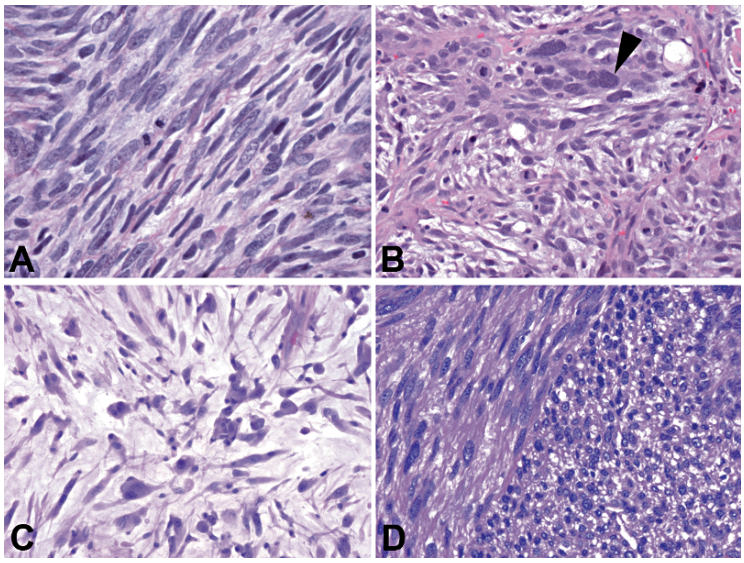


**Figure 28.1.** High grade sarcomas. **(A)** Fibrosarcoma, with densely packed hyperchromatic spindle cells. **(B)** Pleomorphic MFH, with very large and bizarre cells (arrowhead). **(C)** Myxoid MFH or myxofibrosarcoma, showing pleomorphic cells in a myxoid background. **(D)** Leiomyosarcoma, with perpendicular fascicles.

**Table 28.2.** Features of high-grade sarcoma patterns.

| | |
|---|---|
| Fibrosarcomatous appearance | A hypercellular, fascicular tumor with a "herringbone" pattern. Atypia may not be significant. May be seen in fibrosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, and others |
| Malignant fibrous histiocytoma (MFH), pleomorphic | A cellular tumor with bizarre nuclear atypia, including giant cells and highly pleomorphic and hyperchromatic nuclei. Very mitotically active, often with necrosis. Now generally called *pleomorphic undifferentiated sarcoma* |
| MFH, myxoid | A tumor with a myxoid or edematous background containing highly pleomorphic cells, frequent mitoses, and characteristic arcing vessels. The entity of myxoid MFH is synonymous with myxofibrosarcoma, but other sarcoma types (lipo-, leiomyo-, etc.) may take on this pattern |
| Leiomyosarcoma | A fascicular tumor with bundles of cells intersecting at right angles, a high mitotic rate, and significant cytologic atypia, although not as pleomorphic as the MFH. Non–smooth-muscle tumors may occasionally show this pattern |
| Rhabdomyosarcoma | A tumor with large eosinophilic cells with eccentric nuclei, showing significant nuclear pleomorphism (with the exception of the alveolar type). May occur as a component of other high-grade sarcomas |

A reliable clue to a high-grade sarcoma is the presence of malignant nuclei. A sarcoma nucleus has some reproducible features across many tumor types. The nucleus has an irregularly shaped border and has dark, dense, granular chromatin that is fairly evenly distributed throughout the nucleus (Figure 28.2). Unlike carcinoma nuclei, prominent nucleoli and nuclear membranes are *not* a usual feature. Learning to recognize this sort of atypia is critical in identifying some of the subtle sarcomas.

## Tumors of Fat

Throughout this chapter, you will find tables listing some of the more common entities, grouped by clinical behavior. Table 28.3 lists some of the common tumors of fat.

The most common soft tissue tumor is the *lipoma*. A lipoma is defined as a neoplasm of mature fat. It is histologically indistinguishable from ordinary fat; to tell the difference you must know it appeared clinically as a discrete lobular mass. There are many histologic variants of lipoma, classified based on what additional soft tissue component is present, such as the angiolipoma, fibrolipoma, angiomyolipoma, and so forth. The hibernoma is a lipoma of brown fat, in which the fat cells are full of innumerable tiny vacuoles. The lipoblastoma, despite the alarming name, is a benign pediatric tumor of mature fat and benign lipoblasts.

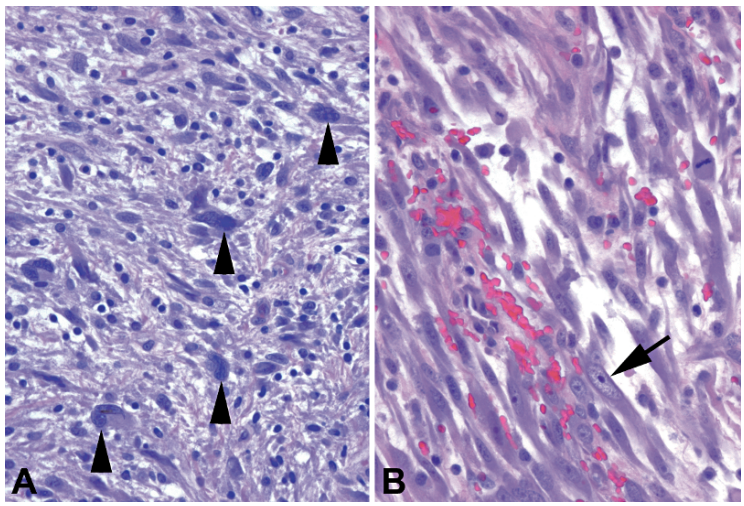


**Figure 28.2.** The sarcoma cell vs. the reactive cell. **(A)** Malignant cells in a MFH or other high-grade sarcoma show large nuclei with irregular shapes and very dark chromatin with a coarse texture (arrowheads). It is as though (in fact, it is likely) the nucleus has way too many chromosomes, and the nucleus is swollen and dark with the extra chromatin (truly hyperchromatic). Nucleoli are not usually prominent. **(B)** Reactive fibroblasts in nodular fasciitis have large nuclei and prominent nucleoli that stand out against a pale nucleus (arrow). The nuclear membrane is smooth and oval.

**Table 28.3.** Common neoplasms of fat.

| Benign | Malignant but indolent | Malignant and aggressive |
|---|---|---|
| Lipoma, including | Atypical lipoma or | Dedifferentiated liposarcoma |
| Angiolipoma | Well-differentiated liposarcoma | |
| Angiomyolipoma | Myxoid liposarcoma | Round cell liposarcoma |
| Hibernoma | | |
| Lipoblastoma (children) | | Pleomorphic liposarcoma (no relation to pleomorphic lipoma) |
| Myelolipoma | | |
| Spindle cell lipoma | | |
| Pleomorphic lipoma | | |

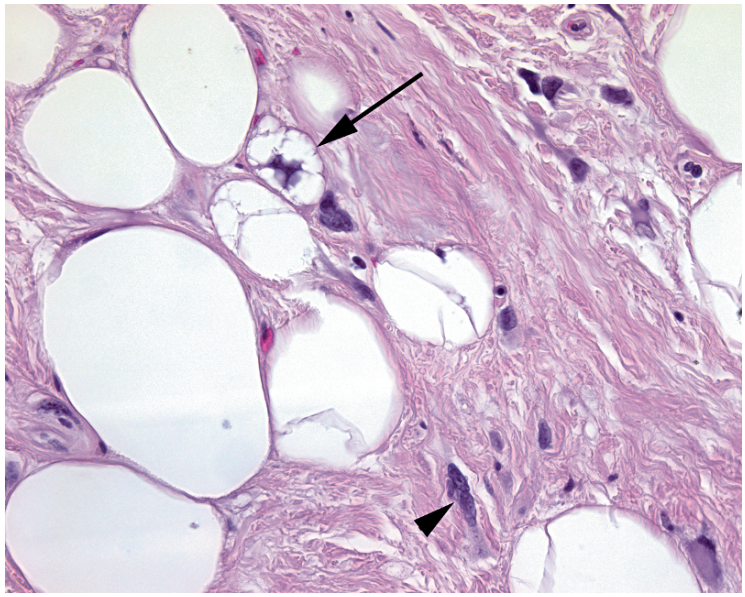

**FIGURE 28.3.** Lipoblast. Small fat vacuoles indent the nucleus of this lipoblast (arrow), seen in a well-differentiated liposarcoma. Other cells within the fibrous septa (arrowhead) have the look of sarcoma cells, with irregular, large, dark nuclei.

There is a lot of fuss about *lipoblasts*. They are immature fat cells in which the nucleus is star shaped, due to being indented on multiple sides by small bubbles of fat (Figure 28.3). They are often associated with liposarcomas, but they can also appear in the benign lipoblastoma, and they are not necessary for a diagnosis of liposarcoma (more on this later). Note that normal adipocytes are not mitotically active cells, so prominent mitoses are generally seen only in high-grade liposarcomas.

Two types of lipoma are notable for their unusual cytologic features. They are both usually found on the back or neck of elderly men and are noticeably fibrous and nonfatty on low power. These are the *pleomorphic lipoma* and *spindle cell lipoma*. The spindle cell lipoma has areas of nondescript spindle cells and collagen and may remind you of a nerve sheath tumor if there is not much fat in the lesion. The pleomorphic lipoma is similar, with the addition of large giant cells and floret cells (wreath-shaped nuclei). These giant cells (Figure 28.4) are an example of a benign lesion simulating malignant atypia; clinical information is helpful in not mistaking these for liposarcomas.

The *well-differentiated liposarcoma* (WDLS) is a tumor of adults. It looks similar to a lipoma on low power except for an increase in fibrous "interstitium" between fat cells and/or fibrous bands (Figure 28.5). A close examination of the fibrous areas reveals hyperchromatic, irregularly shaped nuclei; these are usually large and dark enough to be visible at 4×. Finding a lipoblast is a bonus. A softer feature is an assortment of differently sized fat cells, unlike the monomorphic benign lipoma. The WDLS is so named when it occurs in a nonresectable location, such as the retroperitoneum. By definition, when it occurs on an extremity, it is called an *atypical lipoma*, as the prognosis in these sites is excellent.

When the WDLS has been around for a while, especially in a recurrent or occult retroperitoneal lesion, there is a risk of the tumor transforming into a high-grade pleomorphic sarcoma. When this happens, you will see a tumor with well-differentiated lipomatous areas and an abrupt transition to a high-grade tumor (storiform/spindled, MFH-like, or even rhabdo- or leiomyosarcomatous). Regardless of morphology, this is called a *dedifferentiated liposarcoma*, and the key to diagnosis is recognizing the adjacent WDLS. Because dedifferentiated liposarcoma is the most likely diagnosis in a retroperitoneal pleomorphic sarcoma, if you are grossing such a tumor, be sure to sample anything near the tumor that looks like fat: it may be the well-differentiated component.

