

VASCULAR TUMORS OF THE SKIN

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BENIGN VASCULAR NEOPLASMS

Regardless of their particular histologic appearances, hemangiomas may be observed throughout life and assume relatively uniform macroscopic characteristics (1-3). They are bluish-red, non-ulcerated, relatively well-circumscribed, variably-fluctuant masses that may be macular, plaque-like, or protuberant in nature and commonly blanch when manually compressed by the examiner. The sizes of hemangiomas vary considerably, from 1 to 2 mm to more than 20 cm in greatest dimension. Large areas of the skin surface may be affected by those lesions that are part of the Sturge-Weber syndrome, and these also tend to be confined to one side of the body. Hemangiomas are not uncommonly congenital proliferations, and if so, they usually regress spontaneously with maturation of the host (1,3). Patients with **Kimura's disease** (tentatively included as a form of cutaneous hemangioma) often have multifocal nodular and violaceous lesions of the skin, peripheral eosinophilia, and enlargement of those lymph nodes draining the affected cutaneous area (4). Another distinctive subtype-- "**targetoid hemosiderotic**" (also known as "**hobnail**") **hemangioma**-- is named for its clinical appearance, which may simulate that of an archery target at some stage of lesional evolution (5-7).

Despite the fact that all cutaneous hemangiomas are benign, some variants-- such as lobular capillary hemangioma and infiltrating hemangioma-- may be floridly multifocal and difficult to approach surgically (8). Recurrence of such lesions therefore does not necessarily indicate progression to a biologically aggressive neoplasm.

Histologic Findings:

In the past few years, several microscopic variants of hemangioma of the skin have been recognized. These include the well-known capillary and cavernous subtypes-- composed of small-bore and large ectatic vascular spaces, respectively-- as well as mixed capillary-cavernous/venous hemangiomas (1), lobular capillary hemangiomas ("pyogenic granulomas") (9), "cellular" capillary hemangiomas (1), acquired tufted hemangiomas (10), glomeruloid hemangiomas (11), verrucous hemangiomas (12), infiltrating hemangiomas (13), targetoid/hobnail hemangiomas (6,7), epithelioid ("histiocytoid") hemangiomas (14,15), and Kimura's tumor/disease (4,15).

The basic structure of all of these proliferations is that of *organized formation of complete intercellular lumina*, mantled by pericytic cuffs of variable thickness and lined by bland endothelial cells with a spectrum of appearances (16). Another feature common to all the hemangiomas (possibly excepting "infiltrating" and "targetoid" lesions) is a *lobular* configuration (9,16). Discrete groups of lesional blood vessels and investing pericytes are separated from one another by fibrous stroma, and they contain a central "feeder" vessel in each lobule. Indeed, the **lobular capillary hemangioma** (LCH) is the prototypical example of this morphologic arrangement. Although the latter tumor is most commonly superficial and polypoid-- often with overlying ulceration-- it also may be seen deep in the dermis or subcutis (8). Examples of LCH that are traumatized may show regenerative nuclear atypia and mitotic activity in constituent endothelial cells (17); indeed, we have seen lesions

such as this that were misdiagnosed as vascular sarcomas because of these features. However, attention to the fact that the lobular character of the tumor is retained in these circumstances should help to avoid erroneous interpretations.

"Cellular" capillary hemangioma is simply regarded as a variant form of LCH in which the boundaries between adjacent lobules are indistinct, and the lumina formed by constituent endothelial cells are extremely small. In our opinion, this lesion is synonymous with the "angioblastoma" of Nakagawa (18). Another alternative designation-- that of "juvenile hemangioendothelioma"-- is unacceptable for diagnostic use, because hemangioendotheliomas in general are regarded as potentially-malignant neoplasms.

Verrucous hemangioma is a variant of cavernous hemangioma that is typified by overlying epidermal papillomatosis, parakeratosis, and hyperkeratosis (12). Keratinocytic rete ridges extend downward in this tumor to "embrace" or surround lesional blood vessels, much in the same manner as that observed in angiokeratoma (see below).

Acquired tufted hemangioma is another subtype of LCH, in which the lobules of tumor cells project into ectatic but pre-existing dermal veins and lymphatics (10,19). This arrangement yields a low-power appearance which has been likened to "cannon balls in the dermis" by Wilson-Jones and Orkin (19). In light of this description, it is likely that some examples of "intravenous pyogenic granuloma" described by Cooper et al. (20) would be regarded as acquired tufted hemangiomas currently.

