# 22

# Malignant Vascular Tumors

## OUTLINE



## ANGIOSARCOMA

Angiosarcomas are malignant tumors that recapitulate many of the functional and morphologic features of normal endothelium. They vary from highly differentiated tumors resembling a hemangioma to anaplastic lesions difficult to distinguish from a poorly differentiated carcinoma or pleomorphic sarcoma. Angiosarcomas are no longer subdivided into lymphangiosarcomas and hemangiosarcomas because this distinction cannot be reliably made by conventional methods. In fact, evidence indicates that some angiosarcomas have a mixed phenotype.[1] *Hemangioendothelioma*, a term formerly used as a synonym for *angiosarcoma*, particularly in sites such as the bone, is used for vascular tumors of borderline malignancy only (see Chapter 21).

### Incidence

Angiosarcomas are collectively one of the rarest soft tissue neoplasms. They account for a vanishingly small proportion of all vascular tumors and less than 1% of all sarcomas. Although they may occur at any location in the body, they rarely arise from major vessels and have a decided predilection for skin and superficial soft tissue, a phenomenon that contrasts sharply with the deep location of most soft tissue sarcomas. These tumors infrequently occur during childhood, but when they do, they seem to occur in an epidemiologic pattern different from that of adults.[2,3] For example, angiosarcomas tend to develop more in internal organs or with various disease states (e.g., Klippel-Trénaunay syndrome). Over the past two decades, the distribution pattern of angiosarcomas has changed. *Cutaneous angiosarcomas*, formerly constituting about one-third of all angiosarcomas, now account for about one-half. This increase probably reflects the increasing frequency of cutaneous postirradiation sarcomas. About 10% of angiosarcomas are located in deep soft tissue, and the remainder are located in parenchymal organs such as the breast, bone, heart, and spleen (Table 22.1).[4]

Because there are pathogenetic and behavioral differences among angiosarcomas, it is useful to conceptualize them not as one disease but as several interrelated ones linked by the common presence of the malignant endothelial cell. Angiosarcomas are divided into several clinical groups: (1) primary cutaneous angiosarcoma (unassociated with lymphedema or radiation); (2) lymphedema-associated angiosarcoma; (3) postirradiation angiosarcoma; (4) angiosarcoma of deep soft tissue; and (5) angiosarcoma of parenchymal organs such as bone, liver, spleen, heart, and breast. Angiosarcomas also rarely develop adjacent to foreign material, in the vicinity of arteriovenous fistulas in renal transplant patients, within other tumors, or in association with rare genetic syndromes. Although eclipsed in number by the other forms of angiosarcoma, these unusual associations suggest more than a coincidental occurrence.

### Etiologic Factors

Chronic lymphedema and radiation are the most widely recognized predisposing factors for angiosarcomas of skin and soft tissue. Typically, **lymphedema-associated angiosarcoma** occurs in women who underwent (modified) radical mastectomy for breast carcinoma and had chronic severe lymphedema for years. Virtually all forms of lymphedema have been associated with this complication. To explain the association of lymphedema and angiosarcoma, some suggest that the growth and proliferation of obstructed lymphatics eventually fail to respond to normal control mechanisms. Others believe that carcinogens in lymphatic fluid induce the neoplastic change,

**TABLE 22.1 Anatomic Distribution of Angiosarcomas**

| Location | No. of Cases (*N* = 222) | Percentage (%) |
|---|---|---|
| Skin | 110 | 49.6 |
| Breast (parenchyma) | 32 | 14.4 |
| Soft tissue | 25 | 11.2 |
| Heart | 15 | 6.7 |
| Bone | 9 | 4.1 |
| Other | 31 | 14 |

Data from Lahat G, Dhuka AR, Hallevi H, et al. Angiosarcoma: clinical and molecular insights. *Ann Surg.* 2010;251(6):1098.

or that the lymphedematous extremity represents an immunologically privileged site[5] that is unable to perform immunologic surveillance of normally occurring mutant cell populations.

Radiation has been clearly associated with angiosarcoma, independent of lymphedema. Definitionally, **postirradiation angiosarcoma** must (1) be biopsy proven, (2) arise in the radiation field, (3) occur after a latency of several years, and (4) arise in an area without lymphedema. Previously, postirradiation angiosarcomas followed radiotherapy for carcinoma of the cervix, ovary, endometrium, and Hodgkin lymphoma after an interval of more than 10 years. In the past two decades, this epidemiologic profile has been changing because of the common practice of administering radiation to women following lumpectomy for breast cancer. The interval in these patients is much shorter than the foregoing group.

A number of angiosarcomas have developed at the site of defunctionalized *arteriovenous fistulas*[6-8] in renal transplant patients and have been attributed to immunosuppression. However, this does not explain those cases that have occurred in the absence of immunosuppression or the invariable presence of angiosarcoma in the immediate vicinity of the fistula. Some have proposed that immunosuppression provides the ideal context in which deviant patterns of blood flow upregulate growth factors and adhesion molecules to promote endothelial proliferation and migration.[9] Angiosarcomas also have been reported adjacent to *foreign material* introduced into the body iatrogenically or accidentally. In an extensive review of the literature by Jennings et al.,[10] nine angiosarcomas associated with foreign material were identified. Common to all was a long latent period between introduction of the foreign material and development of the tumor. Although one case occurred within 3 years, the remainder appeared more than a decade later. A variety of solid materials were implicated, including shrapnel, steel, plastic and synthetic (usually Dacron) vascular graft material, surgical sponges, and bone wax. An exuberant host response in the form of a fibrous tissue capsule around the foreign material may represent an important intermediate step in the sarcoma's development.[10] An angiosarcoma occurring in a long-standing gouty tophus suggests that urate deposits may function as the equivalent of foreign material.[11]

Angiosarcomas supervening on other tumors, such as port-wine stains, hemangiomas, lymphangiomas,[12,13] benign and malignant nerve sheath tumors,[14-18] malignant germ cell tumors,[19] and leiomyomas,[20] have been well documented but are extraordinarily rare. In addition, angiosarcomas may develop in association with other diseases such as neurofibromatosis,[16] bilateral retinoblastoma (*RB1* deletion),[21] Klippel-Trénaunay syndrome,[12] xeroderma pigmentosum,[22] and Aicardi syndrome,[23] an X-linked disorder associated with multiple congenital abnormalities, including agenesis of the corpus callosum.

Unfortunately, information is sparse on the possible role of *environmental carcinogens* in the pathogenesis of soft tissue angiosarcomas, although relatively strong evidence links various substances to the induction of **hepatic angiosarcomas**. About one-fourth of hepatic angiosarcomas occur in patients who have received thorium dioxide (Thorotrast) for cerebral angiography, in vineyard workers exposed to arsenic trioxide ($AsO_3$)–containing insecticides, and in industrial workers exposed to vinyl chloride during synthetic rubber production. A few cases have occurred in patients receiving long-term androgenic anabolic steroids. Mutations of the *KRAS2* gene have been detected in both sporadic and Thorotrast-induced hepatic angiosarcomas.[24]

## Molecular Genetic Findings

Angiosarcomas constitute a tight genomic group that differs from other sarcomas by overexpression of genes implicated in the stages of angiogenesis, including genes for vascular-specific receptor tyrosine kinases: *TIE1, KDR (VEGFR2), SNRK, TEK,* and *FLT1 (VEGFR1)*.[25] Angiosarcomas can be further separated into two genomic subgroups: radiation-induced lesions characterized by overexpression of *LYN* and *PRKCθ* and non–radiation-induced lesions characterized by overexpression of *FLT1* and *AKT3*. A small subset of angiosarcoma also harbors activating mutations of *KDR*, suggesting that small-molecule receptor inhibitors (e.g., sunitinib) could be effective therapeutic agents.

High-level *MYC* amplification has recently been demonstrated in 50% to 100% of postirradiation and lymphedema-associated angiosarcoma, but not in other forms.[26-28] Furthermore, amplification status is independent of grade, location, and histologic features. *PTRB* mutations, with or without concurrent mutations in *PLCG1*, are seen exclusively in *MYC*-amplified postirradiation angiosarcomas.[29]

Huang et al.[30] recently reported *CIC* gene abnormalities in a small number of cases classified as "angiosarcoma" on the basis of morphologic features in six cases or immunohistochemistry (IHC) for CD31 and ERG alone in three cases. The six cases of "angiosarcoma" had irregular spaces interpreted as rudimentary vessel channel formation and *CIC* mutations, tending to occur in relatively young patients. In contrast, *CIC* gene rearrangements were seen in three tumors in young adults and were composed of primitive cells with epithelioid and rhabdoid morphology without overt vascular differentiation. Based on the photomicrographs, we believe these cases are better seen as *CIC*-rearranged primitive sarcomas with aberrant expression of CD31[30] rather than angiosarcomas. Others have reported aberrant CD31 expression in *CIC*-rearranged primitive sarcomas.[31] These tumors are discussed in greater detail in Chapter 33.

## Clinical Subtypes

**Primary Cutaneous Angiosarcoma.** Primary cutaneous angiosarcoma (i.e., those unassociated with radiation or lymphedema) is the most common clinical form, accounting for one-half of all cases.[3] It usually occurs after the seventh decade, with men and women equally affected. Almost 90% occur in the white population. About half develop on the head, neck, and face, particularly the area of the scalp and upper forehead. Although often imputed causally, sun exposure has not been proved. Clinically, the appearance of these lesions is variable. Most begin as ill-defined bruiselike areas with indurated borders. Advanced lesions are elevated, nodular, and occasionally ulcerated (Fig. 22.1). It is difficult to determine the clinical extent of these lesions, which coupled with multifocality in about half the cases, seriously complicates therapy and probably results in suboptimal initial

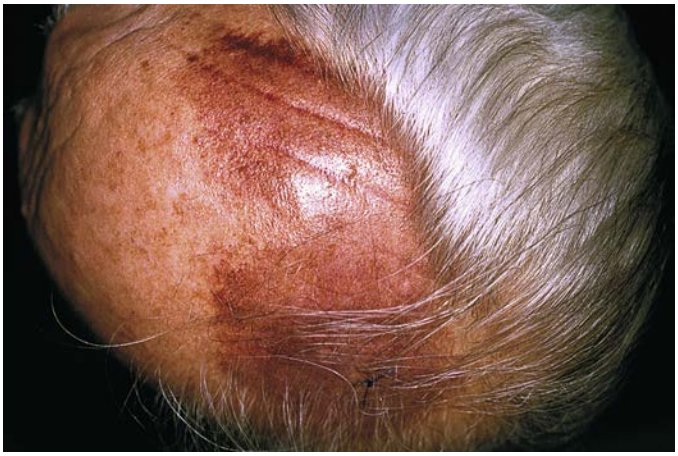


**Fig. 22.1** Angiosarcoma of scalp in elderly man. (Case courtesy of Dr. Vernon Sondak, University of Michigan Hospitals.)


**Fig. 22.2** Angiosarcoma of scalp. Hemorrhagic appearance frequently suggests a diagnosis of dissecting hemorrhage or hematoma.

therapy in many patients. Preoperative mapping of angiosarcoma using grid-pattern biopsies or Mohs surgery has resulted in better delineation of tumor extent and treatment planning.[32]

Grossly, the tumors consist of poorly defined hemorrhagic areas that flatten or ulcerate the overlying skin (Fig. 22.2). Rarely, the epidermis displays verrucous hyperplasia. On a cut section, the tumors have a microcystic or spongelike quality because of blood-filled spaces. The tumors extensively involve the dermis and extend well beyond their apparent gross confines. In poorly differentiated, rapidly growing tumors, deep structures, such as the subcutis and fascia, are invaded. The periphery of the tumors contains a fringe of dilated lymphatic vessels surrounded by chronic inflammatory cells and usually small capillaries in which piling up and tufting of the endothelium suggest incipient malignant change.

Traditionally the diagnosis of angiosarcoma is based on identification of vascular channels of irregular size and shape within a malignant tumor (Figs. 22.3 to 22.6). This, however, can give rise to a wide range of appearances. At one extreme, angiosarcomas can appear so well differentiated that they can be mistaken for a hemangioma. In these cases, evaluation of the architectural pattern is critical. In contrast to hemangiomas, the vascular channels in angiosarcomas are imperfectly formed and anastomose with one another, creating a network of sinuses (Fig. 22.4B-D). They carve their way through tissue, dissecting through the dermal collagen (Figs. 22.3C and 22.4A and B) and fascia, splitting apart groups of subcutaneous fat cells (Figs. 22.3D and 22.4C), and isolating adnexal structures (Fig. 22.4D). In some cases, prominence of nucleoli can be identified within flattened endothelium of the vessels (Fig. 22.5).

At the other extreme, poorly differentiated angiosarcomas are composed of cells of higher nuclear grade with prominent nucleoli, which can vary from spindled to rounded, such that the differential diagnosis embraces a range of tumors from sarcoma to carcinoma (Fig. 22.6). Rudimentary vessels are lined by redundant endothelium often thrown into papillations. In addition to vasoformative areas, poorly differentiated angiosarcomas frequently have expanses of solid-appearing areas.

A rare form of angiosarcoma is the *foamy cell variant*.[33] Composed of sheets of cytologically bland, finely vacuolated endothelial cells, these lesions are easily mistaken for a xanthomatous reaction (Fig. 22.7). Those with more atypia may bring to mind a signet-ring carcinoma.

***Immunohistochemical findings.*** IHC confirmation of the diagnosis of angiosarcoma can usually be accomplished using a panel of vascular markers (see Chapter 6). Using both CD34 and CD31, almost all angiosarcomas, even poorly differentiated ones, can be identified, although with a few caveats. CD34 is expressed by many angiosarcomas and Kaposi sarcoma, but it is also seen in some soft tissue tumors (e.g., epithelioid sarcoma) that may enter into the differential diagnosis of angiosarcoma. CD31 (platelet-endothelial cell adhesion molecule), on the other hand, seems to be the more sensitive and more specific antigen for endothelial differentiation (Fig. 22.8A). In the context of soft tissue neoplasia, virtually all benign and malignant vascular tumors express this membrane protein, whereas nonvascular tumors do not. Because histiocytes are CD31 positive in a granular membranous pattern, it is important to assess accurately the characteristics of positive cells. The prudent approach is to use IHC studies to rule out other diagnoses that may legitimately enter the differential diagnosis, coupled with a panel of vascular markers (e.g., CD31, CD34) that, if positive, support the diagnosis of angiosarcoma.