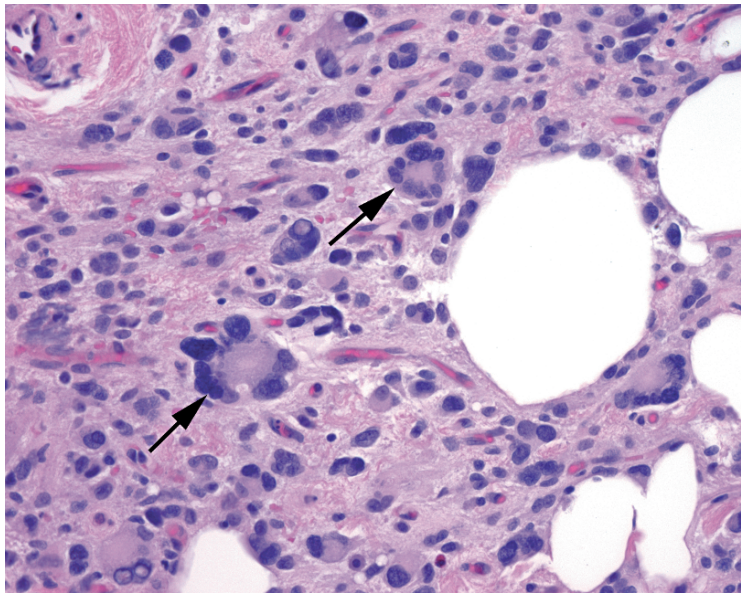

**Figure 28.4.** Pleomorphic lipoma. This type of benign lipoma is known for having very bizarre stromal cells that mimic sarcoma. The classic cell is the floret cell, with a circular wreath of nuclear lobes (arrows). Their presence suggests the diagnosis of pleomorphic lipoma.

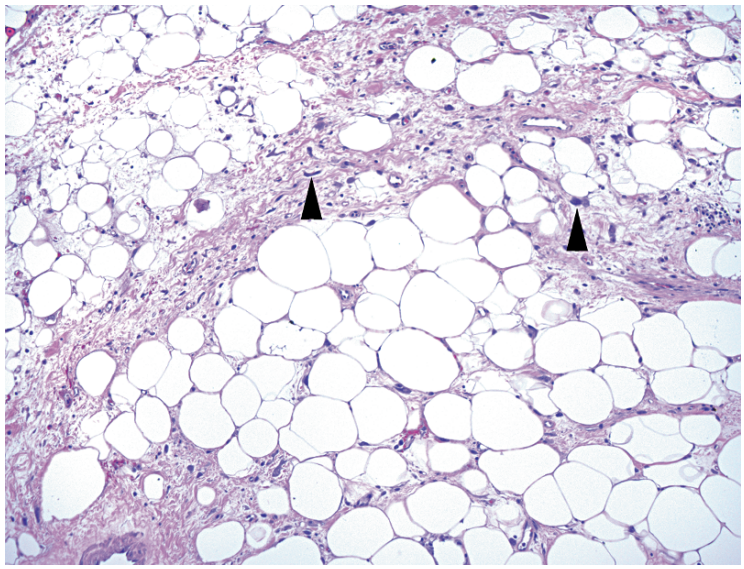

**Figure 28.5.** Well-differentiated liposarcoma. There is an increased amount of fibrous interstitium between fat cells, and atypical cells stand out at low power (arrowheads).

*Myxoid liposarcoma* is a different type of low-grade liposarcoma. It is not as clearly fatty as the WDLS, and the low-power impression is that of a gelatinous tumor with scattered fat cells and a stereotypical capillary network that has been compared to chicken-wire (Figure 28.6). These vessels are very delicate, and, unlike normal capillaries, they have little substance to their walls; they appear as a naked sleeve of endothelium stretched through the tumor. The tumor cells themselves are small spindled or rounded cells and lipoblasts, without the large atypical cells of the WDLS.

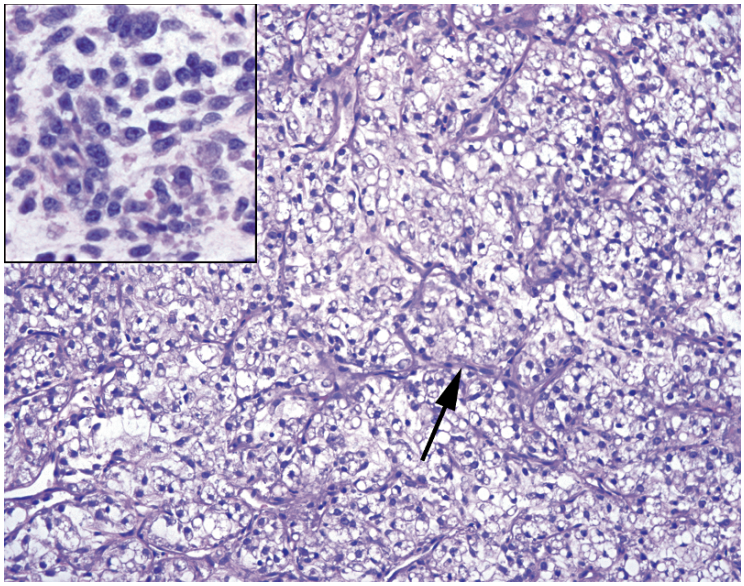

**Figure 28.6.** Myxoid liposarcoma. The fatty component may be very subtle in myxoid liposarcoma; the vessels are more often the tip off. The vasculature is composed of a delicate network of very thin capillaries with three- and four-way branch points, similar to chicken-wire (arrow). The cell population is composed of small cells, which may have fat vacuoles in them, and a myxoid background. Large atypical cells should not be present. **Inset**: Areas of closely packed small cells are indicative of round cell differentiation.

The myxoid liposarcoma can also transform into a higher grade lesion. When the small uniform cells become very densely packed and obscure the vascular pattern, it is indicative of round cell differentiation. The presence of more than 5% round cell differentiation is worth noting; a tumor with more than 75% is called a *round cell liposarcoma*.

The rare pleomorphic liposarcoma describes a high-grade tumor with extremely bizarre pleomorphic lipoblasts. It differs from the dedifferentiated liposarcoma in that it is still recognizable as a lipomatous tumor. It does not arise from, or have any relation to, the pleomorphic lipoma.

## Fibrous Tumors and Myxoid Tumors

The fibroblast and the myofibroblast are ubiquitous cells, in charge of the reparative changes that take place in every part of the body. In resting state, they are fusiform to stellate cells with oblong pale nuclei, and they lay down a collagen matrix. Their job is to proliferate, and therefore mitotic activity is not unusual in reactive lesions. Although myofibroblasts may stain for actin (and are occasionally mistaken for smooth muscle), in general immunostains are not helpful in this tumor family.

Before we discuss the true neoplasms, we will review the collection of reactive (inflammatory or posttraumatic) lesions that present as tumors (lumps). *Keloid* is a common fibrous lesion, occurring at a site of trauma. It is similar to the normal fibroblastic proliferation of a dermal scar, except for its large size and characteristic thick cords of collagen called *keloidal* collagen. It is clinically recognizable and not usually a diagnostic dilemma.

*Nodular fasciitis*, on the other hand, may simulate a neoplasm clinically and is therefore more challenging for the pathologist. It is classically a rapidly growing lesion, sometimes associated with known trauma, sometimes not. On low power, it is a fairly circumscribed lesion with a hypercellular periphery, and it has a heterogeneous, as opposed to monomorphic, look. A microcystic appearance is classic. On high power the fibroblasts show a "tissue culture" appearance (fusiform to stellate with distinct cytoplasmic processes), and they float in a myxoid

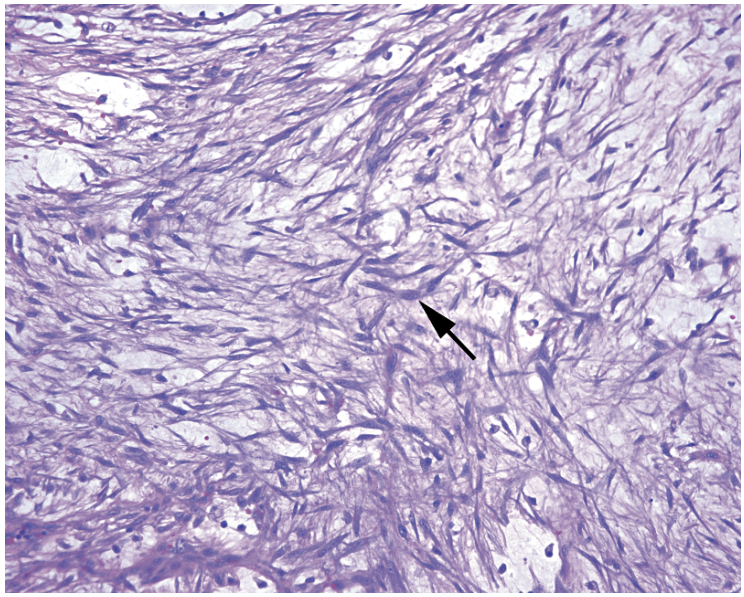

**Figure 28.7.** Nodular fasciitis. In this field the inflammatory component is not prominent, but the "tissue culture" pattern is seen clearly, with fusiform and stellate fibroblasts stretching delicate processes through the myxoid background (arrow).

background with surrounding red blood cells and lymphocytes (Figure 28.7). Older lesions may become more dense, collagenized, and pink and may resemble a fibromatosis (see later) with chronic inflammation. There should be no nuclear atypia, but you will see mitotic activity.

The biggest pitfall in nodular fasciitis is misinterpreting the patchy high cellularity and mitotic activity for a sarcoma. The clinical history is helpful, as is recognizing the reactive versus malignant nuclear features (something that takes practice).

*Proliferative fasciitis* is similar to nodular fasciitis except with the addition of large pink ganglion-like cells. *Proliferative myositis* is essentially the same lesion but in an intramuscular location. *Myositis ossificans* is a variant of proliferative myositis that shows reactive bone formation.

*Inflammatory myofibroblastic tumor* has gone by many names (inflammatory pseudotumor, inflammatory fibrosarcoma, plasma cell granuloma, others), but in this chapter it will be shortened to IMT. While long considered a reactive lesion, occasional cases have spread aggressively and even metastasized. Therefore, it is beginning to be regarded as a neoplasm, and will be included below, despite its histologic similarity to nodular fasciitis.

## Neoplasms

The prototypical benign fibroblastic lesion is the *fibromatosis* (Table 28.4). This is a bland and indistinct tumor composed of normal-looking fibroblasts: fascicles of pink cells with pale tapering nuclei in a collagenous background (Figure 28.8). The very pale nuclei make the capillaries stand out and appear dark in comparison. It is very infiltrative around the edges, much like a normal scar. Superficial fibromatoses can occur on the palm (palmar fibromatosis, Dupuytren's contracture), sole (plantar, Ledderhose disease), or penis (Peyronie's disease), where they are benign but can recur. Axial or deep fibromatoses, such as on the chest wall or mesentery, are typically more aggressive in their expansion and are called *desmoid tumors*. The desmoid tumors are characterized by a specific immunohistochemical trait, the accumulation of β-catenin in nuclei.

*Low-grade fibromyxoid sarcoma* is one of those most troublesome entities; it simulates a benign lesion (fibromatosis) yet has metastatic potential. It may appear hypocellular, myxoid, or vaguely storiform, much like a fibromatosis.