Glomeruloid hemangioma is a newly described variant in which proliferating vascular channels take on the size of dermal venules, and are grouped together in discrete clusters such that they passingly resemble glomeruli of the kidney on low-power microscopy (21). The significance of such tumors resides in their association with the "POEMS" syndrome, a constellation of disorders (polyneuropathy, organomegaly, endocrinopathies, monoclonal gammopathies, and skin lesions) that is usually linked to an underlying lymphoproliferative disease or plasma cell dyscrasia (11,21).

Infiltrating hemangioma is again composed of venule-sized channels, but this lesion differs from the others described thus far because it shows no circumscription. A disorganized proliferation of randomly-arranged (but complete) luminal profiles is seen throughout the dermis and subcutis in this variant, and it may involve underlying fascia and muscle as well. Viscera, bones, and multiple soft tissue sites are affected in some cases, justifying diagnostic use of the term "angiomatosis" (13).

The **targetoid hemosiderotic ("hobnail") hemangioma**, as well as another closely allied variant-- **microvenular hemangioma**-- are probably related to the infiltrating variant just cited (5-7,22). Nonetheless, the first two of these lesions show a greater penchant for formation of incomplete and interanastomosing vascular spaces that "dissect" through dermal collagen and subcuticular tissue (5). Small papillary projections of bland endothelial cells also may project into the lumina of targetoid hemangiomas (6,7). These histologic features often cause considerable concern regarding the potential diagnosis of a vascular sarcoma. Nonetheless, the advancing

boundaries of targetoid hemangiomas are relatively well-defined (unlike those of endothelial malignancies), and an organized rim of dense hemosiderin deposition is often apparent peripherally (5). Other lesions with closely-similar microscopic features include the so-called "**benign lymphangioendothelioma**" (23) and "**multinucleate angioreticulohistiocytoma**" (24). However, the latter tumors do differ from targetoid hemangioma. Benign lymphangioendothelioma contains proteinaceous lymphatic fluid rather than luminal erythrocytes, lacks stromal hemosiderin deposits, has a more regimented superficial constituency by vertically-aligned vascular spaces, and may be invested by lymphoid infiltrates. Angioreticulohistiocytoma contains multinucleated stromal cells that border vascular spaces, and in some foci, may appear to line them.

The lesion now known as **epithelioid hemangioma** (15) has been the subject of considerable terminological debate in recent years. Alternative designations for this tumor include "**angiolymphoid hyperplasia with eosinophilia**" (25) and "**histiocytoid**" **hemangioma** (14). The salient feature of epithelioid hemangiomas is the plump, cuboidal appearance of the endothelial cells that line constituent blood vessels. The latter channels have the dimensions of capillaries or venules, and their lumina are indistinct because of the space occupied by proliferating endothelia. Nuclear contours in the tumor cells are round or slightly indented, chromatin is dispersed, and nucleoli are indistinct (15). These characteristics led Rosai et al. to focus on a morphologic similarity between the nuclei of such neoplasms and those of histiocytes (14). Angiolymphoid hyperplasia with eosinophilia is nothing more than an inflamed version of epithelioid hemangioma, in which the stroma between constituent dermal blood vessels is rich in lymphocytes and eosinophils (25).

Like other morphologic variants of hemangioma, a basically lobular substructure is observed in epithelioid hemangiomas as well. Nevertheless, a unique finding in the latter neoplasms is their potential association with large arteries or veins in the skin, such that the tumoral blood vessels appear to emerge from pre-existing vascular adventitia like a swarm of bees.

Considerable attention also has been given to the possible synonymity between epithelioid hemangioma and **Kimura's disease/tumor** (4). However points of convincing clinicopathologic dissimilarity do exist between these two neoplasms. Kimura's tumor features a striking stromal lymphoid infiltrate-- complete with germinal centers-- and is centered more deeply in the skin. Moreover, constituent vessels are more elongated than those of epithelioid hemangioma, and tumor cell nuclei do not have the complex contours of those in the latter lesion. As already mentioned, Kimura's disease often includes the presence of regional lymphadenopathy and eosinophilia in the peripheral blood, whereas epithelioid hemangiomas are unassociated with these findings (15).