Newer antibodies to FLI1 and ERG proteins are highly sensitive and relatively highly specific markers of angiosarcoma.[34-36] FLI1, a nuclear transcription factor, has been shown to identify more than 95% of vascular tumors, regardless of type and level of malignancy.[34] However, it is also expressed by some adenocarcinomas and melanomas,[35] making it important that one not prejudge a malignant tumor as an angiosarcoma without considering these as well. ERG, an *ETS* family transcription factor, is expressed in normal endothelial cells. Nuclear ERG expression has recently been shown to be an exquisitely sensitive marker of vascular differentiation (Fig. 22.8B). In a study of more than 200 vascular tumors, Miettinen et al.[36] have shown that virtually all benign and malignant vascular tumors express the protein, including lymphatic lesions as well. Because ERG expression is highly retained in angiosarcomas, it indicates that the marker is independent of the level of malignancy. As with FLI1, ERG expression can be seen in nonendothelial tumors,

including Ewing sarcoma, prostatic adenocarcinoma, myeloid malignancies, and epithelioid sarcoma. In general, we find that FLI1 and ERG are best used as secondary markers for the confirmation of endothelial differentiation in tumors where CD31 is less than fully diagnostic. Smooth muscle actin immunostains can be used to judge the presence of pericytes investing the endothelium in histologically ambiguous vascular lesions, since angiosarcomas typically lack pericytes. However, care must be exercised not to misinterpret stromal myofibroblasts as pericytes. Very rare angiosarcomas show aberrant expression of neuroendocrine markers, most often synaptophysin and CD56.[37,38]

As noted earlier, *MYC* amplification and MYC protein overexpression are not generally features of primary cutaneous angiosarcomas. Shon et al.[39] noted MYC overexpression in only 9 of 38 primary cutaneous angiosarcomas (24%), only two of which showed high-level *MYC* amplification by fluorescence in situ hybridization (FISH).[39] Ginter et al.[40] and Requena et al.[41] reported similar findings. Thus, unlike in postirradiation angiosarcoma (see later), where the finding of *MYC* amplification and MYC overexpression may be very helpful in distinguishing angiosarcoma from benign mimics, these tests are not helpful in the evaluation of primary cutaneous angiosarcoma.

***Clinical behavior.*** The overall 5-year survival of patients with cutaneous angiosarcomas varies from 30% to 50%.[4,42,43] Most patient deaths are the result of metastases to lung, liver, and lymph node.[43,44] Outcome is influenced by factors such as age, size, and margin status.[4,42,43,45] Younger patients have a

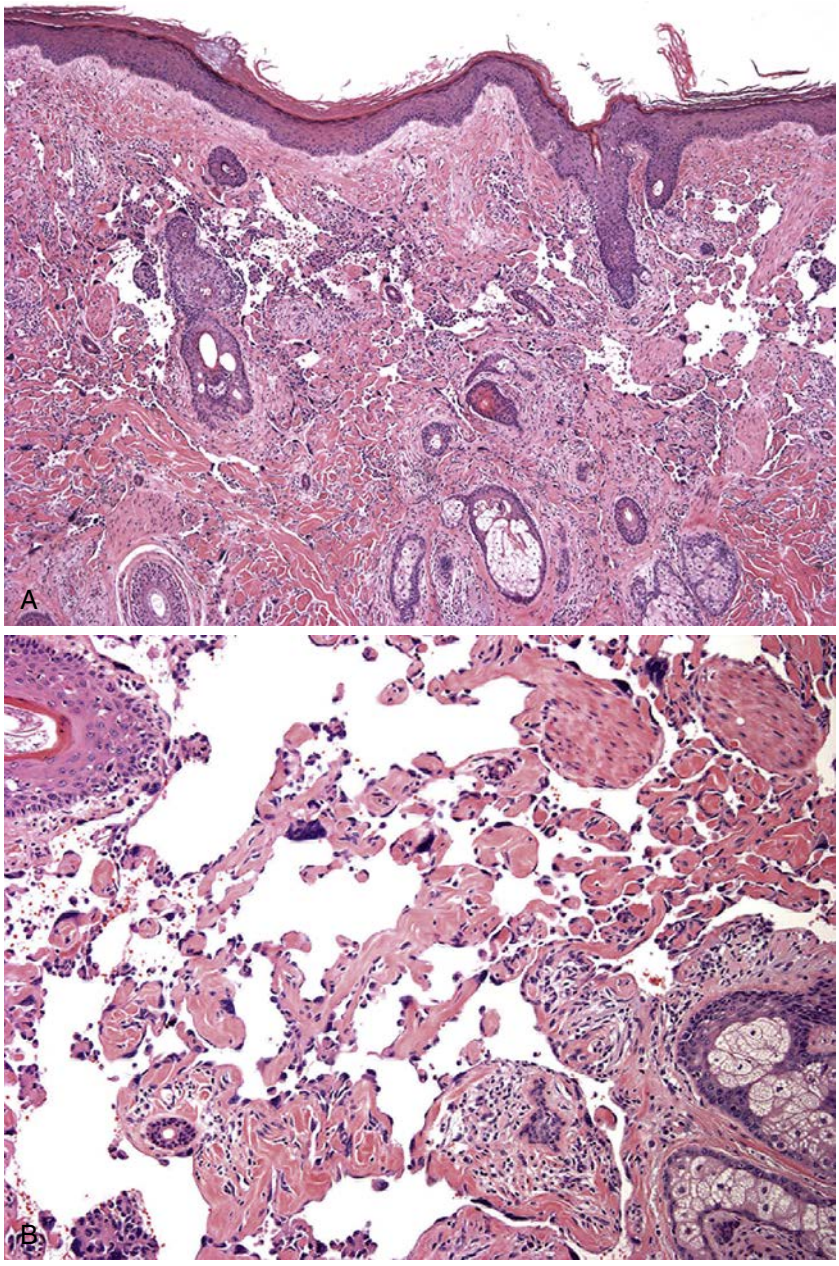



**Fig. 22.3** Cutaneous angiosarcoma composed of irregular vascular channels (A) infiltrating the dermis (B) and lined by atypical cells, which dissect collagen (C) and fat (D).

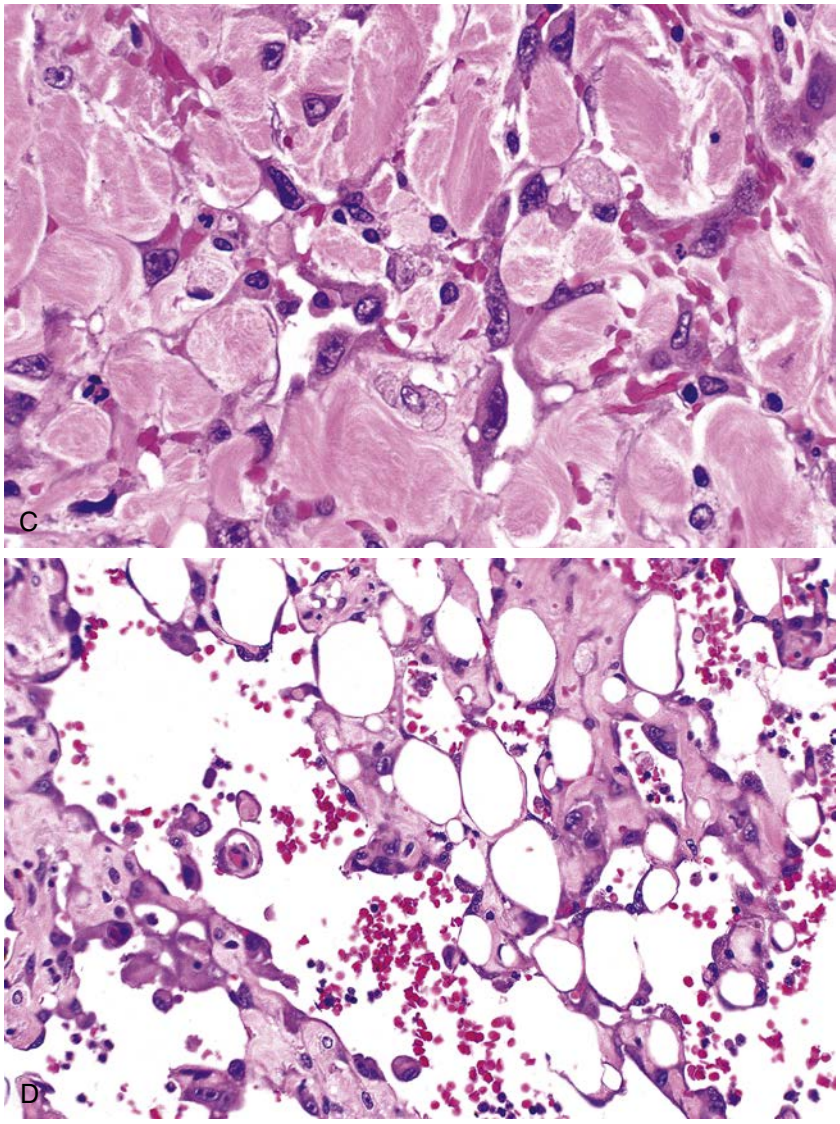



**Fig. 22.3, cont'd**

decidedly better prognosis than older patients. In a retrospective analysis of patients entered into the Surveillance, Epidemiology and End Results (SEER) Program, patients younger than 50 years had a 10-year relative survival rate of 71.7%, compared to 36.8% for those older than 50 years.[46] A similar trend has been reported by others.[42,43]

*Size* is also consistently linked to outcome. In the past, most angiosarcomas were large (>5 cm) at presentation,[44] but this has changed. Approximately one-half of angiosarcomas now are less than 5 cm at presentation.[4,43] Tumors less than 5 cm in diameter (T1) have a significantly better prognosis than larger tumors (T2).[42,44,47-49] Mark et al.[47] reported a 5-year survival of 32% for lesions less than 5 cm compared to 13% for those greater than 5 cm, and Pawlik et al.[42] noted a mortality of less than 10% in patients with lesions less than 5 cm and 75% in those with lesions greater than 5 cm. It should be noted that *pathologic size* correlates better with outcome than clinical size because the latter often underestimates the size.

*Negative margin* status is highly correlated with improved survival,[4,45] although it is both difficult to achieve negative margins in angiosarcoma and to assess them at frozen section. At one institution, as many as two-thirds of margins interpreted as negative at frozen section were judged to be positive on permanent section.[42] For this reason, Pawlik et al.[42] recommend that reconstruction surgery be postponed until the results of permanent sections are available.

Although conventional histologic grading is not widely applied to angiosarcomas, Deyrup et al.[43] proposed a risk stratification scheme based on a combination of *necrosis* and *epithelioid* morphology. Patients whose tumors had both (high-risk histologic group) had a 24% 3-year survival. In contrast, patients whose tumors lacked both (low-risk histologic group) had a 77% 3-year survival. The importance of necrosis[50] and epithelioid appearance[4] in prognosis has been validated by others. A purely epithelioid form of cutaneous angiosarcoma with a predilection for the extremities and an aggressive course has been described.[51,52]

**Angiosarcoma Associated with Lymphedema.** In 1949, Stewart and Treves[53] reported six patients who developed vascular sarcomas (so-called lymphangiosarcoma) following radical mastectomy and axillary lymph node dissection for breast carcinoma. Although some of the patients had also undergone radiotherapy, the common denominator in each appeared to be the presence of *chronic lymphedema*, which usually supervened shortly after mastectomy. Since this original description, many cases of vascular sarcomas complicating chronic lymphedema have been recorded. Not unexpectedly, most have occurred in women after mastectomy, although tumors have been documented on the abdominal wall after lymph node dissection for carcinoma of the penis and the arm or leg affected by congenital, idiopathic, traumatic, and filarial lymphedema. Recently, angiosarcomas have also been reported in **obesity-associated lymphedema** (localized massive lymphedema).[54] This has led to the conjecture that the obesity epidemic may well increase the incidence of angiosarcoma.

***Clinical findings.*** About 90% of all angiosarcomas associated with chronic lymphedema occur after surgery for breast carcinoma, although the estimated frequency of this complication is less than 1% of all women who survive 5 years after mastectomy. These patients are typically women in their seventh decade who have developed a significant degree of lymphedema, usually within 1 year of mastectomy. The tumors develop within 10 years of the original surgery, although the interval may be as short as 4 years or as long as 27 years. In rare instances, the tumor has been reported in postmastectomy

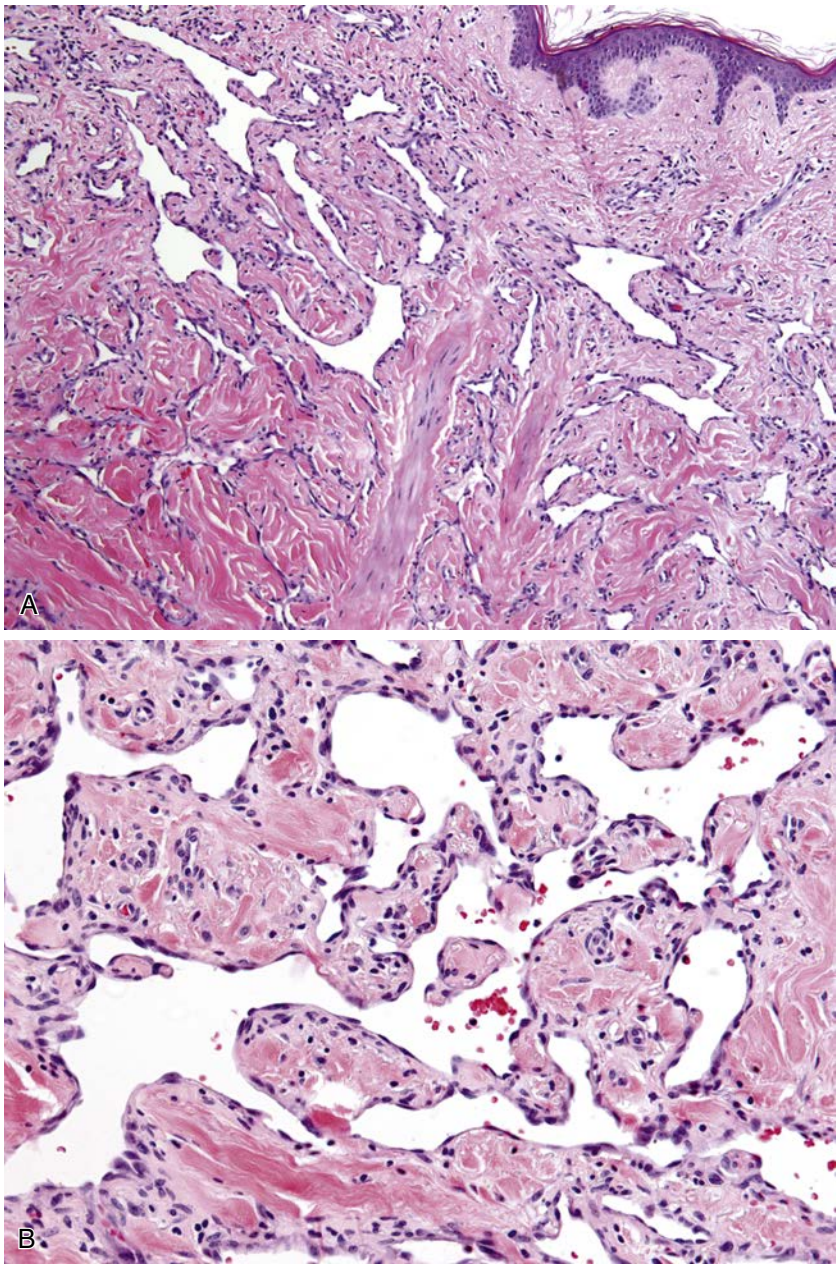



**Fig. 22.4** Well-differentiated angiosarcoma ramifying within the dermis (A) and showing destructive growth in dermal collagen (B), fat (C), and adnexal structures (D).

