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Tumors of the Soft Tissue of the Lower Extremity

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INTRODUCTION

There is some confusion within segments of the medical community as to the precise meaning of "soft tissue." The soft tissue of the human body includes all extraskeletal tissue that is neither epithelial, hematopoietic (marrow derived blood elements), nor parenchymal (constituent of a visceral organ). The nervous system is divided such that neither the glial nor the central neuronal elements are considered to be soft tissue, though by convention the peripheral nervous system is. In sum, the soft tissues consist of adipose tissue, fibrous tissue, musculature, vascular structures, and peripheral nerves.

It should not be surprising that tumors of the soft tissue may arise virtually anywhere in the human body. Although soft tissue predominates in some regions of the human body such as the thigh and retroperitoneum, it is also found throughout the remainder of the human body in the form of vessels and peripheral nerves. Possibly as a direct result of their extensive distribution, soft tissue tumors that are related to those elements may arise in a wide range of locations. For instance, leiomyomas (tumors of smooth muscle differentiation) may arise in the skin (related to vessels of the superficial or deep plexi or erector pili musculature), within parenchymal organs, or within the lumina of vessels themselves. As might be expected, leiomyomas arise more commonly in locations that are richer in smooth muscle, such as the uterine corpus.

Tumors of the soft tissue may be classified into three major categories: nonneoplastic (reactive), neoplastic but benign, and neoplastic and biologically malignant. The same may be said of epithelial tumors and those of the skeletal system. Those tumors that are not neoplastic are composed of a heterogeneous (polyclonal) population of cells. In most instances these lesions arise as the result of a stimulus and regress when that stimulus is removed. In contrast, neoplasms emanate from a single "mother" cell, and as a result each cell is genetically identical. Neoplasms do not necessarily arise as the direct result of an external stimulus, but rather begin as the result of a cascade of genetic mutations that result in cell immortality and uncontrolled proliferation. To be certain, some neoplasms evolve as the direct result of a stimulus (examples: HPV-related carcinoma, radiation-related sarcoma); however, such neoplasms do not regress when such stimuli are removed.

As mentioned, neoplasms may be benign or malignant. As a general rule, benign neoplasms do not become widely invasive and lack the ability to metastasize or cause death. Again, these rules have their limitations. Some benign neoplasms such as uterine leiomyomas may seed the lungs. Fibromatoses may be diffusely infiltrative, and those that arise within the abdomen may even cause death. By convention, malignant neoplasms are those that have metastatic

potential and may cause death. Limitations exist with regard to malignant neoplasms as well. For instance, basal cell carcinoma is quite innocuous in most cases, and both metastases and deaths related to this neoplasm are publishable events.

The classification of many soft tissue tumors is in flux as the result of ongoing research, particularly within genetic arenas. Kaposi's sarcoma and fibromatosis are examples of tumors whose precise characterization has proven controversial. Kaposi's sarcoma was originally classified as a sarcoma because in extreme cases it may involve the lungs and other viscera so extensively as to cause death; however, it is now thought by some investigators to be a form of virally induced hyperplasia. Alternatively, superficial and deep fibromatoses (desmoid) have been traditionally described as benign, though these tumors may be locally destructive and, in the case of desmoid, may lead to death when arising near vital structures. This potentially aggressive behavior has led some to suggest that they would be better classified as low-grade malignancies.

The trunk and proximal extremities play host to the overwhelming majority of all soft tissue neoplasms; however, soft tissue tumors exhibiting virtually every type of differentiation may also arise within the foot.[1,2] Some tumors such as Kaposi's sarcoma, synovial sarcoma, and clear cell sarcoma are seen in the distal extremity at a disproportionally *high* rate relative to more proximal sites.[1] In this author's series of 401 soft tissue neoplasms of the foot, which was assembled at Memorial Sloan-Kettering Cancer Center, the most commonly diagnosed lesions were Kaposi's sarcoma, synovial sarcoma, superficial fibromatosis, giant cell tumor of tendon sheath, and clear-cell sarcoma (in descending order).[1] This study exhibited a pronounced bias toward those tumors that appeared clinically malignant, as is commonly the case with series of the lower extremity that are assembled at facilities that specialize in the treatment of cancer. In addition, this series was largely limited to neoplasms, though the author acknowledged that the neoplastic nature of both Kaposi's sarcoma and superficial fibromatosis is in debate. When nonneoplastic (reactive) tumors of the lower extremity, such as ganglion cysts are included in reviews of the subject, such lesions typically outnumber bona fide neoplasms.[2,3]

Clinical Features

Soft tissue tumors are distinct in that unlike the vast majority of cutaneous carcinomas, most present as nondescript subcutaneous nodules which lack a distinctive clinical appearance. Where most basal cell carcinomas may be readily identified based strictly on their clinical appearance, soft tissue neoplasms and nonneoplastic soft tissue proliferations cannot be accurately characterized based on clinical inspection alone. Such masses typically require histopathologic analysis to be definitively identified. Parenthetically, it may be impossible to distinguish soft tissue tumors from true cysts, granulomatous infiltrates (gout, granuloma annulare, and rheumatoid nodule), and tumors of the cutaneous adnexae (see chapter 16) based strictly on their clinical appearance.

Of greatest concern when managing patients with soft tissue tumors is the potential for confusion between those soft tissue tumors that are malignant and similarly appearing masses that are wholly benign. This concern has been documented on several occasions in relation to synovial sarcoma and its tendency to mimic ganglion cysts when arising on the dorsum of the foot.[1,2,5] A feature that might augment the clinician's ability to assess subcutaneous masses of the distal lower extremity is tumor localization. Certain soft tissue tumors have a predilection for particular sites in the foot. Soft tissue tumors that are most likely to affect the foot's dorsal surface are ganglion cyst, giant cell tumor of tendon sheath, Kaposi's sarcoma, and synovial sarcoma. Epidermal "inclusion" cysts and periosteal chondromas are also commonly seen in this location.[1,2] The most likely tumors to arise within the pedal digits are ganglion cysts, epidermal inclusion cysts, giant cell tumor of tendon sheath, and Kaposi's sarcoma.[1–3] In the Memorial Sloan-Kettering Cancer Center series, the digital region also played host to epithelioid sarcoma in a significant number of cases.[1] The plantar surface of the foot is affected most by superficial fibromatosis, followed by Kaposi's sarcoma and epidermal inclusion cysts.[1,2] The heel is affected by the aforementioned tumors at a slightly reduced rate. The region of the heel is of particular interest because it is among the most common sites for clear-cell sarcoma to manifest.[1] Clear cell sarcoma is a highly malignant neoplasm that is also known as melanoma of soft parts.[1]

Soft tissue tumors may pose problems with respect to both their histopathologic classification and clinical management. There is a wide spectrum of clinical behavior that may be attributed to various tumors of the soft tissue. These tumors may range from overtly benign to highly malignant in nature. Some soft tissue neoplasms may be extremely difficult to classify in terms of their malignant potential based on histopathologic features. In many such cases, even the distinction between "benign" and "malignant" may not be entirely clear. It is now accepted that when attempting to characterize the biologic potential of some soft tissue neoplasms, all is not black or white, but rather, there are often shades of gray.

To convey more accurately the biologic behavior of sarcomas (malignant soft tissue neoplasms) to treating clinicians, the concept of *tumor grade* was introduced. This schema of nomenclature allows tumors to be stratified into those that may be expected to metastasize quickly and those that are

more likely to remain localized. Neoplasms are graded as either low-grade or high-grade, depending on various histopathologic criteria such as the degree of cytologic atypia, the mitotic rate, and presence or absence of necrosis. This is done in a manner similar to that which is applied to malignant neoplasms within the skeletal system. As a general rule, low-grade malignant neoplasms are slow-growing and have a low probability of metastasis. Dermatofibrosarcoma protuberans (DFSP) is an example of a tumor whose malignant status is accepted but, due to its bland histopathologic features and limited metastatic potential, is further qualified by the term *low-grade*. In contrast, high-grade malignant neoplasms grow rapidly and readily metastasize. Synovial sarcoma is the classic example of a high-grade sarcoma that is common within the lower extremity. Of course, metastasis of high-grade sarcoma is a prelude to patient demise in most cases.

As is the case with melanoma and many carcinomas, the duration of any delays prior to the diagnosis of most sarcomas will have an inverse relationship to patient survival. When dealing with sarcomas, such delays result in prolonged periods of time prior to surgical and/or chemo or radiotherapy, which in turn leads to increased tumor size. It has been shown that the incidence of hematogenous spread of malignant soft tissue neoplasms is directly proportional to the size of the primary tumor.[6] Unfortunately, delays prior to diagnosis are not unusual in the setting of soft tissue neoplasia. Scully and colleagues noted delays of up to 21 months prior to the diagnosis of synovial sarcoma of the foot in their series.[5] They further elaborated on the commonality with which sarcomas in the foot may be confused with benign tumors, particularly ganglion cysts, and noted that this was the primary cause of such delays.[5] The potential for such oversights led Scully et al. to recommend that aspiration biopsy should be performed on all suspected ganglion cysts. They felt that "ganglia" that fail to provide cyst fluid upon aspiration should be taken for open biopsy.[5] Although there have been major breakthroughs in the treatment of many sarcomas by nonsurgical means, timely surgical excision remains the most effective therapeutic option for increasing patient survival.

Approximately 23% of patients with primary extremity sarcoma eventually develop distant metastasis, despite profound advances in multimodality therapeutics.[7] Once extremity sarcomas have metastasized, the host's prognosis becomes quite grim with a mean patient survival of approximately 1 year.[7] As mentioned, surgery remains the mainstay in therapy for sarcomas. Limb amputation has long been the standard surgical procedure for the management of high-grade sarcoma of the distal extremities. However, such is no longer the case. Most authorities now perform limb-sparing surgery when possible, followed by adjuvant radiotherapy or, less commonly, chemotherapy. This more conservative surgical approach provides excellent local control and a mean 5- and 10-year survival that is comparable to protocols that include more aggressive surgery.[6,8] In some centers postoperative radiotherapy is reserved for high-grade sarcomas and applied only to low-grade sarcomas that measure greater than 5 cm in maximum dimension.[7]

BIOPSY TECHNIQUES

Most soft tissue tumors lack clinical features that allow them to be distinguished from each other or from other benign and malignant tumors of the skin. For this reason, and because malignant soft tissue neoplasms may be highly aggressive, early biopsy is mandated when assessing non specific subcutaneous or deep masses of the foot. Established criteria that serve as indications for biopsy when investigating soft tissue tumors include a duration of 4 weeks or greater, rapid growth, and a maximum diameter of 5 cm or greater.[9] The lattermost of these indications should be loosely applied when dealing with such tumors in the foot, as because of the anatomic confinement of such tumors when expanding in the foot, sarcomas become symptomatic at an earlier point in their evolution. As a direct result of such limitations in space, masses arising in the superficial tissues of the distal lower extremity may be biopsied when significantly smaller than 5 cm. In sharp contrast, sarcomas arising in the deep soft tissue of the trunk or proximal extremity may grow to exceedingly large sizes prior to discovery. Such biopsies are best performed by clinicians with experience in the subject of soft tissue neoplasia.

There is a broad spectrum of techniques available to sample soft tissue neoplasms of the lower extremities. Unlike squamous cell carcinoma, basal cell carcinoma, and melanoma, soft tissue tumors often lie deep in the subcutis or within the deep soft tissues, making techniques such as shave technique and punch technique inappropriate in many instances. Tissue must be harvested at a depth that is sufficient to ensure that the neoplasm itself is sampled rather than simply the compressed or inflamed perilesional soft tissue. For this reason, *superficial* shave techniques are rarely appropriate for sampling tumors of the soft tissue. Exophytic (outward-growing) or protuberant lesions may be adequately sampled through the use of shave techniques; however, in most instances the technique of choice for sampling tumors of the soft tissue is incisional biopsy (the excision of a small part of a larger lesion), excisional biopsy (the complete excision of the lesion in question), or Tru-cut core needle biopsy.

Tru-cut core needle biopsies sample tumors by a means reminiscent of bone marrow biopsy. When performing this technique, subcutaneous masses or masses lying within the deep soft tissues are penetrated by large-gauge hollow nee-

dles that have been are specially constructed to retain sampled tissue within their lumen upon withdrawal. The needle may be redirected to sample various regions within the neoplasm in question. The tissue that remains within the needle lumen upon withdrawal is processed for histopathologic or cytogenetic analysis. Although Tru-cut core needle biopsy technique acquires a relatively small amount of tissue, because it allows for the sampling of various regions with a neoplasm and is easy to perform, it has been found to be highly effective for the diagnosis of soft tissue sarcomas, allowing for an accurate diagnosis in 94–98% of cases.[10] This high rate of effectiveness has been a consistent finding amongst investigators who have taken it to task.[9] Incisional biopsy (open biopsy) is a procedure whereby a wedge of lesional tissue is sampled without the intention of complete tumor removal. This technique typically provides more tissue than does Tru-cut core biopsy; however, it results in a larger amount of associated wound site complications and samples only a limited area within the lesion in question. In addition, incisional biopsy may complicate the subsequent definitive surgery. In a series of 329 patients with malignant soft tissue tumors, Mankin and colleagues reported that in 10.3% of cases, the tissue obtained at biopsy was insufficient to allow for a precise diagnosis. Interestingly, the vast majority of biopsies performed within their series were of the *incisional* variety, procedures that consistently provide more tissue than core needle biopsy.[11] The distinction lies in the quality of the sample. Core needle biopsies provide a broader sample of tissue and the needle may be redirected to sample additional regions within the tumor.

Wound site complications may be extremely problematic when acquiring samples of soft tissue tumors for histopathologic examination. In 17.3% of the cases in the series assembled by Mankin et al., the biopsy procedure (predominantly incisional biopsies) was followed by complications such as infection, hemorrhage, and local tissue breakdown/dehiscence.[11] The high rate of wound site complications when performing incisional biopsies on soft tissue tumors of the foot mandates that such biopsies be reserved for surgeons with experience in the performance of such techniques. Tru-cut core needle biopsy techniques have become widely used for the diagnosis of soft tissue tumors of all kinds due to a significantly lower incidence of wound site complications and the ease with which they may be performed.[10] Many practitioners consider incisional biopsy as the technique of choice only for exceptionally large soft tissue tumors of the extremities (those measuring greater than 5 cm in dimension).[9]

Histopathologic Challenges Related to Tumors of the Soft Tissue

In some instances, tumors of the soft tissue closely resemble one another by light microscopy, making ancillary diagnostic testing methods such as immunohistochemistry, polymerase chain reaction (PCR), and cytogenetic analysis extremely important to precisely characterize. For instance, high-grade fibrosarcoma may be histopathologically indistinguishable from synovial sarcoma, clear-cell sarcoma, and malignant peripheral nerve sheath tumor. When faced with this diagnostic dilemma, pathologists may escape the resultant conundrum with the aid of ancillary technologies such as those listed above, which allow for the analysis of tumor properties at the antigenic or genetic level. Synovial sarcoma and clear cell sarcoma may be identified through genetic-based studies where they will be shown to exhibit characteristic t(X;18) and t(12, 22) chromosomal translocations, respectively. In many cases, malignant peripheral nerve sheath tumor can be distinguished through the use of immunohistochemical studies, and in this context, high-grade fibrosarcoma will be a diagnosis of exclusion. Thankfully, most soft tissue tumors may be effectively diagnosed based solely on their histopathologic appearance. This is particularly true of benign tumors and low-grade sarcomas, as they are characteristically better differentiated and thus more closely recapitulate the nonneoplastic soft tissue elements after which they are named. It is for this reason that leiomyomas and well-differentiated leiomyosarcomas are readily identified by light microscopy (they more closely resemble nonneoplastic smooth muscle), where the definitive diagnosis of high-grade leiomyosarcoma may be exceedingly challenging based on morphologic features alone.

TUMORS OF FIBROUS / FIBROHISTIOCYTIC DIFFERENTIATION

Dermatofibroma (Benign Cutaneous Fibrous Histiocytoma)

Dermatofibromas (DF) are benign dermal-based tumors whose cells exhibit antigenic properties that resemble those of dermal dendrocytes.[12–14] Recall that dermal dendrocytes are thought to function as part of the immune system, aiding in the presentation and processing of foreign antigens within the skin. Because DF may arise in association with an inciting process such as an arthropod assault and often involute over time, they have been traditionally classified as nonneoplastic (reactive) proliferations; however, using molecular genetic testing, researchers have recently demonstrated clonality in many such tumors.[15–17] The demonstration of clonality provides strong evidence that these tumors are indeed neoplasms. The occasional history of local trauma or insect bites suggests that these proliferations are triggered by

exogenous factors; however, such inciting events are not a consistent finding.[18] The neoplastic nature of DF is not accepted by some authorities.[18] Dermatofibromas most often arise on the lower extremities of young adults. There is a slight female predominance.[12,15,19] The volar (non-hair-bearing) surfaces of the hands and feet, including the subungual region of the nail unit, may occasionally be affected.[20–22] We have seen DF primary to the sole, dorsal foot, digits, and nail units in this author's podiatric pathology practice. A case of subungual DF that mimicked acral melanoma has been reported.[22] Dermatofibromas appear as tan-brown sessile papules or small nodules which may be firm to palpation. Occasional DF may grow quite large in size, mandating that sarcoma be excluded from the clinical differential diagnosis. We have seen a DF measuring 3.5 cm in greatest dimension arising on the dorsal foot. Dermatofibromas usually appear as solitary units; however, multiple lesions may arise concurrently in exceptional instances.[21]

Dermatofibromas have been divided into several subtypes based on their histopathologic features, among them the cellular subtype, aneurysmal subtype, fibrocollagenous subtype, clear cell subtype, and histiocytic subtype.[23–26] The cellular and aneurysmal variants are clinically significant in that they become quite large and will recur locally in a minority of cases when not completely excised.[24,25]

Clinical differential diagnosis

Dermatofibromas are often characteristic in clinical appearance and thus prompt a rather limited clinical differential diagnosis. The umbilication of DF upon lateral compression (Fitzpatrick's sign) may help to further characterize these lesions when the clinical findings are ambiguous. More precisely, Fitzpatrick's sign connotes the tendency for dermatofibromas to dimple when compressed (pinched) from their lateral surfaces. This phenomenon occurs in part due to the nature in which dermatofibromas cause tethering between the superficial and deep reticular dermis. Some DF may be confused with superficial congenital or acquired (Clark's) nevi, particularly during involution when they often present as brown macules or papules (Fig. 17-1). Dermatofibromas may become deeply pigmented or exhibit pigment asymmetry, leading some such lesions to resemble atypical nevi or melanoma. Amelanotic melanoma may masquerade as poorly pigmented forms of DF especially cellular or aneurismal variants.[27] Some nonpigmented variants form dermal nodules that may be confused with cysts or benign and malignant adnexal tumors. Large DF, particularly those of the *cellular* variety, can mimic dermatofibrosarcoma protuberans, a locally aggressive form of low-grade fibrosarcoma.[25] The *aneurysmal* variant of DF, because of its intralesional hemorrhage and hemosiderin deposition, may be mistaken for both benign and malignant vascular neoplasms.[24]

Histopathology

As noted above, there are several variants of DF, predominantly categorized based on disparate histopathologic features within the tumors themselves. In addition, DF typically prompt characteristic changes within the adjacent stroma and within the overlying epidermis. The surface epithelium is often thickened (acanthotic) with elongated retia and induction of adnexal structures emanating from its undersurface. Dermatofibromas that arise on the plantar surface often exhibit superimposed reactive changes (hyperkeratosis, acanthosis, incipient ulceration) secondary to the added friction and pressure that they precipitate (Fig. 17-2). There is often an increased amount of melanin pigment within basal keratinocytes, particularly in lesions originating on persons of color. Intra-epidermal melanocytes are only slightly increased or normal in number and are not scattered into the high reaches of the epidermis as they would be in melanoma. Some investigators have suggested that epidermal growth factor plays a central role in the aforementioned epidermal changes.[28] These dermal-based neoplasms consist of short spindled cells which may exhibit either a storiform or haphazard pattern of growth. Most DF are well circumscribed, though some may not appear so due

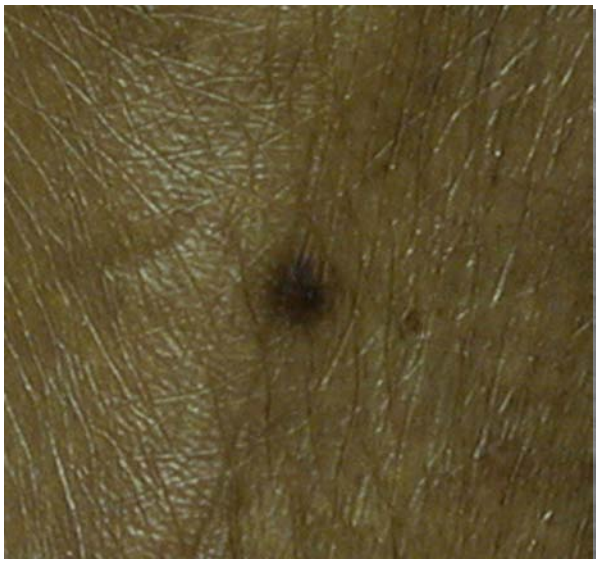

FIGURE 17-1. Dermatofibroma. Dermatofibromas may stimulate the production of melanin pigment within the overlying epidermis, creating the appearance of a melanocytic proliferation (courtesy Sean Van Marter, D.P.M.).

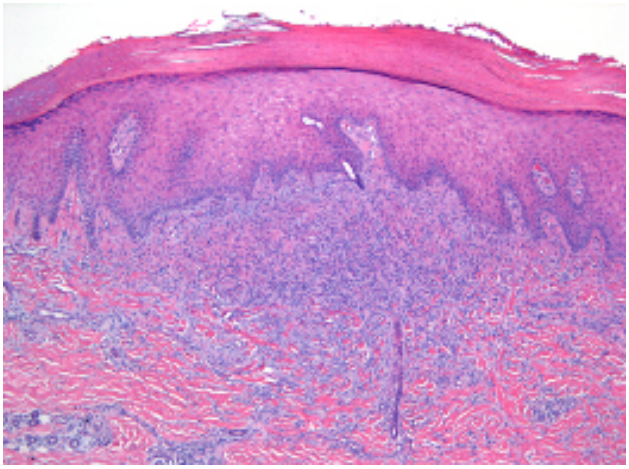

FIGURE 17-2. Dermatofibroma. A well-circumscribed dermal-based proliferation of spindled cells arising in the skin of a plantar surface.

to the fact that they characteristically possess dense cellularity centrally, which tapers off peripherally. Within the less cellular peripheral regions, keloidal bundles of collagen are often seen, many of which are surrounded by lesional cells. Within the central portion of the DF, there is often an admixture of thin fibroblast-like spindled cells and plump histiocytes, some of which may be multinucleated. *Cellular variants* may exhibit dense central cellularity, scattered mitotic figures (up to 3/10 high power fields), and extension into the subcutaneous fat.[25] Aneurysmal variants of DF are defined by blood-filled spaces of varying size and scattered deposits of hemosiderin.[24] Clear-cell variants are composed of cells that possess abundant clear cytoplasm and distinct cytoplasmic contours.[26]

Atypical Fibrous Histiocytoma

Atypical fibrous histiocytoma (AFH) is an uncommon neoplasm that is closely related to cellular and aneurismal variants of dermatofibroma. Because these lesions have a higher rate of recurrence and have been shown to metastasize on rare occasions, AFH will be listed separately in this text. In a series of 59 cases of AFH, Fletcher and colleagues found no gender predilection. The mean age of affected persons was 38 years.[29] Data regarding long-term follow-up were available for 21 of the cases in their series. Among those cases, 3 persons developed local recurrences and an additional two experienced distant metastases. One of those persons who developed distant metastases died of disseminated disease.[29] Forty-two percent of the neoplasms in Fletcher's series arose in the skin of the lower extremity. The foot or ankle played host to nearly 10% of all such lesions.[29] The skin of the hallux has been involved in at least one reported case.[30]

Clinical differential diagnosis

See Dermatofibroma.

Histopathology

Like DF, AFH are dermal-based and moderately well-circumscribed neoplasms. Lesional cells may have a storiform, haphazard, or vaguely fascicular pattern of growth. The cells that constitute AFH are often larger than those of other DF variants and may possess an increased amount of eosinophilic cytoplasm. Features that distinguish AFH from traditional forms of dermatofibroma are high cellularity and moderate nuclear atypia. Occasional cases disclose cells with atypical features that are either mild or marked. Scattered mitotic figures, including atypical forms, should be expected. Tumor necrosis may be present; however, its significance has not been established.