BORDERLINE ENDOTHELIAL TUMORS

Papillary Endovascular (Lymph-)Angioendotheliomas

Clinical Features: Papillary endovascular angioendotheliomas (PEA) were first described by Dabska in 1969 (26), and have subsequently become known using her name as an eponym (i.e., Dabska's tumor). A more recent paper (27) has suggested that a more correct designation for this neoplasm is that of papillary intralymphatic

angioendothelioma. It is apparently seen only in children and adolescents, as a fluctuant, ill-defined reddish plaque or nodule that ranges in size up to 5 cm. A zone of dermal edema may surround such neoplasms (26,28). "Metastases" of PEA to regional lymph nodes were reported in the seminal series of cases, but other authors have since suggested the alternative interpretation that the nodal implants actually represented tumor "satellites" as part of a field neoplasia phenomenon (29).

Nevertheless, PEA does have a marked propensity to recur locally after surgical excision, justifying its inclusion as a "borderline" proliferation (26,30).

Histologic Findings: The microscopic features of PEA are distinctive. As its name suggests, this tumor is confined to pre-existing vascular spaces in the corium, most of which have the properties of dilated lymphatic channels. Also in similarity to deep lymphangiomas of the skin, PEA features contiguous dermal fibrosis and intralesional aggregates of lymphocytes. The latter cells are also evident in intimate admixture with plump endothelial cell clusters inside of the affected vessels (26,27).

The papillae of PEA are composed of polyhedral cells with round nuclei, dispersed chromatin, and small nucleoli. As just mentioned, mature lymphocytes commonly mantle the peripheral aspects of the papillary formations, and they contain internal, globular, intercellular eosinophilic deposits of basement membrane material. These inclusions may be labeled with the periodic acid-Schiff stain or with immunostains for laminin and collagen type IV (17).

Adjacent blood vessels in PEA that do not contain papillae are nonetheless lined by atypical endothelial cells, with hyperchromatic nuclei. Small areas of racemose vascular proliferation also may be apparent in the dermis, as seen in well-differentiated angiosarcomas. Mitotic activity is present but limited in scope.

Epithelioid Hemangioendotheliomas

Clinical Attributes: Epithelioid hemangioendotheliomas (EH) are subcutaneous lesions that only uncommonly involve the dermis. As such, they present as firm tan-pink nodules and plaques measuring several cm in maximum diameter. Adult patients are primarily affected, with a slight predilection for women. The trunk and extremities are the usual sites of origin (31-33). Some patients with EH of the skin will concurrently have histologically-identical tumors in the lung (where they were known in the past as "intravascular bronchoalveolar tumors" [IVBATs]) and the liver (32). Under these conditions, it is impossible to determine whether the visceral and cutaneous lesions are independent primary neoplasms, or whether they represent metastases of one another. EH recurs in up to 40% of cases, and approximately 15% metastasize to distant extracutaneous locations (34).

Histologic Features: EH is typified by disorganized sheets and cords of large polyhedral tumor cells with amphophilic cytoplasm, prominent cytoplasmic vacuoles, and round but eccentric nuclei. Chromatin is vesicular and small nucleoli are often seen. The neoplastic cells make no attempt to form complete intercellular vascular lumina, as seen in epithelioid *hemangiomas* (17). However, like the latter tumor, EH has a proclivity for growth around pre-existing large blood vessels. Mitotic activity and necrosis may be apparent, but they are relatively inconspicuous when present. The background stroma is variably fibrous or myxoid in character (32).

Two diagnostic errors are common in the evaluation of EH. First, one may focus on the cord-like arrays of polygonal cells in some cases, leading to a misinterpretation of metastatic carcinoma. Secondly, those lesions with extensive cytoplasmic vacuolization may erroneously be labeled as adipocytic in nature. The application of electron microscopy or immunohistochemical studies for epithelial and endothelial determinants (see above) is useful in resolving such uncertainties.