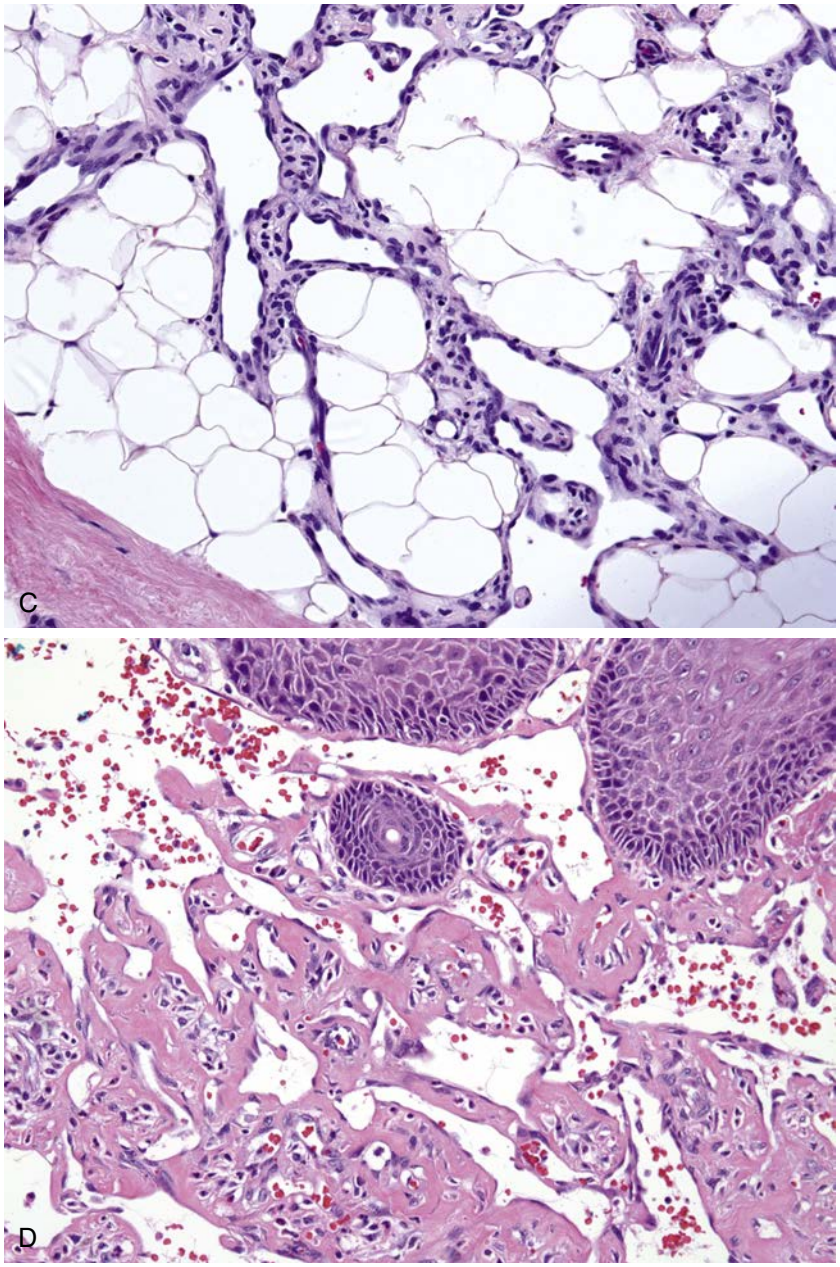



**Fig. 22.4, cont'd**

patients who have experienced little or no lymphedema. Whether some patients truly have no lymphedema is questionable, because minor degrees of lymphedema in obese patients can go undetected clinically.

When these tumors occur in congenital or idiopathic lymphedema, the affected patients are usually younger, the lymphedema is of longer duration, and any extremity may be affected. Most patients are in their fourth or fifth decade and have experienced lymphedema for two decades or longer.

Regardless of the clinical setting, the onset of cancer is heralded by the development of one or more polymorphic lesions superimposed on the brawny, nonpitting edema of the affected extremity. Deeply situated lesions in the subcutis may impart only a mottled purple-red hue to the overlying skin, whereas superficial lesions can be palpated as distinct nodules that coalesce to form large, polypoid growths (Fig. 22.9). Ulceration, accompanied by a serosanguineous discharge, characterizes late lesions. Repeated healing and breakdown give rise to lesions of various stages that spread distally to the hands and feet or proximally to the chest wall or trunk in advanced cases.

***Microscopic findings.*** The hallmark of lymphedema-associated angiosarcoma is capillary-sized vessels composed of obviously malignant cells that infiltrate soft tissue and skin. The lumens may be empty, filled with clear fluid, or engorged with erythrocytes, a finding that has made it difficult to classify these tumors as to blood vessel or lymphatic origin. Lymphocytes are occasionally found around the neoplastic vessels, but because this feature is also seen in other angiosarcomas, it does not provide sufficient evidence of lymphatic differentiation.

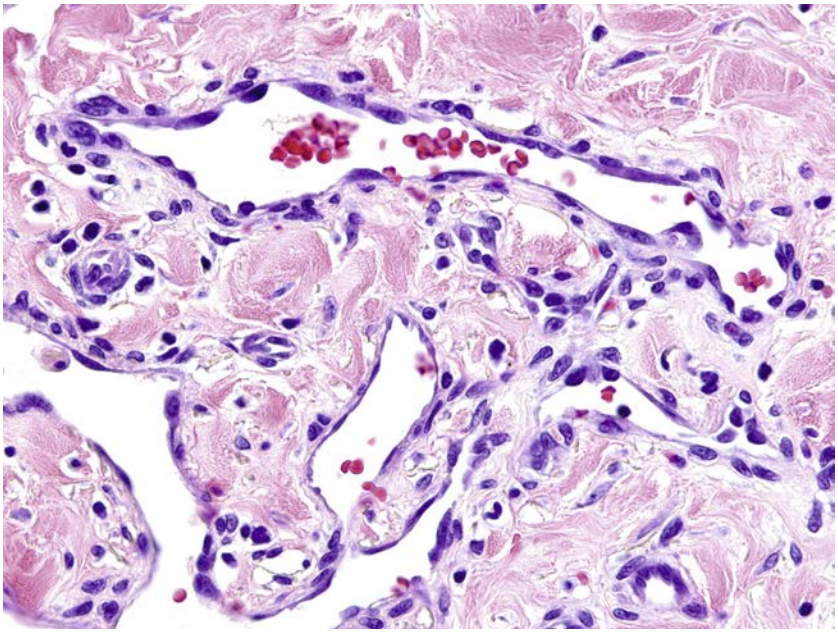
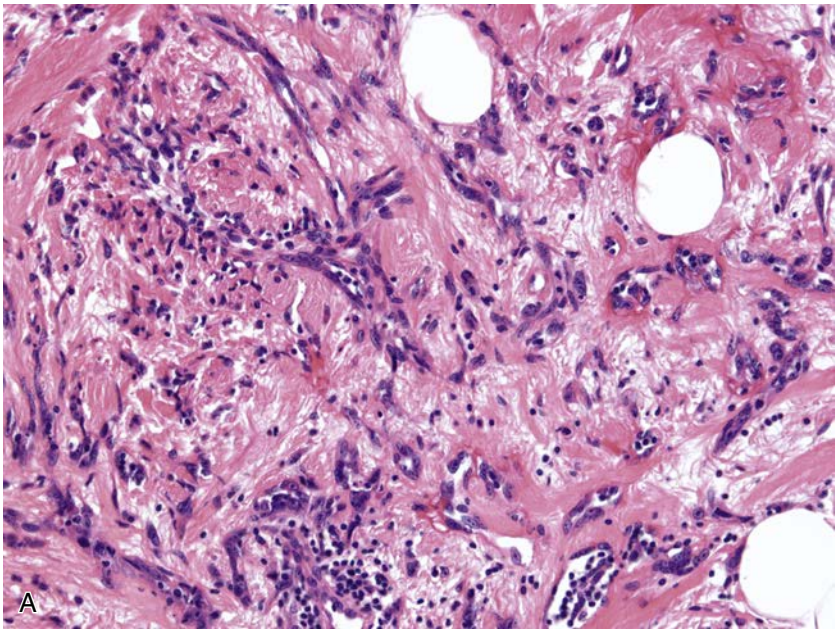


**Fig. 22.5** Ramifying vessels of well-differentiated angiosarcoma (same case as Fig. 22.4) displaying only mild atypia of endothelium. Nucleoli can be appreciated in some cells.



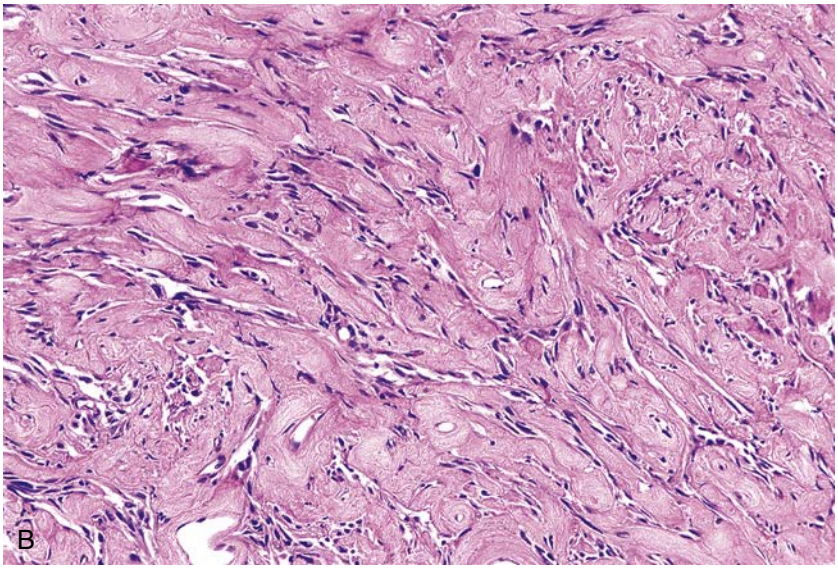
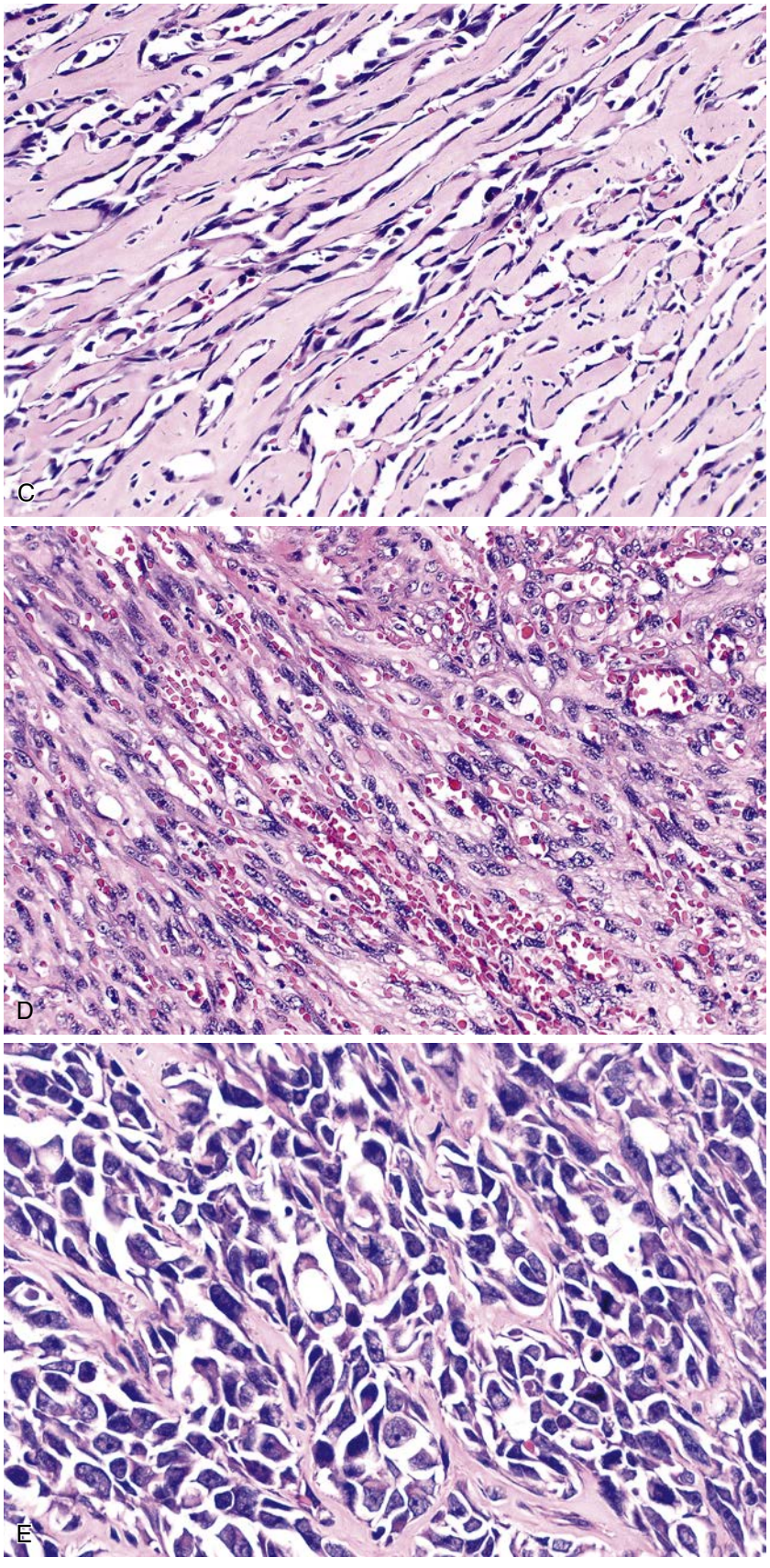




**Fig. 22.6** Patterns within angiosarcoma ranging from well-formed vessels (A), spindled slitlike vessels (B-D), solid areas (E and F), and sievelike areas (G).