**Table 28.4.** Fibrous and myxoid neoplasms.

| Benign | Malignant but indolent | Malignant and aggressive |
|---|---|---|
| Fibromatosis | Low-grade fibromyxoid sarcoma | Fibrosarcoma |
| Palmar/plantar (superficial) | ("Evans tumor") | |
| Desmoid tumor (deep) | Low-grade fibrosarcoma | |
| Dermatofibroma/benign fibrous | Dermatofibrosarcoma | |
| histiocytoma | Atypical fibroxanthoma | |
| Solitary fibrous tumor | Malignant solitary fibrous tumor | |
| Intramuscular myxoma | Low-grade myxofibrosarcoma | Myxofibrosarcoma |
| | | (a.k.a. myxoid MFH) |
| Inflammatory myofibroblastic tumor | | |

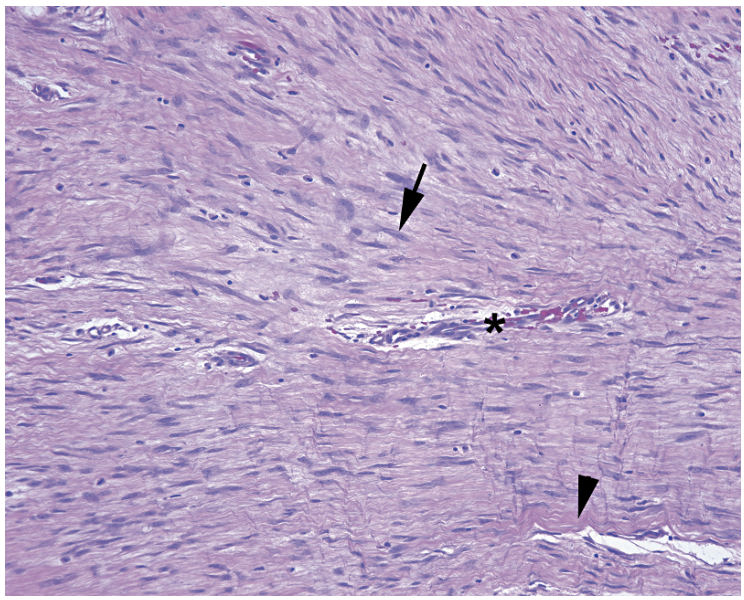

**Figure 28.8.** Fibromatosis. The cells in this lesion are pale and indistinct, with the small wavy nuclei (arrow) noticeably hypochromatic relative to the endothelial cells of the nearby capillary (a good internal control; asterisk). There is abundant collagen in the stroma (arrowhead).

*Fibrosarcoma* is the high-grade endpoint of this spectrum of lesions. It is the classic pure "herringbone" lesion, with fascicles alternating in a zigzag pattern. There is no significant collagen or inflammation to speak of. It has a high mitotic rate, but the cells are not particularly atypical: the nuclei tend to be monomorphic, oval, and euchromatic (Figure 28.9). It is mainly the cellular density and mitotic activity that set this lesion apart as malignant.

However, *what looks like fibrosarcoma is not usually fibrosarcoma*. True fibrosarcoma is quite rare, while its imitators, especially malignant peripheral nerve sheath tumor and synovial sarcoma, are more common. Therefore, fibrosarcoma is a diagnosis of exclusion.

The *solitary fibrous tumor* is included here because of its resemblance to fibroblastic tumors, but in truth the type of differentiation is not known. The solitary fibrous tumor has a unique staining pattern (CD34, CD99, and bcl-2) and typically arises from serosal surfaces. Because of its association with the pleura, it was once called the "benign mesothelioma." On low power, the tumor is described as having a patternless pattern, which evidently means nonstoriform-nonherringbone-nonfascicular. The swirling mass of uniform cells is reminiscent of ovarian stroma, but appears more pink due to abundant collagen (Figure 28.10). Collagen is laid down in parallel bundles, and the cellularity varies from one field to the next. The vessels are of the "staghorn" type, meaning they are gaping,

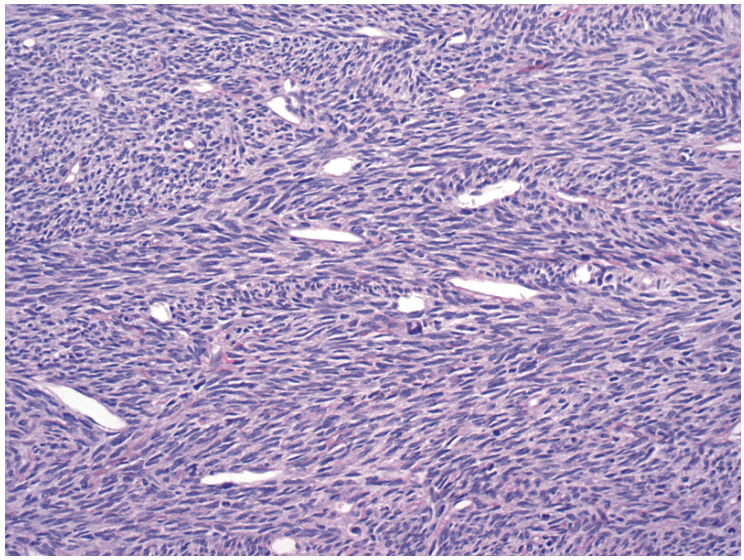

**Figure 28.9.** Fibrosarcoma. This field shows the typical herringbone pattern of fibrosarcoma, with zigzagging bands of spindle cells. Many other tumors can have this pattern.

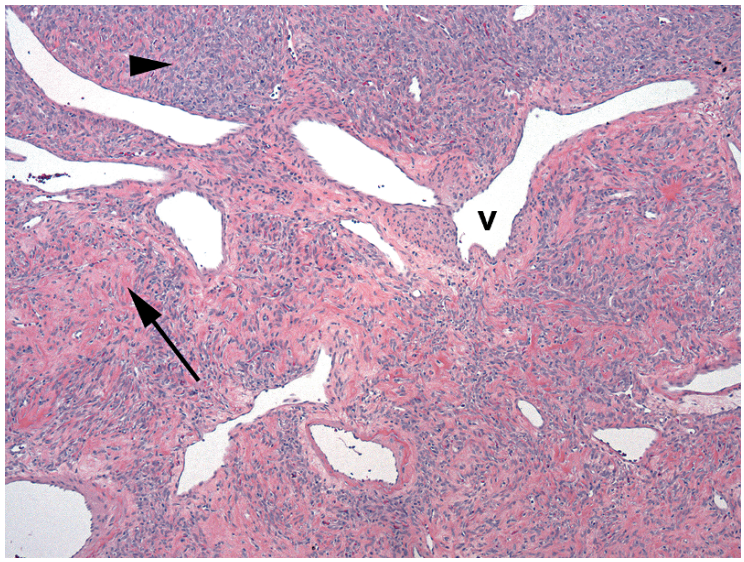


**Figure 28.10.** Solitary fibrous tumor. The most noticeable features at low power are the staghorn vessels (v), which this tumor shares with the related hemangiopericytoma. The tumor is composed of areas of small nondescript spindle cells (arrowhead) and collagenous stroma (arrow). The pattern of the spindle cells is described as "patternless," meaning somewhat chaotic.

branching vessels without an appreciable wall thickness: the tumor appears to extend right up to the endothelium. A mitotic rate of more than 4 per 10 high-power fields (hpf) suggests a malignant solitary fibrous tumor.

### *Fibrous Tumors of the Skin*

The benign fibrous/fibrohistiocytic tumor of the dermis is the *dermatofibroma* or *benign fibrous histiocytoma*. It appears clinically as a little nodule, and at low power you see a diffuse, hazy, indistinct "blueness" occupying and expanding the dermis. On higher power, the dermatofibroma shows a textbook storiform pattern, with spindly cells arranged in little radial

sunbursts, like spokes on a wheel (see Figure 27.23 in Chapter 27). There is also usually accompanying inflammation, including lymphocytes, plasma cells, and foamy macrophages.

The malignant, albeit indolent, counterpart is the dermatofibrosarcoma protuberans (DFSP). This lesion is also distinctly storiform, and the tumor cells, as in the dermatofibroma, are monomorphic, fusiform, and just slightly hyperchromatic. However, the DFSP penetrates more deeply and classically infiltrates the subcutaneous fat, wrapping around fat cells in a distinctive pattern (see Chapter 27). In contrast to the dermatofibroma, the DFSP is ironically more uniform in cytology and lacks the associated inflammatory cells.

The skin also has its own MFH variant, called an *atypical fibroxanthoma*. Despite being histologically equivalent to a pleomorphic MFH, this superficial tumor is easily resected and therefore has a good prognosis.

### *Myxoid Tumors*

The myxoid lesions included here are those that are not myxoid variants of other tumor types (such as myxoid liposarcoma). Many different lesions may converge on the myxoid phenotype, however. What we call *myxoid* is really the accumulation of hyaluronic acid, a gel-like substance that is essentially a form of solid water in the body (as seen in tissue edema). It may appear clear to a very pale blue on routine stains. A myxoid differential diagnosis would include myxoma, angiomyxoma, neurofibroma, and nodular fasciitis (all benign) and myxoid MFH (myxofibrosarcoma), myxoid liposarcoma, myxoid chondrosarcoma, myxoid leiomyosarcoma, and the low-grade fibromyxo- and myxofibro- entities (all malignant). You would also need to exclude tumors that may appear myxoid but are not, including chordoma, cartilaginous tumors, and epithelial mucinous tumors.

The *intramuscular myxoma* is a benign and nearly acellular lesion that presents as a gelatinous mass within a muscle, usually in women. There are rare small stellate cells without atypia. What separates the benign myxoma from other more worrisome lesions is its virtual lack of capillaries.

*Myxofibrosarcoma* is a high-grade tumor also known as *myxoid* MFH, and its low-grade counterpart is the low-grade myxofibrosarcoma (not to be confused with the fibromatosis-like low-grade *fibromyxoid* sarcoma!). The myxofibrosarcomas are tumors that are prominently myxoid but that have an increasing cellularity, nuclear pleomorphism, and mitotic rate compared to myxoma. Because of prominent vessels and bubbly cells (pseudolipoblasts), they may be mistaken for myxoid liposarcoma. However, the vessels are different. Myxofibrosarcoma vessels are "curvilinear," which means they make short thick arcs in the tumor, and the tumor cells appear to drip off of them like wax from a candle (Figure 28.11). Compare these to the delicate branching capillaries of the myxoid liposarcoma (see Figure 28.6). The nuclei of myxofibrosarcoma also set them apart; they are hyperchromatic and pleomorphic, unlike the uniform nuclei of the myxoid liposarcoma.

*Inflammatory myofibroblastic tumor* (IMT) is a neoplasm of mainly young people, often arising in the abdominal cavity. It is a proliferation of plump fibroblasts with abundant associated inflammation, especially plasma cells. It is very similar in appearance to a nodular fasciitis in that there are tissue culture–like fibroblasts in a myxoid, granulation tissue–like background (Figure 28.12). It differs by its visceral location and prominence of plasma cells (not seen in nodular fasciitis). The hypercellularity may be very worrisome for a high-grade sarcoma. However, while the nuclei may be enlarged, with prominent nuclear membranes or large nucleoli, you should not see the irregularly shaped hyperchromatic nuclei of MFH. Many cases show immunoreactivity for ALK.

## Smooth Muscle

There are no reactive smooth muscle lesions, so we will go straight to neoplasms (Table 28.5). Smooth muscle neoplasms may be positively identified by immunoreactivity to actin and desmin but may sometimes show spurious cytokeratin or EMA staining.

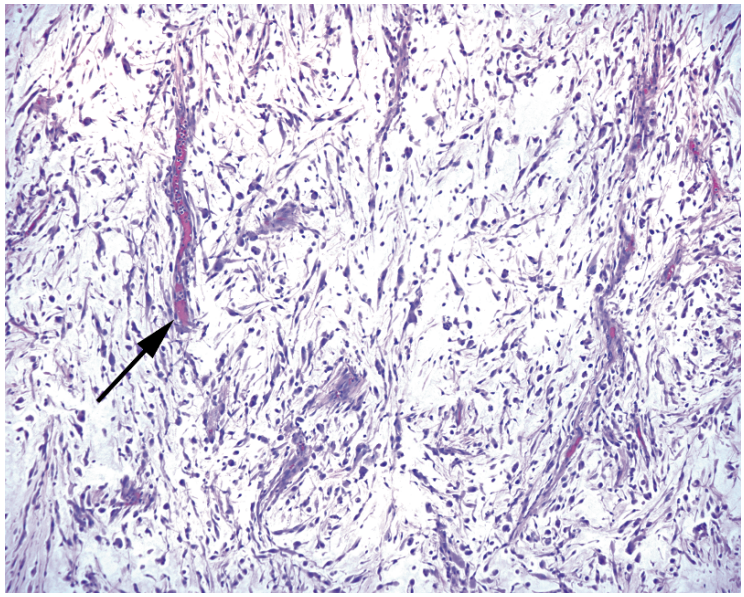

**Figure 28.11.** Myxofibrosarcoma. Although the cells here resemble those of pleomorphic malignant fibrous histiocytoma, the stroma is myxoid, and the vessels are unique (arrow). They appear as short arcs or segments, unlike the complex branching vessels of myxoid liposarcoma, and the tumor cells are intimately associated with the vessels, like wax dripping down the side of a candle.