Spindle-Cell “Hemangioendothelioma” (Hemangioma)

Clinical Characteristics: Spindle-cell “hemangioendothelioma” (SCH)—now regarded as a benign entity (spindle-cell hemangioma [35]) is a tumor entity that is seemingly confined to the skin and subcutis (36,37). It is included in this section with other hemangioendotheliomas mainly because of historical context. This lesion has a long period of evolution-- up to 30 years-- and therefore usually presents in young adulthood (36). It has a marked tendency for multifocality, and a predilection for the skin of the extremities. It also may arise in the setting of Mafucci's syndrome, in which multiple enchondromas of bone are also observed (36-38).

SCH is a multinodular, red-violet, fluctuant lesion that may attain a size of several centimeters. Its original “borderline” status stemmed from the fact that local recurrence after surgical excision was thought to be a common event, being seen in up to 70% of cases (36). However, reanalysis of this point has made it appear likely that such “recurrences” are actually a reflection of multifocality (35). Only one documented instance of distant metastasis by SCH has been reported to date, and this case was unusual in that the patient had received radiation therapy (36). Another controversy surrounding this lesion centers on whether it is, indeed, a neoplasm at all. Some authors instead prefer the view that SCH represents a reactive endothelial proliferation (39,40).

Histologic Features: SCH has a distinctive microscopic appearance that represents an “amalgamation” of the attributes of cavernous hemangioma and Kaposi's sarcoma (33,36). One observes an intimate admixture of large, ectatic vascular spaces in the dermis-- which often contain luminal thrombi and may harbor calcifications as well-- with spindle-cell foci showing extravasation of erythrocytes and intracytoplasmic vacuoles. The latter finding is shared with **epithelioid** hemangioendothelioma, as described above. Nuclei of the tumor cells in both components of SCH are relatively bland, and mitotic activity is limited. The peripheral borders of the proliferation are poorly-defined, and small “satellite” lesions may be observed within several millimeters on either side of the main mass (37). Permeation into the subcutis or deeper soft tissues is relatively common. Small areas featuring racemose, interanastomosing, “dissecting” vascular channels may be noted as well.

Kaposiform Hemangioendothelioma

Clinical Features: Kaposiform hemangioendothelioma (KHE) is a neoplasm that is most commonly observed in children and adolescents, although examples also have been reported in adult patients as well (41-44). There is no apparent gender predilection. This cutaneous tumor may take the form of rapidly-enlarging red-violet plaques, nodules, or grouped telangiectasias, and may reach a maximum size of several cm. Lesions in the skin may be accompanied by concomitant KHEs in the deep soft tissues, and an association with lymphangiomatosis is also common (41,44).

Another peculiar clinical linkage of KHE is with the Kasabach-Merritt phenomenon (peripheral consumption of platelets and other formed blood elements), producing a potentially life-threatening coagulopathy (41).

The preferred therapy for this lesion is complete surgical excision, when possible. However, administration of interferon, steroids, and other agents may be necessary for unresectable KHEs (44). Death may occur as a result of the cited complications of these neoplasms, and their aggressive local growth may produce considerable morbidity, but metastasis has not been documented.

Histologic Features: KHE is typified by an amalgamation of histologic findings that one might expect in lymphangiomas, hemangioma variants, other forms of hemangioendothelioma, and Kaposi's sarcoma. As such, one observes a proliferation of fusiform or compact polygonal endothelial cells, arranged in sheets or irregular nodules in the dermis and subcutis. These also line interconnecting slit-like vascular channels or rounded capillary-type vessels, and some of the lumina in such structures contain microthrombi. Cytoplasmic hyaline droplets, extravasated erythrocytes, and stromal hemosiderin are seen in a proportion of KHEs. Nuclear atypia is slight, and mitotic activity is variable but generally limited. In contrast to true Kaposi's sarcoma, which is the principal differential diagnostic consideration, there is no molecular evidence of infection with the human *Herpes* virus type 8 in KHE (or, for that matter, any of the other hemangioendotheliomas) (45).

Other Hemangioendotheliomas

Two other cutaneous hemangioendotheliomas are now recognized—"retiform" hemangioendothelioma (RHE) and "composite" hemangioendothelioma (CHE). The first has a strong clinicopathologic resemblance to Dabska's tumor, except that it may occur in adults. The principal feature of RHE is the elongated and sinusoidal nature of its vascular channels, such that they resemble the rete testis on scanning microscopy. Its behavior is "borderline," with frequent recurrence but uncommon metastasis (44,47).