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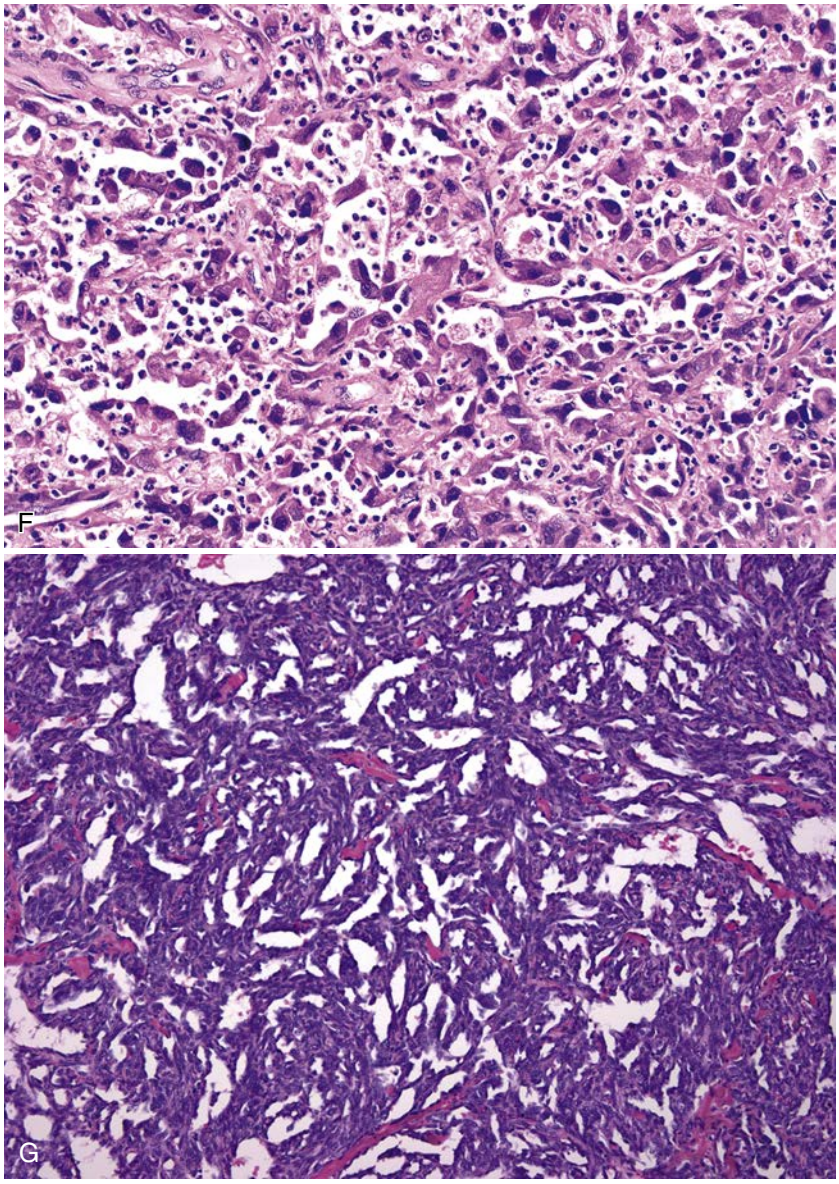


**Fig. 22.6, cont'd**

Perhaps the only feature that sets this tumor apart from the conventional angiosarcomas discussed in this chapter, and that some have used to support lymphatic differentiation, is its association with areas of *lymphangiomatosis*.[55] These changes appear to represent premalignant changes of small vessels, presumably lymphatics. The vessels become dilated and form a diffuse, ramifying network throughout the soft tissue (Fig. 22.10). They are lined by plump endothelial cells with hyperchromatic nuclei. These areas may merge imperceptibly with areas of frank angiosarcoma or may exist alone in patients who have not yet developed discrete clinical lesions. Therapy for this premalignant lesion is problematic. These patients probably are at risk of developing angiosarcoma and deserve scrupulous follow-up care. It seems best to recommend therapy for patients with clinical lesions only.

Interestingly, high-level *MYC* amplification has recently been demonstrated in two cases of angiosarcoma arising secondary to morbid obesity–associated lymphedema.[56] *MYC* amplification has also been reported in other lymphedema-associated angiosarcomas, although the number of studied cases is very small.[41,57]

**Angiosarcoma of the Breast.** Angiosarcomas of the breast are those that originate in the mammary parenchyma, as opposed to those overlying the skin,[58-62] although they may extend secondarily into the skin. This has led to a blurring between angiosarcomas arising in breast parenchyma and those arising in the skin of the breast after radiation. Extracting the behavior of parenchymal breast angiosarcoma from reports is also problematic. Some studies fail to distinguish between the two types or, if they do, combine data from both groups for the purposes of reporting.

True **parenchymal angiosarcomas** account for approximately 1 in 1700 to 2000 primary malignant tumors of the breast. Unlike other angiosarcomas, this type occurs exclusively in women, usually during the third or fourth decade, although occasional cases have been reported in menopausal or pregnant women.[58]

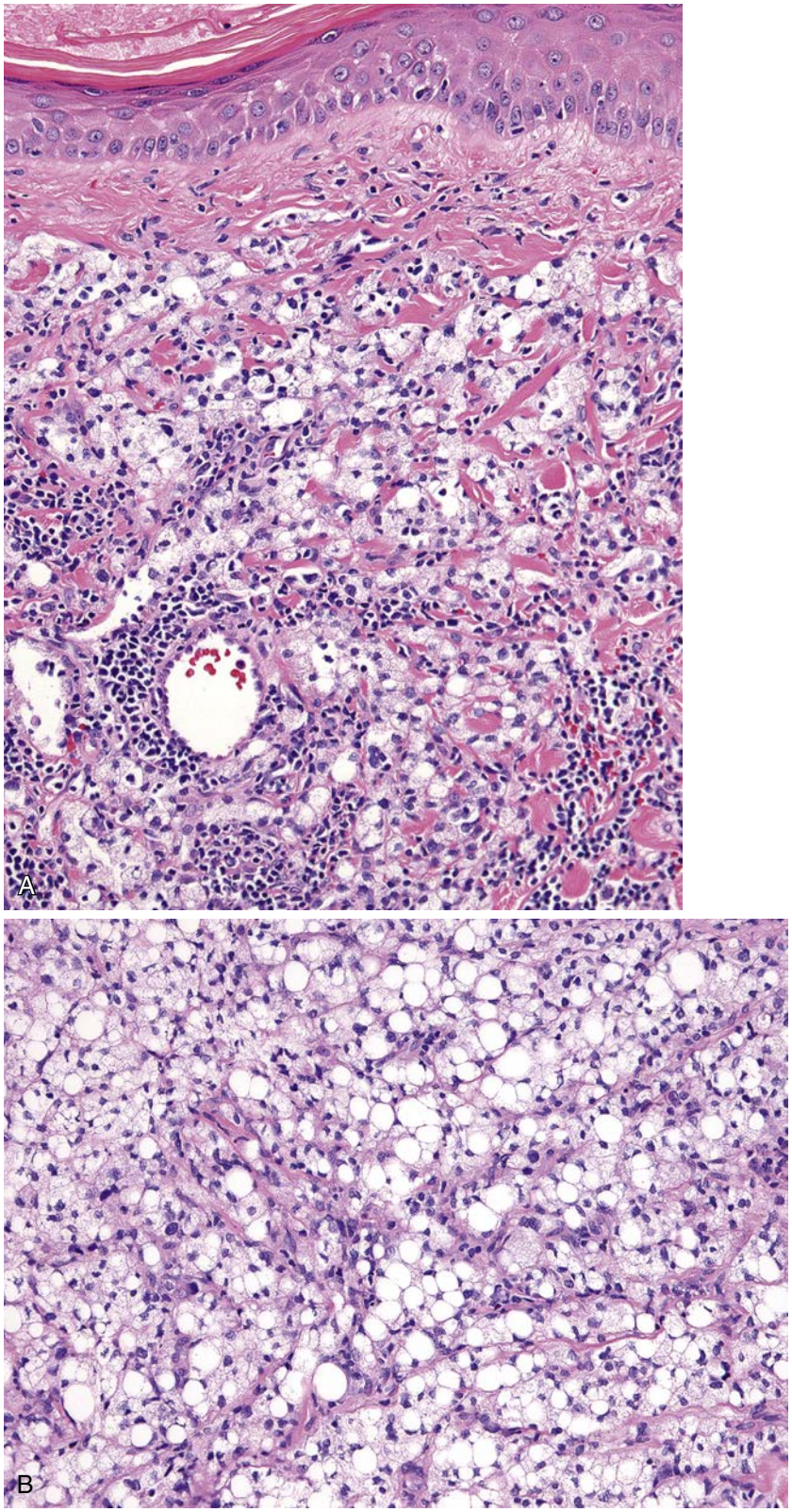


**Fig. 22.7** Rare foamy cell variant of angiosarcoma (**A**) illustrating finely vacuolated endothelial cells (**B**) expressing CD31 (**C**).

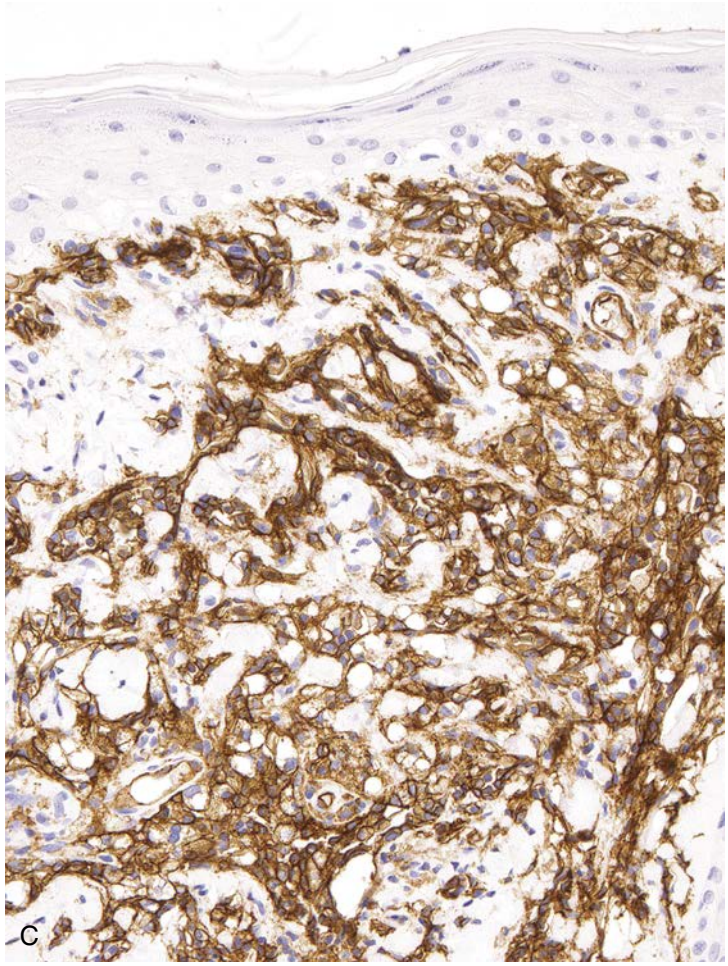


**Fig. 22.7, cont'd**

The typical presentation is an intramammary mass averaging about 5 to 7 cm associated with variable discoloration of the overlying skin (Fig. 22.11). About 80% of women have localized disease at presentation.[59] Rarely, metastases in the regional lymph nodes or contralateral breast are present.[63] Despite the size, classic features of carcinoma, such as nipple retraction, are absent. Located deep in the substance of the breast, they often invade the skin but seldom extend into the pectoral fascia. The tumors are poorly defined, hemorrhagic, spongy masses surrounded by a rim of engorged vessels. The tumors share similar histologic features with other angiosarcomas. The recommendation is to grade breast angiosarcomas.[64] Grade I lesions are composed of well-formed, anastomosing vascular channels that permeate fat and breast. The vessels are lined by a single layer of attenuated endothelium with minimal atypia. Grade II lesions are more cellular; vessels are lined by cells with distinct nuclear atypia and multilayering, but solid areas are not present. Grade III lesions are composed of sheets of cells of high nuclear grade interrupted by intralesional blood lakes. The three grades are represented about equally within breast angiosarcomas.[65] Whether grading actually predicts outcome is controversial. In a large series by Rosen et al.,[63] survival probability among the three grades at 1 year was similar, but at 5 and 10 years, grade III lesions fared worse. Nascimento et al.[62] did not identify statistically significant differences among the three grades. Interobserver variability is likely one of the most important factors limiting the clinical applicability of angiosarcoma grading in this and other locations. Although we make some effort to grade mammary parenchymal angiosarcomas, we also typically emphasize that data are conflicting on the value of this task, and that these lesions are best considered "high grade" for purposes of clinical management.

Whether mammary parenchymal angiosarcoma has similar or different behavior as cutaneous angiosarcoma of the breast is also debated. Some maintain that the two have a comparable course,[60] whereas others cite a higher risk of mortality with primary breast angiosarcoma.[61] In one of the largest series of 59 patients, the 5-year overall survival was 61%, and the 5-year disease-free survival was 44%.[61] Both were significantly associated with tumor size but not with various other factors, including age or administration of chemotherapy. However, grade was not assessed or evaluated.

Unlike postirradiation cutaneous angiosarcomas involving the breast, primary mammary angiosarcomas do not show *MYC* amplification, and testing for MYC is not of value in the differential diagnosis of these tumors.[64,65]

***Differential diagnosis.*** The differential diagnosis of mammary parenchymal angiosarcoma lies principally in

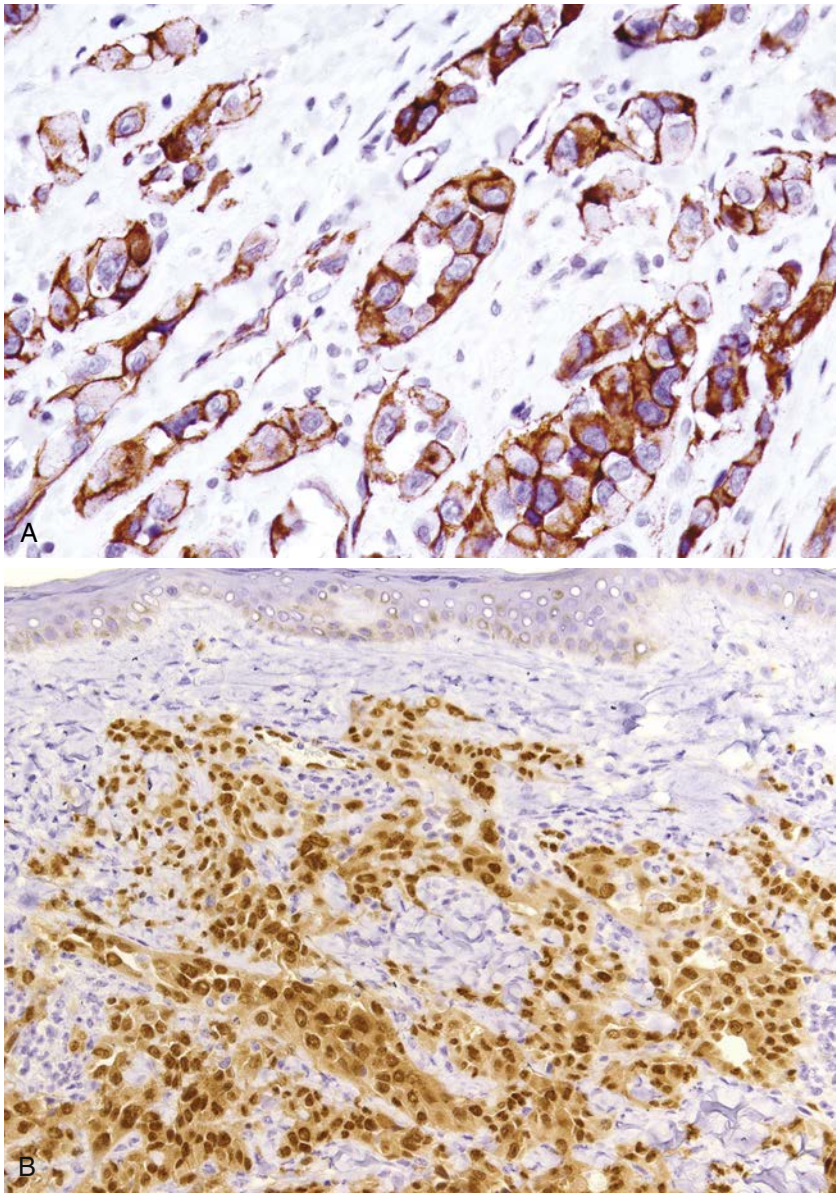


**Fig. 22.8** Immunostains in angiosarcoma. A, CD31 shows membrane staining in most cases. B, ERG is expressed in the nucleus.

distinguishing it from **benign hemangioma** or **angiolipoma**, two *nonpalpable* breast lesions that are increasingly detected and removed because of more sophisticated imaging techniques. Angiosarcomas of the breast are poorly defined lesions that grow infiltratively within fat and breast lobules. It is the pattern of destructive growth that distinguishes them from benign lesions when the degree of atypia is minimal. Hemangiomas and angiolipomas of the breast are usually sharply demarcated from normal breast tissue. The vessels of a hemangioma are regular in shape, and those of angiolipoma have fibrin microthrombi. We have found that it is extremely helpful to correlate the histologic findings in needle biopsies of mammary vascular tumors with the imaging findings, since hemangiomas and angiolipomas typically appear as small, well-circumscribed masses, unlike larger, more infiltrative and less well-delineated angiosarcomas.