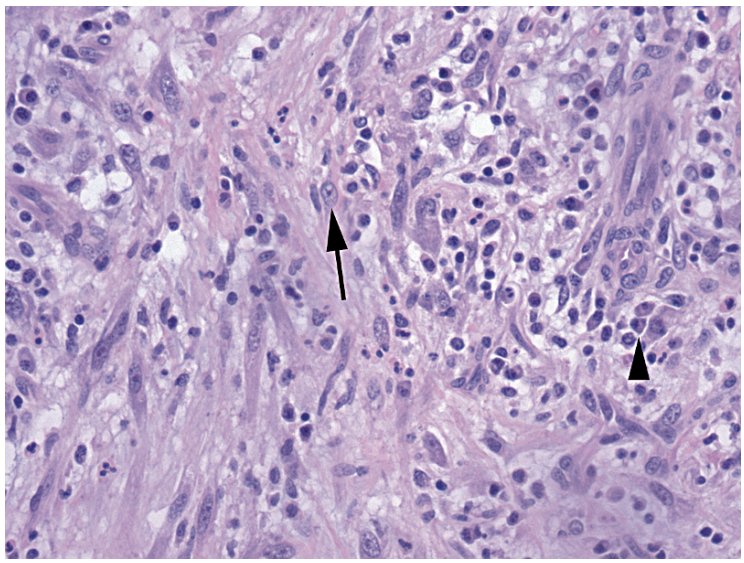

**Figure 28.12.** Inflammatory myofibroblastic tumor. The tumor is composed of a network of reactive-looking fibroblasts (arrow), capillaries, and inflammation, especially plasma cells (arrowhead).

**Table 28.5.** Smooth muscle neoplasms.

| Benign | Malignant but indolent | Malignant and aggressive |
|---|---|---|
| Leiomyoma | Cutaneous leiomyosarcoma | Leiomyosarcoma, retroperitoneal or soft tissue |

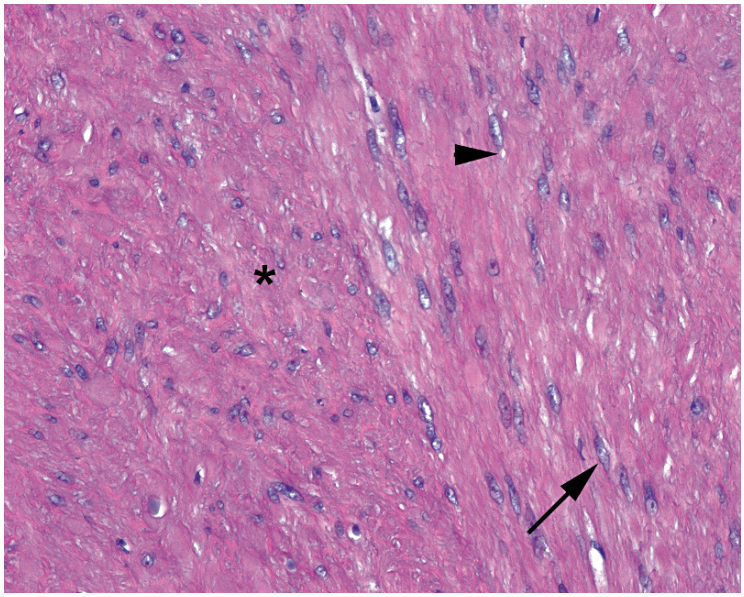

**Figure 28.13.** Leiomyoma of colon. As in the leiomyoma of the uterus, there are smooth muscle cells in bundles running parallel to and perpendicular to (asterisk) the slide. The features of benign smooth muscle include elongated pale nuclei with paranuclear vacuoles (arrowhead) and occasional corkscrew nuclei in which the nuclei appear twisted (arrow). Wavy pink muscle fibers are usually visible between the nuclei.

The *leiomyoma* should be familiar, as it is identical to the uterine tumor. It can occur as a primary neoplasm in cutaneous, gastrointestinal, and other sites. However, unlike in the uterus, in these body sites there is a very low threshold for bumping the lesion up to leiomyosarcoma. In general, greater than 1 mitosis per 10 hpf is worrisome.

The leiomyoma is characterized by long parallel bundles of smooth muscle cells that intersect at right angles, such that some are seen longitudinally and some cut in cross section. The nuclei are often described as cigar or box-car shaped, with blunt ends. You may also see corkscrew nuclei, which appear twisted about themselves and are associated with the contracted state. Paranuclear vacuoles are common (Figure 28.13).

*Leiomyosarcomas* range in appearance from something very similar to leiomyoma to a densely cellular and hyperchromatic tumor with scattered highly atypical nuclei (Figure 28.14). They can occur in the skin, where they are relatively indolent, or in the retroperitoneum, soft tissues, or any organ with smooth muscle, where they are more aggressive.

In a smooth muscle–like lesion arising anywhere near the gastrointestinal tract, you should consider the *gastrointestinal stromal tumor* (GIST) in the differential diagnosis. Many of what were once called *gastric leiomyomas* are now identified as GISTS. The cells differentiate along the line of the interstitial cell of Cajal, the pacemaker cell of the stomach, and like this cell, the GIST stains for c-kit and CD34. The GIST may take a spindle cell morphology, overlapping with leiomyoma or schwannoma, or may be epithelioid with a wide range of morphology. Clinical behaviors range from benign to malignant, depending on site and histologic factors.

## Skeletal Muscle

Tumors of skeletal muscle are uncommon, and, as a terminal cell type with no stem cells or regenerative activity (like neurons), they are mainly seen in children or young adults (Table 28.6). They all get the rhabdo- prefix and should all stain with actin and desmin, plus special skeletal muscle markers myogenin and MyoD1. Other unrelated tumors in other sites sometimes are described as "rhabdoid;" remember that the –oid suffix means "looks like, but is not." Therefore, the rhabdoid meningioma or rhabdoid tumor is not of muscle origin but simply displays similar cell shape and appearance.

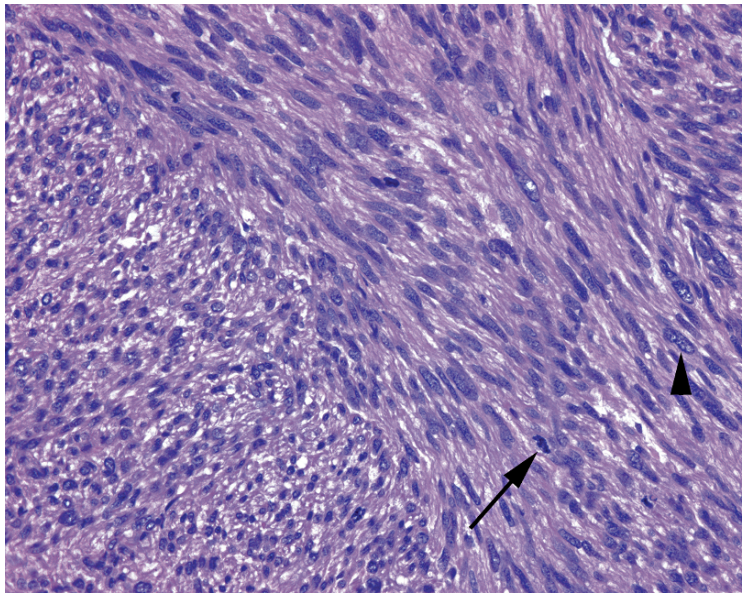

**Figure 28.14.** Leiomyosarcoma. A malignant version of the leiomyoma, this tumor has the architectural pattern and nuclear morphology of its benign cousin but with much higher cellularity, hyperchromatic nuclei, frequent mitoses (arrow), and large atypical cells (arrowhead).

The rhabdomyoma is a rare neoplasm of primitive skeletal muscle cells. The *fetal rhabdomyoma* generally occurs in children, typically in the head and neck, and resembles the embryonal rhabdomyosarcoma but without the atypia and mitoses. In adult men, the *adult rhabdomyoma* usually arises in the head and neck. In this variant, the cells are rhabdoid in shape, with small peripheral nuclei, and pink clumps of myofilaments in the cytoplasm, not unlike mature muscle cut in cross-section. The third variant, *genital*, occurs in adult women. This variant is predominantly composed of strap cells (elongated pink cells with cytoplasmic cross-striations), again without atypia or mitoses.

*Rhabdomyosarcoma* is the most common sarcoma of children and is rare in adults. Remember that any high-grade sarcoma can acquire some rhabdo- differentiation, however. Pure rhabdomyosarcomas can be grouped into three subtypes: embryonal, alveolar, and pleomorphic. The pleomorphic type is found in adults.

*Embryonal rhabdomyosarcoma* comprises about 80% of cases and has a significantly better outcome than the alveolar type. It is composed of sheets of rhabdomyoblasts (plump and eosinophilic with large eccentric nuclei), nonspecific spindled cells, or strap cells (Figure 28.15). The botryoid subtype of embryonal rhabdomyosarcoma refers to tumors occurring in a mucosal site, such as the genital tract.

*Alveolar rhabdomyosarcoma* is a very aggressive variant and equals "unfavorable histology." In this type, fibrous septa divide the tumor into packets, much like renal cell carcinoma, but the discohesive cells tend to fall apart in the middle of the packets (Figure 28.16). The solid variant may be indistinguishable from the small round blue cell tumors. As it turns out, the cytogenetic findings are different in embryonal and alveolar types. As the prognosis is so different, many centers are beginning to routinely do molecular tests on these tumors.

**Table 28.6.** Skeletal muscle neoplasms.

| Benign | Malignant but (relatively) indolent | Malignant and aggressive |
|---|---|---|
| Rhabdomyoma<br>Fetal<br>Adult (head and neck)<br>Genital | Embryonal rhabdomyosarcoma<br>and Botryoid subtype | Alveolar rhabdomyosarcoma<br>Pleomorphic rhabdomyosarcoma |

## Peripheral Nerve/Neuroectodermal

Nerves, as the axonal processes of terminally differentiated neurons around the spinal cord, do not actually form tumors. However, the cells associated with the nerve sheath do commonly produce neoplasms, including schwannoma and neurofibroma. Other tumors of neuroectodermal origin are included here as well.