Plantar Fibromatosis (Superficial Fibromatosis/Ledderhose's Disease)

Despite its namesake, plantar fibromatosis (PF) was initially described by Madelung in 1875. This unusual condition represents one of several forms of superficial fibromatosis, the others being palmar (Dupuytren's) fibromatosis, penile (Peyronie's) fibromatosis, and dorsal knuckle pads.[31,32] Plantar fibromatosis has been traditionally viewed as a benign proliferation; however, due to its high rate of local recurrence and because such lesions may be locally aggressive, some have questioned whether it might be better classified as a form of low-grade fibrosarcoma.[1] Arguing against interpreting these tumors as malignant is their utter lack of metastatic potential.[32] Plantar fibromatosis may arise within individuals who have already been affected by one or more of the other types of superficial fibromatosis, though they rarely arise concurrently. In as many as 69% of cases, PF manifests in persons who have either already developed palmar fibromatosis or eventually will. Others have found this association in far fewer cases.[33,34] Less commonly, dorsal knuckle pads or penile fibromatosis arises in association with PF. Those persons affected by PF and penile fibromatosis are exceedingly few.[35] Plantar fibromatosis is bilateral in roughly 20% of cases.[33] Unrelated conditions that appear to be seen at a higher rate in association with persons with superficial fibromatosis include diabetes mellitus, epileptic seizures, and chronic alcohol abuse.[32] The incidence of PF increases with advancing age in a fashion similar to its palmar counterpart. In contrast to palmar fibromatosis, more than 1/3 (35%) of cases of PF are diagnosed in patients younger than 30 years of age.[34] The average age of patients at the time of surgery for PF was 45 years in the Memorial Sloan-Kettering series.[1]

Plantar fibromatosis is more common in men than in women.[33] Individuals affected by this condition present themselves with a deep focus of induration and/or nodule formation, most often within the medial band of the plantar fascia; however, any portion of the plantar fascia may be affected.[36] Flexion contractures involving the pedal digits may occur.[36] Many investigators believe that in light of the morphologic, immunohistochemical, ultrastructural, and genetic properties of both PF and Dupuytren's contracture, they are likely different manifestations of the same fundamental pathologic process.[37–39] The same adjunctive studies have led many to believe that superficial fibromatoses are in actuality bona fide neoplasms, rather than the reactive proliferations as they have long been considered to be.[38–40]

Clinical differential diagnosis

Plantar fibromatosis may present as a vaguely delineated area of induration, as multiple discrete nodules, or in some instances as a solitary mass. Because its clinical appearance may be variable, the associated differential diagnosis is quite broad. Where a palpably prominent plantar fascia with nodularity allows for a limited differential, consisting mainly of PF and fibrosarcoma, discrete nodules and masses may simulate any of a number of soft tissue neoplasms. Plantar lesions may resemble fibrosarcoma, synovial sarcoma, and both benign and malignant smooth muscle tumors. In the Memorial Sloan-Kettering series, we noted many cases of clear-cell sarcoma of soft parts involving the fascia of the heel. Epithelioid sarcoma may extend for long distances within the subcutis of the forefoot, causing diffuse induration with nodule formation in a manner that could be mistaken for superficial fibromatosis.

Histopathology

Superficial fibromatoses are similar regardless of their site of origin, though those arising on the plantar surface have a tendency toward higher cellularity. Lesional cells form sheets of plump spindled cells that are commonly oriented in the same direction so as to yield the histopathologic appearance of fishes swimming (Fig. 17-3). Lesional cells characteristically infiltrate through preexisting fascia, though aggressive forms may extend into the adjacent soft tissue or skin. Cytologically, lesional cells are embedded within variably dense collagenous stroma. Individual cells possess elongate nuclei that range from oval to cigar-shaped. There is abundant eosinophilic cytoplasm in proliferative lesions.

Superficial Acral Fibromyxoma

Superficial acral fibromyxoma (SAF) is a benign soft tissue tumor described by Fetsch et al. in 2001. In their inaugural series, these investigators described 37 such tumors, which had a distinct predilection for the distal extremities, particularly the toes and fingers.[41] The tumors in their series ranged from 0.6 to 5.0 cm in greatest diameter, with an average size of 1.75 cm. All of the 37 cases in their series arose in the toes (20/37), fingers (13/37), or palms (4/37). Twenty of their cases arose in association with either a fingernail or toenail. In one recent report, SAF was an incidental finding in an avulsed dystrophic nail plate.[42] Although neither metastases nor locally aggressive behavior has been noted, because local occurrence eventuated in association with three of the incompletely excised tumors in the original series, the authors recommended complete excision with narrow margins.[41]

Clinical differential diagnosis

The differential diagnosis for SAF is largely related to its acral location. Once rubbed or traumatized, this neoplasm may closely resemble lesions as disparate as verruca vulgaris, acquired acral fibrokeratoma, glomus tumor, pyogenic granuloma, Dupuytren's (subungual) exostosis, and paronychia. In the original series, these tumors were also confused with giant cell tumor of tendon sheath, hemangioma, atypical fibroxanthoma, and carcinoma.[41] In this author's experience, by far the most common mimics are verruca and acquired acral fibrokeratoma.

Histopathology

Superficial acral fibromyxomas are nonencapsulated, moderately well-circumscribed tumors. These lesions are composed of spindled cells embedded within loose fibrous stroma (Fig. 17-4). There may be a prominent myxoid component, or this feature may be subtle. The cellularity ranges from sparse to moderate from one region to another. Some lesions are paucicellular throughout the entire neoplasm. High cellularity is not a feature of SAF. Within the substance of the tumor there are an increased number of small venules and arterioles, some of which are surrounded by a halo of myxoid material. Such vascularity is most pronounced in lesions with a prominent myxoid component. The cells that comprise SAF are spindled or stellate in configuration and exhibit a pattern of growth that ranges from vaguely fascicular to storiform. Atypical cytologic features are not a feature of SAF, and mitotic figures are rare.[41,42]

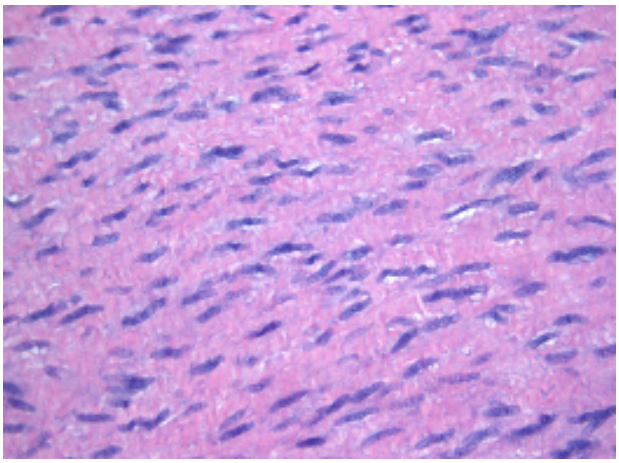

FIGURE 17-3. Superficial fibromatosis. A diffusely infiltrating proliferation of plump spindled cells, often exhibiting parallel orientation.

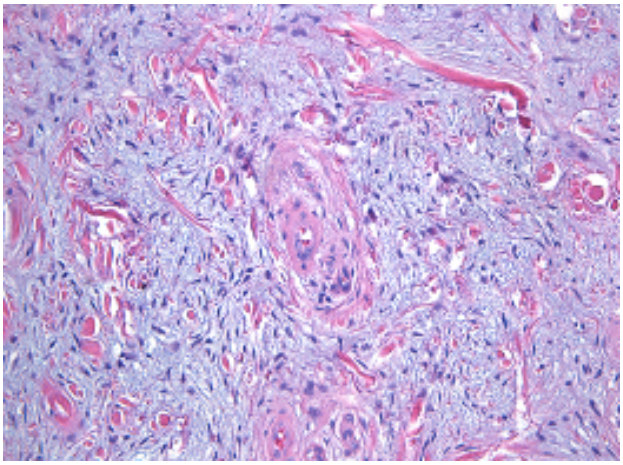

FIGURE 17-4. Superficial acral fibromatosis. A haphazardly arranged proliferation of spindled cells and small vessels within myxoid matrix.

MyxoinFlammatory Fibroblastic Sarcoma (Acral Myxoinflammatory Fibroblastic Sarcoma/ Inflammatory Myxoid Tumor of the Soft Parts with Bizarre Giant Cells/Inflammatory Myxohyaline Tumor of the Distal Extremities with Virocyte or Reed-Sternberg-Like Cells)

Myxoinflammatory fibroblastic sarcoma is an unusual neoplasm first characterized by Weiss and colleagues in 1998 under the designation "inflammatory myxohyaline tumor of the distal extremities with virocyte or Reed-Sternberg-like cells." They noted that this tumor was unique due its distinct predilection for the distal extremities and the presence of bizarre tumor cells of unknown histogenesis.[43] They believed this tumor to possess low-grade malignant potential.[43] This abstract was followed a full-length publication which summarized and expanded upon their earlier findings.[44] During the following year, Meis-Kindblom and Kindblom described the clinicopathologic features disclosed by a series of similar neoplasms under the less lengthy designation "acral myxoinflammatory fibroblastic sarcoma." Michal then reported on five identical cases, naming them "inflammatory myxoid tumor of the soft parts with bizarre giant cells."[45,46] Largely as the result of the concise nature of the nomenclature offered by Meiss-Kindblom et al., it is their terminology that has been most utilized in subsequent reports.[47–50] The modifier "acral" has now been largely omitted because these tumors have been described in the skin or subcutaneous soft tissue proximal to the acral regions.[48]

Despite their predilection for the distal extremities, MFS remain rare as compared to other soft tissue tumors of the feet, accounting for only one of 401 pedal soft tissue tumors in the Memorial Sloan-Kettering series.[1] This bizarre neoplasm commonly involves the fingers and toes of middle-aged adults. There appears to be no particular gender predilection.[43,45] Most cases of myxoinflammatory fibroblastic sarcoma have measured between 1 and 6 cm in greatest dimension; however, one such neoplasm measuring at least 18 cm has been reported.[45,48] Among the 34 patients for whom follow-up information was available in the series by Meis-Kindblom et al., 24 (67%) endured local recurrences.[45] The rate of local recurrence was significantly lower in the series by Weiss and colleagues.[43] Also notable within the series by Meis-Kindblom et al. were one case in which there was a histologically proven lymph node metastasis and another case with a presumed lung metastasis.[45] In keeping with the low-grade characterization of this tumor as given by Weiss et al., such metastases appear to be rare events.[43] In one case of MFS from the dorsal foot, investigators demonstrated a unique reciprocal chromosomal translocation t(1;10) (p22;q24) and evidence of clonality.[47]

Clinical differential diagnosis

Myxoinflammatory fibroblastic sarcoma usually presents itself as a nonspecific subcutaneous mass; as such, it may be closely simulated by virtually any subcutaneous mass-forming lesion of the distal extremity. On the fingers and toes MFS is most closely simulated by giant cell tumor of tendon sheath, fibroma of tendon sheath, fibrolipomatous hamartoma, and superficial acral fibromyxoma. On the mid- and rearfoot, more likely mimics include ganglion cysts, superficial fibromatosis, synovial sarcoma, clear-cell sarcoma, and fibrosarcoma.

Histopathology

Myxoinflammatory fibroblastic sarcomas are poorly circumscribed neoplasms which may disclose a nodular or partially lobulated configuration. Lesional cells are haphazardly positioned within collagenous stroma. Patchy fibrosis and myxoid material are commonly present. There is usually an associated mixed inflammatory infiltrate composed of neutrophils, eosinophils, histiocytes, and lymphocytes. As initially described by Weiss, scattered large cells with atypical nuclei and prominent nucleoli are seen within the inflammation (Fig. 17-5). These bizarre cells may have a striking resemblance to the Reed-Sternberg cells that are characteristic of Hodgkin's disease.

Atypical Fibroxanthoma (Superficial Malignant Fibrous Histiocytoma)

Unlike the vast majority of soft tissue tumors, atypical fibroxanthoma (AFX) is by definition seen only in the skin, where it typically arises on the sun-exposed surfaces of the scalp, face, ears, or less commonly shoulders of elderly persons.[51–53] Most cases appear as firm pink-red papules or nodules. Some investigators recognize a subtype of AFX that characteristically arises on the trunk and extremities of young and middle-aged adults.[56] Cases of AFX involving the skin of the foot have been described.[54,55]

Tumors with histopathologic features that are identical to AFX, but lie deep to the skin, are by convention designated *malignant fibrous histiocytoma* (described elsewhere). Some use the term *AFX* to denote only those skin tumors that possess histopathologic features typical of the *pleomorphic* variant of malignant fibrous histiocytoma;[32] however, such seems inappropriate, as some AFX exhibit features closer to those of the classic or storiform types of malignant fibrous histiocytoma. Because atypical fibroxanthoma may be histopathologically and immunophenotypically indistinguishable from malignant fibrous histiocytoma, some authors have equated them,[53] however, because there are dramatic differences in terms of prognosis, it is important to distinguish them in a clear manner. Those neoplasms that arise within the skin (AFX) usually follow a benign course.[51] Only rare metastases of AFX to regional lymph nodes and visceral organs have been reported.[57–59] Such is not the case for those tumors arising in the deep soft tissue, where metastases and eventual patient death are common.

Clinical differential diagnosis

Atypical fibroxanthoma may clinically resemble benign cutaneous fibrous histiocytoma (dermatofibromas), particularly the cellular variant, which most often forms nodules. There also may be similarities between AFX and other dermal or subcutaneous tumors such as dermatofibrosarcoma protuberans, inflamed cysts, adnexal tumors, and amelanotic melanoma. Ulcerated lesions may resemble basal cell carcinoma or squamous cell carcinoma.

Histopathology

The most consistently recognized form of AFX is composed of profoundly atypical cells growing in haphazard array. There is marked nuclear pleomorphism, and mitoses are easily identified (Fig. 17-6). There may be

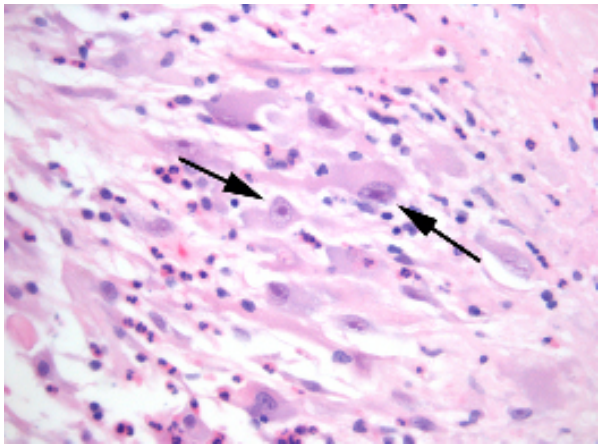

FIGURE 17-5. Myxoinflammatory fibroblastic sarcoma. Bizarre cells with abundant eosinophilic cytoplasm and prominent nucleoli.

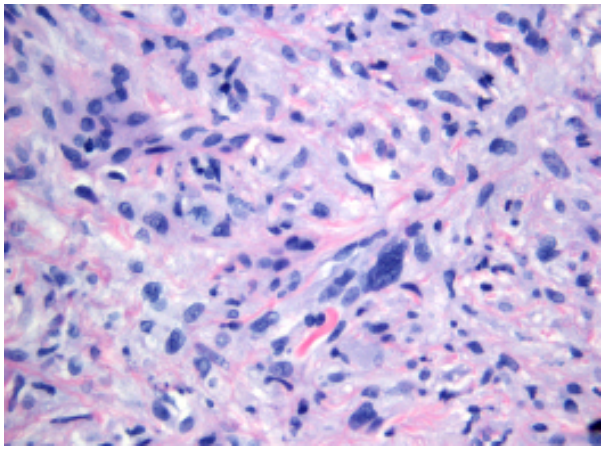

FIGURE 17-6. Atypical fibroxanthoma. Pleomorphic and hyperchromatic cells in haphazard array with scattered mitotic figures (arrow).

scattered giant cells, some of which may be multinucleated. A variably dense inflammatory infiltrate composed of lymphocytes and histiocytes may be present. An alternative morphologic expression of AFX is the classic (spindle-cell) variant, which discloses a dense population of hyperchromatic spindled cells with nuclear pleomorphism that ranges from mild to moderate. In spindle-cell AFX the neoplastic cells exhibit haphazard, storiform, or fascicular patterns of growth. In all forms of advanced AFX, there may be marked epidermal attenuation or ulceration.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans **(**DFSP) is a relatively common form of low-grade fibrosarcoma whose name relates to its tendency to originate within the dermis (dermato) and form firm potato (tuber)-like masses. This malignant soft tissue neoplasm is low in grade as reflected by its characteristically high rate of local recurrence (exceeding 30%), with only exceptional examples of distant metastasis.[60–63] Such metastases, although particularly uncommon, are well documented from primary sites that include the skin of the foot.[64–67] Similar to the pattern of metastasis shown by most other sarcomas, once tumor cells gain access to the systemic circulation, lesions cells spread by hematogenous routes. Thus, the lymph node metastases that are common to carcinomas and melanomas are not typical of DFSP; rather, these tumors tend to spread first to the bone or viscera, particularly the lungs.[64,66,67]

Dermatofibrosarcoma protuberans most often arises in persons of middle age; however, individuals of any age may be affected.[60,68] Most DFSP arise in the skin of the trunk or proximal extremity, though involvement of the foot, and even toes, has been reported.[69–73] In addition, we have noted pedal involvement among the many cases of DFSP reported within our own podiatric pathology practice. Curiously, those neoplasms that arise on acral surfaces do so at a higher rate within the pediatric population.[74] *Bednar tumor* is the eponym given to cases of DFSP that are colonized by benign melanocytes, resulting in the accumulation of intratumoral melanin pigment. Such tumors appear blue-brown upon clinical inspection. Bednar tumors account for approximately 5% of all DFSP and have been well documented in the skin of the foot.[69,70,75]

The precise line of differentiation for DFSP has been debated. The absence of antigenic markers indicative of differentiation towards other forms of soft tissue suggests that cells of DFSP are most closely related to fibroblasts or primitive mesenchyme.[76] Progression from bona fide DFSP to classic fibrosarcoma has been described in several instances, including some with foot involvement.[60,69,77] From a genetic perspective, investigators have consistently identified a limited number of distinct genetic mutations in association with DFSP. Such mutations typically involve either chromosome 17 or 22 and include translocation t(17;22) (q22;q13), amplification of 17q and/or 22q, and ring chromosome 17 or chromosome 22.[78–80]

Clinical differential diagnosis

Dermatofibrosarcoma protuberans may clinically resemble dermatofibromas, particularly those of the cellular variety, dermal- or subcutaneous-based cysts, and cutaneous adnexal tumors. More advanced tumors may be confused with other low- and high-grade sarcomas, including myxoinflammatory fibroblastic sarcoma, epithelioid sarcoma, and fibrosarcoma. Some cases form ill-defined zones of induration rather than discrete exophytic (outgrowing) masses.

Histopathology

Dermatofibrosarcoma protuberans are moderately to poorly delineated dermal-based neoplasms that typically extend into the subcutaneous fat. Advanced lesions may become significantly more infiltrative, extending well beyond their clinically apparent boundaries. Lesional cells may exhibit a haphazard, storiform, or herringbone pattern of growth. Often multiple patterns of growth are seen within the same neoplasm. Cytologically, these tumors are composed of small hyperchromatic spindled cells. Prominent nuclear atypia in the form of pleomorphism (variation in nuclear shape) is not seen. The tendency for cells of DFSP to diffusely infiltrate the subcutaneous fat, often encircling individual adipocytes, is a key feature of DFSP and may allow for its distinction from its mimics (Fig. 17-7). Mitotic figures are characteristically few in number, and tumor necrosis is not present.

Fibrosarcoma

Fibrosarcomas are amongst the most poorly understood of all soft tissue tumors, despite the fact that they are not uncommon in relative terms. The difficulty that investigators have had in accurately characterizing fibrosarcoma is largely a function of its many histopathologic variants and the absence of specific surface antigens that permit study by ancillary tests such as immunohistochemistry. The lack of specific findings by ancillary testing methods leads pathologists to consider the diagnosis of fibrosarcoma to be one of exclusion. The diagnosis of fibrosarcoma may only be rendered when the neoplasm in question fails to exhibit either antigenic or genetic features that could suggest an alternate line of differentiation. In many instances, those neoplasms designated as malignant fibrous histiocytoma (atypical fibroxanthoma) are believed in actuality to represent high-grade pleomorphic fibrosarcoma.[32]

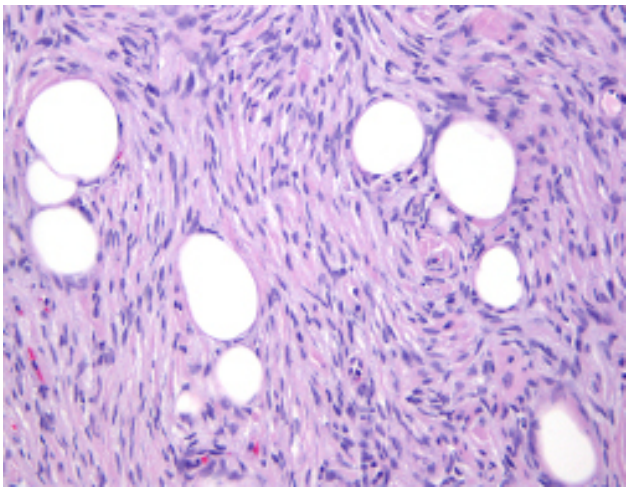

FIGURE 17-7. Dermatofibrosarcoma protuberans. Malignant spindled cells diffusely infiltrating subcutaneous fat.

Fibrosarcoma is a variably aggressive neoplasm whose cells exhibit fibroblastic differentiation. As a direct result of their differentiation, all but the most poorly differentiated variants possess highly collagenous stroma. As with all high-grade sarcomas, high-grade examples of fibrosarcoma are accompanied by a significant risk for distant metastasis. This risk is further enhanced in those sarcomas that arise within the deep soft tissue. The potential for metastasis declines dramatically for tumors that manifest in the skin or subcutis, locations that are commonly related to a history of radiation exposure or extensive scar formation.[32] One insidiously progressive low-grade variant of fibrosarcoma that is associated with a marked propensity for local recurrence and uncommon metastases has been designated as *low-grade myxofibrosarcoma*. This neoplasm often results in patient demise when arising in the trunk; however, because complete excision may be readily accomplished in the distal extremities, this low-grade sarcoma may be cured surgically in most cases when arising in the foot.

Fibrosarcoma is predominantly a disease of middle-aged individuals; however, persons of all ages may be affected.[81,82] Pediatric populations are affected by a distinct variant of fibrosarcoma.[83] Men are at slightly higher risk for developing fibrosarcoma than are women.[84] The deep soft tissue of the proximal lower extremity and the retroperitoneum are the most common locations for fibrosarcoma; however, involvement of the foot has been extensively documented.[85,86] Fibrosarcoma accounted for 8.3% of all such malignant soft tissue tumors in the Memorial Sloan-Kettering Cancer Center series.[1]

Clinical differential diagnosis

The clinical differential diagnosis for fibrosarcoma includes all neoplastic and nonneoplastic lesions that form deep-seated painless masses. In the foot, such lesions would include lesions such as epidermal inclusion cyst, ganglion cyst, plantar fibromatosis, myxoinflammatory fibroblastic sarcoma, and synovial sarcoma, to name a few.

Histopathology

In prototypical fibrosarcoma, small neoplastic spindled cells with hyperchromatic nuclei grow diffusely. Neoplastic cells are embedded within collagen-rich stroma. In classic examples of fibrosarcoma, there is a characteristic herringbone pattern of growth (Fig. 17-8). Mitotic figures are uniformly present but widely variable in number. Those cases of fibrosarcoma that possess a prominent myxoid component to the background stroma are designated as so-called myxofibrosarcoma. Low-grade fibrosarcomas may be relatively paucicellular and may disclose only subtle cytologic atypia, in the form of nuclear hyperchromasia. Low-grade myxofibrosarcoma has these low-grade cytologic features in conjunction with distinctly myxoid stroma and thick chicken wire-like vascularity. Unlike the low-grade counterparts, high-grade lesions are more likely to exhibit prominent nuclear pleomorphism, pronounced hypercellularity, an accelerated mitotic rate, and tumor necrosis (Fig. 17-10).