**Angiosarcoma of Soft Tissue.** Angiosarcomas arising from and essentially restricted to deep soft tissue account for about 10% of all angiosarcomas (see Table 22.1). Unlike their cutaneous counterpart, soft issue lesions occur at any age and are evenly distributed throughout all decades.[12] About one-third develop in association with other conditions, such as inherited diseases (neurofibromatosis, Klippel-Trénaunay syndrome, Maffucci syndrome), synthetic vascular grafts, and other neoplasms. Similar to the more common adult soft tissue sarcomas, they develop on the extremities or in the abdominal cavity, where they present as a large, hemorrhagic mass (Fig. 22.12). These tumors may be confused with a chronic hematoma, even after biopsy of the tumor, especially if the biopsy material is limited or nonrepresentative. In very young patients, the large size of this tumor may result in hematologic abnormalities, such as thrombocytopenia, high-output cardiac failure from

arteriovenous shunting, or even death as a result of massive exsanguination.[2] Unlike angiosarcomas of the skin, deep angiosarcomas more often have an epithelioid appearance[12,13] (Fig. 22.13). These "epithelioid angiosarcomas" consist of sheets of high-grade rounded endothelial cells with prominent nucleoli, some of which contain intracytoplasmic lumens. Because many express keratin, it is essential that CD31 and sometimes FLI1/ERG immunostains be performed in parallel.

Based on the largest series so far, soft tissue angiosarcomas are aggressive neoplasms.[12] Altogether, 53% of patients were dead of the disease within 1 year; another 31% had no evidence of disease at 46 months. Overall, 20% of patients experienced local recurrences and 49% distant metastasis, most often to the lung, followed by lymph node, bone, and soft tissue. The features statistically associated with poor outcome included older age, retroperitoneal location, large size, and high Ki67 values (>10%). In a smaller series of epithelioid angiosarcomas, four of six patients died of the disease.[13]

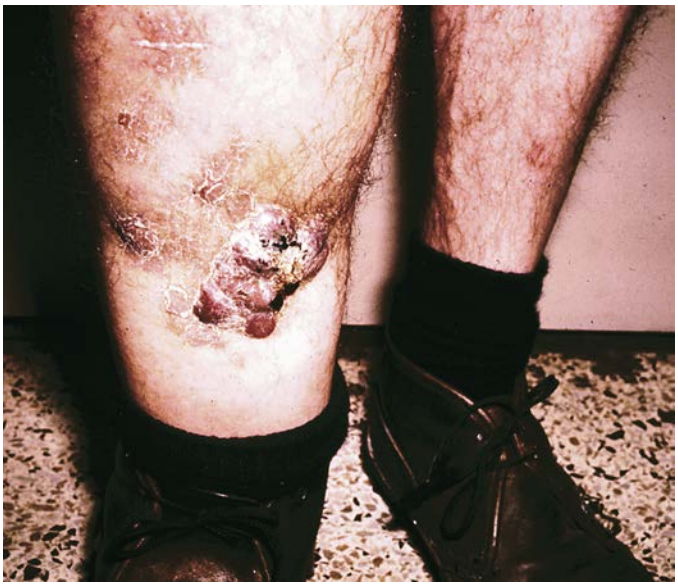

**Fig. 22.9** Angiosarcoma in lymphedematous extremity.

**Radiation-Induced Angiosarcoma.** About one-quarter of angiosarcomas occur after radiation therapy. In previous decades, these angiosarcomas usually presented in the abdominal wall or cavity after irradiation for carcinoma of the cervix, ovary, or uterus, with a small number of cases for various other malignant or benign conditions. This demographic profile has changed in recent years. Currently, about one-half of postirradiation angiosarcomas develop on the skin of the breast in women who have had breast-sparing surgery and whole breast irradiation.[4] The incidence of this complication has been estimated at 0.05% to 0.14% of all patients.[66,67]

Most develop within 5 years following high doses of radiation (median: 50 Gy), but a significant subset occurs with a latency as short as 3 years.[68] The onset of these lesions is heralded by ecchymoses or thickening of the skin with one or more elevated lesions that develop in the background of little or no lymphedema, but with changes of radiation damage in the epidermis (Fig. 22.14). Typically multifocal, they vary greatly in size (0.4-20 cm) but on average are significantly larger than the atypical vascular lesion described later in the chapter. Histologically, they involve dermis and rarely extend into the underlying breast parenchyma. Their features are similar to other cutaneous angiosarcomas (Fig. 22.15A), except that MYC expression can be documented in a significant percentage of these lesions (Fig. 22.15B) by IHC because of amplification of the gene (see earlier). Approximately 50% of patients experience recurrences and 40% metastases, which occur most often in the lung, contralateral breast, and bone. To date, histologic

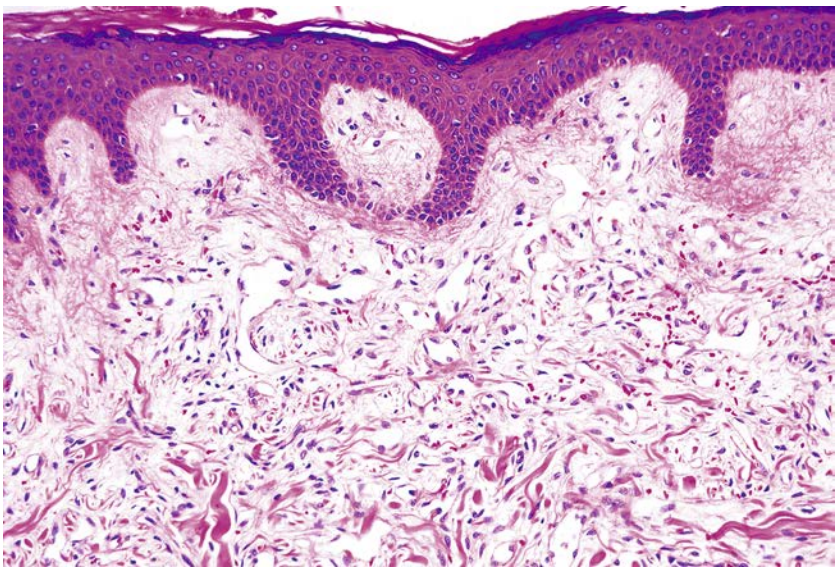

**Fig. 22.10** Diffuse proliferation of dermal lymphatic vessels (lymphangiomatosis) containing atypical endothelium. This lesion occurred in a patient a few years after mastectomy for breast carcinoma. Minimal lymphedema was present. Such changes have been considered premalignant and may herald the onset of frank angiosarcoma.

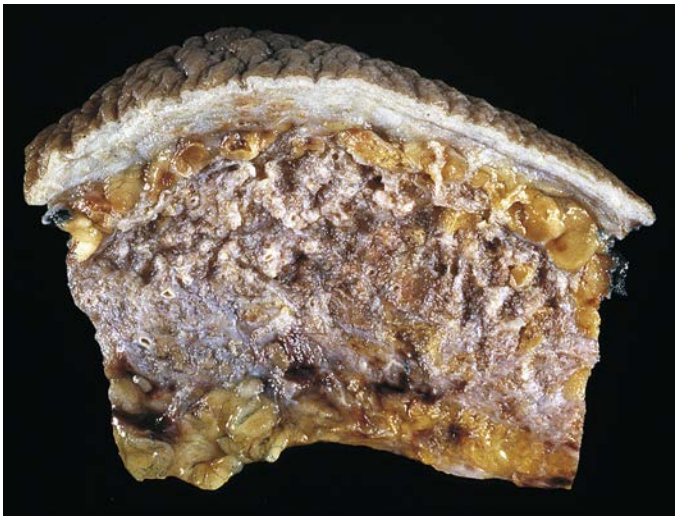

**Fig. 22.11** Angiosarcoma of breast with spongelike quality.

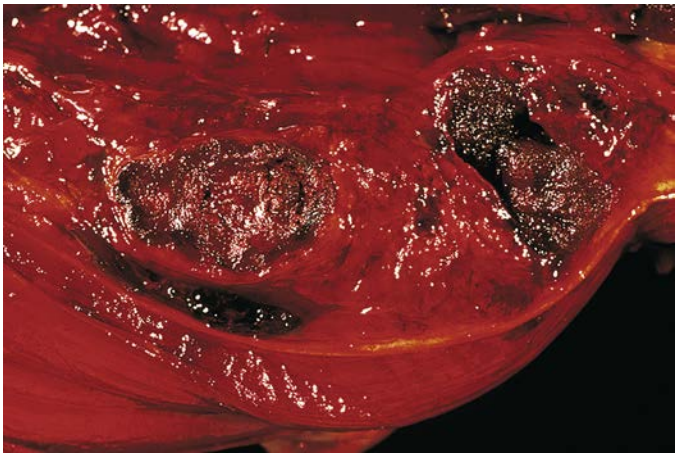

**Fig. 22.12** Angiosarcoma in deep soft tissue with prominent hemorrhage.

features have not been especially helpful in predicting outcome. Although a few reports have suggested that tumors with low-grade features have a good prognosis, there have been too few cases of this type for statistical analysis.[68] The overall prognosis for patients with postirradiation angiosarcoma is poor, with a median disease-specific survival of slightly over 3 years noted in 35 patients from the Netherlands and Sweden.[69] Similar findings were reported in 33 patients from the Dana-Farber Cancer Institute in Boston.[70]

This form of postirradiation angiosarcoma differs from others by the relatively short interval between radiation and development of a tumor. The reason for this shorter latency is not well understood, but the large volume of skin encompassed in the radiation field is one explanation.[68]

## Prognostic Factors and Clinical Behavior

Although angiosarcomas are considered several interrelated clinical diseases, most large studies combine them to analyze outcome.[4,50] This approach has the advantage of providing cohort sizes amenable to statistical analysis, but it also runs the risk of obscuring differences that may exist among the various clinical subtypes. Nevertheless, the themes that emerge from such studies underscore that *clinical factors* are more relevant in determining prognosis than histologic features, because the features typically used in histologic grading systems do not lend themselves well to angiosarcomas. Again, risk stratification schemes using angiosarcoma-specific histologic criteria may prove useful in the future.[43]

Collectively, patients with angiosarcomas have an average 5-year survival of 30% to 40%.[4,45] Many prognostic factors have been studied in this disease, including patient age, location, size, depth, extent, and margin status (Table 22.2). Although the importance accorded to each varies from study to study, there is general agreement that older patients have a worse prognosis than their younger counterparts, as noted previously for cutaneous angiosarcomas.[4,42,46,71,72] Tumor size, which has been most extensively studied in cutaneous lesions,[45-47] is strongly linked to outcome in all angiosarcomas.[4] Clinical extent, resectability, and margin status are important determinants of outcome, based on several studies (Table 22.3). Studies also reaffirm the belief that angiosarcomas of deep soft tissue, body cavities, or body organs fare worse than cutaneous lesions.[45] For postirradiation angiosarcoma, a reduced rate of local recurrence has been seen in patients treated with chemotherapy (most often containing a taxane).[74] Also, patients who receive resection of all previously irradiated skin may have better local disease control than those with more limited excision.[70]

Treatment for localized regional disease consists of complete surgical excision with negative margins. Because of the risk of local recurrence and the difficulty in achieving negative margins, adjuvant radiotherapy is typically combined with surgery.[42,75-77] No conclusive evidence supports the use of adjuvant chemotherapy for localized disease after surgery and radiation.[66,67]

*Cytotoxic chemotherapy*, which includes the use of anthracyclines, ifosfamide, and taxanes, is the primary treatment for metastatic angiosarcoma. *Taxanes* have become increasingly popular over the past decade because of their antiangiogenic activity, with some evidence that head and neck angiosarcomas are more responsive to taxanes than those in other sites.[77] Studies from Japan have shown a significantly better prognosis and distant metastasis–free rate in patients with face and scalp angiosarcomas,[78] as well as those in other cutaneous locations,[79] treated with docetaxel than in those treated with other agents. At the vanguard of therapeutic research is the use of tyrosine kinase inhibitors, such as sorafenib, to target the VEGFR signaling pathways.[77] Results from a Phase II trial of sorafenib for patients with advanced angiosarcoma from the French Sarcoma Group have shown only limited antitumor activity, however, chiefly in patients who had already received other types of chemotherapy.[80] Expression of PD-L1 has been associated with worse outcome in patients with cutaneous angiosarcoma, suggesting a possible role for immune checkpoint inhibitors targeting this molecule.[81] In angiosarcoma cell lines, promising preliminary results have been noted with vadimezan (a vascular disrupting agent), selumetinib (MEK inhibitor), and everolimus (mTOR inhibitor).[82]