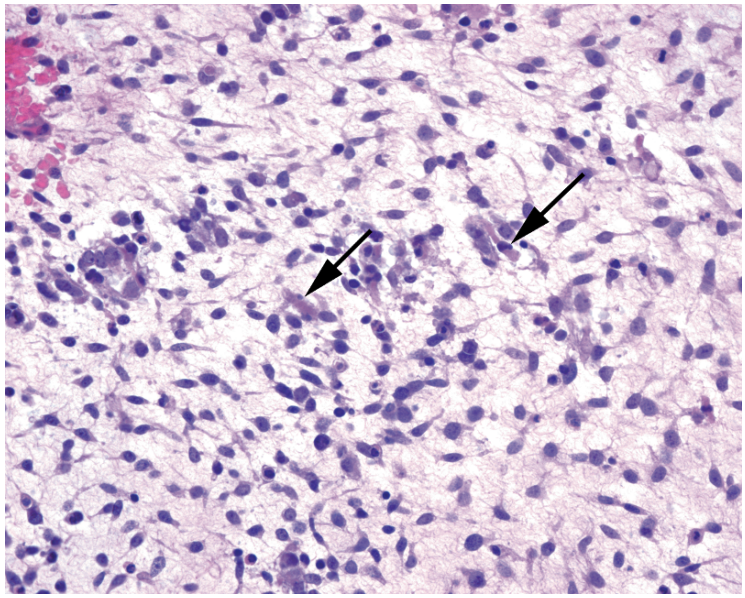

**Figure 28.15.** Embryonal rhabdomyosarcoma, botryoid type. The background is gelatinous, and the small spindle cells are nonspecific in appearance. Occasional strap cells are visible, with cytoplasmic muscle fibers (arrows).

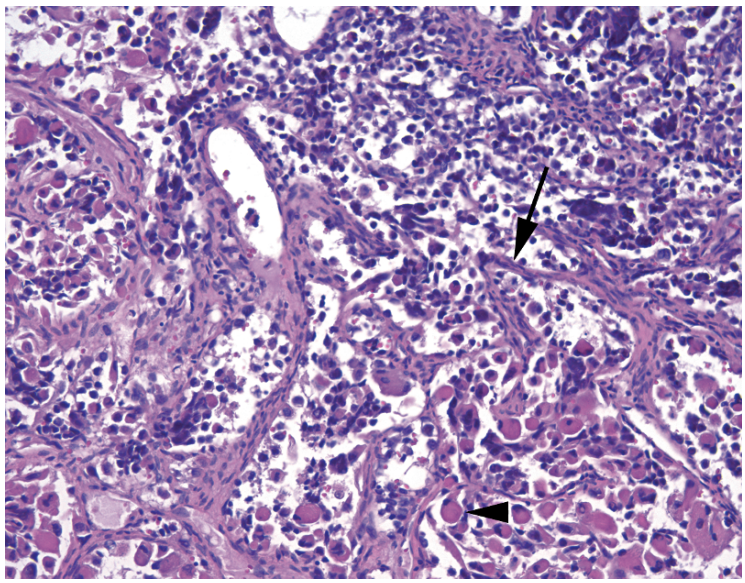

**Figure 28.16.** Alveolar rhabdomyosarcoma. The alveolar pattern is outlined by fibrovascular septa (arrow), and the tumor cells tend to fall out of the centers of their nests. This example shows prominent rhabdomyoblast differentiation (arrowhead), with large cells full of dense pink cytoplasm and eccentric nuclei. Other specimens may show only small round blue cell phenotype.

The only lesion that could be called reactive, in this group, is the traumatic neuroma. This is a disorganized tangle of nerve endings, including Schwann cells, perineurium, and axons, that may be found at the location of prior surgery or trauma. On the slide, it looks like a large, frayed nerve.

The benign peripheral nerve sheath tumors include the schwannoma and the neurofibroma (Table 28.7). Both of these lesions are S100 positive. Both can undergo malignant transformation into the malignant peripheral nerve sheath tumor, although this is much less common in the schwannoma. However, the nerve sheath lesions, just like the pleomorphic lipoma, may occasionally acquire bizarre cytology that does not indicate malignancy. This degenerative atypia is called *ancient change*.

The *schwannoma* is an encapsulated lesion that arises from a peripheral nerve and can therefore be found anywhere in the body. It usually shows alternating hypercellular (Antoni A) and myxoid (Antoni B) areas, as well as characteristic parallel arrays of palisading cells called *Verocay bodies* (Figure 28.17). The cells themselves have euchromatic, fusiform nuclei that stream in parallel within a pink fibrillary background. Thick-walled, hyalinized vessels are typical, which look as though they have a layer of amyloid replacing the vessel wall.

The *cellular variant* of schwannoma is still benign but can get quite hypercellular, and mitotically active (up to 10 mitoses per 10 hpf). The capsule and hyaline vessels should help to point you toward schwannoma. Foamy macrophages are common within this tumor.

The *neurofibroma*, in contrast, is an unencapsulated lesion that may appear as a nodule, a poorly circumscribed tumor, or a plexiform ("bag of worms") tangle. It is pale to pink at low power, with a myxoid background and thin curly tendrils of collagen between the cells (Figure 28.18). The nuclei are pale, thin, and slightly undulating, as in a normal nerve, and there should be no mitoses. Unlike in the schwannoma, special stains may reveal axons trapped within the lesion.

**Table 28.7.** Nerve-related neoplams.

| Benign | Malignant |
|---|---|
| Schwannoma, neurofibroma | Malignant peripheral nerve sheath tumor |
| Granular cell tumor | Malignant granular cell tumor (rare) |
| Paraganglioma | |

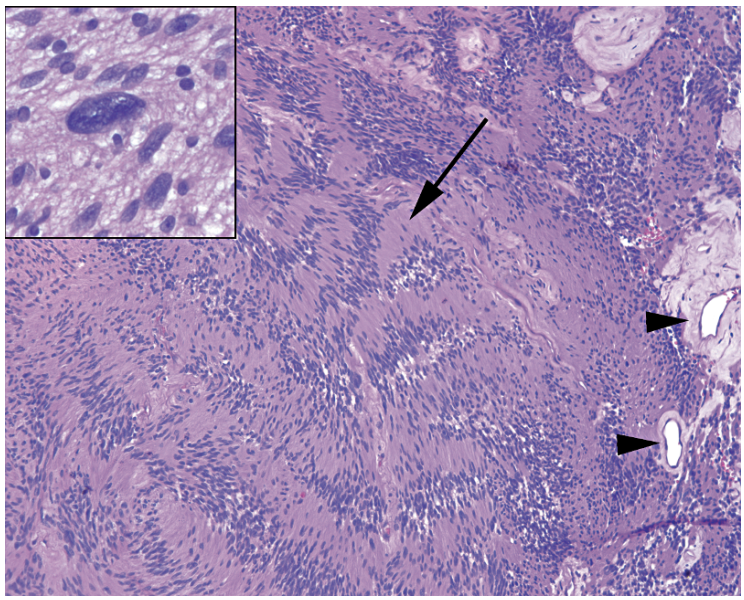

**Figure 28.17.** Schwannoma. In this spindle cell neoplasm, the long tapered nuclei tend to clump together and form arrays called Verocay bodies (arrow). Hyalinized vessels (arrowheads) are common. **Inset**: Occasional large atypical cells indicate ancient change, not malignancy.

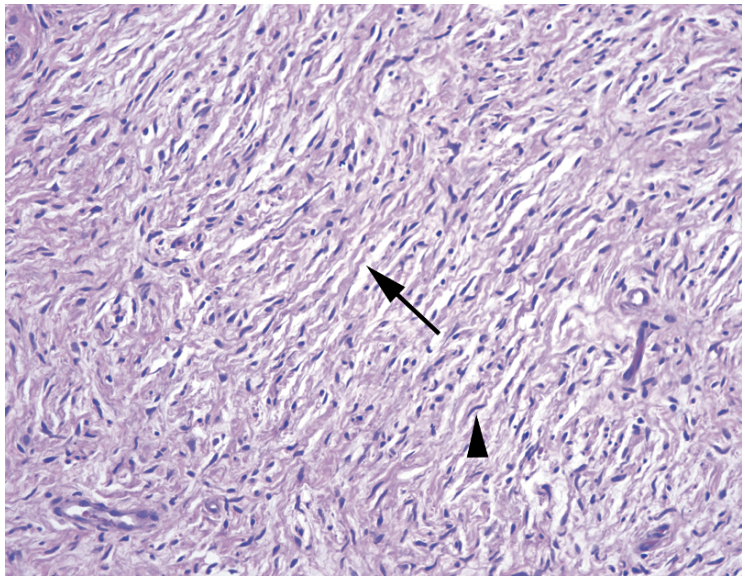

**Figure 28.18.** Neurofibroma. The nuclei tend to be thin and wavy (arrowhead), much like in a normal nerve. The tumor is usually paucicellular, with a myxoid background and delicate curly strands of wispy collagen (arrow).

The *malignant peripheral nerve sheath tumor* is usually a high-grade sarcoma and often takes the morphology of the fibrosarcoma (Figure 28.19). It may retain some nerve sheath features, such as the wavy nuclei, nuclear palisading, or hyalinized vessels, but tends to lose most of its S100 reactivity. Mitoses should be present, unlike in a neurofibroma.

The *granular cell tumor* is a benign tumor that shows neural differentiation but that resembles a collection of foamy macrophages. It is often associated with striking pseudoepitheliomatous hyperplasia in mucosal sites. These epithelial changes may be mistaken for squamous cell carcinoma if the subtle underlying diagnostic granular cells are overlooked.

The *paraganglioma* is actually a neuroendocrine tumor but is included here as it is sometimes presents as a soft tissue mass. It is a (usually) benign tumor with neuroendocrine-type nuclei, arranged in an alveolar pattern (Figure 28.20).

## Vascular Tumors

Reactive lesions of capillaries are very common, as an inherent part of the healing process is the formation of new vasculature. Granulation tissue, which fills in a defect in the body tissues, has very prominent capillaries with large endothelial cells (see Figure 3.2 in Chapter 3). The capillaries of granulation tissue are plump and round, with at least two cell layers (endothelium and pericytes), and may be crowded but do not appear interconnected. Neoplastic vessels, on the other hand, are often lacking the pericyte component and typically form anastomotic channels and slit-like spaces with sharp angular profiles. Extravasated blood cells are common in vascular neoplasms. The immunohistochemical markers for the vascular tumors are CD31 and CD34.

*Papillary endothelial hyperplasia* is a pattern of organizing thrombus that may occur within a vessel or hematoma. It may be seen incidentally in a surgical specimen or represent a symptomatic small mass by itself, in which case it is called a *Masson's tumor*. It is composed of tiny fibrin papillae covered by thin endothelium (Figure 28.21).

A *hemangioma* is a benign neoplasm of vascular elements, and there are many subtypes, including the common capillary hemangioma, the cavernous hemangioma, and the juvenile hemangioma (Table 28.8). The hemangiomas generally have round, nonbranching vessels,

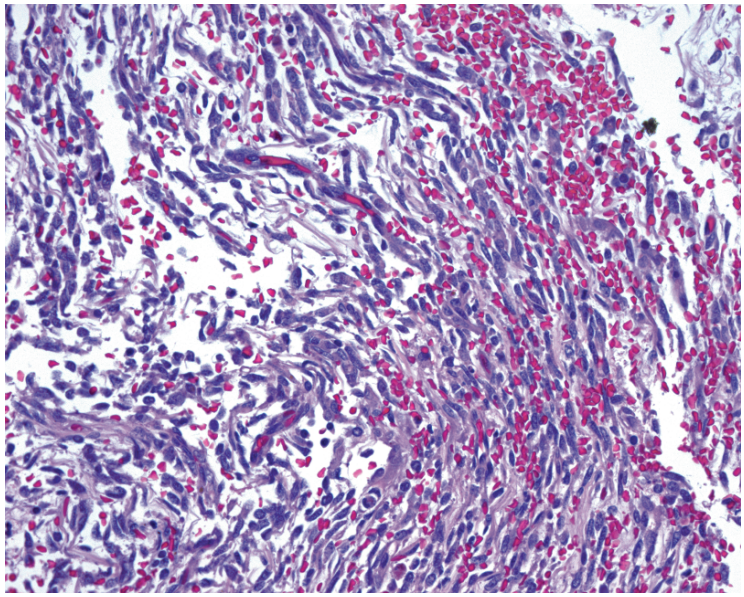

**Figure 28.19.** Malignant peripheral nerve sheath tumor. Although the malignant peripheral nerve sheath tumor sometimes resembles a fibrosarcoma, in this example it is more reminiscent of a neurofibroma, which was probably the origin in this case. There is a myxoid background and wavy collagen, but the cells are much more hyperchromatic and atypical than in a neurofibroma.