Malignant Fibrous Histiocytoma (Pleomorphic Malignant Fibrous Histiocytoma/Undifferentiated High-Grade Pleomorphic Sarcoma)

Malignant fibrous histiocytoma (MFH) is the deep-seated correlate to the more superficially located AFX

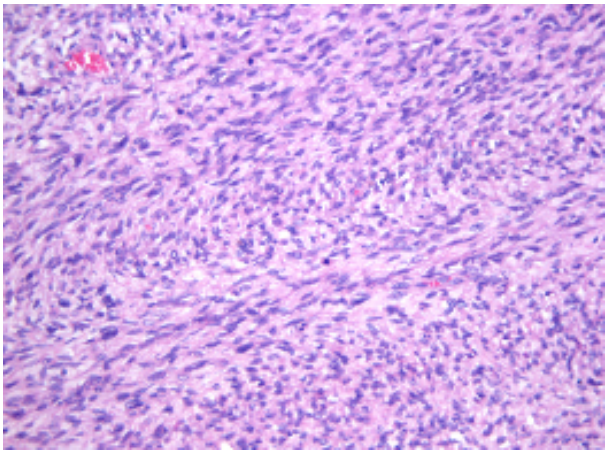

FIGURE 17-8. Low-grade fibrosarcoma. A densely cellular proliferation of spindle cells with a herringbone pattern of growth.

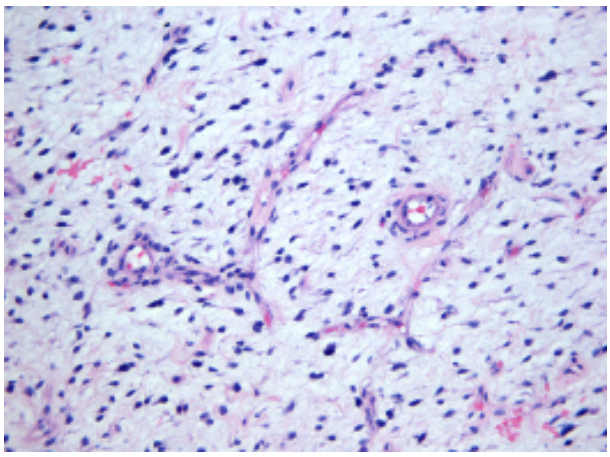

FIGURE 17-9. Low-grade myxofibrosarcoma. A paucicellular neoplasm with abundant myxoid matrix and fine vascularity.

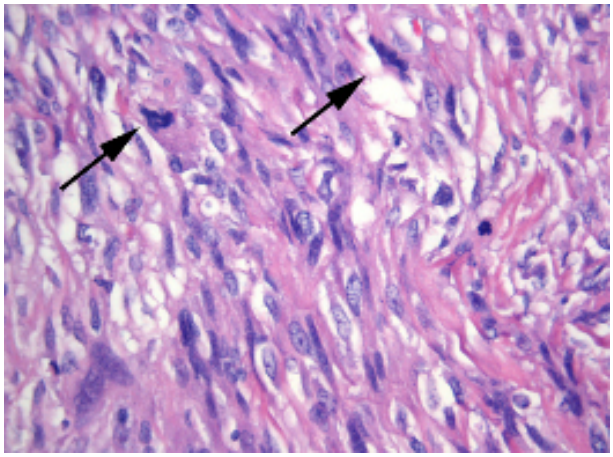

FIGURE 17-10. High-grade fibrosarcoma. Bizarre cells with a vaguely fascicular pattern of growth. Atypical mitoses are present (arrow).

(see previous). These high-grade sarcomas may arise in the foot; however, they do so at a relatively low rate. They accounted for almost 7% of the sarcomas summarized at the Memorial Sloan-Kettering Cancer Center.[1] It is now accepted that many of those tumors that were once classified as MFH are actuality poorly differentiated sarcomas of other types where the determination of lines of differentiation may be exceedingly difficult (see pleomorphic liposarcoma and high-grade fibrosarcoma).[87] In addition, in contrast to traditionally held beliefs, it is now accepted that MFH do not actually exhibit histiocytic differentiation.[87] In sum, the tumor designated as malignant fibrous histiocytoma may not be a distinct entity; rather, this may be a wastebasket diagnosis given to all high-grade sarcomas that have become so profoundly mutated as no longer to possess characteristics that are specific to any particular line of differentiation.

Clinical differential diagnosis

Malignant fibrous histiocytomas are characteristically seated within the deep soft tissue. As these neoplasms are essentially high-grade (poorly differentiated) by definition, they may be clinically confused with virtually any high-grade sarcoma of the deep soft tissue, in particular, synovial sarcoma, high-grade liposarcoma, rhabdomyosarcoma, and high-grade fibrosarcoma. Other mimics include benign soft-textured neoplasms such as lipomas.

Histopathology

Malignant fibrous histiocytoma is by definition a poorly differentiated neoplasm that lacks (or appears to lack) specific lines of differentiation. As such, these neoplasms are composed of highly atypical cells that may be spindled or irregular in shape (Fig. 17-11). Neoplastic cells may be embedded within a myxoid stroma, acute and chronic inflammation, collagen, or necrotic debris. Mitotic figures, including those that are atypical, are characteristically present.

TENOSYNOVIUM-ASSOCIATED TUMORS

Ganglion (Synovial) Cysts

Ganglion cysts are pseudocysts, meaning they lack a bona fide epithelial lining. These mass-forming lesions may be lined by fibrous tissue or metaplastic synovial tissue. Synovial cells may be distinguished from epithelium by the absence of an underlying basal lamina and the manner in which these cells blend imperceptively with the underlying stroma. Synovial tissue, when present, is a chief producer of hyaluronate, one of the primary components of synovial fluid. When synovial tissue is present, the designation *synovial cyst* is preferred. When synovial cells are not seen the lesion is most precisely referred to as a *ganglion cyst*. For the purpose of this discussion, unless otherwise specified, the term *ganglion cyst* will connote both those pseudocysts with lining synovial tissue and those without it.

Ganglion cysts may arise as the result of any of several distinct pathological processes. Ganglions may arise within peripheral nerves, articular spaces, tenosynovium, supportive soft tissue, or bone. They may represent outpouchings of bona fide synovial tissue near a joint space or tendon sheath (soft tissue ganglia), the product of end-stage soft tissue degeneration secondary to trauma

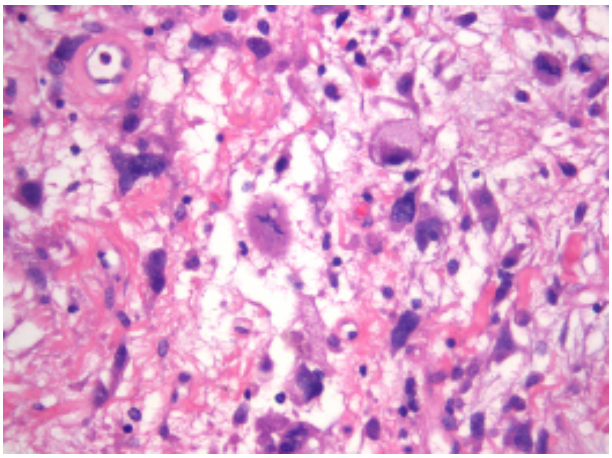

FIGURE 17-11. Malignant fibrous histiocytoma. Bizarre cells without discernible lines of differentiation.

or infarct (intra-osseous ganglia), or the aberrant production of mucosubstances by neoplastic or nonneoplastic stromal elements (digital mucous cysts).[88–91] At least some of the soft tissue "ganglia" are in actuality juxta-articular myxomas that through the production of copious mucin have become cystic.[91] A stalk connecting the cyst with a nearby joint or tendon sheath may in exceptional cases be grossly demonstrated. Some authors have equated digital mucous cysts with ganglion cysts, a reasonable approach when considering the nonspecific nature of the term *ganglion cyst*.[92]

The most common sites of occurrence for ganglion cysts are the distal extremities, especially near the hand and dorsal wrist.[93] Women are involved roughly three to four times more commonly than are men.[92,94] When the lower extremities are involved, the dorsal surface of the foot has been listed as the most common site of involvement; however, if one equates digital mucous cysts with ganglia, that ascertation would be called into question.[92,94,95] The low percentage of ganglion cysts in the series of 196 tumors of the foot and ankle assembled by Ozdemir et al. (1.5%) was most likely due to selection bias, as most such tumors are not surgically treated, and when excised, the procedure is commonly performed in an outpatient setting.[3] This series did not account for such lesions managed in an outpatient setting. Persons of all ages may be affected, though those in the fourth, fifth, and sixth decades of life seem to predominate.[94,95] Pain is the most common complaint, occasionally in the form of radiating or neuritic pain secondary to nerve entrapment.[94] Ganglia that arise in association with peripheral nerves or within closed spaces such as the sinus tarsi may cause neurological symptoms secondary to entrapment-related irritation.[89,94]

Clinical differential diagnosis

Ganglion cysts may mimic a host of soft tissue neoplasms and nonneoplastic tumors. Not uncommonly, ganglia are clinically mistaken for epidermal inclusion cysts, acquired digital fibrokeratomas, rheumatoid nodules, nodular giant cell tumors, or tumors of the cutaneous adnexae. In the Memorial Sloan-Kettering Cancer Center series, several synovial sarcomas and a high-grade fibrosarcoma were followed for extended periods of time as ganglia before a belated biopsy was performed.[1] The profound morbidity associated with such oversights led Scully and colleagues to suggest needle aspiration biopsy with cytopathologic examination for all ganglion-like masses. They recommended open biopsy or excision of all those lesions that failed to sufficiently aspirate.[5]

Histopathology

There are subtle histopathologic differences among ganglion cysts, depending on the manner in which they arise. All have in common the presence of abundant mucinous material dispersed amidst fibrous tissue without an epithelial lining (Fig. 17-12). Some are partially or completely lined by synovial tissue of varying thickness. Most have distinct lumina; however, some simply exhibit pools of mucin amidst loose fibroconnective tissue. There may be a dense fibrous capsule, particularly in longstanding lesions. When a capsule is present, myxoid degeneration is a typical finding. Upon cytologic examination, the product of an aspiration from a ganglion cyst is not entirely specific. Scattered mucin, histiocytes, and inflammatory cells are standard findings. In this context it is the *lack of* malignant cells that is of significance.

Fibroma of Tendon Sheath (FTS)

FTS was the diagnosis rendered in only 1% of the 401 soft tissue neoplasms described in the Memorial

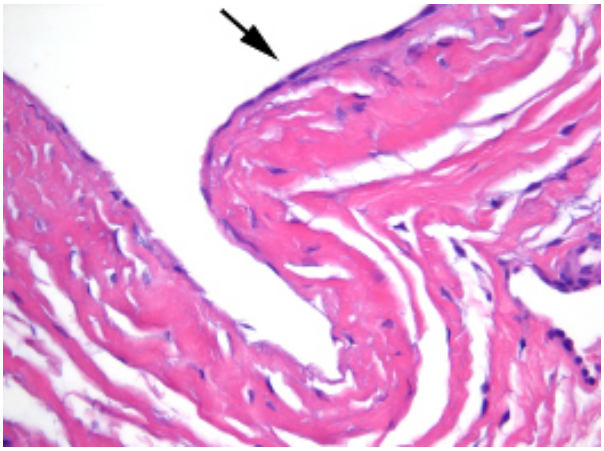

FIGURE 17-12. Ganglion cyst. Fibrous pseudocyst with an incomplete attenuated synovial lining.

Sloan-Kettering Cancer Center series.[1] There were none in the series of 196 tumors of the foot and ankle assembled by Ozdemir et al.[3] The lack of such tumors in large series is almost surely secondary to the fact that such tumors are highly unlikely to find their way into cancer centers or consultation files. A compelling argument for the existence of a transitional lesion that lies midway between fibroma of tendon sheath and giant cell tumor of tendon sheath was offered by Satti. The presence of such a lesion and antigenic similarities between these tumors suggest that FTS and giant cell tumor of tendon sheath represent the same process at varying stages in their evolution.[96,97] Militating against this notion is the fact these lesions appear to develop in association with different chromosomal breakpoints.[98,99] Although FTS have traditionally been considered to be reactive (nonneoplastic) lesions, the presence of a t(2;11) chromosomal translocation in at least one case and seemingly autologous growth seem to favor a neoplastic origin.[98]

In most instances, FTS present themselves as painless insidiously growing subcutaneous masses in young to middle-aged adults.[100,101] Men are affected twice as often as are women.[101] The extremities are most often involved, with the hands being affected at a higher rate of frequency than the feet.[101] Tumors rarely exceed 3 cm in greatest diameter.[102] Upon gross examination, most FTS are well-circumscribed, round, or slightly lobulated tumors with a firm consistency and solid cut surface.

Clinical differential diagnosis

Fibroma of tendon sheath may resemble giant cell tumors of tendon sheath, epidermal inclusion cysts, Schwannomas, or adnexal neoplasms. Possibly, the lesion most commonly mistaken for FTS is ganglion or synovial cyst.[103] This distinction may in most cases be made with transillumination (positive in cysts) or fine-needle aspiration biopsy, which will not elicit cyst fluid in cases in FTS. Because other solid tumors, including those that are malignant, may result in a "dry tap," clinicians should consider open biopsy for tumors that fail to aspirate.

Histopathology

Histopathologic sections demonstrate a solid hypocellular tumor with a dense collagenous surface. There is often a vaguely lobulated configuration. Most lesions exhibit slit-like vascular spaces scattered throughout the lesion or at minimum present focally (Fig. 17-13). The tumors are extremely well circumscribed, though true capsules are not present.

Tenosynovial Giant Cell Tumor, Localized Type (GCTL) (Nodular Tenosynovitis/Tenosynovial Giant Cell Tumor, Nodular Type)

GCTL is a relatively common, benign soft tissue neoplasm, accounting for almost 17% of the benign soft tissue neoplasms of the foot in the Memorial Sloan-Kettering Cancer Center series.[1] These tumors are distinct from and should not be confused with giant cell tumor of low malignant potential and giant cell malignant fibrous histiocytoma, which although histologically similar, represent different clinicopathological entities.[32] It has been suggested that GCTL represent the initial phase of a spectrum that eventuates into fibroma of tendon sheath; however, their contrasting chromosomal changes and epidemiological features argue otherwise.[96,97,101,104,105] Some have concluded that the antigenic profile of GCTL most closely resembles that of synovial tissue.[105] GCTL have demonstrated a spectrum of chromosomal abnormalities; however, translocation t(1;2) appears to be most consistently identified.[99] The clonal nature of many of the GCTL that have been studied, further argues in favor of a neoplastic process rather than one that is wholly reactive in nature as once suspected.[99]

Unlike fibroma of tendon sheath, GCTL is more common among young to middle-aged females.[104] In addition, these slow-growing neoplasms are much more often identified in the fingers and toes than are fibroma of tendon sheath, which are typically seen more proximally on the extremities.[101,104] The hands are involved roughly six times more often than are the feet.[104] This upper extremity bias may be in part secondary to the underdiagnosis of such lesions when they occur in the feet. GCTL may arise on the plantar or extensor surface; however, some authorities have touted a flexor predominance.[106,107] There may be a history of trauma; however, this is not a consistent finding.[104] Roughly 80% GCTL are painless and freely moveable beneath the overlying skin. Pain is a more routine finding when such lesions involve the soft tissue of the foot.[104,108]

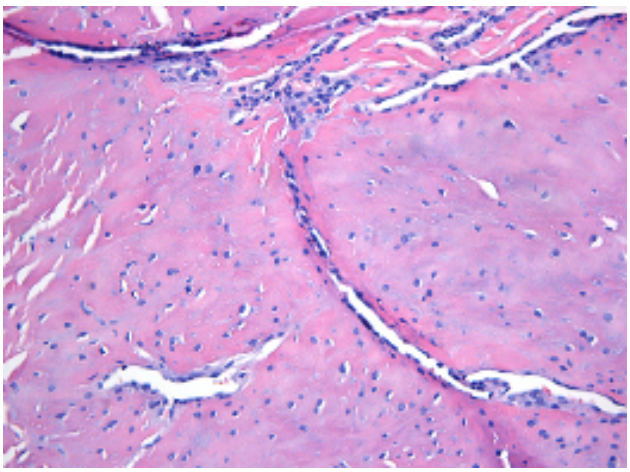

FIGURE 17-13. Fibroma of tendon sheath. Scattered tumor cells within dense collagenous stroma. Scattered slit-like vascular spaces are seen.

Clinical differential diagnosis

The differential diagnosis for GCTL is quite lengthy; however, some notable entities to be considered include fibroma of tendon sheath, ganglion (synovial) cyst, epidermal inclusion cyst, superficial fibromatosis, aggressive digital papillary adenocarcinoma of the extremities, and synovial sarcoma. A case resembling a periungual fibroma has been reported.[109] Erosion of nearby bones may in some cases be evident, especially in association with lesions of the distal forefoot and toes.[110]

Histopathology

Tenosynovial giant cell tumor, nodular type is comprised of an admixture of large osteoclast-like giant cells, small synovial-like mononuclear cells, and foamy histiocytes (Fig. 17-14). Giant cells are variable in number, ranging from rare to extremely numerous. The mononuclear cell population is a consistent finding. These cells have round to reniform nuclei with longitudinal grooves and a moderate amount of pale cytoplasm. Although hemosiderin is a common finding, it is not seen to the degree that it is in pigmented villonodular tenosynovitis. Stromal hyalinization is a common feature.

Tenosynovial Giant Cell Tumor, Diffuse Type (GCTD) (Pigmented Villonodular Tenosynovitis, Proliferative Synovitis)

GCTD is a poorly circumscribed and locally aggressive proliferation of synovium-like tissue that typically arises within a joint space; however, in exceptional cases it may be extra-articular. Some have used the designation “diffuse type giant cell tumor” to describe those occurring within the soft tissue and “pigmented villonodular tenosynovitis” to denote those arising within the joint space.[111] The former of the two has been said to behave in a more aggressive fashion.[111] Most cases of so-called extra-articular GCTD likely represent unrecognized contiguous spread from a nearby joint.[32] The term *malignant giant cell tumor of tendon sheath* should be reserved for tumors that show both areas of traditional giant cell tumor and areas that are overtly malignant histopathologically.

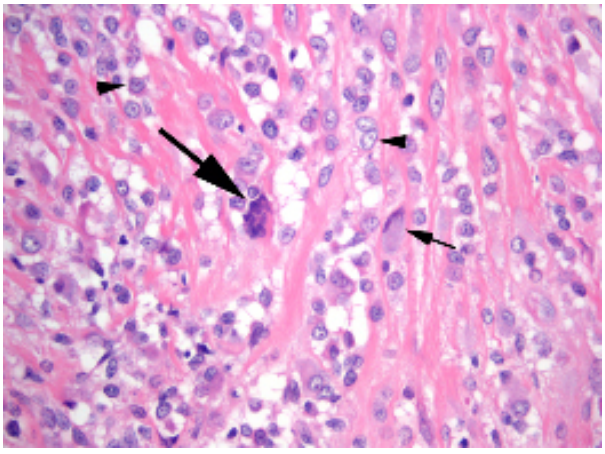

FIGURE 17-14. Giant cell tumor of tendon sheath. A variable collection of giant cells (large arrow), foamy histiocytes (small arrow), and mononuclear cells (arrow heads).

Based on morphologic findings, immunophenotype, and genetic studies, most investigators consider GCTD to be closely related to giant cell tumors of the localized type.[99,105,108] Militating against such a relationship is the presence of chromosome 5 and 7 additions in some cases of GCTD, a feature not described in association with the localized form.[99] In addition, there are epidemiological differences. The diffuse form of tenosynovial giant cell tumor tends to affect a slightly younger age group than does the localized form. Most cases of GCTD arise in persons under 40 years of age, and there is only a slight female predominance.[112]

Roughly 90% of intra-articular GCTD (pigmented villonodular synovitis) involve the knee and hip, with the ankle involved to a much lesser extent.[113] Toe and midfoot involvement has been reported.[114] When the soft tissue is primarily affected, there is a far more even anatomic distribution.[115] In one large series of extra-articular GCTD, nearly 20% of cases involved the foot and ankle.[115] Patients with GCTD commonly present with articular or peri-articular pain and swelling with decreased range of motion.[116] Hemarthrosis, degenerative osteochondral findings, and bone invasion are expected findings.[113,114] These tumors should be regarded as benign, but locally aggressive, neoplasms that are prone to recurrence when inadequately excised.[115] Cases that exhibit frankly malignant histopathologic features are better characterized as bona fide sarcoma.[115]

Clinical differential diagnosis

Tenosynovial giant cell tumor, diffuse type, may resemble a number of different clinical conditions, depending on where they arise. Intra-articular GCTD may mimic a loose body, chronic synovitis, gout, rheumatoid synovitis, or degenerative joint disease. Those that arise within the extra-articular soft tissue may be entirely nonspecific, appearing as an ill-defined soft tissue mass that may or may not extend to a nearby joint.

Histopathology

Upon histopathologic examination, GCTD grows as infiltrative sheets with a variably villous configuration. Cleft-like spaces are often present. Cytologically, GCTD are composed of an admixture of small mononuclear histiocyte-like cells, larger round cells, multinucleated giant cells, foamy histiocytes, and lymphocytes (see GCT of tendon sheath). Giant cells may be less numerous than would be

typical of the nodular variant. In contradistinction to GCT of tendon sheath, diffuse GCT often shows abundant fresh hemorrhage and hemosiderin scattered within the tumor.

TUMORS OF ADIPOSE TISSUE

There is a spectrum of neoplastic and nonneoplastic processes that are composed of adipose tissue or exhibit cells that express adipocyte-like differentiation. A nonneoplastic proliferation that is of particular interest in podiatric circles is so-called juxtamalleolar lipoma. This physiologic expansion of juxtamalleolar fat pads in some overweight postmenopausal women has been confused with bona fide lipomas by some. In addition, there are numerous true neoplasms, hamartomatous proliferations such as fibrolipomatous hamartoma and angiolipoma, and various metaplastic processes that may result in an adipose-rich mass or growth. Among neoplasms, there is a wide spectrum of tumors that exhibit adipose differentiation. These neoplasms range from benign tumors that are rarely of clinical significance to high-grade malignancies that readily metastasize and cause death. Despite the fact that they all exhibit at least focal fatty differentiation, their histopathologic appearance and patterns of growth may be strikingly dissimilar.

Lipoma

Lipomas are benign neoplasms composed of cells that closely resemble those in normal adipose tissue. They are by far the most common tumor of the soft tissue when assessing the entire body, accounting for at least 16% of such benign tumors.[32,116] In actuality, because the overwhelming majority of these lesions go undiagnosed, their frequency is certainly much higher.[32] Despite their frequency elsewhere, lipomas accounted for only 2% of the "tumors" of the foot in the series by Ozdemir et al. and only 1.7% of all soft tissue neoplasms in the Memorial Sloan-Kettering Cancer Center series of 401 such tumors of the foot.[1,3] As lipomas are neoplastic, they tend to harbor a characteristic subset of mutations involving the long arm of chromosome 12 or 13 or the short arm of chromosome 6.[117,118] In contrast, subcutaneous angiolipomas appear to have a normal karyotype, suggesting that they represent hamartomatous proliferations rather than true neoplasms.[119]

Lipomas may be seen in persons of any age; however, they are most frequently identified after the first two decades of life, particularly in obese individuals.[120] Men are affected slightly more commonly than are women.[120] Lipomas may arise superficially within the subcutaneous tissue or deep within the muscle or fascia. Within the foot, the subfascial space is routinely involved.[121] Most lipomas present as slow-growing dome-shaped masses, though their shape may be distorted by overlying tendons or retinaculae. Superficial lipomas are well circumscribed; however, intramuscular variants may disclose a diffuse pattern of growth. Although lipomas are rarely painful, cases presenting as symptomatic macrodactally and plantar fasciitis have been described.[122–124] Pain may be a prominent feature in association with some angiolipomas due to the presence of intra-vascular fibrin thrombi and the resultant local ischemia. Both genuine lipomas and abnormally prominent nonneoplastic fat pads may cause pain secondary to nerve entrapment.[125–127]

Apart from conventional lipoma, there are several distinct lipoma variants, each classified based on its particular histopathologic and/or genetic features. These variants include spindle cell lipoma, pleomorphic lipoma, chondroid lipoma, and benign lipoblastoma.[128,129] Based on clinical and genetic observations, angiolipoma is better classified as a hamartomatous process than a true neoplasm.[119] Each lipoma variant boasts its own epidemiological profile and sites of predilection; for instance, spindle cell lipoma typically arises on the neck of upper-middle-aged men where chondroid lipoma tends to arise in the soft tissue of the proximal extremities. A description of the particular features of each of these variants would be beyond the scope if this chapter. Suffice to say, each is benign and rarely of clinical significance.