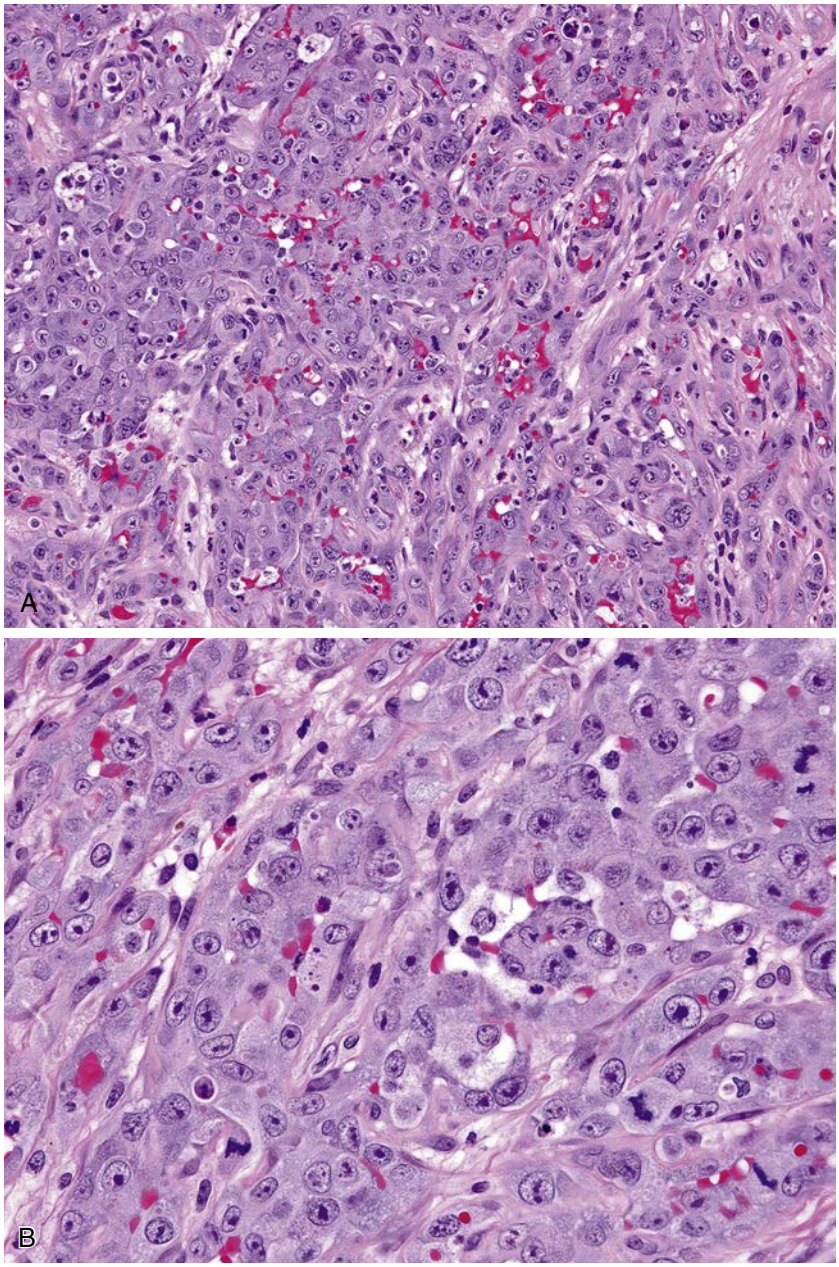


**Fig. 22.13** Epithelioid angiosarcoma of deep soft tissue (A) composed of epithelioid endothelial cells with prominent nucleoli and slate-gray cytoplasm (B).

## ATYPICAL VASCULAR LESION

The term *atypical vascular lesion* (AVL) refers to a continuum of cutaneous lesions that develop following radiation and have some, but not all, of the features of angiosarcoma[83-87] (Figs. 22.16 to 22.19). The term was first used by Fineberg and Rosen[88] to refer to small, sharply circumscribed intradermal vascular lesions that resembled a lymphangiectasia or lymphangioma and pursued a benign course. It is now evident that the spectrum of histologic changes that occur in this clinical setting is more diverse than originally appreciated and that some lesions, although not diagnostic of angiosarcoma, are still worrisome and deserve careful scrutiny (Table 22.4).

Clinically, AVLs are small, pink-brown cutaneous papules (<1 cm) that are frequently multifocal and usually develop within 3 years of radiation. Histologically, AVLs embrace a histologic spectrum that ranges from banal-appearing lesions resembling a lymphangioma circumscriptum to capillary vascular proliferations with nuclear atypia. This has led to the proposal that AVLs be divided into two types: a *lymphatic type* (LT) and a *capillary vascular type* (VT). The more common LT consists of ectatic lymphatic vessels usually confined to the superficial dermis and often referred to as *benign lymphangiomatous papules*. The vessels are lined by flattened or slightly protuberant (hobnail) lymphatic endothelium, which expresses CD31, podoplanin (D2-40), and variably, CD34. Although the nuclei may appear hyperchromatic, they are not enlarged or irregular in shape (Figs. 22.16 to 22.19).

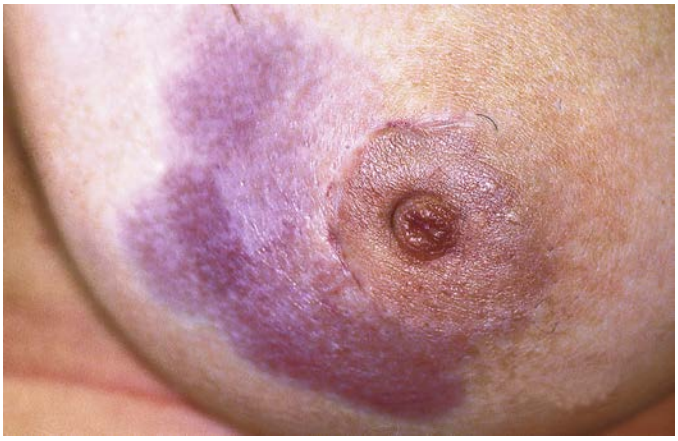

**Fig. 22.14** Cutaneous angiosarcoma of breast after breast-conserving surgery and irradiation for carcinoma.

In a minority of LT-AVLs, the vessels infiltrate and intercommunicate more extensively within the dermis (Fig. 22.18). Such lesions are reminiscent of progressive lymphangiomas. VT-AVLs resemble capillary hemangiomas and consist of blood-filled, pericyte-invested capillary vessels involving the superficial and/or deep dermis. Extravasated erythrocytes and hemosiderin may be present in the dermis (Fig. 22.19). A small number of VT-AVLs display nuclear atypia.

A relatively large number of studies have now shown that *MYC* amplification by FISH and/or MYC overexpression by IHC may be very helpful in the discrimination of AVLs and postirradiation angiosarcomas.[40,64,65,89] In general, an excellent correlation has been found between FISH and immunohistochemical results. One should exercise caution since we have seen AVLs with apparent MYC protein overexpression, but without *MYC* amplification by FISH. These

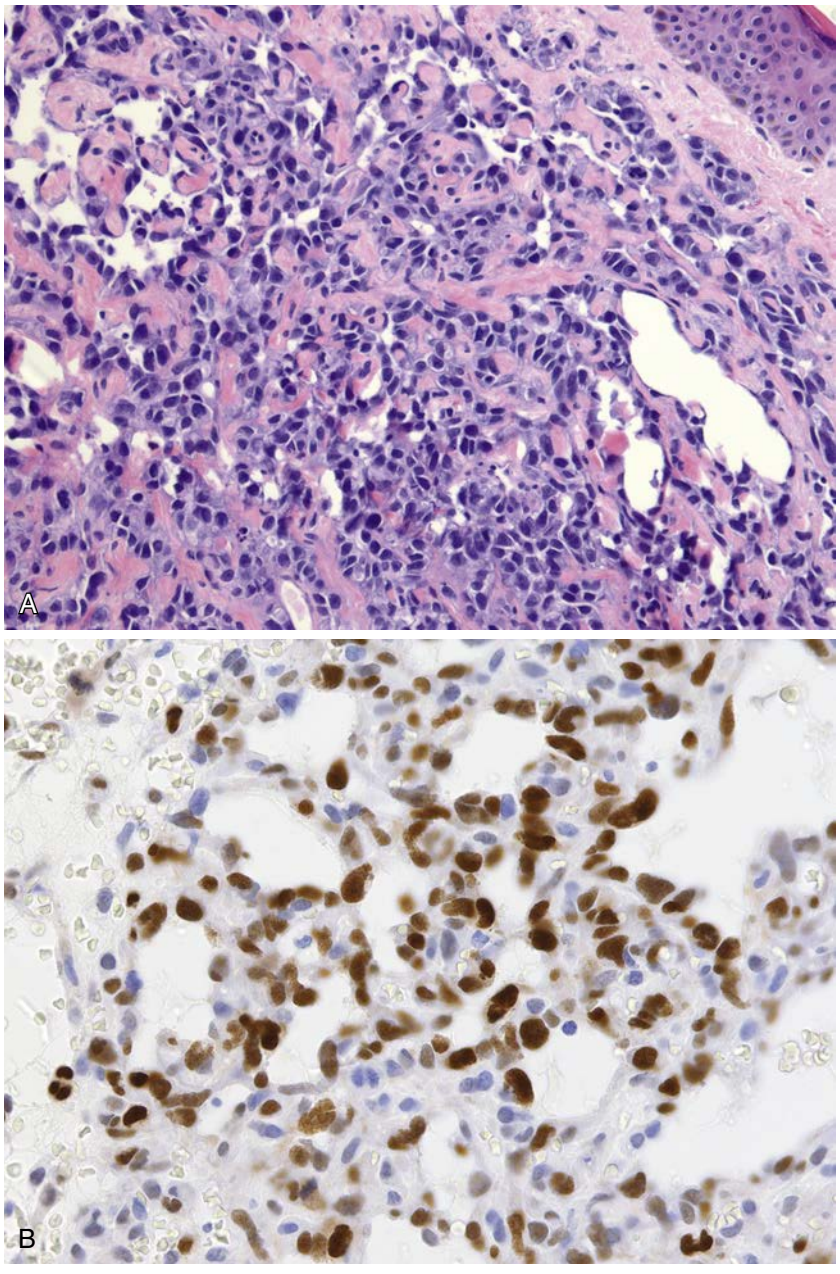


**Fig. 22.15** Postirradiation angiosarcoma (**A**) with MYC expression (**B**).

**TABLE 22.2 Prognostic Factors in Angiosarcoma: All Sites**

| | Favorable Prognostic Factor | Unfavorable Prognostic Factor |
|---|---|---|
| Age[42,46] | <50 yr | >50 yr |
| Location[46] | Trunk[46] | Head/neck |
| Focality | Unifocal[42] | Multifocal |
| Clinical extent[44,46] | Local | Regional/distant |
| Size[4,46-48] | <5 cm[4,46] | >5 cm |
| Depth[45] | Superficial | Deep soft tissue-body cavity |
| Margin status[4] | Negative | Positive |
| Histology | Nonepithelioid | Epithelioid[4,43] |
| | No necrosis | Necrosis[43,50] |

**TABLE 22.3 Relationship Between Prognostic Factors and Outcome in Angiosarcoma**

| All Sites | Median Survival |
|---|---|
| **Excision[4]** | |
| Complete | 66 mo |
| Incomplete | 19 mo |
| **Margins[45]** | |
| Negative | 4.9 yr |
| Positive | 2.0 yr |
| **Size[46]** | |
| <5 cm | 3.6 yr |
| >5 cm | 2.3 yr |
| **Location[45]** | |
| Superficial | 3.6 yr |
| Deep soft tissue | 2.3 yr |

most likely represent false positives related to excessive antigen retrieval. For this reason, FISH is the test of choice, when available.

Understanding the behavior of these lesions continues to evolve. Approximately 10% to 20% of patients with AVLs will develop additional lesions.[86,87] The critical question is whether these lesions carry an increased risk for angiosarcoma; opinions are divided. One view maintains that the two are unrelated, based on the vast majority of patients with AVLs having a favorable clinical course after excision of one or more lesions. This is borne out by a recent large study from the French Sarcoma Group.[91] That radiation-associated angiosarcomas display *MYC* amplification and AVLs do not has buttressed this view.[27,28,87] On the other hand, others maintain that the two are related and represent a histologic continuum.[85-87] This view is supported by the rare instances in which sequential biopsies of patients with AVLs document histologic progression of the lesion to angiosarcoma,[85-87] as well as by *TP53* mutational analysis defining common mutations in both.[92] Patton et al.[87] proposed that the risk for angiosarcoma varies, depending on the type of AVL, and suggested that the LT-AVLs, which represent the overwhelming majority of lesions reported, probably carry negligible risk, whereas the VT-AVLs have a higher, but as-yet undefined, risk. VT-AVLs displaying nuclear atypia are at greatest risk for angiosarcoma and may be a direct precursor lesion. Patton et al. recommended a diagnostic biopsy for the ordinary LT-AVL, complete excision with excellent follow-up care for VT-AVLs, and more extensive surgery for those with atypia.

## KAPOSI SARCOMA

In 1872, Kaposi[93] described five cases of an unusual tumor that principally affected the skin of the lower extremities of elderly men in a multifocal, often symmetric fashion. Called "idiopathic multiple pigmented sarcoma of the skin" by Kaposi, this form of the disease later became known as *sporadic* or *classic* Kaposi sarcoma (KS). Other forms were subsequently recognized and included an *endemic* form prevalent in sub-Saharan Africa, a rapidly progressive or *epidemic* form associated with acquired immunodeficiency syndrome (AIDS), and an *iatrogenic* form following organ transplantation. Despite these apparent differences, epidemiologic data strongly indicated an infectious etiology for all. A seminal study by Chang et al.[94] identified DNA fragments within KS tissue that shared a sequence identity to Epstein-Barr virus (EBV) and herpesvirus saimiri (HVS). The agent, subsequently classified as a gamma 2 herpesvirus, is known as **Kaposi sarcoma–associated herpesvirus** (KSHV) or human herpesvirus 8 (HHV8). This virus is also responsible for primary effusion lymphoma and multifocal Castleman disease. KSHV, unlike other herpesvirus infections, does not occur ubiquitously but has distinct pockets of prevalence. It is most common in sub-Saharan Africa (>50%), moderately prevalent in the Mediterranean (20%–30%), and less common in Europe and the United States (<10%).

KSHV is now considered the causative agent for all forms of KS, based on a number of key observations[95,96]: (1) the incidence of KS mirrors the prevalence of KSHV in all populations studied; (2) KSHV seroconversion is a predictor of KS and occurs before clinically evident lesions in all forms of the disease; (3) KSHV can be identified in KS cells and is capable of transforming endothelial cells;[97] (4) KS is never observed in the absence of KSHV; and (5) the genome of KSHV contains homologues of cellular genes (e.g., v-cyclin) that can stimulate cell growth and angiogenesis. The marked variation in the incidence of KS in various risk groups implies that KSHV per se is not sufficient for the development of KS. In the course of the infection, the virus preempts various host genes.