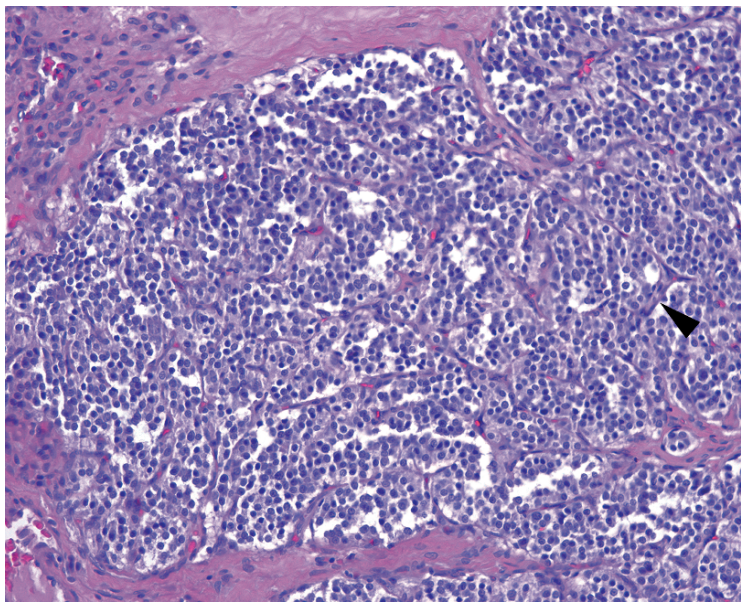

**Figure 28.20.** Paraganglioma. Fibrovascular septa (arrowhead) divide the neoplasm into small balls of cells (the "zellballen" pattern). The cells have small, perfectly round nuclei with neuroendocrine chromatin. Despite the paraganglioma's classification as an extraadrenal pheochromocytoma, it resembles the carcinoid tumor more closely than the pheochromocytoma.

although they may be very crowded or dilated, and the capillaries are surrounded by a pericyte layer. The *pyogenic granuloma*, once thought to be a reactive lesion, may in fact be a true neoplasm and is now called *lobular capillary hemangioma*. It is a circumscribed mass of capillaries with associated inflammation and ulceration. This lobular (circumscribed with rounded contours) appearance is characteristic of benign vascular lesions in general.

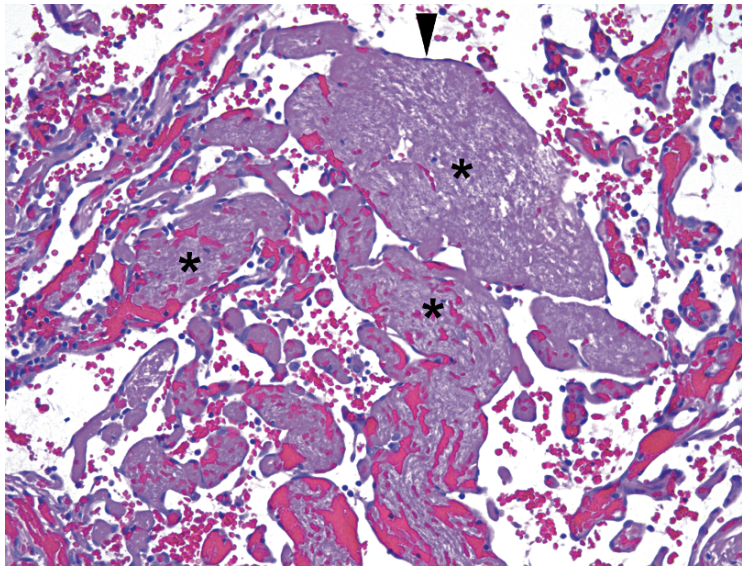

**Figure 28.21.** Papillary endothelial hyperplasia. Fingers of fibrin and red blood cells (asterisks), not true fibrovascular cores, are lined by bland endothelial cells (arrowhead).

**Table 28.8.** Vascular neoplams.

| Benign | Malignant but indolent | Malignant and aggressive |
|---|---|---|
| Hemangioma | Hemangioendothelioma | Angiosarcoma |
| | Kaposi's sarcoma | |
| Perivascular tumors | Malignant examples of perivascular tumors are rare | |
| Glomus tumor | | |
| Perivascular epithelioid cell tumor | | |

For every category of endothelial lesions there is an epithelioid variant, in which the endothelial cells acquire a lot of cytoplasm, becoming plump and epithelial-looking, often with cytoplasmic lumina that are their attempts at vessels. These variants are challenging because they may not look particularly vascular. Negative epithelial markers (cytokeratins, EMA) are helpful, but unfortunately some epithelioid vascular neoplasms may express some keratins.

The indolent malignant lesions of endothelium are called *hemangioendothelioma*. The epithelioid hemangioendothelioma is a sclerosing lesion with cords of vacuolated cells, some of which may contain red blood cells within the vacuoles, a diagnostic feature (Figure 28.22). It can be very difficult to distinguish from carcinoma without stains.

*Kaposi's sarcoma*, a virally induced (human herpesvirus type 8) low-grade sarcoma seen primarily in patients with HIV, has several stages and appearances, ranging from the most subtle of slit-like spaces in the dermis (see Chapter 27) to a dense spindle cell lesion. Because of the many variants, and a considerable array of "Kaposiform" mimickers, the differential diagnosis is beyond the scope of this chapter.

*Angiosarcoma* is the high-grade endothelial tumor, and it too has many variants. It can occur in organs, such as the liver or breast, especially after exposure to toxins or radiation. However, it can also arise in soft tissues de novo. Lymphedema is a recognized risk factor. Angiosarcoma classically shows branching, anastomotic irregular spaces with bulbous atypical cells lining the spaces (the hobnail pattern; Figure 28.23). Pericytes are typically absent, and at the periphery the tumor infiltrates into the surrounding tissue. This infiltrative border is very helpful in identifying malignant lesions.

Naturally, there is an epithelioid variant of angiosarcoma. The epithelioid angiosarcoma may look like a generic "very bad tumor" composed of sheets of plump cells with large nuclei

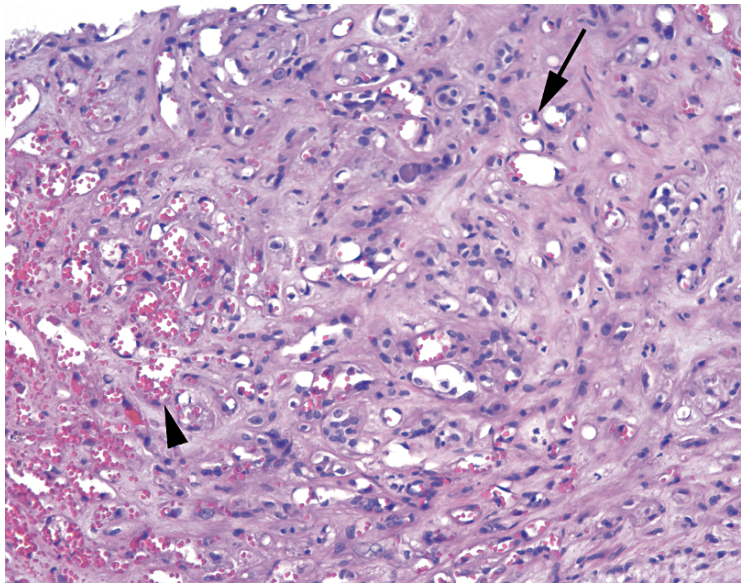

**Figure 28.22.** Epithelioid hemangioendothelioma. A rare but distinctive tumor, the epithelioid hemangioendothelioma is characterized by a dense fibrotic or sclerotic background, with small capillary spaces (arrowhead) and single cells with intracytoplasmic lumens complete with red blood cells (arrow).

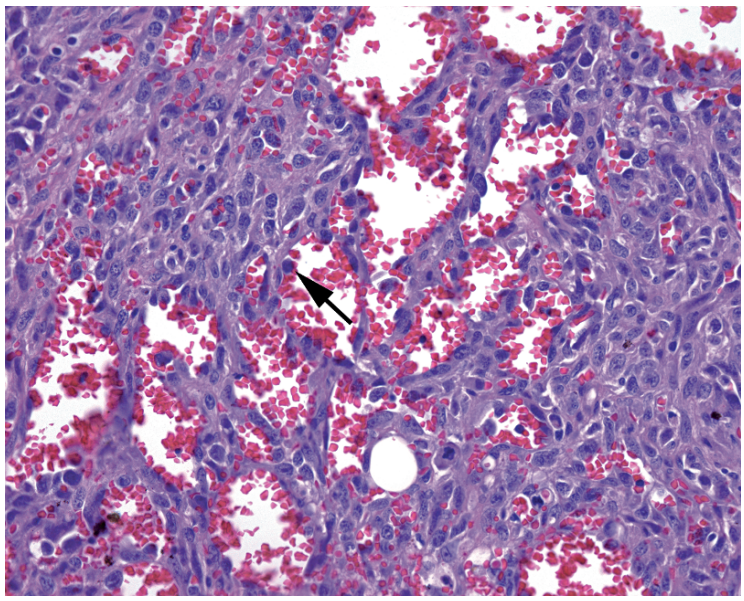

**Figure 28.23.** Angiosarcoma. In some areas the tumor cells have begun to grow as a solid sheet, but there are still vascular spaces visible, and full of blood. Large and hyperchromatic malignant cells protrude into the lumina (arrow) in a hobnail pattern. The tumor cells also show prominent nucleoli.

and prominent nucleoli, having almost no vascular differentiation. This sort of tumor may be identified only after a large battery of stains.

There are several tumors with *pericyte* differentiation, those cells that surround and support the endothelial cells. They are not exactly smooth muscle cells and have their own phenotype and immunostaining profile. The *glomus tumor* is one such lesion, and the hemangiopericytoma was once thought to be of pericyte origin. The perivascular epithelioid cell tumor family

of lesions are a unique group of neoplasms that share immunoreactivity for the melanoma markers HMB45 and Melan-A. This group includes the angiomyolipoma, covered in more detail in Chapter 13.

## Malignant Tumors of Unknown Differentiation

The following malignant tumors of unknown differentiation are all high grade by definition and mostly occur in younger people, adolescents to people in their thirties. Most are defined by translocations, with the exception of the epithelioid sarcoma (at least to date), which may explain why they do not particularly look or stain like other mesenchymal elements we are familiar with. An interesting general rule is that translocation tumors, despite being high grade, tend to have monomorphic populations of cells. The cells may be ugly, but they are uniformly so. This is in contrast to the pleomorphic MFH like cells of other high-grade sarcomas, which show complex karyotypes.

*Synovial sarcoma*, despite the name, is neither synovial in origin nor found in joint spaces. It does share characteristic cleft-like spaces with some benign synovial tumors and usually arises somewhere in the vicinity of a joint. The most recognizable form is the biphasic synovial sarcoma, in which packets of cytokeratin-positive, gland-forming, epithelial cells are scattered in a spindle cell background (Figure 28.24). Not much else looks like that. However, the synovial sarcoma more commonly presents in monophasic form, which is just the spindle cell component. It is a blue and hypercellular tumor, with a monomorphic population of nondescript spindle cells, and it should be in the differential diagnosis for fibrosarcomatous or storiform tumors.