Clinical differential diagnosis

Superficially located lipomas of the lower extremity may resemble ganglion cysts, rheumatoid nodules, epidermal inclusion cysts, or subcutaneous granuloma annulare. Variants that are firm to palpation may resemble other low-grade soft tissue tumors. Benign tumors that might be considered within the differential diagnosis are nerve sheath tumors and juxta-articular myxomas. The most common malignancies to be mistaken for classic lipomas in the distal lower extremity are high-grade fibrosarcoma, synovial sarcoma, and clear-cell sarcoma (melanoma of soft parts), due to their typically soft texture.

Histopathology

Both classic lipoma and its variants have in common a line of differentiation toward that of adipose tissue which, with the exception of lipoblastoma, is mature in appearance. Most are well circumscribed and some possess a thin capsule-like layer of compacted fibrous tissue around the periphery (Fig. 17-15). Individual adipocytes disclose a single attenuated nucleus compressed to one side of the cell membrane due to a single intracytoplasmic lipid-containing vacuole that distends the cell and produces the characteristic clear and distended appearance. In conventional lipoma, the fibrous septae are

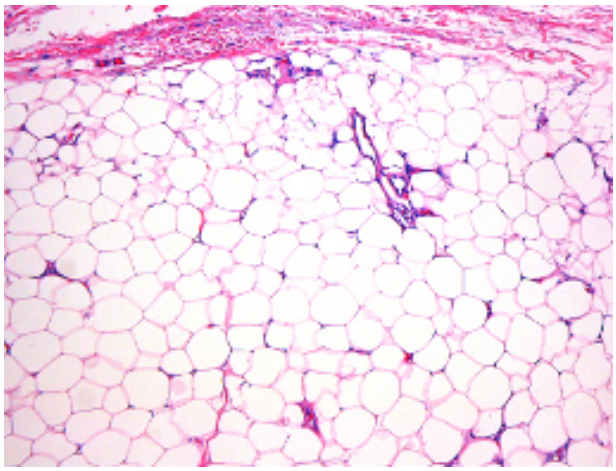

FIGURE 17-15. Lipoma. A lobulated proliferation of mature adipose tissue surrounded by a delicate fibrous membrane.

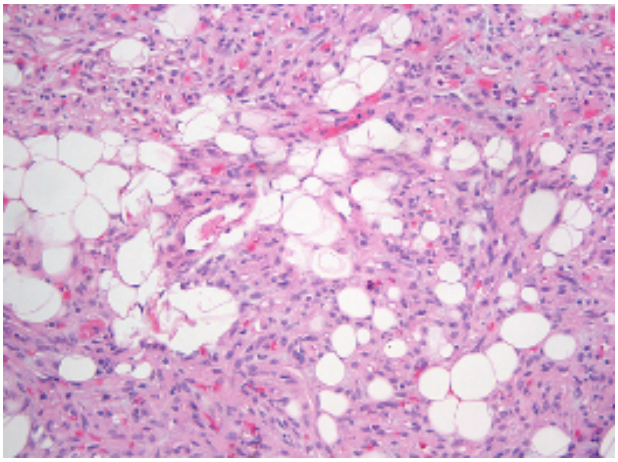

FIGURE 17-16. Spindle cell lipoma. Bland spindled cell blended with mature adipocytes, resulting in a histopathologic appearance reminiscent of dermatofibrosarcoma protuberans.

delicate and lack significant cellularity. Neither nuclear atypia nor hyperchromasia is an expected finding in routine cases; however, sporadic large and multinucleated cells are characteristic of the pleomorphic variant. Conventional lipomas may possess within them, areas of metaplastic bone (osteolipoma), paucicellular zones of fibrous tissue (fibrolipoma), or copious myxomatous material (myxolipoma). The fat content within lipoma variants may vary from scant to abundant. Spindle cell lipoma is thought to be part of the same spectrum as pleomorphic lipoma. These tumors may be quite cellular and to an unsuspecting pathologist might be confused with an infiltrative fibrocytic neoplasm that has invaded into fat rather than one neoplasm with two morphologically distinct components (a biphasic neoplasm) (Fig. 17-16). Chondroid lipoma is a newly described neoplasm that is significant only in that it may closely resemble extraskeletal chondrosarcoma. Benign lipoblastoma is unique among the lipoma variants in that it boasts a prominent component of immature-appearing fat cells (lipoblasts) and arises in children under three years of age.[130]

Fibrolipomatous Hamartoma of Nerve (Neural Fibrolipoma, Lipomatosis of Nerve)

Fibrolipomatous hamartoma of nerve is an uncommon hamartomatous proliferation of fibrous tissue and fat within the epineurium of peripheral nerves of the distal extremities.[131] The overwhelming majority of fibrolipomatous hamartoma (FH) arise in association with the median or ulnar nerve of the upper extremity; however, involvement of the lower extremity's dorsal cutaneous nerves, superficial peroneal nerve, and the more distally located nerves of the foot has been described.[132–138] In roughly 30% of cases, FH present as macrodactyly, and in this setting females appear to predominate.[132,138] In a small percentage of cases, localized gigantism is compounded by hypertrophy of the underlying bone.[132] Fibrolipomatous hamartomas typically become clinically apparent during early childhood as a fusiform enlargement along a neural tract; however, few are formally diagnosed prior to the second decade of life.[132] In some cases, FH are solitary and asymptomatic; however, with enlargement there may be associated motor or sensory deficits.[102] For symptomatic lesions, a tissue diagnosis will provide a definitive diagnosis, though for asymptomatic lesions that will likely not be excised, MRI imaging studies are pathognomonic.[139] Conservative surgical treatment is largely limited to eliminating compressive forces such as overlying retinaculae.

Clinical differential diagnosis

The clinical differential diagnosis for FH includes nearly all soft tissue masses, in particular, those that involve peripheral nerves or may lead to compression neuropathy. Intraneural ganglia, intraneural neurofibroma, plexiform neurofibroma, intraneural lipoma, and benign and malignant nerve sheath tumors may be clinically indistinguishable, though most may be readily excluded with MRI imaging studies.

Histopathology

Histopathologic sections reveal a bulbous expansion of the involved nerve secondary to a diffuse infiltration of benign fibroadipose tissue within the epineurium. The remaining nerve fascicles are gathered in lobule-like collections that are separated by the soft tissue infiltration. The endoneurium appears largely uninvolved by the process.

Cytologically, the fibroadipose tissue is without significant cellularity and nuclear atypia is not seen. There is a highly variable ratio of fibrous tissue to fat with adipose tissue predominating in most instances.

Liposarcoma

Liposarcoma is a term that denotes a sarcoma that exhibits at least focal differentiation toward that of adipose tissue. There are several distinct entities that fall within this general category, each having distinct clinical, histopathologic, and genetic features. On the low-grade end of the spectrum is atypical lipomatous tumor (well-differentiated liposarcoma) and low-grade myxoid liposarcoma, lesions that when arising in the extremities are cured with complete excision. In sharp contrast are high-grade myxoid sarcoma (round cell sarcoma), dedifferentiated liposarcoma, and pleomorphic liposarcoma, which metastasize readily and may cause death.

Atypical Lipomatous Tumor (Well-Differentiated Liposarcoma)

Atypical lipomatous tumor is a slow-growing but locally aggressive neoplasm that may bear a striking resemblance to benign lipoma both clinically and histopathologically. In most instances, these tumors may be distinguished cytogenetically by the presence of a supernumerary ring chromosome with amplification of region 12q14-15.[140] This neoplasm was once uniformly designated as *well-differentiated liposarcoma*, however, because it rarely if ever metastasizes and complete surgical excision is curative. The term *atypical lipomatous tumor* is now applied these tumors when they arise in sites that are amenable to complete excision.[141] The term *well-differentiated liposarcoma* is reserved for the same tumor when it arises within the abdomen, mediastinum, or other sites where complete excision is hampered by the presence of vital structures. Atypical lipomatous tumor (ALT) accounted for only 1% of the soft tissue tumors of the foot that were summarized at Memorial Sloan-Kettering Cancer Center.[1] In general, liposarcoma (of which almost half are of the well-differentiated/atypical lipomatous type) is much more common elsewhere in the body, accounting for roughly 23% of all soft tissue sarcomas.[142,143] The literature describing atypical lipomatous tumor in the foot is limited to scattered case reports.[144]

Atypical lipomatous tumors may arise superficially or within the deep soft tissue. Those arising within deep sites outnumber those presenting superficially by a ratio of 5:1.[140] The deep soft tissue of the thigh is a particularly common site of involvement.[142] The sexes are affected equally and most cases manifest during the sixth decade of life.[142,145] Most present as well-circumscribed masses that are entirely painless, one reason that these tumors may grow to an exceedingly large size prior to diagnosis.[102] Although ALT do not carry with them a significant risk for metastasis, in approximately 2% of cases that arise in the extremities, these tumors will "dedifferentiate" (lose differentiation through a series of mutations) into a much more aggressive tumor.[146] "Dedifferentiated" liposarcoma may manifest in more than 20% of cases from the retroperitoneum.[146] Overall, the prognosis for persons affected by ALT is excellent when the distal extremities are involved, with a mortality rate that approaches 0%. When internal sites such as the retroperitoneum are affected, the mortality rate may be as high as 80% if followed over a 20-year span.[146,147]

Clinical differential diagnosis

The differential diagnosis of ALT could include virtually any benign or malignant soft tissue tumor. Foremost, due to its gross and histologic similarities, the lipoma-like variant must be distinguished from benign lipomas. Low-grade myxofibrosarcoma may be clinically and radiologically indistinguishable. The soft consistency and potentially large size of ALT may bring various high-grade sarcomas to mind, as these neoplasms exhibit similar textural properties.

Histopathology

Atypical lipomatous tumor may be divided into four subtypes: lipoma-like (adipocytic), sclerosing, spindle cell, and inflammatory. The most common variant is lipoma-like liposarcoma, followed by sclerosing liposarcoma.[102] There is often overlap between the subtypes or expression of two or more elements within the same neoplasm.[102] The *lipoma-like (adipocytic) variant* resembles normal fat. Fibrous septae may be slightly more prominent than would be expected in a lipoma, and scattered large and hyperchromatic cells are an expected finding within both the fatty component and the fibrous stroma (Figure 17-17). The adipocytic cells resemble mature fat cells with clear lipid-containing cytoplasm and a single attenuated nucleus pressed tightly against the cell membrane. In most cases scattered lipoblasts with multiple intracytoplasmic lipid vacuoles and a scalloped nuclear membrane may be identified. The *sclerosing variant* may be largely void of constituents that resemble normal fat. This variant often displays large areas of sclerotic fibrous tissue with only rare adipose-like foci. Large atypical cells with nuclear hyperchromasia are a consistent finding. Rare multinucleated lipoblasts are typically seen within sheets of hypocellular stroma. The *spindle cell* and *inflammatory* variants are extremely rare and most often reported in the deep soft tissue of the retroperitoneum.

Myxoid Liposarcoma (Low-Grade Myxoid Liposarcoma and Round Cell Liposarcoma)

Myxoid liposarcoma (MLS) and round cell liposarcoma, although once classified separately, are now known to

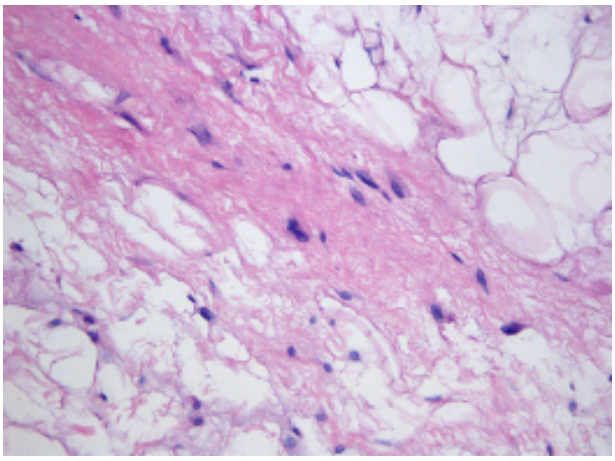

FIGURE 17-17. Well-differentiated (lipoma-like) liposarcoma. A lipoma-like neoplasm with thickened fibrous septae that displays scattered large hyperchromatic cells.

be opposite ends of a common spectrum.[32,148] These sarcomas are often seen as components of the same tumor and have shown identical genetic abnormalities, in the form of translocation t(12;16)(q13;p11), which is identified in over 90% of cases.[148,149] Round cell sarcoma is only rarely seen without an associated component of conventional myxoid sarcoma.[150] Pure myxoid liposarcomas are at the low-grade end of the sarcoma spectrum in that they rarely metastasize but are locally aggressive and notoriously recurrent following inadequate excision. In contrast, because round cell liposarcoma is at the high-grade end of the myxoid liposarcoma spectrum, when at least 5% of the tumor is of this type, distant metastasis can be expected in over 20% of cases.[150,151] Unlike the vast majority of sarcoma, metastases from myxoid liposarcoma are often to extrapulmonary sites.[151]

Myxoid liposarcoma rarely arises within the foot, though its most common site of occurrence is the more proximal portions of the lower extremity. Up to 60% of all myxoid liposarcomas arise in the deep soft tissue of the thigh.[152] Of the 252 soft tissue malignancies of the foot reported at Memorial Sloan-Kettering Cancer Center, only 3 (1.2%) were designated as "myxoid liposarcoma."[1] Due to their rarity in the distal lower extremity, reports have been largely limited to descriptions of exceptional cases.[153,154] Myxoid liposarcoma is most commonly diagnosed in persons in their fourth or fifth decades of life; however, involvement of persons as young as 16 years of age has been described.[150,152] There is no distinct gender predilection. Patients typically present with a painless mass which may have grown to be of substantial size prior to presentation.[152]

Clinical differential diagnosis

Myxoid liposarcoma may closely resemble virtually any soft tissue neoplasm that has a soft to only slightly indurated consistency. Notorious mimics include benign lipomas, atypical lipomatous tumors, low-grade myxofibrosarcoma, and virtually any form of high-grade sarcoma.

Histopathology

Low-grade myxoid liposarcoma is composed of small hyperchromatic stromal cells and scattered lipoblasts embedded within abundant myxoid stroma. The myxoid substance may form pools that are essentially acellular. There is a delicate network of small vessels that may have a "chicken-wire" appearance upon low-power inspection (Fig. 17-18). There is often a lobular pattern of growth with areas of hypercellularity distributed at the periphery of each lobule. In contrast, high-grade round cell areas are largely devoid of myxoid stroma, and rather, show sheets of round atypical cells with scant cytoplasm (Fig. 17-19). Hemorrhage and/or necrosis may be present in association with high-grade histologic features (round cell component).

Pleomorphic Liposarcoma (PLS)

Pleomorphic liposarcoma is one of the rarest forms of liposarcoma. Cases with pedal involvement are profoundly unusual. Only 1 of 252 (0.4%) sarcomas of the foot that were reported at the Memorial Sloan-Kettering Cancer Center was of this subtype.[1] There has been a report of PLS arising in association with a burn scar on the sole.[155] Many cases of what has been designated as "pleomorphic malignant fibrous histiocytoma" may in fact represent examples of pleomorphic liposarcoma that have gone undiagnosed due to insufficient sampling.[87]

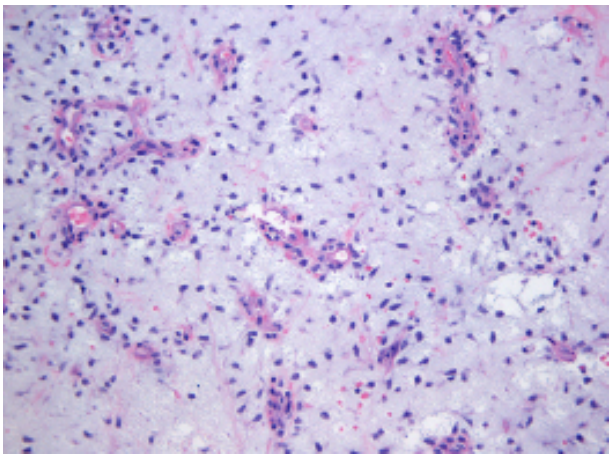

FIGURE 17-18. Myxoid liposarcoma. A delicate network of thin-walled vessels with interposed mucin and small round neoplastic cells.

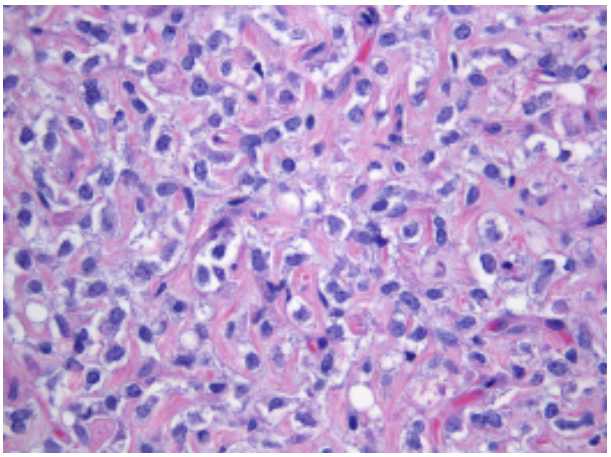

FIGURE 17-19. Round-cell liposarcoma. The high-grade correlate to low-grade myxoid liposarcoma, disclosing much less pronounced vascular and myxoid components.

The most common site for PLS is the deep soft tissue of the thigh.[156,157] Pleomorphic liposarcoma is typically a rapidly growing tumor that may be painless until eroding into, or impinging upon, adjacent structures. There is no clear gender predilection; however, few large series have been compiled to allow for precise epidemiological characterization. Most patients present after the age of 40, and the peak incidence appears to be within the seventh decade of life.[156,157] Pleomorphic liposarcoma is the most aggressive variant of liposarcoma, leading to distant metastasis in over 40% of cases.[151,158]

Clinical differential diagnosis

From a clinical perspective, pleomorphic liposarcoma may present similar to any quickly growing soft tissue neoplasm. Virtually all high-grade sarcomas may be considered within the differential diagnosis as might benign tenosynovial giant cell tumor, lipoma, and low-grade myxofibrosarcoma.

Histopathology

Pleomorphic liposarcoma appears as a sheet-like proliferation of highly atypical spindle cells admixed with scattered bizarre polygonal cells and atypical lipoblasts (Fig. 17-20). In some cases relatively few lipoblasts are seen, making close inspection necessary to avoid resorting to descriptive diagnoses such as “pleomorphic high-grade undifferentiated sarcoma” or malignant fibrous histiocytoma. In some instances PLS is well marginated, while in alternative cases there is a decidedly infiltrative pattern of growth.

Mixed-Type Liposarcoma

In rare cases liposarcomas disclose a combination of two or more of the aforementioned subtypes. Biphasic tumors of this type have been designated as *mixed-type liposarcoma*. This rare liposarcoma subtype is distinctly unusual and largely limited to elderly patient populations.[159]

BENIGN TUMORS OF VASCULAR TISSUE

Pyogenic Granuloma (PG) (Lobular Capillary Hemangioma)

Pyogenic granuloma is a term that has been used within podiatric circles to describe many discrete highly vascularized mass-forming soft tissue proliferations. This might include exuberant granulation tissue at sites of chronic inflammation or, alternatively, distinct vascular proliferations that arise on the skin and mucous membranes (lobular capillary hemangioma). On the skin of the lower extremity, the former of these predominate, particularly in periungual regions. It must be noted that from a dermatopathological perspective, pyogenic granuloma is thought only to be synonymous with lobular capillary hemangioma, a vascular tumor that may or may not be associated with inflammation or ulceration.[160] This also appears to be the most prevalent viewpoint in both the dermatological and pathological literature.[161,162] Although technically speaking PG are variants of capillary hemangioma, because of the unique context in which this designation is used among clinicians of the lower extremity and its importance with regard to its differential diagnosis, the granulation tissue type of “pyogenic granuloma” will be included herein.

Pyogenic granulomas are red-pink dome-shaped lesions that may bleed profusely after minimal trauma.[163]

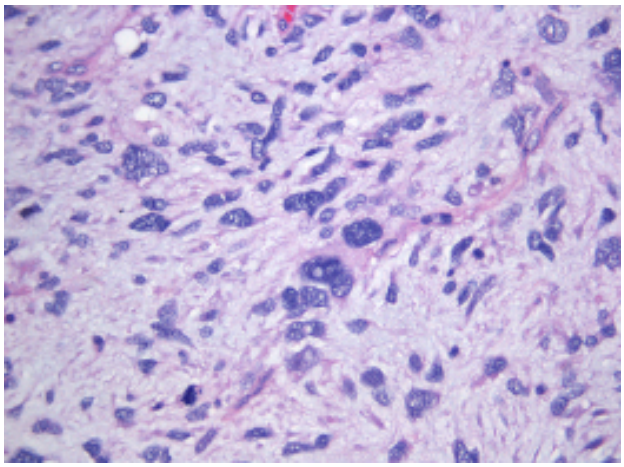

FIGURE 17-20. Pleomorphic liposarcoma. Cytologic atypia in the form of nuclear pleomorphism is pronounced.

They may arise on the mucous membranes, especially in gravid females, or on the skin, in which case young males predominate.[164] Most cases of bona fide pyogenic granuloma (lobular capillary hemangioma) arise on the head and neck, with only about 5% involving the skin of the lower extremity.[161] Because PG are often eroded or ulcerated, they may have a pyogenous appearance; however, this is not a requisite for the diagnosis. Moreover, PG is not a true granuloma. Most persons with PG present with a painless mass with an average size of 1.2 cm.[165] The majority of PG arise spontaneously; however, there is a history of trauma in roughly 26% of cases.[161] The form of pyogenic granuloma that is composed of exuberant granulation tissue uniformly arises in association with persistent inflammation such as one sees in association with a common paronychia. Other associations include retinoids, pregnancy (epulis gravidarum), and alternative vascular proliferations.[166–169] A curious finding is the association between oral retinoids and the formation of chronic paronychias with pyogenic granuloma formation within the lower extremities.[166,167]

Clinical differential diagnosis

There are few lesions in podiatric dermatology that represent diagnostic pitfalls of the magnitude as do pyogenic granulomata. These lesions may be confused with a wide array of benign and malignant tumors of skin and soft tissue. Of particular concern is the resemblance of PG to nodular and amelanotic melanoma, squamous cell carcinoma (especially those arising within the nail unit), basal cell carcinoma, and cutaneous metastases.[170–175] The commonality with which PG may masquerade as a malignancy mandates all such lesions arising in adults be handled with a high index of suspicion and early biopsy.

Histopathology

Lobular capillary hemangiomas are sessile or pedunculated proliferations of thin-walled capillary-like vessels. The vessels form lobules separated by fibrous septae. At the periphery of well-developed lesions there may be a collarette of squamous epithelium, though this is not a common finding when arising on the skin of the foot (Fig. 17-21). In many instances, there are inflammatory changes with or without ulceration overlying the lesion. Cytologically, the endothelial cells are plump and may form solid clusters without an associated lumen. Mitotic figures may be present; however, frank cytologic atypia is not typically seen. The pseudo-pyogenic granulomata that represent exuberant granulation tissue arising at sites of persistent inflammation (such as within a longstanding paronychia) are uniformly inflamed and most commonly exhibit dermal scarring and epidermal ulceration.

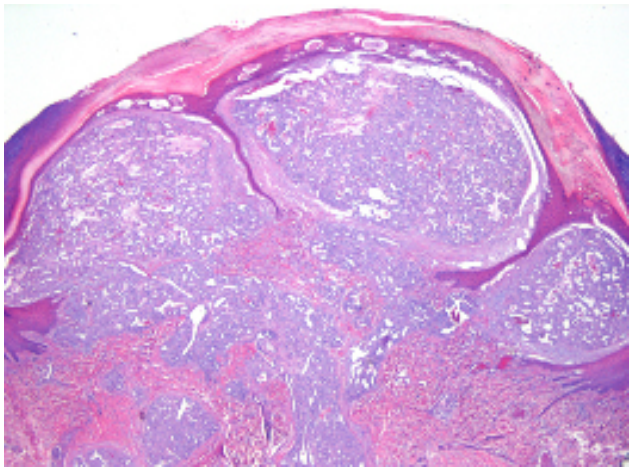

FIGURE 17-21. Pyogenic granuloma. A lobulated proliferation of vascular spaces supported by larger feeder vessels at the lesion's base.