As its name suggests, CHE demonstrates microscopic features that represent a potential admixture of those seen in epithelioid, spindle-cell, and retiform hemangioendotheliomas (48). In addition, CHE may contain foci that simulate angiosarcoma or variants of lymphangioma. Again, it is a biologically-borderline proliferation.

OVERTLY MALIGNANT ENDOTHELIAL NEOPLASMS

Those mesenchymal neoplasms that demonstrate a reproducible tendency for recurrence *and* distant metastasis are rightly considered to be overtly malignant. In specific regard to cutaneous vascular tumors, there are only two that truly fulfill those criteria; namely, Kaposi's sarcoma and angiosarcoma.

Kaposi's Sarcoma

Clinical Findings: The clinical characteristics of Kaposi's sarcoma (KS) are by now all-too-familiar to most physicians, because of the tremendous increase in the incidence of this tumor occasioned by the advent of the AIDS epidemic in the 1980's. Prior to that time, KS was a relatively rarely encountered lesion outside of the Mediterranean basin and Africa (49).

This neoplasm occurs in four well-defined clinical settings (49-51). **Classical Kaposi's sarcoma** is a disease that predominantly affects elderly men of Middle-Eastern or Italian heritage, and which manifests itself as multiple, coalescent, red-brown macules and plaques on the distal lower extremities. A subset of patients has lesions that resemble deep lymphangiomas, accompanied by lymphedema of the extremities. Nodular, sometimes-ulcerated tumors of the skin and viscera eventually supervene in this variant, but only after a prolonged period of time. **African KS** is seen in young black patients from restricted portions of the African continent. Women are almost as frequently afflicted as men, and their mean age is less than that of classical KS patients by two to three decades. The disorder is more rapidly progressive in African KS, with relatively early appearance of nodular lesions and involvement of lymph nodes and internal organs. **KS associated with iatrogenic immunosuppression** shares clinical features with both the classical and African subtypes, and primarily affects recipients of allogeneic organ transplants. **AIDS-related KS** is precipitated by infection with the HIV. At the outset of the AIDS pandemic, it was first noted in young homosexual men (52), with lesser numbers of cases in intravenous drug abusers and recipients of infected blood products.

Although the other manifestations of AIDS have become more evenly-distributed among all infected patient populations, KS has remained largely confined to gay males. In fact, its incidence has already begun to decline, even though the number of HIV-infected individuals continues to rise on a worldwide scale. The reasons for these epidemiologic peculiarities are unknown at the present time (53).

AIDS-related KS has a deceptively innocuous appearance at its onset, taking the form of ill-defined macular "patches" that often resemble ecchymoses (54). In contrast to the topographic confinement of the classical variant, KS in AIDS patients may affect virtually any skin field and also is seen in the mucosae (52). Visceral involvement also appears rapidly, in likeness to that seen in the African form.

Interestingly, several common threads have emerged that bind all of the variants of KS together. One factor is the HLA-DR5 allele, which is greatly overrepresented in KS patients when compared with the population at large (55). The second is seropositivity for the cytomegalovirus (CMV) (56). In reference to that observation, some authors have advanced the hypothesis that KS is not a neoplasm at all, but instead represents an unusual tissue reaction to the latter infectious agent (57). We do not subscribe to the latter view. It has been shown that KS cells express an activated oncogene, termed "K-FGF" (58). Moreover, the features of this proliferation in transfection studies are most consistent with those of a true neoplasm, and the pattern of visceral involvement seen in advanced cases is unlike that of any known viral disease. Lastly, genomic sequences of human *Herpes* virus type 8 (HHV8) have been detected in Kaposi's sarcoma by molecular analyses (59). It would therefore appear tenable to conclude that KS may result from the effects of HIV-CMV-HHV8 co-infection in susceptible (HLA-DR5-positive?) individuals, allowing viral agents to express a latent potential for cellular transformation and oncogenesis (59,60).

Classical KS is an indolent process that only infrequently causes death of the patient directly. African, transplant-associated, and HIV-related variants evolve more rapidly and are often fatal (50).

Histologic Features: The reason that KS was included in this section is that its histologic spindle-cell pattern is most well-known to pathologists. Nevertheless, all subtypes of the tumor will be described here for the sake of convenience.