Transmission of KSHV occurs principally through saliva.[98] Once introduced, the virus is capable of infecting a number of cell types, including B lymphocytes and endothelium, where it establishes a latent infection. Reactivation of latent virus, believed to be pivotal in the development of KS, results in the expression of a number of viral genes that dysregulate the immune response and signaling pathways. These genes, which bear homology to cellular genes of humans, include cyclins, inhibitors of apoptosis, and cytokines and receptors. Tumor growth is further enhanced by human immunodeficiency

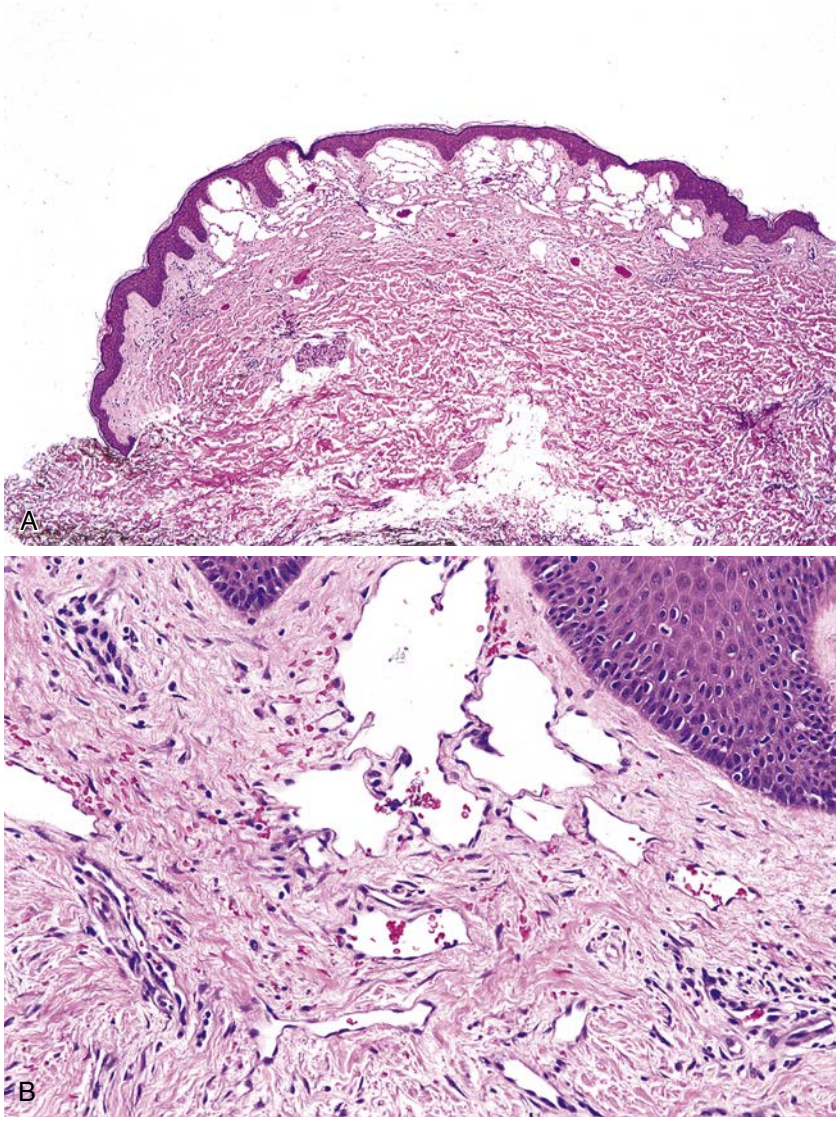


**Fig. 22.16** Atypical vascular lesion of breast, lymphatic type, after breast-conserving surgery and irradiation for carcinoma. This lesion is a circumscribed dermal nodule (A) without endothelial atypia but with some anastomotic growth (B).

virus (HIV) coinfection. HIV-1 induces various inflammatory cytokines and growth factors (e.g., fibroblast growth factor) that enhance tumor growth, and the HIV-1 Tat protein, secreted extracellularly, stimulates KS cells to produce a metalloproteinase that promotes tumor invasion and angiogenesis. Further, KS cells themselves produce a number of cytokines (e.g., VEGF), which through their own receptors, autoregulate growth.[99]

## Clinical Findings

**Classic Kaposi Sarcoma.** The chronic or classic form of KS occurs primarily in men (90%) during late adult life (peak incidence: sixth and seventh decades). The disease is prevalent in certain parts of the world, including Poland, Russia, Italy, and the central equatorial region of Africa. In the last region it accounts for up to 9% of all reported cancers.[100] It is rare in the United States and accounts for only 0.02% of all cancers. This form is statistically and significantly associated with a second malignant tumor or altered immune state.

The disease commences with the development of multiple cutaneous lesions, usually on the distal portion of the lower extremity. Less frequently, the lesions occur on the upper extremity and rarely in a visceral organ in the absence of cutaneous manifestations. The initial lesion is a blue-red nodule often accompanied by edema of the extremity, which some interpret as indicating deep soft tissue or lymphatic involvement by the tumor. The lesions slowly increase in size and number, spreading proximally and coalescing into plaques or polypoid growths that may resemble pyogenic granuloma. Occasional lesions even ulcerate. In some patients the early lesions regress, whereas others evolve so that many stages of the disease are present at the same time. The course of the disease is characteristically indolent and prolonged.

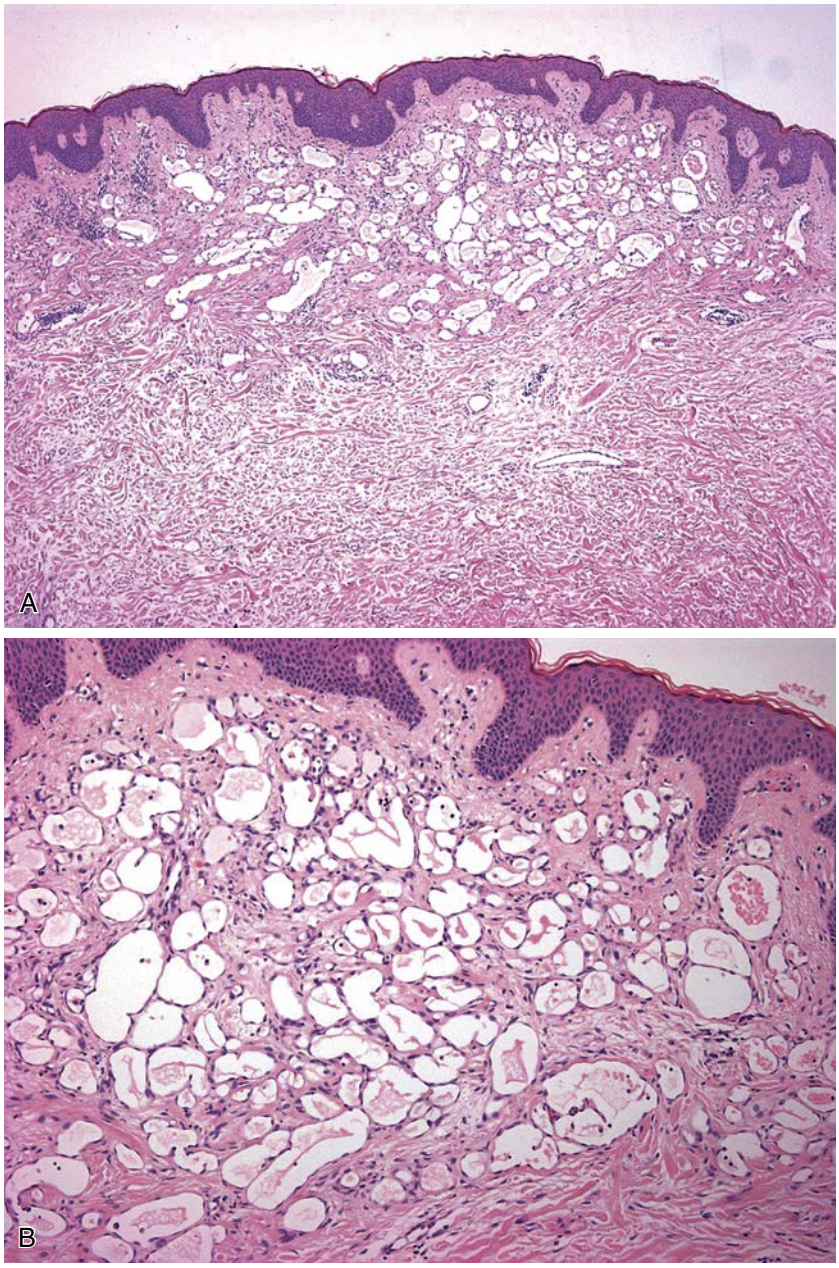


**Fig. 22.17** Atypical vascular lesion of breast, lymphatic type, showing more irregular vascular proliferation in dermis (**A**) consisting of anastomosing vessels (**B**).

**Endemic (African) Kaposi Sarcoma.** Before the development of the AIDS pandemic, African KS was a disease primarily encountered in young males and very young children who presented with bulky lymph node disease. Its prevalence, furthermore, coincided with that of *podoconiosis,* a form of lymphedema associated with barefoot exposure to soil containing silica, a substance thought to result in localized immune suppression.[95] With the advent of AIDS, it has become increasingly difficult to delineate a pure (non-AIDS) endemic form of KS. KS is more common in women and children in this region than anywhere else in the world and occurs in several forms, one of which resembles classic KS and the others similar to the progressive KS of AIDS. One of the latter forms in particular occurs in very young children (<3 years), who present with localized or generalized lymphadenopathy and occasionally ocular and salivary gland disease. Skin lesions are usually minimal. The fulminant course of the disease is attributed to a tendency for internal involvement.

**Iatrogenic (Transplantation-Associated) Kaposi Sarcoma.** The development of KS in transplant patients is well established, although the incidence varies, depending on the patient population, again suggesting the importance of cofactors. KS occurs almost exclusively in renal transplant recipients and not recipients of solid-organ or bone marrow transplants. Renal transplant recipients who are seropositive for KSHV before the transplant or who receive cyclophosphamide as part of their immunosuppressive regime are also more likely to develop KS

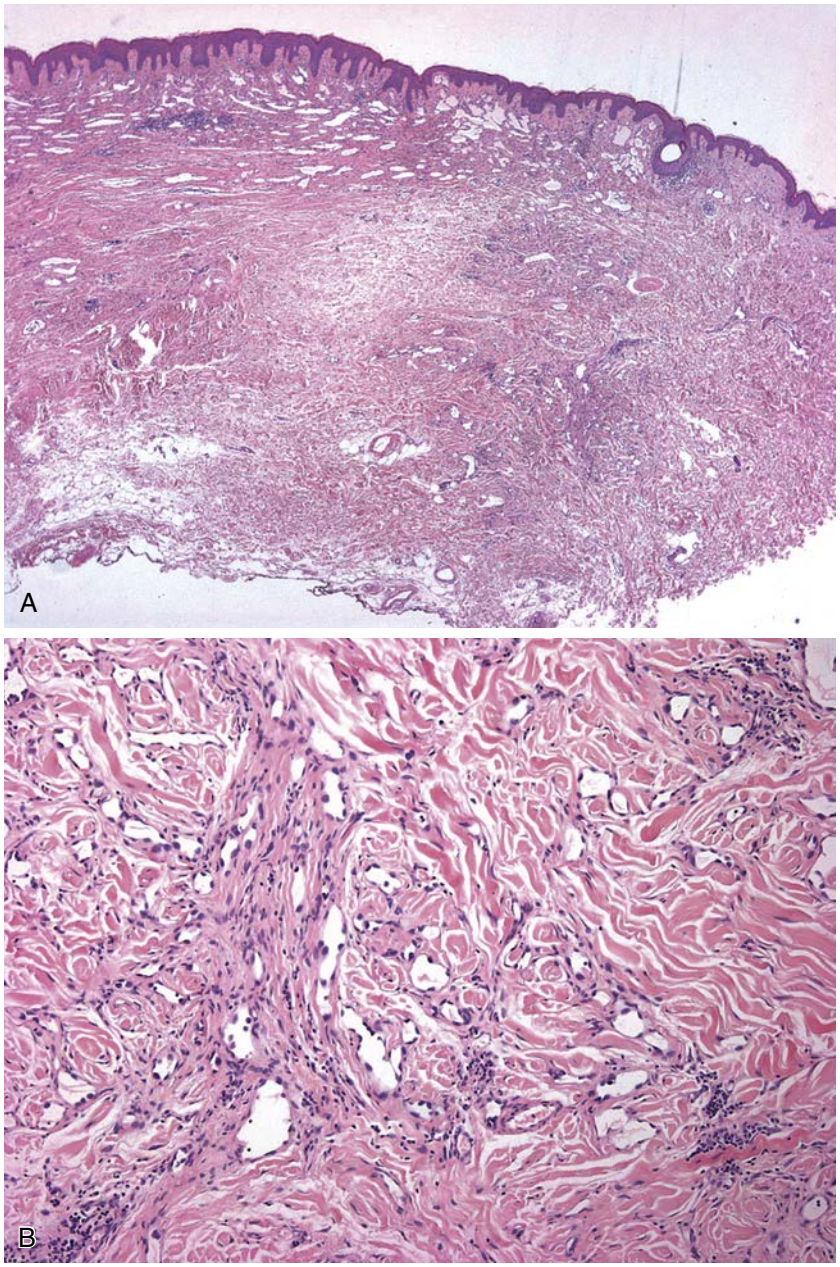


**Fig. 22.18** Atypical vascular lesion of breast, lymphatic type, with involvement of deep dermis (A) and more permeative growth of vessels (B).

than others. The disease develops several months to a few years after the transplant (average: 16 months), and the extent of the disease can be correlated directly with the loss of cellular immunity. Interestingly, renal transplant patients receiving cyclosporine-based immunosuppression have a regression of KS when their regimen is changed to rapamycin, a drug now thought to have direct antitumor activity.[98]

**AIDS-Related Kaposi Sarcoma.** Caused by HIV-1, AIDS produces profound immunodeficiency and susceptibility to opportunistic infections and various tumors. AIDS originated in Africa, where its epidemic proportions have been attributed to heterosexual transmission and to transmission through contaminated medical equipment (e.g., syringes). In the United States, most cases occur in the male homosexual population, although other risk groups, including intravenous drug users and hemophiliacs receiving factor VIII–enriched blood fractions, are also well recognized. During the zenith of the AIDS epidemic, approximately 30% of patients with AIDS developed KS, but this incidence has been greatly reduced by antiretroviral therapy (ART). KS, however, does not equally affect the known risk groups. At one time, as many as 40% of homosexual patients with AIDS developed KS, compared to less than 5% in the other recognized risk groups. KS has only rarely occurred in transfusion recipients. The typical presentation is a young adult male who presents with multiple small, flat, pink patches (Fig. 22.20), which later acquire the classic blue-violet papular appearance (Fig. 22.21). They occur in almost any location but have a predilection for lines of cleavage, mucosal surfaces, and internal organs.