*Epithelioid sarcoma* is notorious for being misdiagnosed, as it does not look much like a sarcoma. It presents as ulcerated nodules on the extremities of young men and at low power resembles a large granulomatous reaction with central geographic (continent-shaped) necrosis. On higher power the tumor cells range from monomorphic spindle cells to large epithelioid cells with pink cytoplasm. Epithelioid sarcoma is unusual in that it shows reactivity to both vimentin, a sarcoma marker, and cytokeratin, a carcinoma marker.

*Alveolar soft part sarcoma* is a translocation tumor involving the *TFE3* gene. It is divided into small packets of cells by a capillary network, similar to a renal cell carcinoma, and in fact

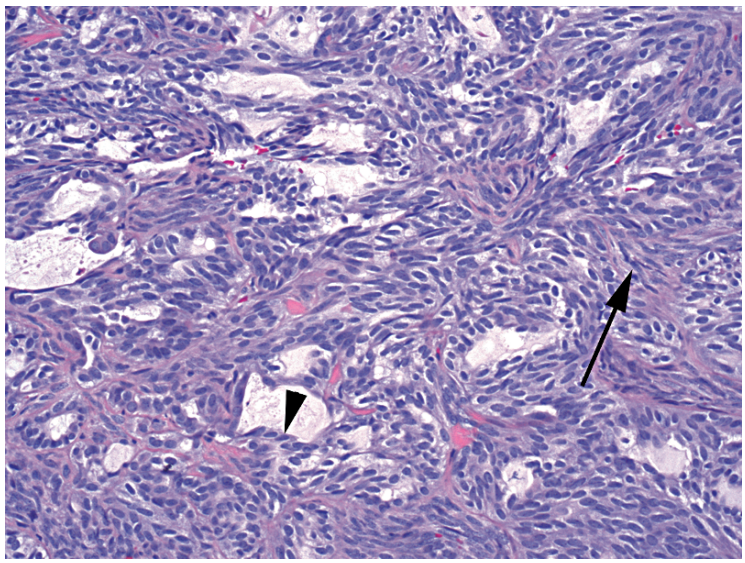

**Figure 28.24.** Biphasic synovial sarcoma. There are gland-like spaces surrounded by epithelial cells (arrowhead), set in a background of spindle cells (arrow). Monophasic synovial sarcoma lacks the epithelial component and can resemble fibrosarcoma.

looks somewhat carcinoma-like. The cells are large and eosinophilic with round nuclei and prominent nucleoli.

*Clear cell sarcoma of soft tissue* is one of several translocation tumors linked to the *EWS* gene. It is called *melanoma of soft parts*, as it stains with melanoma markers and may even produce melanin. Another *EWS* tumor is the *desmoplastic small round cell tumor*, which like it sounds is a small round blue cell tumor in a sclerotic background. The third tumor in this group is Ewing's sarcoma, which is cytogenetically identical to the peripheral neuroectodermal tumor. It is discussed with bone tumors.

## Tumors of Bone

For tumors of bone, involving bone, or simulating bone, the radiograph is the gross examination. As in vascular lesions, a well-differentiated neoplasm may be classified as benign or low-grade malignant largely by the degree to which it infiltrates or invades surrounding tissue or bone. In bone, this infiltration of the periphery is best assessed by a radiologist. General features are the following:

- Benign lesions tend to be clearly defined, well circumscribed, and walled off by a layer of reactive bone (a thin rim on x-ray). Benign entities also tend to evoke a thick and smooth periosteal reaction (thickening).
- Aggressive lesions, which include infectious or malignant lesions, tend to be poorly circumscribed, reflecting their infiltration of surrounding bone. Aggressive lesions tend to produce an onion-skin, spiculated, or discontinuous periosteal reaction.

The second major principle is that primary bone tumors are rare and mainly occur in young adults and children. For any patient over 50 years, the first three items in the differential diagnosis for a bony lesion are metastasis, metastasis, and metastasis. Number four is a hematopoietic malignancy such as myeloma.

### *Bone-Forming Tumors*

First, how does bone form? In the fetus, the main pathway is by endochondral ossification, in which new bone is laid down in the cartilage scaffolding. However, in the membranous bones of the fetal skull, and in the adult at sites of reparative bone, the first step is the synthesis of osteoid (a salmon-pink acellular matrix) by osteoblasts and its subsequent mineralization with calcium hydroxyapatite. This immature bone has a disorganized collagen framework and is called *woven bone*. Continuing development and remodeling produce bone with organized sheets of collagen visible as parallel seams within the trabeculae or cortex; this mature configuration is called *lamellar bone*. Neoplastic or reactive bone is always woven type; fragments of lamellar bone within a lesion must be entrapped native bone.

Second, how do we look at bone? Most histologic sections of bone are decalcified, so the pink fragments of "bone" you see are the osteoid left behind. Calcium phosphate itself is dark purple on H&E. In lesions with osteoid formation, which may include anything from reactive metaplastic bone to fibrous dysplasia to osteosarcoma, the osteoid (pink) can be differentiated from collagen or amyloid (also pink) by the process of mineralization, seen as a purple tinge within the seams of osteoid. Dystrophic calcification in soft tissue, such as tumoral calcinosis, is not the same as bone formation. Reactive bone formation, such as in myositis ossificans, is true bone but is not neoplastic.

The most common benign bone-forming neoplasm is the *osteoid osteoma* (Table 28.9). This lesion is composed of a small (<1.5 cm) nidus of lace-like woven bone surrounded by a dense sclerotic zone (Figure 28.25). The nidus is the source of intense bone pain. It is rarely seen on a slide these days, as radiofrequency ablation is effective treatment. The *osteoblastoma* is essentially the same lesion histologically but is larger (>1.5 cm).

At the other end of the spectrum lies *osteosarcoma*. The conventional type is a high-grade sarcoma. The usual appearance is that of a high-grade spindle cell neoplasm in which the

**Table 28.9.** Bone-forming tumors.

| Benign | Malignant but indolent | Malignant and aggressive |
|---|---|---|
| Osteoma | Parosteal osteosarcoma | Osteosarcoma, conventional type |
| Osteoid osteoma | | Periosteal osteosarcoma |
| Osteoblastoma | | Telangiectatic osteosarcoma |

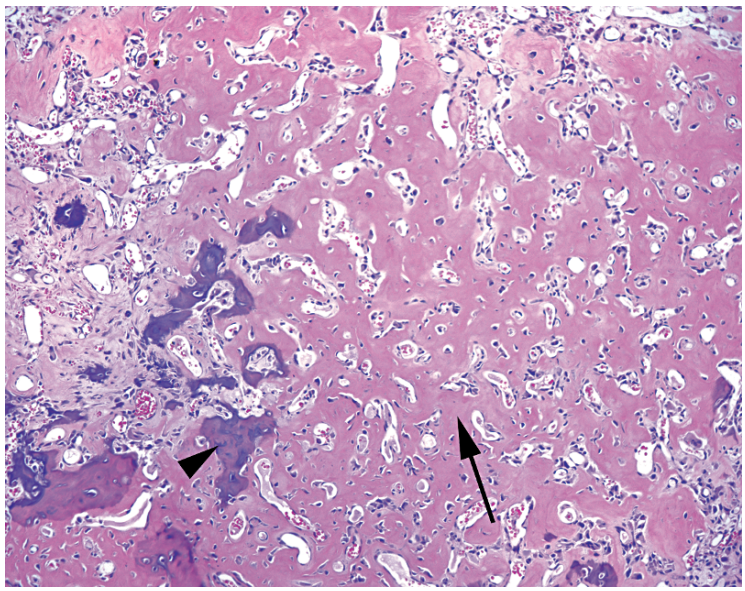

**Figure 28.25.** Osteoid osteoma or osteoblastoma (depending on size). At the nidus of the lesion, osteoid is laid down in a lace-like pattern (arrow) by benign osteoblasts. The hyaline pink substance can be identified as osteoid by the dark purple seams of mineralization (arrowhead).

tumor cells are associated with osteoid deposition (Figure 28.26). The osteoid is laid down in a lace-like pattern, very much like the inside of an osteoma. In fact, a well-differentiated osteosarcoma may be difficult to differentiate from an osteoblastoma. The difference is in the associated population of spindled or atypical cells and in the infiltrative periphery (best appreciated on x-ray). Osteosarcomas may have a wide range of morphologies, including chondroblastic, fibroblastic, and small cell. The unifying and defining feature is the production of osteoid by tumor cells, but osteoid may be sparse and focal. Resections of osteosarcoma are usually done postchemotherapy, at which time the goal is quantifying the amount of viable tumor that remains.

Some variants of osteosarcoma are more indolent. The *parosteal osteosarcoma* occurs on the surface of the bone, usually behind the knee of a young adult. This tumor is a low-grade sarcoma and is therefore not very cellular or atypical. It may resemble an osteochondroma, with well-formed cartilage and bone, but it is not in continuity with the marrow cavity. The similarly named but quite different *periosteal osteosarcoma* is also a surface lesion but is primarily chondroblastic and consists of a low-grade spindle cell population with cartilage formation.

### *Cartilage-Forming Tumors*

Cartilage-forming tumors produce a characteristic fluffy or concentric-ring pattern of calcification on x-rays (Table 28.10). The *osteochondroma* is almost diagnosable by x-ray alone, as it stands out from the bone surface like a mushroom. Histologically, it is a bony stalk in continuity with the main marrow space, capped by mature cartilage, looking very much like a duplicated joint surface. Osteochondromas carry a small risk of transformation to chondrosarcoma.

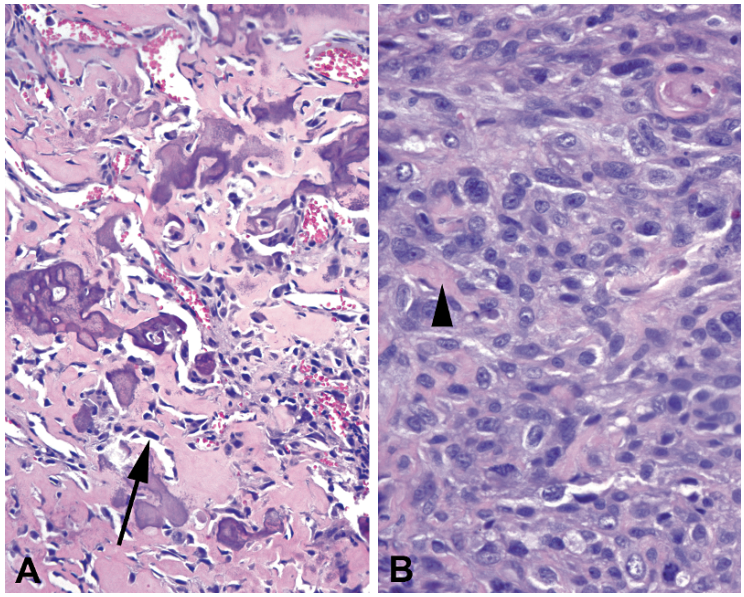


**Figure 28.26.** Osteosarcoma. **(A)** The most-well differentiated tumors can be very difficult to distinguish from osteoblastoma by histology alone. The osteoid deposition is similar, except the osteoblasts may appear more hyperchromatic and atypical (arrow). **(B)** A less differentiated tumor can be difficult to identify as osteosarcoma because of the focal and subtle production of osteoid (arrowhead).