Clinically "early" KS most often takes a macular or "patch" form (54). Microscopically, this variant is extremely subtle. One often sees only a limited proliferation of small, attenuated, interanastomosing but bland blood vessels in the periappendageal reticular corium, together with an excess of nondescript spindle cells throughout the dermal connective tissue. In addition, small pre-existing blood vessels are often invested by a lymphoplasmacytic infiltrate. The "promontory" sign, wherein neovascular channels are formed around native vessels-- yielding profiles that simulate the promontory of a cliff-- is a helpful diagnostic finding (54). Small groupings of venule-like blood vessels are also interspersed randomly throughout the dermis in some cases, and extravasated erythrocytes are inconspicuous if present at all (50). McNutt et al. have also called attention to the fact that endothelia within "new" (neoplastic) blood vessels of KS are often apoptotic in the patch-stage (61). This observation is unique, and would not be expected in benign vascular proliferations.

"Plaque" stage KS features the appearance of more organized aggregates of spindle cells, forming small fascicles in admixture with capillary-sized neovascular channels, extravasated erythrocytes, and stromal hemosiderin granules (50,62). The groupings of neoplastic cells are most often diffusely dispersed throughout the dermis, but they sometimes assume a pseudolobular configuration (50). Another useful diagnostic clue that appears at this phase of tumor evolution is the presence of hyaline globules in the neoplastic endothelial cells. These represent phagocytosed erythrocytes, as documented by the peroxidase reaction, and they also may be stained with the periodic acid-Schiff-diastase method (49). Hyaline globules are not sufficient unto themselves for a diagnosis of KS, because they can rarely be seen in non-neoplastic vascular proliferations of the skin (62). However, they are helpful when interpreted in the proper context. Finally, small papillary projections of tumor cells may be observed within ectatic neovascular spaces in this stage of KS, together with racemose, "dissecting" luminal profiles throughout the dermis.

The truly spindle-cell stage of KS is its "nodular" phase, where fusiform elements comprise the bulk of the proliferating cell population. Their nuclei are only modestly hyperchromatic, with indistinct nucleoli, and cytoplasm is scant and amphophilic. A notable diagnostic feature is the presence of cytoplasmic vacuoles in the spindle cells, probably representing a primitive attempt at vascular lumen formation (50). Another helpful microscopic finding is that the fusiform cells of KS appear to "spare" dermal zones that surround pre-existing vessels, leaving hypocellular cuffs around the latter structures (63). Extravasated erythrocytes and stromal hemosiderin deposition are maximal in scope in the nodular stage of KS, and hyaline globules often are numerous in the neoplastic cells.

Another continuing controversy regarding KS focuses on the "nature" of the proliferating elements in its spindle-cell form. There is no question that patch stage

and plaque stage disease features reproducible immunoreactivity for endothelial markers, but these determinants are only occasionally detected in the spindle cell variant. Some authors contend that KS is a modified lymphatic endothelial tumor (64), whereas others have concluded that it is not endothelial at all (65). I prefer the premise that KS begins as a vascular endothelial neoplasm that undergoes reproducible clonal evolution, to yield a cellular population that predominantly resembles myofibroblasts but retains immunoreactivity for HHV8-latent nuclear antigen-1 (66,67).

Differential diagnosis includes leiomyosarcoma, spindle-cell melanoma, spindle-cell squamous carcinoma, malignant peripheral nerve sheath tumor, and spindle-cell angiosarcoma. All but the last of these possibilities are easily excludable by attention to histologic detail or application of special studies.

Spindle-cell angiosarcoma (SCA) is a rare lesion (see below), the microscopic attributes of which are nearly identical to those of nodular KS (33). Nevertheless, the clinical features of the two conditions usually differ substantially, as detailed below. SCA also exhibits a much higher degree of nuclear atypia and mitotic activity. Moreover, immunostains for thrombomodulin, FLI-1, CD31, and CD34 are typically positive in SCA but not in spindle-cell KS, and only the latter tumor contains genomic sequences of HHV8 and immunoreactivity for the latent nuclear antigen-1 of that virus (33,68).

Angiosarcoma

Clinical Features: Angiosarcoma of the skin is characteristically seen in one of several well-defined clinical contexts. These encompass idiopathic proliferations on the scalp or face of elderly patients; occurrence in a field of prior therapeutic irradiation after a "lag" period of 5 or more years; and development in an area of chronic cutaneous lymphedema (the so-called **Stewart-Treves syndrome**) (69). An exceedingly small minority of tumors do arise outside of the situations just cited, as lesions of the extremities or trunk in individuals with no apparent predisposing conditions.