Capillary Hemangioma (Cherry/Senile Hemangioma, Superficial Hemangioma of Infancy)

Capillary hemangioma is a somewhat descriptive term which describes several distinct benign vascular lesions of skin. Within this category are lobular capillary hemangioma (described elsewhere), cherry or senile angioma, and hemangioma of infancy (cellular hemangioma/strawberry hemangioma). These lesions are all composed of thin capillary-like vessels, some of which contain red blood cells. Due to the vascular nature of the lesions in question, they present themselves as red papules or nodules that vary considerably in size depending on the subtype. Hemangiomas of infancy (HOI) range from inconspicuous to quite large, whereas cherry (senile) angiomas usually measure less than 4 mm in greatest diameter. Cherry (senile) angiomas may be further distinguished by the fact that they present during late adulthood, while, as their name implies, HOI are often present at birth or manifest during the first year of life.[160,161] It has been reported that HOI affect up to 12% of all infants within their first year of life and females are predominantly affected with a ratio of 5:1.[176,177] Hemangiomas of infancy are most common on the head and neck (60%) with only 15% involving the extremities.[178] During their initial growth phase HOI may be quite disfiguring; however, involution of these painless lesions occur in 10% of cases per year, whereas 90% of all lesions have undergone involution by the age of 9.[179] It is during this initial growth phase that superficially located lesions may form red nodules, termed *strawberry hemangioma*. In contrast to HOI, cherry (senile) angiomas predominate on the trunk and proximal extremity and persist throughout life.[160]

Clinical differential diagnosis

The diagnosis of cherry angioma is rarely a diagnostic dilemma; however, large lesions may resemble pyogenic granulomata or melanocytic nevi. Like many benign lesions of the skin, once traumatized, cherry angiomas may acquire a more worrisome appearance, resembling "nodular" melanoma. Hemangiomas of infancy are similarly characteristic upon gross examination and thus are most often appropriately diagnosed upon clinical inspection. In some instances, HOI may closely resemble Spitz nevus, an atypical melanocytic neoplasm of childhood.

Histopathology

Histopathologic sections reveal a superficial, deep, or mixed proliferation of thin-walled capillary-like vessels that may exhibit a lobular configuration; however, this may not be as pronounced as is expected in pyogenic granuloma (PG) (Fig. 17-22). Although superficial ulceration or inflammation may be seen, this is also not an expected finding as it is in PG. There may be a collarette of squamous epithelium at the lesion's periphery, especially in cherry (senile) angioma; however, this is often not a prominent finding. Cytologically, endothelial cells are without atypical nuclear features.

Cavernous Hemangioma (Venous Malformation/Deep Hemangioma of Infancy)

Cavernous hemangioma (CH) is similar to capillary hemangioma in many epidemiological respects; however, there are important distinctions. CH typically arises deeper within the dermis, thus imparting a bluish hue. In addition, CH does not share the tendency to spontaneously regress, but rather will persist or in some cases, progress. Because these lesions cannot be expected to regress and may be responsible for local destruction, many cases must be managed surgically. Although like capillary hemangioma these tumors most commonly involve the head and neck, their occurrence within the foot is well documented.[1,180–184] Most CH are painless; however, tendinitis secondary to impingement on neighboring structures has been described.[185] Alternatively, discomfort may arise secondary to intralesional vascular thrombosis.

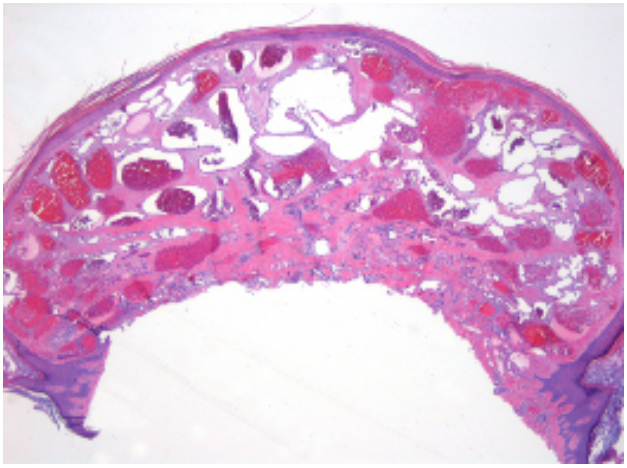

FIGURE 17-22. Cherry (senile) hemangioma. An admixture of small and intermediate-sized vascular spaces with less pronounced lobularity than would be expected in association with pyogenic granuloma.

Clinical differential diagnosis

Similar to superficial hemangioma of infancy, the diagnosis of CH is usually made upon simple visual inspection. Within the differential diagnosis are other vascular proliferations, such as various vascular malformations, hobnail hemangioma, acquired tufted angioma, and low-grade angiosarcoma (hemangioendothelioma).

Histopathology

Upon histopathologic analysis, CH is found to be composed of thin-walled vessels resembling those in capillary hemangioma except of larger diameter. Some vessels may exhibit an attenuated smooth muscle wall. The vessels may disclose a lobular arrangement; however, in some cases they may be haphazardly disposed. The collarette of squamous epithelium that typifies capillary hemangiomas is most often not seen in CH, in part due to their deeper location. The endothelial cells lining the vessel luminae are flat and devoid of cytologic atypia.

Arteriovenous Malformation (Vascular Malformation, Arteriovenous Hemangioma)

This is a designation that may be applied to vascular proliferations composed of well-developed veins, or an admixture of veins and arteries. These lesions are not bona fide neoplasms, but rather, develop congenitally or in exceptional instances as a reactive phenomenon secondary to localized trauma.[186,187] The overwhelming majority of arteriovenous malformations (AVM) are the result of faulty fetal vascular development, particularly among those that arise in the deep soft tissue.[188] Vascular malformations may be loosely classified into deep variants, which most commonly present themselves in the head and neck or limbs of children or young adults, and superficial variants that are seen most often in the skin of the head and neck of middle-aged or elderly persons, with a predilection for the lip. It is the deep type that may be

associated with severe arteriovenous shunting leading to sequelae ranging from soft tissue hypertrophy to Kasabach-Merritt syndrome or cardiac failure.[189] In most instances, AVM are solitary lesions that are not associated with a named syndrome; however, associations with Osler-Rendu-Weber, Sturge-Weber, Fabry, Gorham, Klippel-Trenaunay, Maffucci, and Hippel-Lindau syndromes have been reported.[190] Where superficial AVM commonly present as a solitary blue papule, the deep type may have an extremely variable appearance. Deeply situated lesions may vary from grossly unapparent to Kaposi sarcoma-like due to associated changes within the superficial dermal soft tissue. A similar "pseudo-Kaposi sarcoma" change may be observed in the lower extremity, in association with stasis, where it has been designated as *acro-angiodermatitis*.[191]

Clinical differential diagnosis

Arteriovenous malformations have a variable differential diagnosis depending on whether they arise superficially or within the deep soft tissue. The superficial types may be confused with eccrine or apocrine hydrocystomas, blue nevi, or melanomas, or, once traumatized, may mimic epithelial tumors of the skin. The deep variant may be characteristic when accompanied by soft tissue hypertrophy. Exceptional cases may mimic Kaposi's sarcoma or angiosarcoma.

Histopathology

Superficial AVM are typically well-circumscribed collections of thin and thick-walled muscular vessels that resemble arteries and veins. Veins often predominate. Close histopathologic inspection may demonstrate arteriovenous anastomoses; however, we have found such a connection to be exceedingly difficult to demonstrate. Deep AVM are more diffuse in nature and may be associated with a significant fibrous stromal component. Focal thrombosis and evidence of organization may be present.

Spindle Cell Hemangioma (Spindle Cell Hemangioendothelioma)

Spindle cell hemangioma was originally described in 1986 as a low-grade variant of angiosarcoma.[192] It is now widely accepted that these unusual vascular proliferations are nonneoplastic and lack malignant potential.[193,194] Most examples present in the extremities as burgundy-blue papules or nodules. Cases involving the foot are particularly common.[192–196] All ages may be affected, but most arise in persons in the second or third decades of life.[192–194] The condition is usually indolent; however, some persons will continue to develop additional lesions over long periods of time. Spontaneous regression is not the rule but may occur.[192–194] There is a loose association between spindle cell hemangioma and Klippel-Trenaunay syndrome and Maffucci's syndrome.[194,197]

Clinical differential diagnosis

Spindle cell hemangioma may exhibit a clinical appearance that is frankly reminiscent of angiosarcoma. Alternatively, these proliferations may simulate Kaposi's sarcoma. Solitary lesions may be impossible to distinguish from cavernous hemangioma and other benign vascular proliferations.

Histopathology

Spindle cell hemangioma is composed of a combination of dilated thin-walled vascular spaces and semisolid areas composed of plump spindled cells, some of which surround slit-like spaces (Fig. 17-23). Spindle cell hemangiomas are notorious for their poor circumscription. Random cases may be predominantly intravascular, affecting medium-sized veins.

Glomus Cell Tumor (Glomangioma)

This is a probable neoplasm that is composed of cells that exhibit differentiation towards the regulatory cells of the Sucquet-Hoyer canal. These modified smooth muscle cells function in the regulation of body temperature by selectively permitting or restricting blood flow through arteriovenous anastomoses within the integument.

Glomus tumors are rare, accounting for only 2% of all soft tissue tumors.[198] The overwhelming preponderance of glomus tumors arise in the skin, particularly the fingers and toes.[32] *Glomus cell tumor* is the designation given to solid collections of glomus cells. This variant accounts for roughly 75% of all such lesions.[32] Glomus cell tumor is the variant that most commonly arises in subungual locations, and is painful upon palpation.[199–201] Glomus cell tumors form solitary blue-purple papules or nodules in persons of all ages, but particularly in adults. There is no gender bias except in the case of subungual lesions, which are more common in women.[200,201]

Glomangioma is a closely related proliferation distinguished by the presence of large hemangioma-like dilated vascular spaces. Most glomangiomas are solitary; however, multiple lesions may be seen in association with an autosomal dominant mode of inheritance linked to a mutation involving the short arm of chromosome 1.[202] These tumors are less likely to arise in subungual locations.[199] Rare atypical and malignant variants have been documented, including a case of glomus cell sarcomas arising within an otherwise benign glomus cell tumor.[203,204] Such lesions characteristically disclose size greater than 2 cm, atypical mitoses, or frank cytologic atypia in the form of nuclear pleomorphism and hyperchromasia.

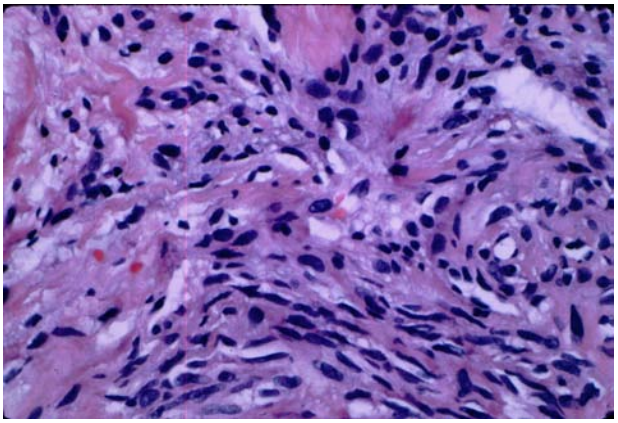

FIGURE 17-23. Spindle cell hemangioma. Densely cellular regions composed of plump spindled cells forming slit-like luminae.

Clinical differential diagnosis

Both glomus cell tumors and glomangiomas may be confused with various benign vascular tumors. In some instances these lesions may be confused with leiomyomas of both vascular and erector pili types. Subungual lesions may simulate pyogenic granulomas and trauma-related changes. Glomangiomas may mimic angiomatosis, spindle cell hemangioma, or angiosarcoma when multiple.

Histopathology

Glomus cell tumors are composed of uniform round cells with central nuclei creating a "fried egg" appearance. Glomus cell tumors disclose nests and sheets of glomus cells surrounding small capillary-like vascular spaces. Glomangiomas are composed of identical cells; however, they surround large vein-like vessels. The cells constituting glomangiomas are much less likely to form sheets, but rather, form thin cuffs around the intratumoral vessels (Fig. 17-24). Some pathologists recognize an additional, extremely rare variant designated as glomangiomyoma. This final subtype most closely resemble solid glomus cell tumor, but with more prominent smooth muscle differentiation.

MISCELLANEOUS BENIGN VASCULAR PROLIFERATIONS

Acquired Tufted Angioma (Angioblastoma of Nakagawa)

This is a benign but progressive vascular proliferation that was first detailed in the Japanese literature under the designation *angioblastoma*.[205] Acquired tufted angioma (ATA) is most often identified on the head, neck, or trunk of young children. There is no distinct gender predilection.[206] Lesions are slowly progressive forming patches, papules, and/or nodules.[206,207] Because ATA are poorly marginated and show a tendency for extensive infiltration of affected areas, excision is typically not possible. These tumors are comprised of scattered aggregates of thin-walled vessels that may permeate throughout the dermis and underlying subcutis (Fig. 17-25)

Hobnail Hemangioma (Targetoid Hemosiderotic Hemangioma)

Hobnail hemangloma is a benign vascular proliferation first described in 1988 by Santa Cruz under the designation *targetoid hemosiderotic hemangioma*.[208] This lesion characteristically presents on the trunk or extremities of young to middle-aged adults. There is a slight male predominance.[208–211] Just as the name implies, these tumors may in some instances exhibit a central violaceous focus surrounded by a pale halo and then an additional peripheral ecchymotic or brown-yellow ring.[208] Most examples do not have such characteristic features. Some investigators believe these benign lesions to be related to other low-grade vascular proliferations such as *Dabska's tumor* and *retiform hemangioendothelioma*; however, due to the potentially aggressive behavior that may be noted in relation with these latter lesions, a distinction must be maintained.[211] A clear understanding of the histopathologic features of hobnail hemangioma must be maintained to avoid confusion between this lesion and vascular neoplasms of either borderline malignancy or those that are frankly malignant. These lesions are composed of convoluted collections of thin-walled vessels lined by plump endothelial cells, the nuclei of which tend top protrude into the vascular lumen (Fig. 17-26). This cytologic finding has been designated as a hobnail configuration.

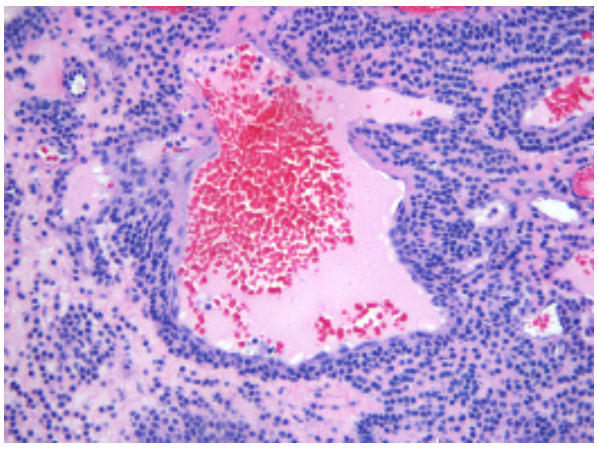

FIGURE 17-24. Glomangioma. Round monomorphous cells form layers around intratumoral vessels.

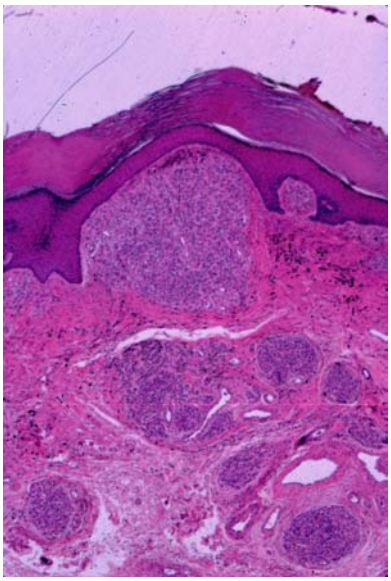

FIGURE 17-25. Acquired tufted angioma. Collections of benign vessels scattered throughout the dermis of volar skin.

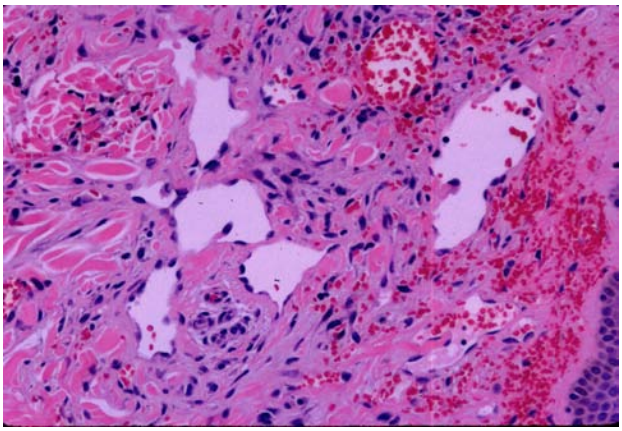

FIGURE 17-26. Hobnail hemangioma. Thin-walled vessels with endothelial cells with nuclei that appear to hang into the vascular luminae.

Verrucous Hemangioma (Neviform Verrucous Acrohemangioma)

Verrucous hemangioma is an unusual form of capillary hemangioma that occurs most commonly on the legs of children.[212,213] These lesions are typically blue to black and, though forming papules, nodules, or plaques (Fig. 17-27), consistently exhibit a keratotic verrucous surface. Eruptive and liner variants have been described.[214,215] Though in some instances verrucous hemangioma may resemble angiokeratoma, it characteristically extends into the reticular dermis and often recurs if incompletely excised.[212,213] Histologically, verrucous hemangioma disclose capillary-like vascular spaces, some of which may be markedly ectatic (Fig. 17-28). There is course papillomatosis and hyperkeratosis of the surface epithelium. Vascular spaces are most prominent within the superficial reticular and papillary dermis; however, extension into the deep dermis may be evident.

VASCULAR TUMORS OF INDETERMINATE POTENTIAL

Kaposi's Sarcoma (KS)

This was described by Kaposi in 1872 under the lengthy designation *idiopathic multiple pigment-sarcoma of the skin.*[216] Interest peaked again during the last three decades as the result of the emergence of an epidemic form in association with acquired immunodeficiency syndrome (AIDS).[217,218] The proliferative cells in KS appear to demonstrate endothelial differentiation based on their morphologic features and antigenic properties. There is much debate as to whether KS is indeed a malignant neoplasm or simple a reactive hyperplastic process. The finding of monoclonality between multicentric vascular proliferations argues in favor of the former; however, this topic remains one of constant debate.[219] There are four clinical variants of KS: classic, endemic (African), immunosuppressive therapy-related, and epidemic (HIV-related).[220] All forms of KS are associated with human herpes virus type 8; however, the causative serotype may be different depending on geographic location.[221,222]

The *classic form* of KS is most often observed on the lower extremities of upper-middle-aged and elderly persons of Jewish, eastern European, or Mediterranean descent.[223]

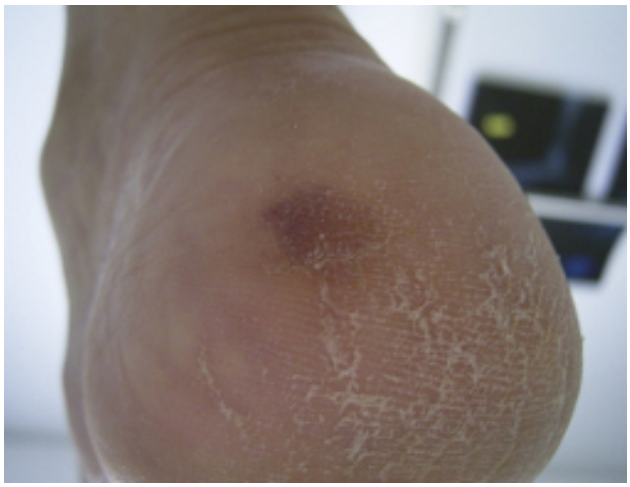

FIGURE 17-27. Verrucous hemangioma. Some verrucous hemangiomas form plaques, particularly when arising on volar surfaces (courtesy Patrick Campbell, D.P.M.).

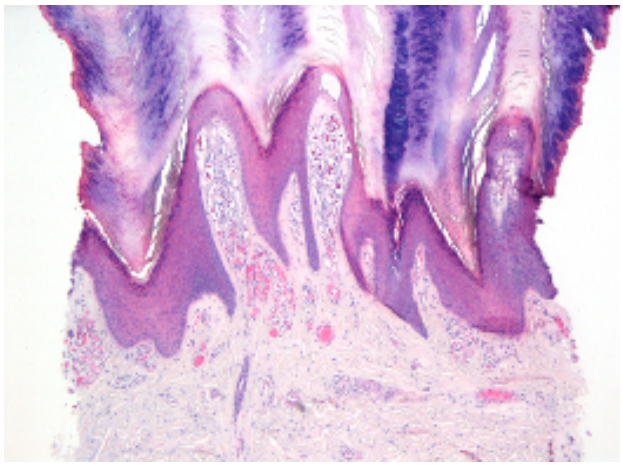

FIGURE 17-28. Verrucous hemangioma. A proliferation of thin-walled vessels within the dermis beneath a verruca-like digitated epithelial surface.

Although chronic and occasionally progressive, this form of KS does not typically cause death, as visceral involvement is uncommon. A relationship between classic KS and the development of non-Hodgkin's lymphoma has been established.[224] The *endemic (African)* variant of KS is most prevalent in sub-Saharan Africa, particularly western Uganda.[225] There are two general subtypes of African KS: a highly aggressive form which arises in children, who usually present with generalized lymphadenopathy and eventually succumb to the disease; and a second form that follows an indolent course, affecting the lower extremities of middle-aged adults.[226,227] *Immunosuppression-associated* KS is the rarest of the four subtypes of KS, affecting persons whose immunological status is being iatrogenically suppressed.[225,228] This form of KS characteristically follows an indolent course and affects organ transplant recipients.[228] The *epidemic (HIV-associated)* variant of KS manifests in persons infected with either HIV-1 or HIV-2.[229] In the United States and Europe, this form of KS is most common in homosexual and bisexual men; however, women and children may be affected in exceptional cases. Unlike the classic form of KS, persons affected by the epidemic form usually exhibit lesions beyond the lower extremity.[217] Such lesions may involve the mucosal surfaces, head and neck, upper extremities, and trunk. Also in sharp contrast to the classic form, in epidemic KS visceral involvement is considerably more common, sometimes without associated skin lesions.[230]

Kaposi's sarcoma usually presents itself as multiple bluish-brown macules or patches; however, cases may progress to form nodules or tumors. Advanced lesions may ulcerate. Oral involvement is common.

Clinical differential diagnosis

Kaposi's sarcoma may mimic low-grade angiosarcoma (hemangioendothelioma), high-grade angiosarcoma, angiokeratomas, and spindle-cell hemangioma. We have seen plantar lesions with superimposed reactive change mimic verruca vulgaris and pyogenic granuloma.

Histopathology

Kaposi's sarcoma is seen histopathologically in three distinct stages: patch, plaque, and nodular. The patch stage discloses as an extremely infiltrative proliferation of slit-like jagged vascular spaces that appear to dissect through the collagen of the reticular dermis. The proliferation is often more prominent around the normal dermal vasculature and adnexal structures. Lesional cells may have a somewhat hobnail appearance, and atypical features are subtle. Extravasated erythrocytes and hemosiderin deposits are expected findings. Sometimes normal vascular channels are noted protruding into lesional vessels, a features designated as the *promontory sign*. In the plaque stage, the proliferation is much more exaggerated, with extension of lesional cell throughout the reticular dermis. In some areas the density of the spindle cell population may make vascular spaces difficult to identify. Eosinophilic globules (intra-cytoplasmic degenerated erythrocytes) may be easily identified as collections of pale pink particles within the cytoplasm of lesional cells. The nodular phase is characterized by a well delineated dermal proliferation of plump spindled cells (Fig. 17-29). Lesional cells form interlacing fascicles around scattered slit-like vascular spaces. Cytologic atypia is mild but mitotic figures may be numerous. Extravasated red blood cells is a consistent finding, as are the presence of eosinophilic globules (Fig. 17-30). There may be erosion or ulceration of the overlying epidermis.