**Table 28.10.** Cartilage-forming tumors.

| Benign | Malignant |
|---|---|
| Osteochondroma | Chondrosarcoma |
| Enchondroma | Dedifferentiated chondrosarcoma |
| Chondroblastoma | |
| Chondromyxoid fibroma | |

The *enchondroma* is merely an island of benign, hypocellular, mature cartilage occurring within the marrow space of the bone. It is usually asymptomatic in long bones but is more often found in the small bones of the hands and feet, where it leads to a visible swelling. The tumor consists of mature cartilage, which is a pale blue matrix with varying amounts of calcification (purple) and single chondrocytes sitting in bubble-like lacunae (Figure 28.27).

The *chondroblastoma* is also benign and is notable for a peculiar pattern of calcification that rings the lacunae, creating a chicken-wire or honeycomb effect. The chondromyxoid fibroma is rare but is in the differential diagnosis for a well-differentiated cartilage lesion in bone. It has both a fibrous component and a cartilaginous component.

*Chondrosarcoma* is typically a mass of atypical but recognizable cartilage, ranging from the low-grade chondrosarcoma (histologically resembling enchondroma) to the high-grade chondrosarcoma (Figure 28.28) based on cellularity, pleomorphism, and mitotic activity. It may be located on the surface of the bone or in the medullary cavity. Features that separate the well-differentiated chondrosarcoma from benign enchondromas include erosion of the inner cortex of bone, entrapment of trabeculae, myxoid change, and a tendency to involve the axial skeleton. Chondrosarcomas are tumors of adults (those in their thirties to fifties).

Chondrosarcomas, even high-grade ones, do not typically have a spindle cell component. A well-differentiated chondrosarcoma with an abrupt transition to high-grade sarcoma (of any pattern) is most likely a *dedifferentiated chondrosarcoma*. As in the liposarcoma family, this diagnosis relies on seeing the previous or adjacent chondrosarcoma. However, a tumor that

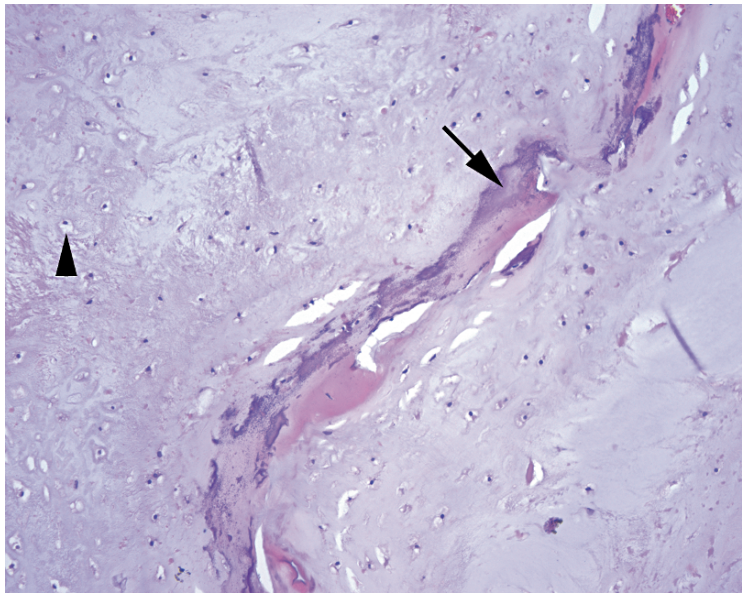

**FIGURE 28.27.** Enchondroma. This example shows a sheet of well-differentiated cartilage, with the characteristic blue, somewhat glassy matrix and small chondrocytes embedded in lacunae (arrowhead). The seam of mineralization (arrow) should not be mistaken for osteoid formation. A well-differentiated chondrosarcoma could look very similar histologically.

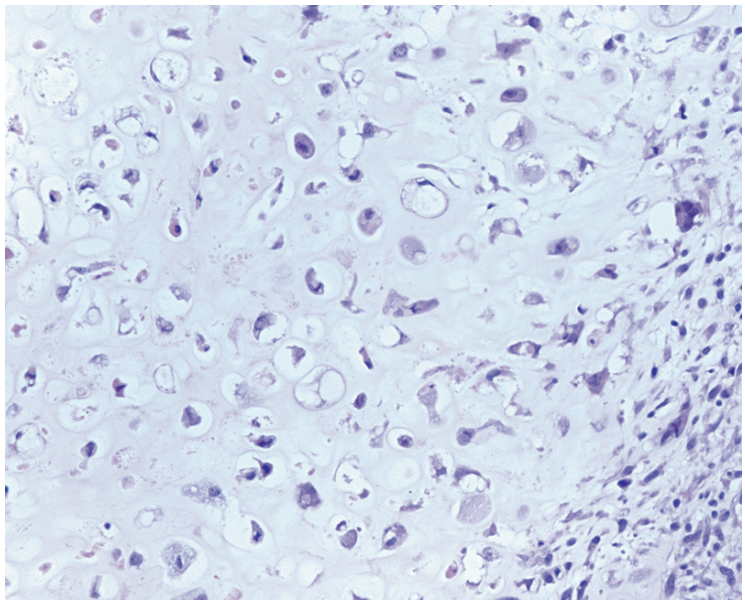

**FIGURE 28.28.** Chondrosarcoma. The cartilage matrix resembles normal cartilage, but the chondrocytes are pleomorphic in size and shape.

shows a gradual transition from cartilaginous areas to high-grade spindle cell areas is more likely a chondroblastic osteosarcoma. Confused? Keep reading.

Osteosarcomas often form cartilage ("chondroblastic"), and chondrosarcomas may mineralize into bone. How do we identify the primary nature of the neoplasm? Chondrosarcoma is a neoplasm of recognizable cartilage without a spindle cell sarcoma component, and the bone formation is through the direct mineralization or ossification of the cartilage, not by osteoid

deposition. A cartilage-forming osteosarcoma, on the other hand, should have areas of spindle cells that are producing osteoid. A spindle cell neoplasm intermixed with cartilage, even if the osteoid is not obvious, is more likely to be in the osteosarcoma family.

### *Fibrous and Miscellaneous Tumors in Bone*

*Fibrous dysplasia* is a lytic and fibrotic lesion (a developmental abnormality, not really a neoplasm) seen mainly in long bones and craniofacial bones (Table 28.11). Microscopically, the lesion consists of a low-grade spindle cell population in which thin trabeculae of woven bone are laid down in a distinct pattern resembling (to English speakers) Chinese letters. Unlike typical reactive bone in an inflammatory lesion, osteoblasts are not visible surrounding the trabeculae. *Ossifying fibroma* is a very similar lesion that occurs in the shins (tibia, fibula) of very young children, only ossifying fibroma *does* show prominent osteoblastic rimming. Finally, we have the *nonossifying fibroma*, which is the low-grade fibroblastic population seen in the above lesions, except without the woven bone formation. It is essentially equivalent to a benign fibrous histiocytoma in other sites. The malignant correlates of malignant fibrous histiocytoma (not uncommon) and fibrosarcoma (rare) can occur in bone as well.

The *giant cell tumor of bone* is a lytic, destructive lesion seen at the ends of long bones in adults. It is composed of a mixture of osteoclast-like giant cells, often with over 50 nuclei, mixed with a background population of mononuclear cells (the true neoplastic component). Mitoses may be seen, but atypia is not. Giant cells, however, are not a unique feature, as they can be seen in almost any bony lesion. The principal differential is with the giant cell reparative granuloma.

*Adamantinoma* is a rare lesion of the tibia that may be composed of squamous, fibrous, or adamantinomatous (see discussion of craniopharyngioma in Chapter 26) cells. The main reason to know about it is to avoid calling it metastatic carcinoma.

*Ewing's sarcoma* is a tumor of adolescents and young adults and appears as a small round blue cell tumor involving the bone. Like most embryonal-type tumors, the cells have hyperchromatic, round, blue nuclei without prominent nucleoli, high nuclear to cytoplasmic ratios with scant cytoplasm, and prominent necrosis and apoptosis (Figure 28.29). It is classically positive for CD99 and overlaps with the peripheral neuroectodermal tumor, which has identical cytogenetics. The differential diagnosis includes true metastases from other small round blue cell tumors, lymphoma/leukemia, and the small cell variant of osteosarcoma.

### *Joint Lesions*

*Synovial chondromatosis* is one of the few true tumors of the joint space (Table 28.12). It is characterized by the accumulation of nodules of benign cartilage in the synovium.

The *giant cell tumor of tendon sheath* actually describes two entities. The diffuse form is also known as pigmented villonodular tenosynovitis, and it is the second of the few lesions to actually involve the joint space. It is composed of a villous or papillary mass of small bland cells, multinucleated giant cells, and foamy macrophages. There are prominent clefted spaces at low power and sometimes pigment (hemosiderin).

**Table 28.11.** Fibrous and miscellaneous tumors in bone.

| Benign | Malignant |
|---|---|
| Fibrous tumors | |
| Fibrous dysplasia | Malignant fibrous histiocytoma |
| Osteofibrous dysplasia (ossifying fibroma) | Fibrosarcoma |
| Cortical fibrous defect (nonossifying fibroma) | |
| Other tumors | |
| Giant cell tumor of bone | Metastatic carcinoma |
| Adamantinoma | Lymphoma |
| | Ewing's sarcoma/peripheral neuroendocrine tumor |

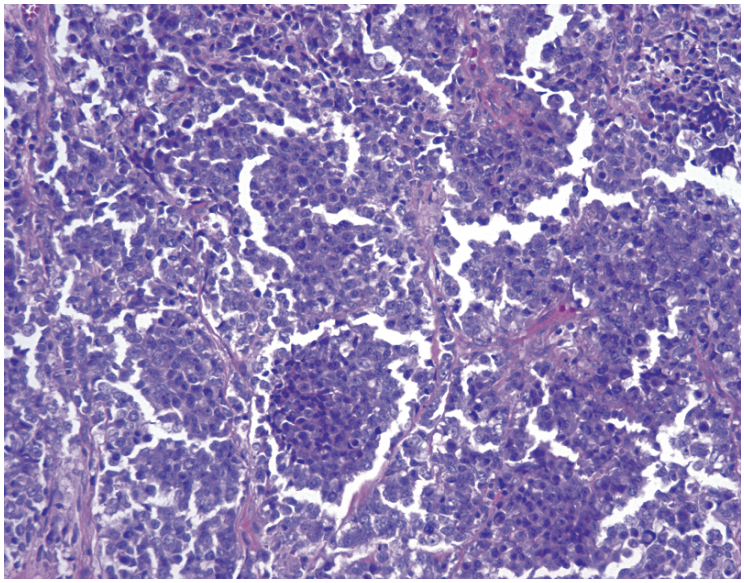

**FIGURE 28.29.** Ewing's sarcoma. The medullary cavity of bone is replaced by a small round blue cell tumor.

**TABLE 28.12.** Joint lesions.

| Benign | Malignant |
|---|---|
| Giant cell tumor of tendon sheath<br>Synovial chondromatosis | Malignant giant cell tumor (rare) |

The nodular or localized giant cell tumor is also called *nodular tenosynovitis*, and, aside from presenting as a nodule on a tendon, its appearance is very similar to the diffuse giant cell tumor. The lesion is composed of bland mononuclear cells, giant cells, foamy histiocytes, cleft-like spaces, and hemosiderin, all set in a collagenous stroma. Both of the giant cell tumors of tendon sheath are distinguished from the giant cell tumor of bone by their immunoreactivity to CD68, a histiocyte marker, as well as by their clinical presentation. However, they do resemble each other on H&E.