Angiosarcomas likewise show a variety of macroscopic presentations. They may be large, multinodular, ill-defined, violaceous, bloody, and sometimes-ulcerated masses; vague ecchymosis-like macular lesions; ligneous, "brawny" alterations in the skin that simulate erysipelas; and multifocal, seemingly-discrete bluish-red nodules that imitate cavernous hemangiomas (17).

The behavior of angiosarcoma is uniformly aggressive. Those patients whose neoplasms are less than 10 cm in maximum dimension may derive some benefit from radical surgical excision and postoperative irradiation, but almost all affected individuals will eventually die of unmanageable local tumor growth or distant metastases (70).

Histologic Findings: In classical form, angiosarcoma is a disorganized proliferation of polyhedral atypical endothelial cells with hyperchromatic nuclei and scant amphophilic cytoplasm. The tumor cells mantle racemose, interconnecting, "sieve-like" vascular channels in the skin that "dissect" through dermal collagen and deeper tissues and contain luminal red blood cells (71-74). Cutaneous appendages are variably entrapped or destroyed by the proliferation; hemosiderin and chronic

inflammatory cells may be interspersed throughout the lesion. Large tumors may ulcerate the overlying epidermis multifocally. Micropapillae of neoplastic cells are frequently seen projecting into the neovascular channels of angiosarcomas, and the supporting (stromal) blood vessels also may show nuclear atypia in endothelial cells. Mitotic activity is variable in scope but always present. Necrosis may or may not be observed.

Several well-documented microscopic variants of angiosarcoma have been recognized. These include the spindle-cell subtype, as described above, a solid "epithelioid" form (75), "minimal-deviation" (hemangioma-like) angiosarcoma (76), a granular-cell variant (77), and a pleomorphic subtype with the potential to simulate atypical fibroxanthoma or malignant fibrous histiocytoma (69). Akiyama et al. also have reported two cases in which benign melanocytes and melanophages were intermixed with the neoplastic endothelial cells in the dermis (78).

Among these histologic forms, several merit further comment because they may be the sources of diagnostic error. Minimal-deviation angiosarcoma (MDAS) shows minimal cytologic atypia of constituent endothelial cells, and forms more complete (tubular) vascular lumina in the upper dermis than those seen in other variants (76). Nonetheless, specimens including the deep dermis and subcutis inevitably reveal the racemose "dissecting" endothelial profiles that are characteristic. The danger here is in the interpretation of shallow punch biopsies or shave biopsies, such that MDAS may be mistaken for "targetoid" or "microvenular" hemangiomas. As described above, the latter hemangioma subtypes have a permeative pattern of growth in the dermis which mimics the superficial aspect of MDAS. Thus, all tumors demonstrating an atypical, disorganized pattern of neovasogenesis should be excised totally.

Epithelioid angiosarcoma is composed entirely or predominantly of plump polyhedral cells that imitate true epithelia (75). These occupy much of the lumen in vascular spaces formed by such lesions, and therefore the latter channels often contain few discernible erythrocytes and are not readily recognized as endothelial in nature.

Simulants of spindle-cell AS have been discussed above in connection with KS. Epithelioid vascular tumors may simulate true epithelial neoplasms (particularly "pseudovascular" or "angiomatoid" squamous carcinomas [79]), melanoma and clear-cell sarcoma, epithelioid sarcoma, epithelioid leiomyosarcoma, and large-cell lymphoma (17). Pleomorphic variants of angiosarcoma can be confused with atypical fibroxanthoma, primary or metastatic undifferentiated carcinomas, melanoma, and malignant fibrous histiocytoma. In these contexts, immunohistologic analysis is the most useful diagnostic tool. Endothelial tumors are reactive for vimentin, CD31 & CD34 antigens, FLI-1, and thrombomodulin. Even though epithelioid vascular neoplasms may occasionally label for keratin (80), as a general category, endothelial tumors lack epithelial membrane antigen, desmin, muscle-specific actin, and p63 & S100 proteins, in contrast to the alternative diagnostic entities cited above.

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