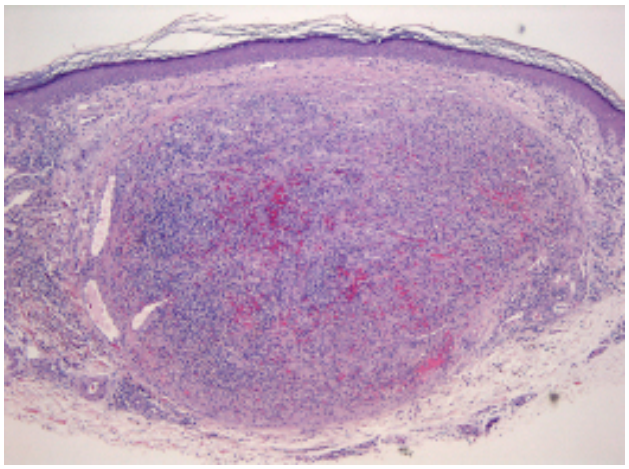

FIGURE 17-29. Kaposi's sarcoma (nodular). A well-circumscribed dermal-based proliferation of spindled cells.

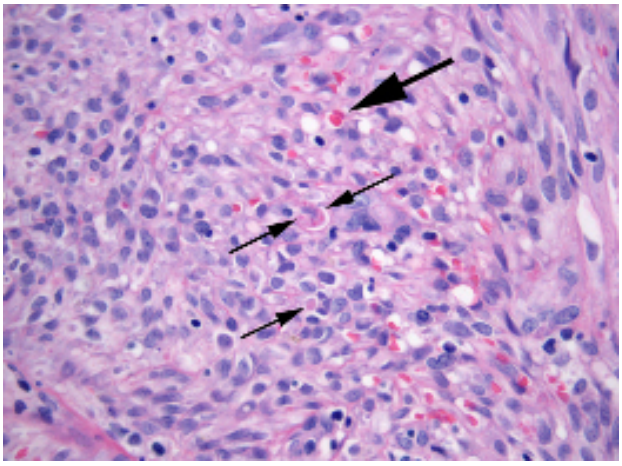

FIGURE 17-30. Kaposi's sarcoma. Sheets of spindled cells with abundant extravasated erythrocytes (large arrow) and scattered intracytoplasmic eosinophilic globules (small arrows).

MALIGNANT TUMORS OF VASCULAR TISSUE

Epithelioid Hemangioendothelioma (EHE)

This is a distinctive low-grade malignant vascular neoplasm first described by Enzinger and Weiss in 1982.[231] Although technically a form of angiosarcoma, this neoplasm is best considered separately due to its distinctive epidemiologic features and characteristic genetic abnormalities, particularly translocation t(1;3), which has been identified in at least two cases.[232,233] Epithelioid hemangioendothelioma may present in the skin, soft tissue, or bone of the lower extremity, though its potential sites of origin are significantly more diverse than this.[231,234–236] It represented but 3 of 252 malignant soft tissue tumors of the foot described at the Memorial Sloan-Kettering Cancer Center.[1] When arising in the bone of the lower extremity, multicentricity is not uncommon.[237,238] Unlike traditional angiosarcoma, EHE of the soft tissue occurs at a similar rate across all age groups, with the exception of childhood, when it is only rarely reported.[236,237] There is no particular gender predilection.[231,239] Roughly half of all cases of EHE arise from within a vascular space, usually a vein.[239,240] Soft tissue and cutaneous EHE characteristically present as firm painful nodules. Symptomatology may in some cases be related to local vascular compromise. Unlike many sarcomas, EHE may metastasize first to lymph nodes.[238] The mortality rate from primary soft tissue EHE is approximately 17%.[239]

Clinical differential diagnosis

The differential diagnosis for EHE varies greatly depending on the site of occurrence and the extent of intratumoral vascularity. When these neoplasms arise in the skin and deep soft tissue they may be quite nondescript, resembling soft tissue tumors such as angioleiomyoma, schwannoma, and virtually any soft tissue-based sarcoma. Well-vascularized lesions may mimic hemangioma, vascular malformation, angiokeratoma, Kaposi's sarcoma, or angiosarcoma. A case presenting as a suspected subungual hematoma of the hallux has been reported.[238]

Histopathology

Epithelioid hemangioendothelioma is characterized by plump polygonal or slightly spindled endothelial cells arranged in cords, nests, or small sheets. Some cells may line small vascular spaces; however, this is not typically a prominent feature. These neoplasms may be deceptively infiltrative within the surrounding soft tissue. The intervening stroma ranges from loosely fibrous to hyalinized, and there may be a somewhat myxoid appearance. Cytologically, lesional cells possess abundant pink cytoplasm and vesicular nuclei with inconspicuous nucleoli. Occasional cells disclose intracytoplasmic luminae containing red blood cells (Fig. 17-31). Such luminae may represent the formation of primitive vascular spaces.

Angiosarcoma (Hemangiosarcoma)

This is a malignant neoplasm that exhibits differentiation toward normal blood vascular or lymphatic vascular endothelium. Angiosarcoma (AS) is relatively uncommon to arise in the foot, accounting for only 2.4% of the malignant soft tissue tumors in that location in one large series.[1] This highly aggressive neoplasm may arise in the skin, soft tissue, or bone (see chapter 15). There are three clinical settings within which AS typically involves the skin: idiopathic (spontaneous development), postirradiation (following external beam radiotherapy), and lymphedema-associated (usually post-lymph node dissection).[241–243] Angiosarcoma arising in the soft tissues accounts for only about one quarter of all cases of AS.[32] Roughly 40% of all soft tissue AS arise within the deep soft tissue of the lower extremity; however, the proximal extremity is far more commonly involved than the foot.[102]

With regard to AS of the skin, the idiopathic cases most often involve the head and neck of elderly males.[241–243] Postirradiation AS usually arises within the field of radiation after adjuvant therapy for an alternate malignant process. This form of AS is classically described in association with treatment for carcinoma of the breast; however, it may be seen in association with radiotherapy directed at other benign and malignant processes.[244,245] Lymphedema-associated AS, also referred to as lymphangiosarcoma, arises in association with longstanding lymphatic congestion. Though classically described in association with post-mastectomy

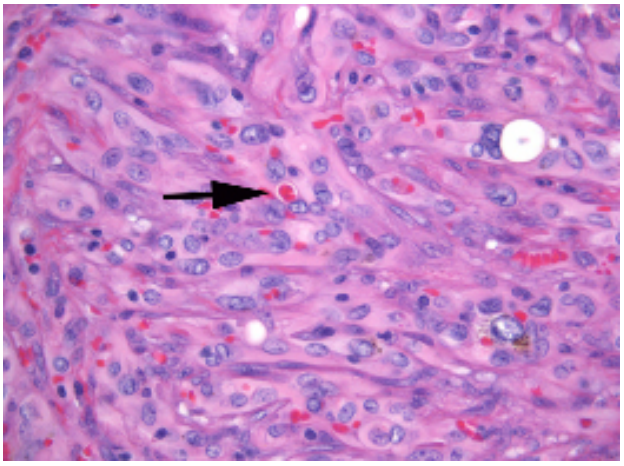

FIGURE 17-31. Epithelioid hemangioendothelioma. Sheets of large polygonal to slightly spindled cells, on of which possesses an intra-cytoplasmic lumen containing erythrocytes (arrow).

lymphedema (Stewart-Treves syndrome), involvement of the lower extremity may occur as the result of lymphedema that manifests as the result of alternate mechanisms such as inactivity or stasis.[245,246]

Angiosarcoma may present in a number of ways, ranging from a deep-seated blue-red nodule to an ecchymotic patch. Those AS that arise within the soft tissue tend to form firm nodules or tumors, whereas those that are primary to the skin are more likely to form plaques or flat areas of purpura.[241,245,247] All forms of angiosarcoma are profoundly aggressive, with half of all affected persons dying within approximately one year of diagnosis.[32] The expected five-year survival is roughly 25%.[247,248] The lungs, bone, and lymph nodes are common sites for metastasis.

Clinical differential diagnosis

The differential diagnosis for angiosarcoma depends on the location within which it arises. Deep-seated tumors may mimic virtually any dense soft tissue tumor. More superficially located neoplasms may mimic granulation tissue, spindle cell hemangioma, diffuse angiokeratoma, and Kaposi's sarcoma, among various other highly vascularized lesions.

Histopathology

The histopathologic appearance of AS varies depending on the degree of its differentiation. Well-differentiated AS may closely simulate a benign hemangioma, particularly in small biopsies. Nuclear enlargement, often with a hobnail configuration (nuclei protruding into the vascular liminae), may be expected. Vessels may be poorly formed and slit-like, with an infiltrative pattern of growth (Fig. 17-32). Moderately and poorly differentiated lesions are usually less diagnostically challenging, as the degree of nuclear pleomorphism and hyperchromasia is marked and well beyond what might be expected in benign lesions (Fig. 17-33). In poorly differentiated AS, vascular spaces become less well-developed or absent. In such cases, ancillary testing methods (immunohistochemistry, electron microscopy) may be necessary to characterize the neoplasm as vascular in nature.

TUMORS OF SMOOTH MUSCLE DIFFERENTIATION

Leiomyomas

Leiomyomas are benign neoplasms composed of spindled cells which recapitulate normal smooth muscle. In the subcutaneous tissue and skin, leiomyomas exhibit patterns of growth that closely simulate vascular smooth muscle (angioleiomyoma) or erector pili musculature (piloleiomyoma). Where piloleiomyomas are limited to the skin, angioleiomyomas more commonly arise in the subcutis or deep soft tissue. There is a third subset of cutaneous leiomyomas that are not seen in the lower extremity as they are limited to the genitalia and areola.

Angioleiomyomas are most commonly well-circumscribed and solitary lesions. They account for roughly 4% of all benign soft tissue tumors that arise in the human body, while maintaining a similar proportion in the skin and soft tissue of the foot.[1,249] Angioleiomyomas manifest as firm papules or nodules in the extremities, particularly the lower leg, where approximately half occur. Other, less common sites of occurrence include the trunk, head and neck.[250,251] Middle-aged persons are usually affected, and there is a slight female predominance.[249,251] This neoplasm has been described as one of the "painful tumors of skin," a feature that is seen in association with about half of affected persons.[251] Interestingly, painful symptomatology is more often witnessed in association with those leiomyomas that arise in the distal extremities.[251,252]

Piloleiomyomas (PL) contrast with angioleiomyomas in several respects. Like angioleiomyomas, these neoplasms may produce papules or nodules; however, they are less well circumscribed and always intimately related to the skin rather than deeper structures. Piloleiomyomas usually present as multiple firm deep-red or brown papules or nodules, whereas angioleiomyomas are usually solitary and less pigmented.[253,254] Piloleiomyomas may be arranged in

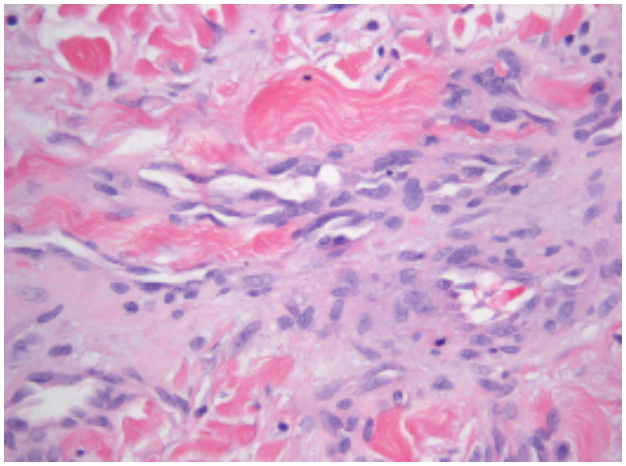

FIGURE 17-32. Angiosarcoma (low-grade). Bland malignant cells infiltrating dermal collagen while forming slit-like vascular spaces.

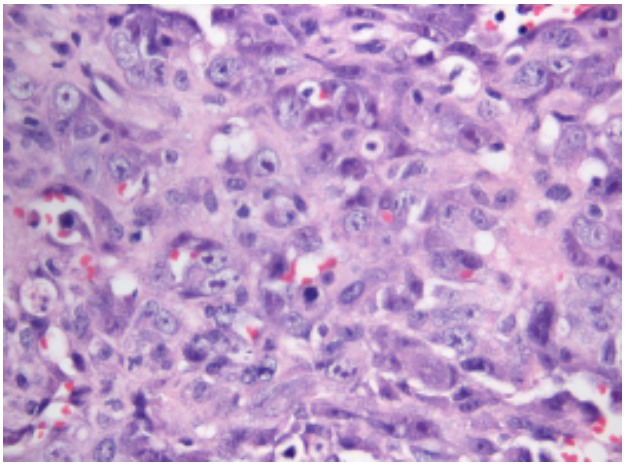

FIGURE 17-33. Angiosarcoma (high-grade). Markedly atypical neoplastic cells infiltrating dermal collagen, forming few poorly delineated vascular spaces.

clusters, they may be linear, or they may form rough plaques.[255] The majority of cases are painful, with sensations ranging from burning, pinching, or stabbing in character.[253,255,256] These tumors predominantly affect young adults and persons of either gender may be involved.[253–255] In exceptional cases, piloleiomyomata are familial.[254,257]

Clinical differential diagnosis

In the lower extremity, solitary leiomyomas may clinically simulate dermatofibromas, adnexal tumors (particularly eccrine spiradenoma), and glomus tumors. Subcutaneous angioleiomyomas may be mistaken for benign cysts. Because piloleiomyomas are typically multiple, their clinical appearance is usually quite characteristic; however, in some instances plaques may resemble epithelioid sarcoma or dermatofibrosarcoma protuberans.

Histopathology

Angioleiomyomas are exceedingly well circumscribed, often possessing a fibrous pseudocapsule (Fig.17-34). The tumor is composed of fascicles of smooth muscle arranged in haphazard array. In most cases, there are numerous vessels within the lesion with prominent muscular walls. Neoplastic smooth muscle cells blend imperceptibly with those of some vessels. Cytologic atypia is an exceptional finding, and mitotic figures are rare or absent (Fig. 17-35). Piloleiomyomas are composed of similar cells; however, in these tumors individual fascicles of smooth muscle may be splayed between collagen bundles within the dermis. There may be a loosely whorled pattern without interposed collagen; however, neither a capsule nor a pseudocapsule is present. Just as may be expected in angioleiomyoma, atypia is uncommon and mitoses are largely absent.

Leiomyosarcoma (LMS)

LMS is a malignant neoplasm of smooth muscle differentiation which may arise within the skin, subcutaneous tissue, or deep soft tissue. There is a distinct predilection for the extensor surfaces of the lower extremity.[258] This tumor accounted for 3% of all soft tissue tumors of the foot in the Memorial Sloan-Kettering series.[1] Leiomyosarcomas of the lower extremity may be divided into those that arise in the skin and those that arise in the subcutaneous and deep soft tissue. A rare additional subtype arises within large veins of the trunk and proximal lower extremity, with only rare examples reported in the smaller veins of the foot, where it may mimic a ganglion cyst.[259] The most common subtype of leiomyosarcoma is intra-abdominal and thus is beyond the scope of this text.

Dermal leiomyosarcoma should be distinguished from deeper variants due to both clinical and prognostic differences. Dermal leiomyosarcomas are thought to be derived from arrector pili muscles and as such are usually lack good circumscription, as do their benign counterpart (piloleiomyoma). Like piloleiomyomas, they may be deep-red to brown in appearance, in contrast to subcutaneous and deep leiomyosarcoma, which usually lack significant cutaneous discoloration. Dermal leiomyosarcoma is solitary in the vast majority of cases unlike piloleiomyoma.[258] Males are involved slightly more often than are females, and the peak incidence is in young to middle-aged adults.[258,260,261] Leiomyosarcomas of the skin are characteristically painful,

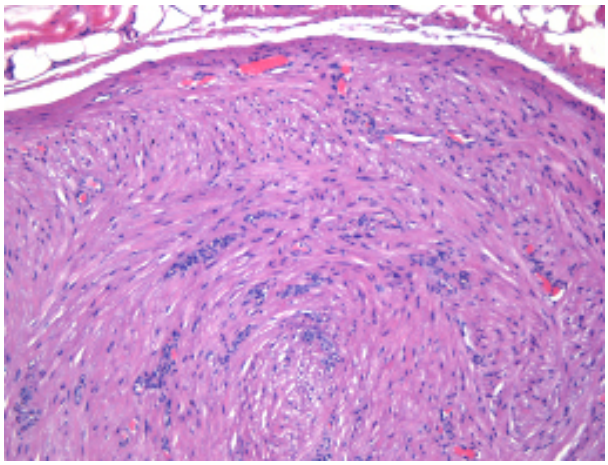

FIGURE 17-34. Angioleiomyoma. An exceedingly well-circumscribed proliferation of spindled cells.

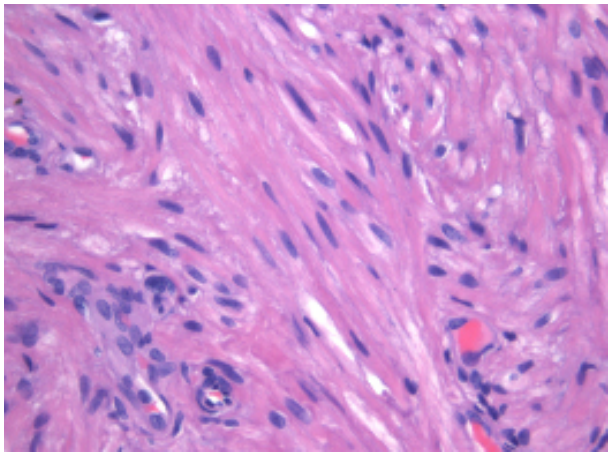

FIGURE 17-35. Leiomyoma. Individual smooth muscle cells possess abundant eosinophilic cytoplasm and elongated cigar-shaped nuclei and lack both nuclear hyperchromasia and significant numbers of mitoses.

most often with a burning sensation; however, such is not always the case.[255,258] Dermal leiomyosarcoma may recur locally following excision in as many as 30% of cases. In sharp contrast to leiomyosarcomas that arise in deeper locations, metastases rarely if ever occur, leading some to question whether these neoplasms should carry the designation "sarcoma."[260,262]

Leiomyosarcoma of the subcutaneous and deep soft tissue is thought to be more closely related to vascular smooth muscle. Due to their deeper location, these neoplasms are often discovered at a later point in their evolution, allowing them to become larger by the time they are diagnosed.[258] In many instances, such tumors exhibit good circumscription akin to their benign counterparts (angioleiomyoma). These sarcomas are slightly more common in men, and the thigh is the most common location.[263,264] Upper-middle-aged adults are usually affected.[263,264] When arising deep to the skin, the rate of local recurrence for leiomyosarcoma is roughly twice that of the dermal variety.[265] In sharp contrast to leiomyosarcomas of the dermis, when arising in deeper locations, metastases are common, manifesting in more than a third of cases.[258,260,264,265] Following metastasis, death ensues in most cases.

Clinical differential diagnosis

The clinical differential diagnosis for dermal leiomyosarcoma includes a host of superficially located tumors, among them piloleiomyoma, cellular and aneurysmal fibrous histiocytoma (dermatofibroma), large glomangiomas, adnexal neoplasms (eccrine spiradenoma), and dermatofibrosarcoma protuberans. Large deeply located lesions may resemble virtually any well-circumscribed mass-forming process. In the lower extremity, synovial sarcoma and clear-cell sarcoma should be foremost excluded. Upon receiving the diagnosis of superficial leiomyosarcoma, metastases from the abdomen or deep soft tissue should foremost be ruled out.

Histopathology

Dermal leiomyosarcoma is by definition predominantly located in the dermis, whereas subcutaneous leiomyosarcoma is largely limited to the subcutis. Dermal leiomyosarcomas are poorly circumscribed and infiltrative with extension into the underlying subcutis in many cases. There may be attenuation of the overlying epidermis. Leiomyosarcomas of the subcutaneous tissue and deep soft tissue are usually well circumscribed, and may posses a thin fibrous pseudocapsule. From a cytologic perspective, the single most important reflection of the tumor's cytologic appearance is the degree of differentiation, or tumor grade. In low-grade leiomyosarcoma, a category within which most dermal leiomyosarcomas are placed, cells may closely resemble benign smooth muscle. Usually such neoplasms are distinguished only by increased cellularity, the presence of mitotic figures, and often subtle nuclear atypia, including hyperchromasia (Fig. 17-36). High-grade neoplasms disclose dense cellularity, scattered mitoses (including those that are atypical), and prominent cytologic atypia in the form of pleomorphism, hyperchromasia, and less cytoplasm relative to the size of the nucleus (Fig. 17-37). Necrosis is common in high-grade lesions. Some high-grade leiomyosarcomas may require ancillary testing to definitively identify smooth muscle differentiation.

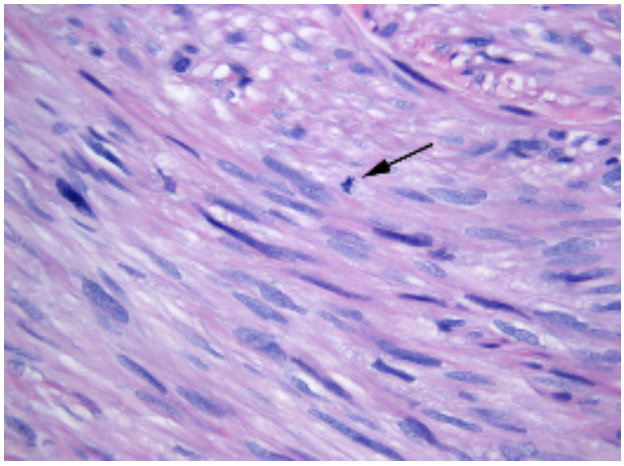

FIGURE 17-36. Leiomyosarcoma (low-grade). Fascicles of spindled cells demonstrating nuclear hyperchromasia and pleomorphism. Note mitotic figure (arrow).

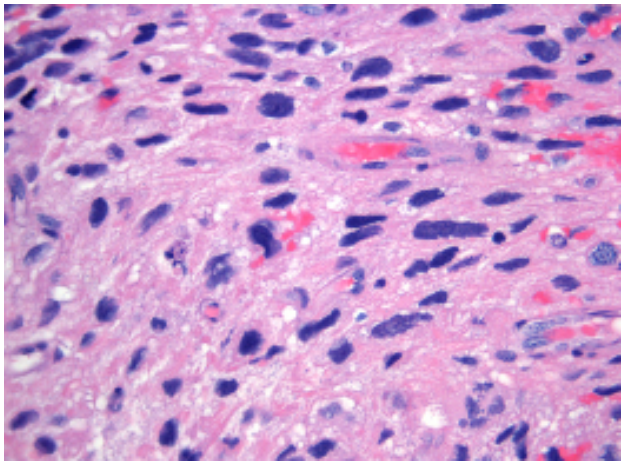

FIGURE 17-37. Leiomyosarcoma (high-grade). Malignant smooth muscle cells disclosing profound cytologic atypia. The microscopic resemblance to benign smooth muscle is largely lost in this high-grade sarcoma.

TUMORS OF SKELETAL MUSCLE DIFFERENTIATION

Rhabdomyoma

Rhabdomyoma is a benign neoplasm composed of cells that demonstrate skeletal muscle differentiation. These rare neoplasms are subdivided into cardiac and extracardiac type. Those that arise within the extracardiac soft tissue are further divided into adult and fetal types. As these neoplasms are virtually limited to the region of the heart, head, and neck, they will not be further described herein.

Rhabdomyosarcomas (Embryonal/Alveolar/Pleomorphic)

Rhabdomyosarcomas are high-grade sarcomas that exhibit varying degrees of skeletal muscle differentiation. Three distinct variants exist, each possessing disparate genetic, epidemiologic, and prognostic profiles. Collectively, they accounted for 2.2% of all soft tissue tumors of the foot in the Memorial Sloan-Kettering series and 3.6% of those that were malignant.[1] Just as has been the case with high-grade osteogenic sarcoma and many childhood leukemias, the prognosis for patients with rhabdomyosarcoma has grown much more favorable in recent decades. With combination, surgical, chemotherapeutic, and radiologic therapy, the overall 5 year survival now approaches 70%, with almost 50% of patients obtaining a clinical cure.[266] Poor prognostic features include advancing age, high stage, recurrence, hand or foot involvement, and non-embryonal subtype.[266]

The *embryonal* subtype is the most common form of rhabdomyosarcoma (RMS), accounting for roughly 50% of all such sarcomas.[267] Spindle cell, botryoid, and anaplastic subtypes of RMS are now classified under the designation *embryonal*. Embryonal RMS is the most common soft tissue sarcoma amongst children and adolescents.[268] The overwhelming majority of embryonal RMS occur in patients of less than 10 years of age, with most of those arising in patients under 5.[268] This RMS variant arises most commonly in the soft tissue of the head and neck or genitourinary system; however, roughly 9% occur in the skeletal musculature of the extremities.[269] Genetic studies have identified allelic losses in chromosomal region 11p15 in most cases of embryonal RMS.[270]

Alveolar RMS is less common than the embryonal variant, accounting for roughly 20% of all cases of RMS.[269,271] This form of RMS usually presents in children or in young adults. However, persons of all age groups may be affected. Affected persons have a median age of 9 years, and there is no particular gender or racial predilection.[269] Unlike embryonal RMS, the alveolar variant is more variable with regard to its sites of predilection. Though this neoplasm may arise in any location, almost 40% are located in the extremities.[272] There were 3 alveolar sarcomas described among the 401 soft tissue tumors of the foot published in the Memorial Sloan-Kettering series.[1] Alveolar RMS demonstrates a higher level of aggressiveness than the embryonal subtype.[266] Most cases of alveolar RMS posses genetic translocation t(2;13) or, less commonly, translocation t(1;13).[273]

In contrast to embryonal and alveolar RMS, the *pleomorphic* variant is found exclusively in adults, most of whom are middle-aged or older.[274,275] There is a slight male predominance.[274,275] The most common location for pleomorphic RMS is the deep soft tissue of the lower extremities; however, they may arise virtually anywhere.[275,276] The prognosis attributed to this form of RMS is exceedingly poor, with nearly three-quarters of all affected patients dieing as the result of their disease.[274,276] Pleomorphic RMS possess complex chromosomal aberrations distinct from those noted in other RMS variants.[277]

All forms of RMS may arise within the soft tissue of the foot.[1] As alluded to earlier, for unknown reasons, tumors affecting the distal lower extremity carry a worse prognosis than those arising elsewhere, with a median survival of roughly 19 months and a 5-year survival approximating 27%.[278] This poor prognosis may be expected despite the fact that tumor affecting these sites are typically smaller at diagnosis than those arising elsewhere.[278] Rhabdomyosarcomas often present as rapidly expanding masses within the deep soft tissue, sometimes causing bowing of the short tubular bones of the foot.[279]

Clinical differential diagnosis

Most rhabdomyosarcomas that arise in the lower extremity do so in the deep soft tissue. As such, they may form ill-defined masses that may be confused with soft tissue swelling. Because they are rapidly growing high-grade malignancies, they may be confused with virtually any such neoplasm that is peculiar to the lower extremity, such as synovial sarcoma, clear-cell sarcoma, and fibrosarcoma. Depending on location, occasional cases may masquerade as soft tissue ganglia.

Histopathology

Each variant of rhabdomyosarcoma is histopathologically distinct. Embryonal RMS is composed of primitive cells with features identical to rhabdomyoblasts (fetal skeletal muscle cells). These cells range from small and round with no perceivable cytoplasm or bullet-shaped with an eccentric tail of eosinophilic cytoplasm, to elongated and strap-like with a central nucleus (Fig. 17-38). The cells grow in no particular pattern. Alveolar RMS is composed of small, round basophilic cells with scant cytoplasm that resemble immature lymphocytes. In classic cases, the neoplastic cells form nests within which lesional cells are closely packed and appear attached around the periphery and become more loosely associated centrally. Cells often appear to float freely within the central aspect of aggregates (Fig. 17-39). Pleomorphic RMS is composed of large cells with bizarre shapes. There may be foci in which spindled cells or round cells predominate. Because these tumors may virtually lack histopathologically perceptible differentiation, arriving at the correct diagnosis may require ancillary testing (genetic, immunohistochemical).

TUMORS OF NEURAL/NERVE SHEATH DIFFERENTIATION

Morton's (Traumatic) Neuroma

In contrast to the overwhelming majority of the tumors described herein, traumatic neuromas, of which Morton's

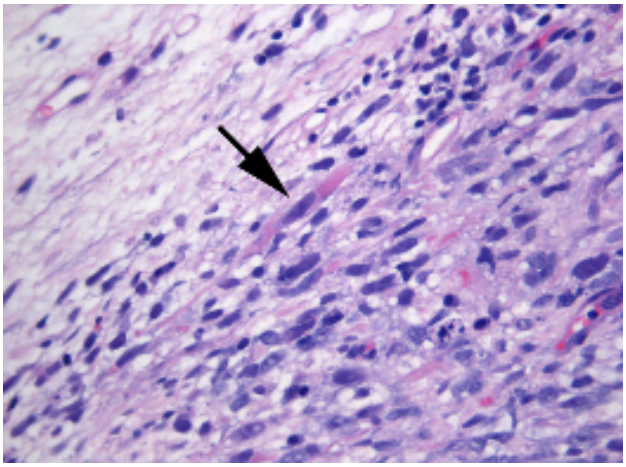

FIGURE 17-38. Emryonal rhabdomyosarcoma. Primitive skeletal muscle cells, one of which has features characteristic of a "strap cell" (arrow).

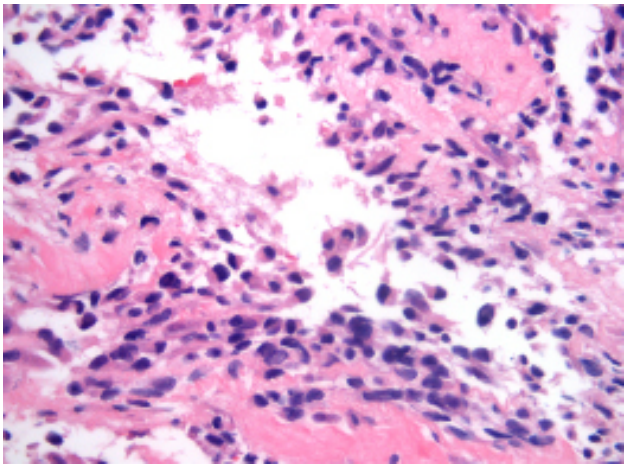

FIGURE 17-39. Alveolar rhabdomyosarcoma. Aggregates of discohesive malignant cells. Cells within the central region of nests appear to be floating freely within a lumen.

neuroma is one type, are not true neoplasms. These mass-forming lesions develop as the result of acute or chronic trauma to a peripheral nerve. In most instances, traumatic neuromas form as the result of an acute traumatic event which has left a peripheral nerve truncated at some point before its peripheral nerve endings. As regeneration proceeds, the nerve and nerve sheath elements become trapped within scar tissue and as a result form convoluted collections of nerve elements. In classic Morton's neuroma, the nerve and nerve sheath damage is the result of a either compression between the third and fourth metatarsal heads, excessive traction placed upon an intermetatarsal nerve, or both. The third common digital nerve is most commonly affected by Morton's neuroma, in part due to the fact that this nerve is pulled around the third transverse intermetatarsal ligament and tethered within the third webspace.[280,281] Similar compressive forces may affect the other intermetatarsal nerves, although much less commonly. Where most traumatic neuromas have no gender or age predilection, Morton's neuroma most commonly affects women of middle age.[280] Women who wear high-heeled, pointed-toe dress shoes are particularly at risk. In some affected individuals, a palpable click and reproduction of symptomatology may be elicited upon compression of the metatarsal heads in the transverse plane. This clinical test has been designated as Mulder's sign. In many instances, palpation or compression of other traumatic neuroma variants will result in similar neuritic pain ranging from low-grade and burning to sharp.

Clinical differential diagnosis

The clinical differential diagnosis for traumatic neuroma is limited due to its associated symptomatology and localization. In exceptional cases, schwannoma may cause similar symptoms, as may intraneural neurofibromas. Finally, nerve compression that is not associated with bona fide neuroma formation may result in symptomatology that is indistinguishable from that of a fully formed Morton's neuroma. As such, an actual mass-forming lesion may not be clinically evident in all patients who are experiencing the type of discomfort that would be characteristic of Morton's neuroma.

Histopathology

Histopathologic evaluation of traumatic neuromas demonstrates nerve fascicles and fibrous-appearing nerve sheath elements in haphazard array. There is peri-fascicular fibrosis causing small neural twigs to splay apart. Inflammation is most commonly scant or absent. Most traumatic neuromas form well-circumscribed nodules. Morton's neuromas often contrast slightly in that the nerve fascicle's basic architecture is preserved. Such lesions disclose parallel nerve fibers/fascicles surrounded by reactive perineural fibrosis and scattered hyperplastic nerve twigs. There may be inordinately wide spaces between individual nerve fibers and fascicles as the result of the aforementioned fibrosis (Fig. 17-40).

Schwannoma (Neurilemmoma)

Schwannomas are benign slow-growing neoplasms that exhibit differentiation toward nerve sheath. Though such tumors may arise anywhere, there is a predilection for the head, neck, and extremities.[282] There were eight schwannomas among the 401 soft tissue tumors of the foot described in the files of Memorial Sloan-Kettering.[1] The overwhelming majority of cases arise within the subcutaneous tissue. Each gender is affected with roughly equal frequency.[282,283] Persons of all ages may be affected; however, most schwannomas present themselves in patients between 20 and 50 years of age.[284] Because schwannomas are tumors of the nerve sheath, they are often intimately associated with peripheral nerves, a feature which may precipitate neuritic symptomatology in some cases. Schwannomas involving the superficial peroneal nerve resulting in webspace pain, branches of the posterior tibial nerve leading to heel pain, and branches of the medial plantar nerve and tibial nerve causing tarsal tunnel syndrome have been described.[285–288] Rarely, patients are affected by multiple schwannomas.[289,290]

Several subtypes of schwannoma exist. Variants include cellular, plexiform, epithelioid, ancient, and those associated with neurofibromatosis type 2.[32] Such lesions have been reported in the foot.[291–294] Cellular schwannomas are particularly significant because they may grow to become

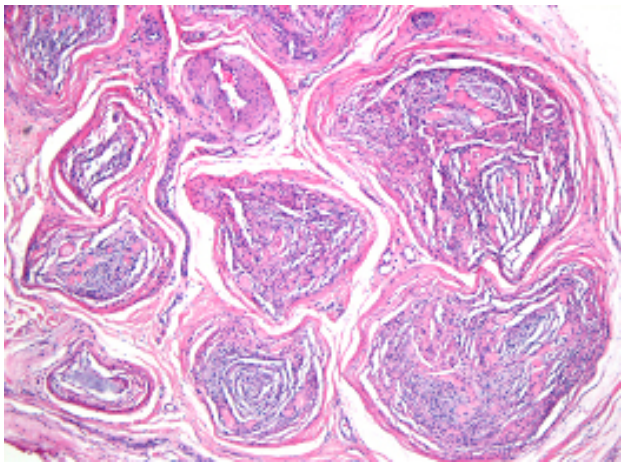

FIGURE 17-40. Morton's neuroma. Nerve fascicles within a peripheral nerve have been splayed apart by dense fibrosis (cut in cross-section).

relatively large and, because of their dense cellularity, may be confused with various malignant neoplasms such as melanoma, malignant peripheral nerve sheath tumors, and synovial sarcoma.[291] Such lesions may ulcerate in exceptional cases.[295] Although there is a malignant correlate designated as malignant peripheral nerve sheath tumor, development of such a sarcoma within a benign schwannoma is an exceedingly rare event.

Clinical differential diagnosis

Schwannomas may or may not have a clinically distinct appearance. Encapsulated, well-circumscribed, and slow-growing soft tissue masses that arise in close association with a peripheral nerve should be considered schwannoma until proven otherwise; however, in most instances such nerves cannot be readily demonstrated by clinical examination or imaging studies. When an associated nerve cannot be demonstrated, the differential should include all well-circumscribed soft tissue tumors, including ganglion cysts, angioleiomyoma, malignant peripheral nerve sheath tumor, and any other mass-forming lesion that may form a capsule or pseudocapsule. Plexiform variants may be clinically identical to plexiform neurofibroma, a lesion that is pathognomic for neurofibromatosis-1. Depending on the site of involvement, schwannomas may not present as a palpable mass, but rather, manifest as a source of neuritic pain or compression syndrome.

Histopathology

Schwannomas are extremely well-circumscribed neoplasms with a true fibrous capsule (Fig. 17-41). These tumors represent one of the few soft tissue neoplasms that form a true capsule, rather than a pseudocapsule (a surrounding layer of compressed fibrous tissue). Schwannomas are characterized by areas of relatively high cellularity (termed Antoni A regions) and areas of relatively low cellularity (termed Antoni B regions). Antoni A regions disclose plump spindled cells with oval to elongate nuclei and brightly eosinophilic cytoplasm. Nuclear membranes are indistinct in Antoni A regions (cells form a syncitium). Schwann cell nuclei may occasionally be aligned in rows separated by fibrillary collections of cell processes, structures designated as Verocay bodies (Fig. 17-42). Schwann cells in Antoni B regions are more loosely arranged, allowing for the distinction of cytoplasmic membranes. Vessels within schwannomas may possess thick hyalinized walls.

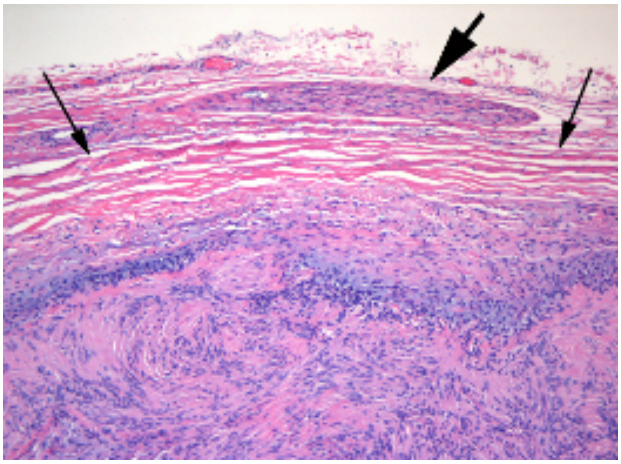

FIGURE 17-41. Neurilemmoma (schwannoma). Nerve sheath tumor (bottom) covered by a thin fibrous capsule (small arrows). Note a peripheral nerve overlying the capsular surface (large arrow).

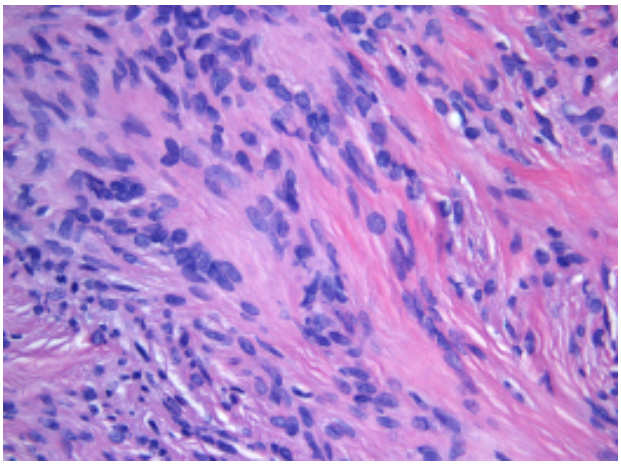

FIGURE 17-42. Schwannoma. Neoplastic cells form short palisades with interposed fibrillary collections of cell processes, designated as Verocay bodies.

Granular Cell Tumor, Neuroectodermal Type (Granular Cell Myoblastoma)

Neuroectodermal granular cell tumor (NGCT) is an uncommon neoplasm whose histogenesis has been long debated. This unusual tumor was previously designated as granular cell myoblastoma due to the resemblance of its cells to primitive myocytes; however, ultrastructural and immunohistochemical studies have shown them to be more closely related to Schwann cells.[296,297] The antiquated term granular cell myoblastoma should no longer be used. Because several neoplasms may have histopathologic features that are identical to NGCT, and the term *granular cell tumor* has been used in the past to describe all such tumors, it has now become commonplace to more precisely designate these neoplasms as granular cell tumors of the *neuroectodermal type* to avoid confusion.

Granular cell tumors of the neuroectodermal type most commonly arise in the skin or subcutaneous tissue of middle-aged adults; however, persons of all ages may be affected.[298,299] There is a slight female predominance, and among races, persons of color are affected with increased frequency.[298–300] Most NGCT arise in the skin and mucosa of the head and neck; however, cases involving the skin and subcutis of the foot have been well described.[1,301–304] In most instances, NGCT are largely asymptomatic. Most cases present as poorly circumscribed nodules ranging from 0.5 to 2 cm. We have seen one case of NGCT that formed a large plaque over the dorsal foot which measured well over 3 cm (unpublished observation). These skin-colored nodules may be multiple in exceptional cases.[305] Though the overwhelming majority of NGCT are benign and follow an indolent course, rare malignant variants have been described.[298,299]

Clinical differential diagnosis

The clinical differential diagnosis for granular cell tumor should include dermatofibroma, various benign adnexal neoplasms, dermal scar, morphea-form basal cell carcinoma, and spindle cell melanoma. Larger lesions may be confused with dermatofibrosarcoma protuberans, particularly when polypoid.

Histopathology

Granular cells tumors range from moderately to poorly circumscribed. Neither capsules nor pseudocapsules are typically seen. Most cases exhibit foci within which lesional cells infiltrate the dermal collagen or less commonly the subcutaneous fat. In many cases, the neoplastic cells induce hyperplasia of the overlying epidermis which may be marked, leading to a pseudoepitheliomatous (carcinoma-like) appearance. Lesional cells are exceedingly monomorphous, with small, centrally located, round-to-oval nuclei. The single most remarkable feature observed in association with NGCT is the presence of richly eosinophilic granules filling the cytoplasmic space of lesional cells (Fig. 17-43). These granules represent secondary lysosomes, possible formed as part of a degenerative phenomenon. Although a characteristic feature of NGCT, such granules may be seen in association with a variety of neoplasms, including meningiomas and leiomyomas. Malignant variants may be virtually identical. Findings such as increased mitotic figures and the presence of nuclear atypia, though not specific for malignancy, should trigger suspicion on the part of the histopathologist.

Neurofibroma

Neurofibromas are common benign neoplasms that are customarily classified as localized, diffuse, or plexiform, depending on their pattern of growth.[32,306] The localized form, when solitary, is of little consequence; however, the diffuse and plexiform variants serve as markers for neurofibromatosis, type 1 (NF-1). The plexiform variant is virtually pathognomonic for that condition.[32] Solitary *localized* neurofibromas present themselves as asymptomatic flesh-colored papules, nodules, or polyps.[307] Roughly 90% of all neurofibromas are of the solitary localized (sporadic) type.[308] Most localized lesions arise during adulthood, and there is no correlation with NF-1.[307] A case of solitary subungual neurofibroma has been reported.[309] Though most neurofibromas are small and clinically insignificant, rare large lesions may arise. One such massive neurofibroma was described in the soft tissue of the foot.[310] Unlike those neurofibromas that are associated with neurofibromatosis, there is not convincing evidence for the malignant degeneration of solitary localized variants, except when arising in the deep soft tissue.

Plexiform neurofibromas are closely related to neurofibromatosis, type 1. These neoplasms arise during childhood and may precede their cutaneous counterparts.[32] When involving large portions of an extremity, these lesions may cause diffuse limb enlargement, a phenomenon designated as *elephantiasis neuromatosa*. Similar gigantism may be seen on a smaller scale and has been reported in the foot.[311] The skin overlying plexiform neurofibroma may be loose and hyperpigmented, adding to the gross deformity. Because plexiform neurofibromatas diffusely infiltrate the involved nerve, affected patients commonly experience associated sensory or motor deficits. Involvement of the common peroneal nerve has led to foot drop in at least one report.[312] Involvement of the deep peroneal nerve has also been described.[313] Plexiform neurofibromas are typically managed by complete resection of the tumor in question with the sacrifice of the affected nerve. Recurrence may be expected if the resection is incomplete.[314]

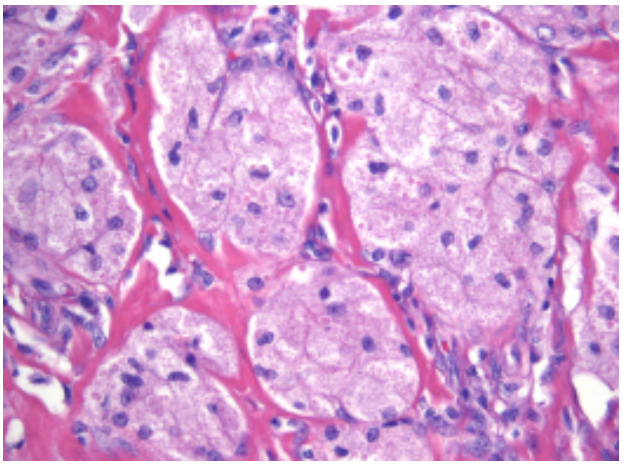

FIGURE 17-43. Granular cell tumor. Nests of neoplastic cells are characterized by distinctly granular cytoplasm.

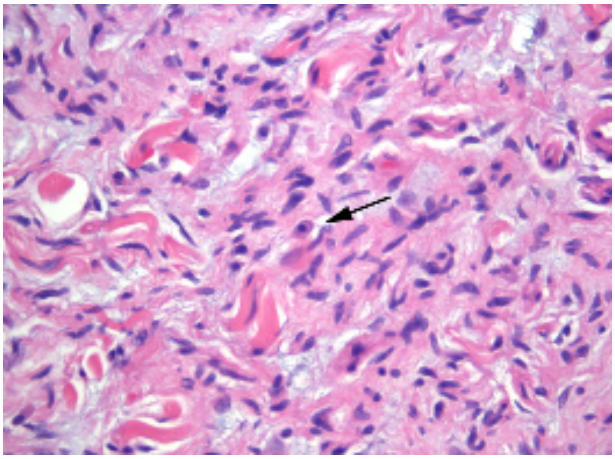

FIGURE 17-44. Neurofibroma. Fibroblasts and Schwann cells are noted within fibrillary stroma. Scattered mast cells are seen (arrow).

Malignant degeneration of plexiform neurofibromas, though not common, has been described, including at least two cases involving the distal extremities.[315,316]

Diffuse neurofibromas present as broad, ill-defined plaques in children and young adults.[32] These neoplasms infiltrate the subcutaneous layer, surrounding anatomic structures as it extends along fascial planes. Roughly 10% of persons with diffuse neurofibromas have neurofibromatosis type 1.[32]

Clinical differential diagnosis

Localized neurofibromas may resemble virtually any skin-colored papule-forming lesion. Among potential mimics are pedunculated neurotized dermal nevi, fibroepithelial polyps, fibrous papules, and clear-cell acanthomas. A characteristic, but not entirely specific, feature of neurofibromas is the "buttonhole sign," which represents the tendency for localized neurofibromas to invaginate into the surrounding skin when direct pressure is applied. Diffuse neurofibromas may simulate connective tissue nevi, dermatofibrosarcoma protuberans, and epithelioid sarcoma. The plexiform variant, because it characteristically arises in association with NF-1, is rarely a diagnostic dilemma. If manifesting prior to the development of other features indicative NF-1, plexiform neurofibromas may mimic Proteus syndrome or fibrolipomatous hamartoma.

Histopathology

Localized and plexiform neurofibromas are characteristically well-circumscribed but nonencapsulated tumors. Localized cutaneous forms are often centered within the reticular dermis; however, extension to epidermal undersurface or subcutis may be seen. Intraneural and plexiform variants are confined to the involved nerve, diffusely infiltrating and expanding the endoneurial space. Diffuse variants are, and as the name denotes, poorly circumscribed, with extension along fascial planes in all directions. Cytologically, neurofibromas are composed of a combination of fibroblasts, Schwann cells, and neuronal elements embedded within loose fibrillary stroma (Fig. 17-44). In most cases of localized and diffuse neurofibroma, the neuronal elements are not apparent by routine microscopy, but may be demonstrated with immunohistochemical stains. Neurofibromas may focally resemble the Antoni B regions of schwannomas. However, such tumors uniformly lack Antoni A-like regions. Mast cells are characteristically seen scattered throughout the interstitium.

Malignant Peripheral Nerve Sheath Tumor (Malignant Schwannoma)

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon neoplasm that accounted for roughly 2% of the 401 soft tissue tumors of the foot in the Memorial Sloan-Kettering series.[1] This tumor was most likely overrepresented in this series secondary to the fact that it was compiled at a cancer referral center. Though more than 50% of all MPNST are believed to be related to, if not derived from, benign nerve sheath tumors, this relationship may be subtle and inconsistently demonstrated by routine testing methods.[317,318] Massive neurofibromas and those of the plexiform subtypes should be considered precursors of MPNST.[319] As many as half of all MPNST arise in persons who have the genetic stigmata of neurofibromatosis type 1, though estimates range from 30–50%.[317,320,321] The lifetime risk for persons with NF-1 to develop MPNST is roughly 3%.[322] The remainder of cases are sporadic.

Sporadic cases of MPNST typically affect middle-aged adults, with no particular gender predilection.[317,320,321] Cases of MPNST that are associated with NF-1 are more likely to involve a younger patient population and demonstrate a male predominance.[323] The extremities represent the most commonly affected sites, followed by the trunk and then head and neck.[324] Two cases of MPNST involving the medial plantar nerve have been reported.[325,326] Malignant peripheral nerve sheath tumors are typically large at diagnosis, owing to their origin in the deep soft tissue. Due to the limited volume of deep soft tissue in the foot, cases are discovered somewhat earlier. By all accounts MPNST are aggressive high-grade malignancies. The median survival for affected patients is less than three years.[327] Though one recent series noted similar survival statistics for sporadic cases and those associated

with NF-1, most investigators have noted an appreciably worse prognosis for persons who suffer from NF-1.[317,320,321,328]

Clinical differential diagnosis

From a clinical perspective, because most MPNST arise within the deep soft tissue, its gross findings are identical to those of any high-grade soft tissue tumor. In the lower extremity synovial sarcoma, clear cell sarcoma, and fibrosarcoma should be foremost excluded. Embryonal rhabdomyosarcoma should be ruled out when such clinical features arise in the pediatric population. Clues to its neuroectodermal nature would include fast-growing tumors arising in persons with NF-1 genotype, an associated neurofibroma, and/or those with a physical relationship to a peripheral nerve.

Histopathology

Most MPNST are composed of plump spindled cells that exhibit features reminiscent of those seen in synovial sarcoma and high-grade fibrosarcoma. There is usually a vaguely fascicular or wavy pattern of growth. Not uncommonly, there are areas of dense cellularity which alternate with regions of decreased cellularity (Fig. 17-45). As with many high-grade sarcomas, divergent differentiation may be seen. Cases that are shown to possess skeletal muscle differentiation have been designated as *triton tumor*. Such differentiation often requires ancillary testing. Because a relatively large proportion of MPNST arise in association with a benign nerve sheath neoplasm, remnants of such tumors may be histopathologically evident. Cytologically, MPNST are usually high in grade and thus lesional cells exhibit features indicative of rapid proliferation such as a high mitotic rate and tumor necrosis. Though most MPNST are composed of spindled cells (Fig. 17-46), epithelioid variants have also been described.[329]

TUMORS OF DISPUTED HISTOGENESIS

Myxomas (Cutaneous/Juxta-articular/Intramuscular)

Myxomas are benign and somewhat poorly understood neoplasms of uncertain histogenesis. Though quite similar in histologic appearance, cutaneous myxomas, juxta-articular myxomas, and intramuscular myxomas appear to be distinct lesions. Militating in favor of this premise is their unique epidemiologic and genetic profiles. True *cutaneous myxomas* are benign neoplasms that are commonly seen in association with the genetic syndrome designated as Carney's complex.[330,331] These tumors should be distinguished from digital mucous cysts, which uniformly arise on the dorsal-distal surfaces of the fingers and toes. Genetically, Carney's complex (cardiac myxomas, lentigines, endocrine overactivity) has been linked to chromosomal locus 2p16.[332] *Juxta-articular myxomas* most commonly arise within the vicinity of the knee; however, the soft tissue around virtually any large joint may be involved.[333] Patients often present themselves with a painful or tender swelling immediately adjacent to a major joint. These neoplasms usually arise in adults, and there is a slight male predominance.[333] Juxta-articular myxomas do not undergo malignant degeneration; however, local recurrences following excision are common (34%).[333] Clonal genetic

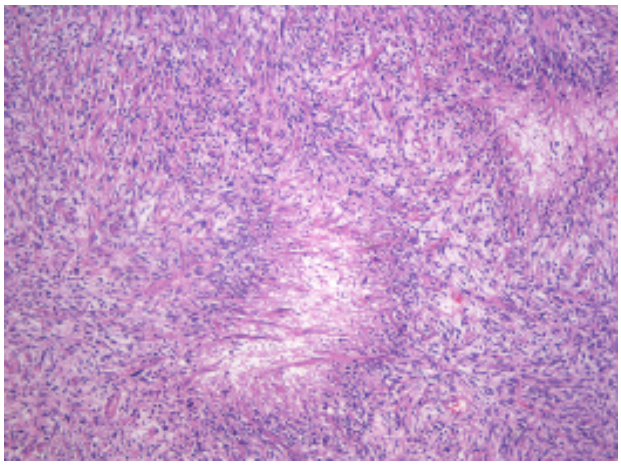

FIGURE 17-45. Malignant peripheral nerve sheath tumor. Alternating areas of high cellularity and low cellularity are a common finding.

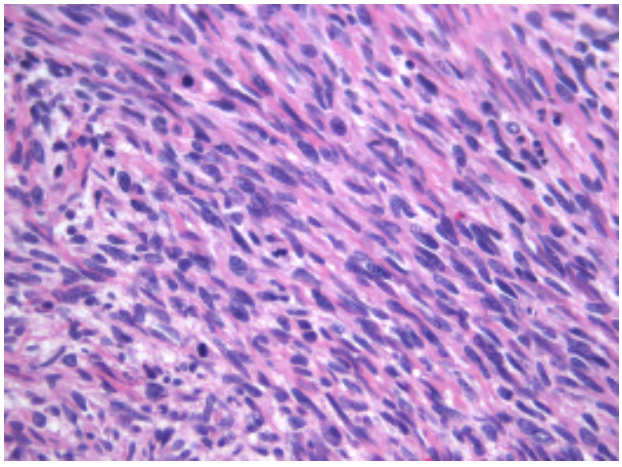

FIGURE 17-46. Malignant peripheral nerve sheath tumor. Spindled cells reminiscent of synovial sarcoma or fibrosarcoma are characteristic.

abnormalities inv(2) and t(8;22) have been identified in one report.[334] In contrast to juxta-articular myxoma, *intramuscular myxoma* more commonly affects middle-aged women. This neoplasm too has a predilection for the lower extremity; however, it most commonly arises as a painless mass within the musculature of the thigh or limb girdle.[335,336] Also in contrast to the juxta-articular variant of myxoma, intramuscular myxomas do not typically recur at the site of origin following local excision.[337] Clonal point mutations in the GNAS1 gene have been identified in the vast majority of intramuscular myxomas.[338] This mutation, also identified in cases of fibrous dysplasia, appears to be an important link between these two conditions and surely explains why they may be seen in common individuals.[338]

Clinical differential diagnosis

The differential diagnosis varies dramatically depending on the type of myxoma in question. When solitary, cutaneous myxomas may resemble other conditions which lead to mucin deposition such as focal mucinosis, digital mucous cysts (digital myxomas), and superficial acral fibromyxoma. In addition, other simple cysts of the skin must be excluded, as should benign lipomas that could be pushing up from the subcutis below. When large or multiple, cutaneous myxomas may resemble disorders of mucin deposition that may be linked to paraproteinemia, such as scleromyxedema. It is important to note that even in cases of cutaneous myxoma that are associated with a syndrome (Carney's complex, LAMB or NAME syndrome) the tumor may be the only clinical findings, as the myxoma may be the earliest manifestation of the condition.[339] The clinical differential diagnosis for juxta-articular myxomas includes localized edema when poorly marginated. When better delineated, they may resemble ganglion cysts, lipomas, myxoinflammatory fibroblastic sarcoma, other low-grade sarcomas, and occasional high-grade sarcomas (see below). For intramuscular myxomas, the chief mimics are intramuscular lipoma, intramuscular hemangioma (easily distinguished with imaging studies), and of primary concern, low-grade sarcoma (myxoid liposarcoma, myxofibrosarcoma) and high-grade sarcoma (rhabdomyosarcoma, synovial sarcoma, clear-cell sarcoma).

Histopathology

Myxomas are usually paucicellular neoplasms with prominent myxoid stroma and minimal vascularity. There may be slightly increased cellularity and vascularity in some cases of juxta-articular myxoma (designated as the *cellular* variant). Scattered bland spindled or stellate cells are embedded within copious myxoid matrix (Fig. 17-47). The presence of either cytologic atypia or nuclear hyperchromasia should raise the index of suspicion for low-grade sarcoma, in particular, myxofibrosarcoma or myxoid liposarcoma. In contrast to its intramuscular and cutaneous counterparts, juxta-articular myxomas are characteristically poorly delineated, owing to their predilection for local recurrence. It is of paramount importance to exclude the possibility of low-grade sarcoma through thorough sampling and diligent inspection, as in some cases their histopathologic features may be quite similar.

Epithelioid Sarcoma

This high-grade sarcoma was first characterized by Enzinger in 1970.[340] It is unique in that it lacks both the clinical and histopathologic features that are common to most other high-grade malignancies, leading to common misdiagnoses and delays in treatment.[340,341] Epithelioid sarcoma most commonly arises in males during adolescence or early adulthood.[342,343] Though overall epithelioid sarcoma is uncommon, it is likely overrepresented in the foot, accounting for 2.3% of all soft tissue neoplasms in one large series.[1] The majority of cases arise in the distal extremities, particularly the flexor surface of the wrist and forearm, followed by the distal lower extremity.[341] Involvement of the toes, medial arch, and ankle region has been well-described.[340–346] Other anatomic locations may also be involved.[342,343] Epithelioid sarcoma usually presents as superficially located slow-growing painless nodules or ill-defined areas of induration. Exceptional cases have presented as chronic ulcerations or have triggered symptoms resembling reflex sympathetic dystrophy.[345,347]

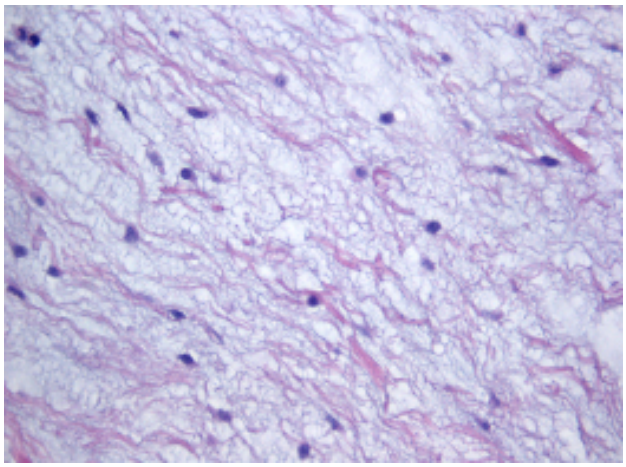

FIGURE 17-47. Myxoma. Few stellate or slightly spindled cells embedded within a diffusely myxoid matrix.

The prognosis for persons with epithelioid sarcoma is poor. This neoplasm cannot be accurately delineated, as it propagates along fascial planes, tendons/tendon sheaths, and nerve sheaths in all directions. This diffuse pattern of infiltration mandates that affected patients be foremost treated with amputation in the overwhelming majority of cases.[340–343] The rate of local recurrence depends somewhat on the magnitude of the initial excision, with reported rates ranging from 34 to 77%.[340,341,348] Metastases occur in approximately 40% of patients.[340,342] Although roughly half of affected persons survive 5 years, because this neoplasm is relentlessly progressive, approximately 80% will succumb within a decade.[340,342,349]

Clinical differential diagnosis

Epithelioid sarcoma may clinically resemble virtually any dermal or subcutaneous-based neoplasm or nonneoplastic mass-forming lesion. Because it may present as a nodule, epithelioid sarcoma must be distinguished from ganglion cyst, dermatofibroma, atypical fibroxanthoma, and various benign and malignant adnexal tumors. Tumors that acquire a plaque-like configuration may be identical to dermatofibrosarcoma protuberans and granuloma annulare. More deeply seated tumors may closely resemble superficial fibromatosis or tenosynovial giant cell tumor, particular when showing attachment to the underlying fascia. Large mass-forming tumors may be identical to clear-cell sarcoma and synovial sarcoma, particularly when arising around the heel.

Histopathology

Epithelioid sarcoma is exceedingly deceptive in terms of its infiltrative qualities and its tendency toward distant metastasis. Lesional cells commonly form dermal or subcutaneous-based nodules that are quite reminiscent of granulomas such as one could see in granuloma annulare. In many cases, the combined cytologic and histologic features are suggestive of carcinoma of possible metastatic origin. Nodules composed of neoplastic cells may contain a central zone of necrosis (Fig. 17-48); however, this is not a constant finding. Cytologically, most epithelioid sarcomas are composed of polygonal (epithelioid) cells with abundant eosinophic cytoplasm. Nuclei are often without significant atypia, and mitotic rates are usually low. Occasional cases demonstrate slightly spindled cytology (Fig. 17-49).

Malignant Melanoma of Soft Parts (Clear-Cell Sarcoma)

Malignant melanoma of soft parts is a high-grade sarcoma that exhibits melanocyte-like differentiation. This unusual neoplasm demonstrates a striking predilection for the distal extremities where over 90% of cases manifest.[350,351] The foot and ankle are most commonly involved, particularly within the soft tissue of the posterior heel, where they may present as painful nodules.[1,350,351] Malignant melanoma of soft parts (MMSP) accounted for almost 6% of all soft tissue tumors from the foot in the Memorial Sloan-Kettering series.[1] Most cases affect adolescents or young adults, and females are involved more often than are males.[350,351] As is the case with most tumors that arise within the distal extremities, most MMSP measure less than 5 cm at presentation. Similar to epithelioid sarcoma, MMSP is often intimately associated with the fascia and/or

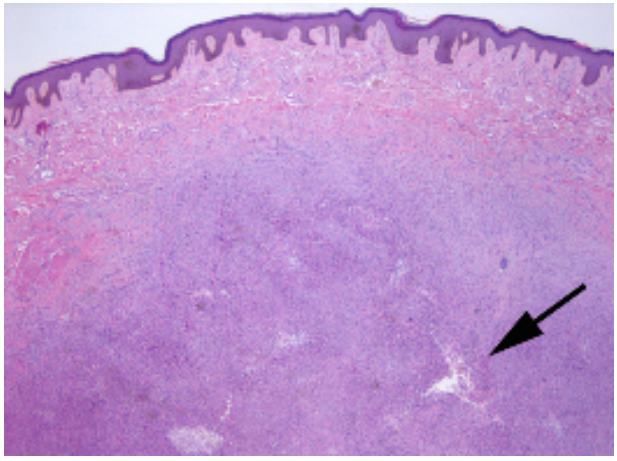

FIGURE 17-48. Epithelioid sarcoma. Dermal-based nodules composed of malignant cells with central necrosis (see arrow).

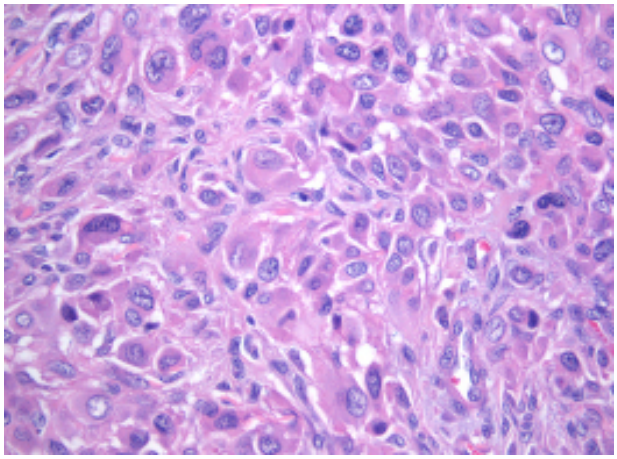

FIGURE 17-49. Epithelioid sarcoma. Polygonal malignant cells with abundant eosinophilic cytoplasm.

tendoaponeurotic structures with secondary extension into the subcutis or reticular dermis.[350,351] The epidermis is usually unaffected.

Malignant melanoma of soft parts exhibits striking antigenic homology with melanoma. Melanocytic antigens such as S100 protein, HMB45, and others are also routinely present in MMSP.[350,351] In addition, melanosomes at varying stages of development may be visualized through electron microscopy.[352] Though antigenically almost identical to melanoma, the genetic profile of MMSP is unique in that such tumors consistently disclose the reciprocal translocation t(12;22).[277] Prognostically, those that harbor MMSP may be expected to have a clinical course that parallels bona fide melanoma in its severity. Metastases to regional lymph nodes are common. At the Mayo Clinic, the 5-, 10-, and 20-year survivals were 67%, 33%, and 10%, respectively.[350]

Clinical differential diagnosis

Malignant melanoma of soft parts may be expected to form nondescript masses emanating from the fascia or aponeuroses but reaching superficially into the deep layers of the overlying skin. These tumors are typically softer to palpation than superficial fibromatoses and most adnexal tumors. They may easily be confused with ganglia by unsuspecting clinicians and, because of their relationship with the underlying structures, may mimic giant cell tumors of tendon sheath. Of course, MMSP may be indistinguishable from other high-grade sarcomas that commonly arise in the distal extremities such as synovial sarcoma and epithelioid sarcoma.

Histopathology

Clear-cell sarcoma (MMSP) are characterized by a nested or fascicular proliferation of epithelioid or slightly spindled cells. Nests of malignant cells may be separated by thin fibrous septae. Lesional cells characteristically disclose clear to slightly eosinophic cytoplasm (Fig. 17-50). Some cases exhibit scattered wreath-like multinucleated cells. Similar to aforementioned epithelioid sarcoma, the degree of cytologic atypia and mitotic rate may be relatively low relative to the highly aggressive clinical behavior that may be expected with this neoplasm. Melanin, though present by electron microscopy and immunohistochemistry, is usually not evident in routinely stained histologic sections.

Synovial Sarcoma

This was the second most common malignant soft tissue tumor of the foot reported in the Memorial Sloan-Kettering series, trailing behind only Kaposi's sarcoma.[1] This high-grade sarcoma accounted for 11.5% of all soft tissue tumors of the foot in that series and 18.3% of those that were malignant.[1] Synovial sarcoma represents nearly 10% of all soft tissue sarcomas and a yet higher proportion of those manifesting in the distant extremities.[1,353] Synovial sarcoma may arise in persons of any age; however, most series have shown an average age during young adulthood.[1,354–356] Males are affected slightly more commonly than are females.[354–356] Roughly 60% of all synovial sarcomas arise in the lower extremities, where notoriously long delays may occur prior to diagnosis.[5,354–356] Scully and colleagues noted an average 14-month delay prior to diagnosis in their series of 14 cases from the foot.[5] Synovial sarcoma may masquerade as seemingly unrelated conditions such as posterior tibial tendon dysfunction, tarsal tunnel syndrome, or Morton's neuroma.[357–360]

Synovial sarcoma may be distinguished genetically by its characteristic translocation t(X:;18).[277] This mutation may be of paramount importance when distinguishing synovial sarcoma from other high-grade spindle-cell malignancies such as malignant peripheral nerve sheath tumor and high-grade fibrosarcoma. Prognostically, roughly half of all synovial sarcomas recur following the initial excision.[32] The expected 5-year survival for persons with synovial sarcoma is roughly 50%; however, this percentage falls to 20–30% at 10 years.[145] When metastases occur, the most common locations include the lung, bone, or regional lymph nodes.[32] Small tumor size (< 5cm), early clinical stage, and young patients age (< 10 years) are indicators of a slightly improved prognosis.[145,355,361]

Clinical differential diagnosis

Of primary importance to clinicians of the lower extremity is the significant propensity of synovial sarcoma to

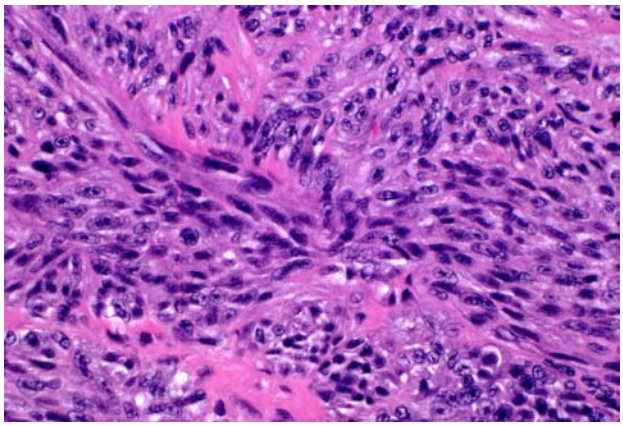

FIGURE 17-50. Melanoma of soft parts (clear cell sarcoma). Malignant spindle cells with pale to clear cytoplasm.

mimic common benign masses of the lower extremity. Scully noted the introduction of long delays prior to diagnosis as the result of confusion with ganglion cysts, particularly those of the midfoot region.[5] Similar findings were noted at the Memorial Sloan-Kettering Cancer Center.[1] This tendency and the grave implications led Scully and colleagues to suggest needle aspiration of all ganglia followed by open biopsy of all lesions from which fluid could not be obtained.[5] Other potential clinical miscues include tenosynovial giant cell tumor, lipoma, fibromatosis, and various other forms of low- and high-grade sarcoma.

Histopathology

There are two histopathologic forms of synovial sarcoma; monophasic and biphasic. Both types form moderately well-circumscribed, nonencapsulated masses within the deep tissue. In some cases a fibrous pseudocapsule composed of compressed connective tissue forms around the neoplasm's periphery. Monophasic synovial sarcomas are more common. This variant is composed of plump spindled cells with uniform nuclei, scant cytoplasm, and ill-defined cytoplasmic membranes (Fig. 17-51). The spindle cell component is arranged in fascicles. Some foci with a herringbone pattern reminiscent of fibrosarcoma may be present. The biphasic variant exhibits an identical spindle cell component; however, this form of synovial sarcoma possesses a second cell population composed of cuboidal or columnar cells arranged in glandular structures (Fig. 17-52). Both variants usually disclose a background of sclerotic collagen of variable density. As this is a high-grade neoplasm, mitotic figures and other features indicative of rapid proliferation are seen. There are often areas of exceedingly high cellularity admixed with areas of lesser cellularity.

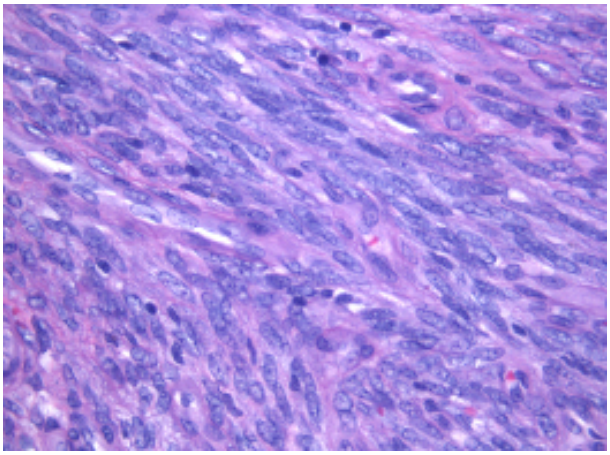

FIGURE 17-51. Synovial sarcoma (monophasic). Densely cellular neoplasm composed exclusively of spindled cells with scant cytoplasm.

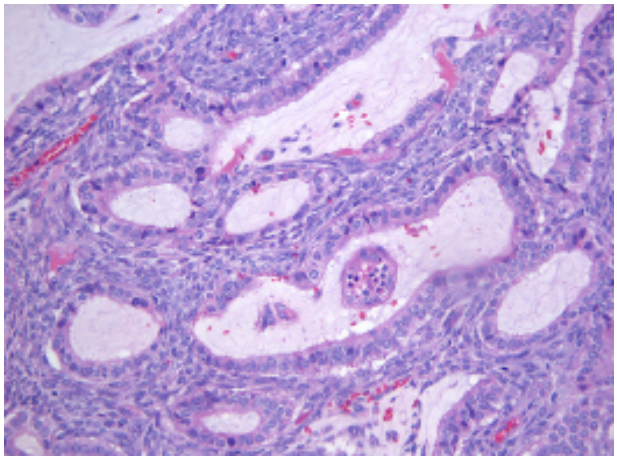

FIGURE 17-52. Synovial sarcoma (biphasic). Scattered glandular structures disposed amidst the spindle cell population that characterizes the monophasic variant.

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