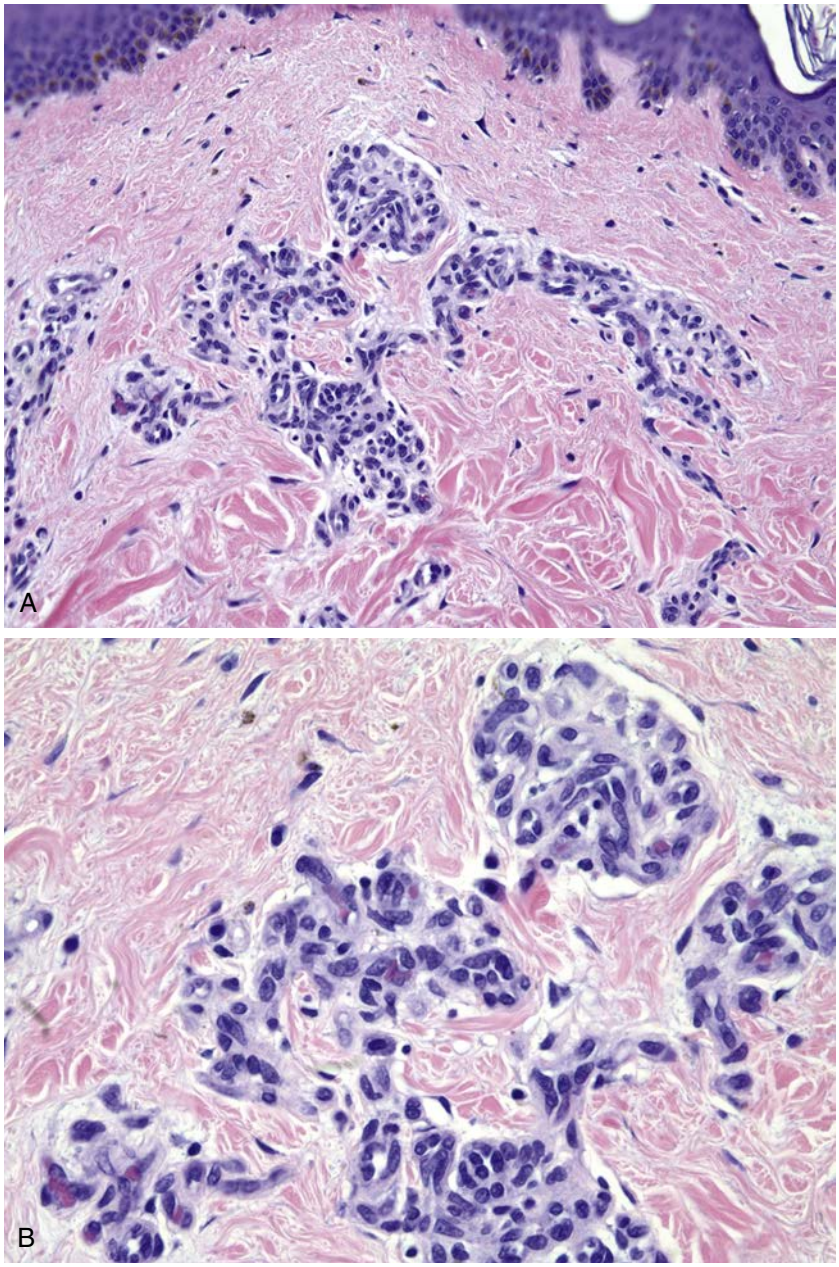


**Fig. 22.19** A and B, Atypical vascular lesions of breast, vascular type, showing proliferation of small, capillary-type vessels within dermis.

## Microscopic Findings

There is no fundamental difference in the appearance of KS among the various clinical groups. The early lesions of KS are now seen most often in the AIDS patient, and in many patients the subtlety of changes presents an ongoing challenge to the surgical pathologist.

The earliest (*patch*) stage of KS is a flat lesion characterized by a proliferation of miniature vessels surrounding larger ectatic vessels. A slightly more advanced patch lesion also displays a loosely ramifying network of jagged vessels in the upper dermis (Figs. 22.22 and 22.23). In some respects this stage resembles a well-differentiated angiosarcoma, except that the cells are so unimpressive that they resemble normal capillary or lymphatic endothelium. There is also a sparse infiltrate of lymphocytes and plasma cells surrounding the patch lesion. The histologic changes seen in patch lesions have also been noted in clinically normal areas of skin in patients who have KS elsewhere. This observation underscores the diffuseness of the disease process.

The more advanced (*plaque*) stage of the disease produces a slight elevation of the skin. It is at this point that the vascular proliferation usually involves most of the dermis and may extend to the subcutis. A discernible but relatively bland spindle cell component, initially centered around the proliferating vascular channels, appears at this stage. In time the spindle cell foci coalesce and produce the classic nodular lesions of KS. Diagnosis of the well-established case is seldom difficult.

**TABLE 22.4 Comparison of Atypical Vascular Lesion and Postirradiation Angiosarcoma**

| | Atypical Vascular Lesion | Angiosarcoma |
|---|---|---|
| Size | Usually <1 cm | Typically >1 cm<br>Average: about 4.0 cm |
| Multifocality | Common | Common |
| Circumscription | ++ | – |
| Subcutaneous extension | Rare | Common |
| Anastomotic vessels | ++ | +++ |
| Cytologic atypia and prominent nucleoli | – | +++ |
| Multilayered endothelium | – | +++ |
| Blood lakes | – | ++ |

Data from Brenn T, Fletcher CD. Radiation-associated cutaneous atypical vascular lesions and angiosarcoma: clinicopathologic analysis of 42 cases. *Am J Surg Pathol.* 2005;29:983.

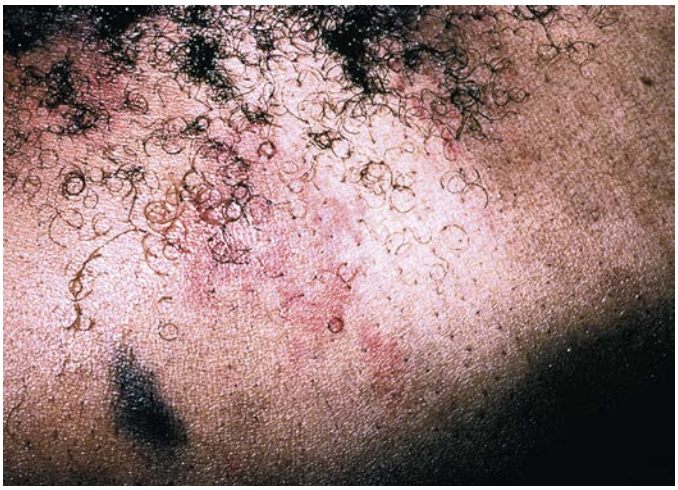

**Fig. 22.20** Early patch stage of Kaposi sarcoma, as seen in patient with AIDS. Lesion is flat and mottled. (Courtesy of Dr. Abe Macher.)

Graceful arcs of spindle cells intersect one another, as in a well-differentiated fibrosarcoma (Figs. 22.24 to 22.28). Unlike fibrosarcoma, however, slitlike spaces containing erythrocytes separate the spindle cells and vascular channels (Fig. 22.25). In cross section these arcs of spindle cells are equally diagnostic by virtue of the sievelike or honeycomb pattern they create. Inflammatory cells (lymphocytes and plasma cells), hemosiderin deposits, and dilated vessels are usually seen at the periphery of nodular lesions (Fig. 22.26). A characteristic but not specific feature of the well-established lesion is the presence of the *hyaline globule*. These periodic acid–Schiff–positive, diastase-resistant spherules may be located both intracellularly and extracellularly (Fig. 22.28B). Some of the hyaline globules are effete erythrocytes, as supported by the finding of erythrocytes in phagolysosomes on ultrastructural analysis and by certain common histochemical features (positive for toluidine blue and endogenous peroxidase).

Although the typical lesions of KS are devoid of pleomorphism and a significant number of mitotic figures, histologically aggressive forms of KS may result from progressive histologic dedifferentiation in otherwise typical cases. Poorly differentiated tumors may also arise from the start and seem to be more common in KS cases originating in Africa. In these tumors the cells not only appear more pleomorphic, but also may have a brisk level of mitotic activity. KS, particularly in the setting of AIDS, may show transitional areas that appear more akin to angiosarcoma. These areas may contain large ectatic vascular spaces similar to a hemangioma or lymphangioma and also have papillary tufts lined by atypical endothelial cells (Fig. 22.27). These tumors have been termed *lymphangioma-like Kaposi sarcoma*.[101]

Just as the early changes of KS in the skin present a diagnostic challenge, so do early changes of this tumor in other organs (Fig. 22.29). A particularly common problem is the evaluation of lymph nodes in the AIDS patient. The earliest changes in lymph nodes may be represented by a mild angiectasia and proliferation of vessels in the subcapsular sinus. The interfollicular sinuses are gradually involved and expanded. The earliest stages may closely resemble the reactive lymph node condition, known variously as *nodal angiomatosis* and vascular transformation of the subcapsular sinus, which results from lymph node obstruction. Others have noted the similarity of these lymph nodes to Castleman disease when the proliferating vessels are centered around the follicles. Fortunately, immunostaining is extremely helpful because even subliminal lymph node lesions express HHV8 (see later). Well-advanced cases of KS involving lymph nodes do not present a problem because they exhibit partial or complete lymph node effacement by a monotonous spindle cell proliferation. Because patients with AIDS are prone to develop mycobacterial pseudotumors of the lymph node, special stains may be needed to distinguish these changes from KS of the node.

## Immunohistochemical Findings

Identification of KSHV as the causative agent of KS allows targeting of viral antigens as markers for the diagnosis. Latency-associated nuclear antigen (LANA-1), encoded by the open reading frame 73 of KSHV, is responsible for anchoring viral DNA to host heterochromatin and is constitutively expressed in infected tissues. Commercially available antibodies to this protein have high sensitivity and specificity for identifying KS. More than 90% of KS of all types display strong nuclear immunoreactivity for this protein in both endothelium and spindled components[102-104] (Fig. 22.30B), whereas other vascular tumors, even those from HIV-infected patients, are negative for this antigen. Although usually not needed to diagnose classic examples of KS, LANA-1 antibodies have proved useful for diagnosing the early or subtle lesions of KS and for distinguishing spindled cell angiosarcomas from KS.

A pan-endothelial marker, CD31 is expressed by both the spindled and the endothelial components of KS lesions (Fig. 22.30A). Other endothelial markers, such as FLI and ERG, are also routinely positive.[105,106] In addition, VEGFR3 and podoplanin (D2-40), generally considered markers of lymphatic endothelium, are strongly expressed by these tumors.[107-110] Although usually cited as evidence that KS is a lymphatic

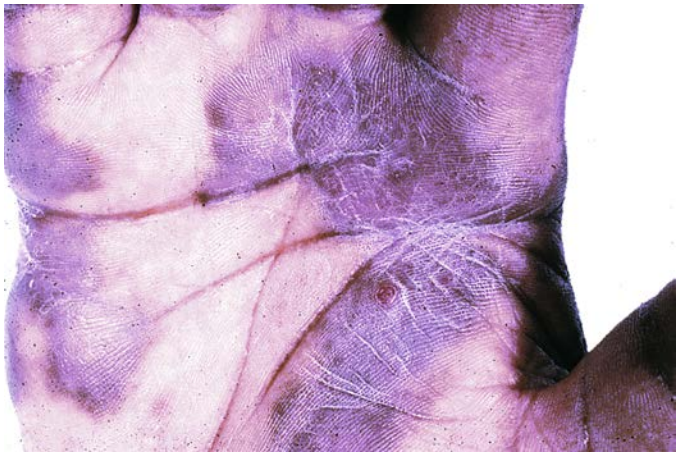

**Fig. 22.21** Advanced stage of Kaposi sarcoma in AIDS patient with combination of patch, plaque, and nodular lesions. (Courtesy of Dr. Abe Macher.)

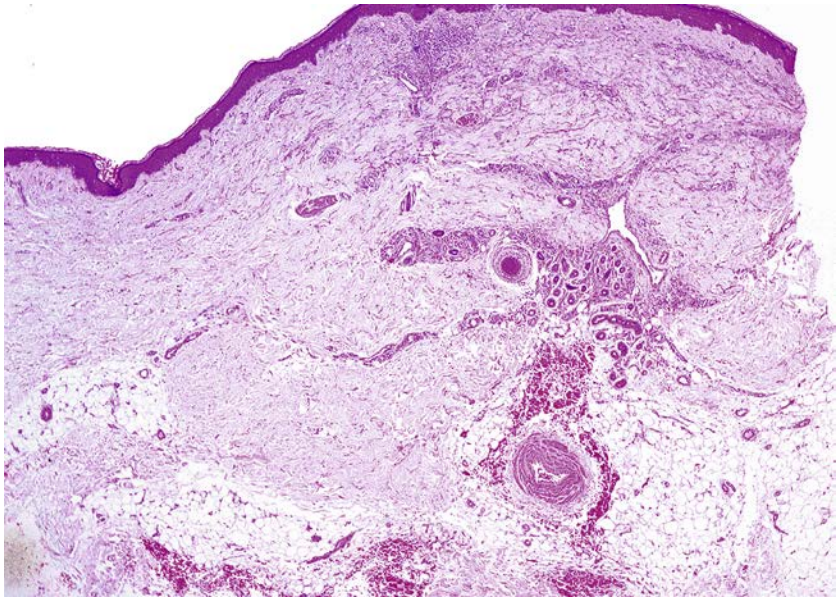

**Fig. 22.22** Early lesion of Kaposi sarcoma in AIDS patient. Lesions are flat or slightly elevated.

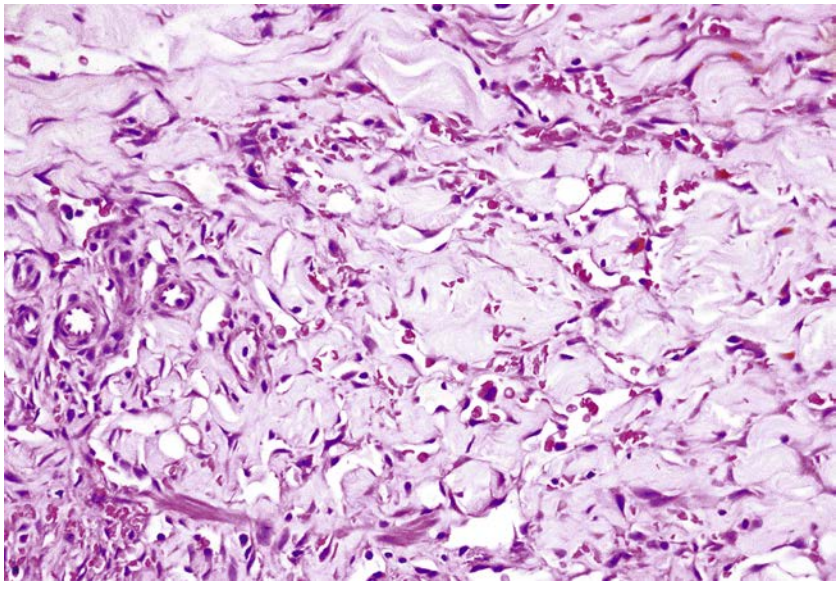

**Fig. 22.23** Early lesion of Kaposi sarcoma illustrating irregular proliferation of miniature vessels in the dermis somewhat reminiscent of the pattern of angiosarcoma.

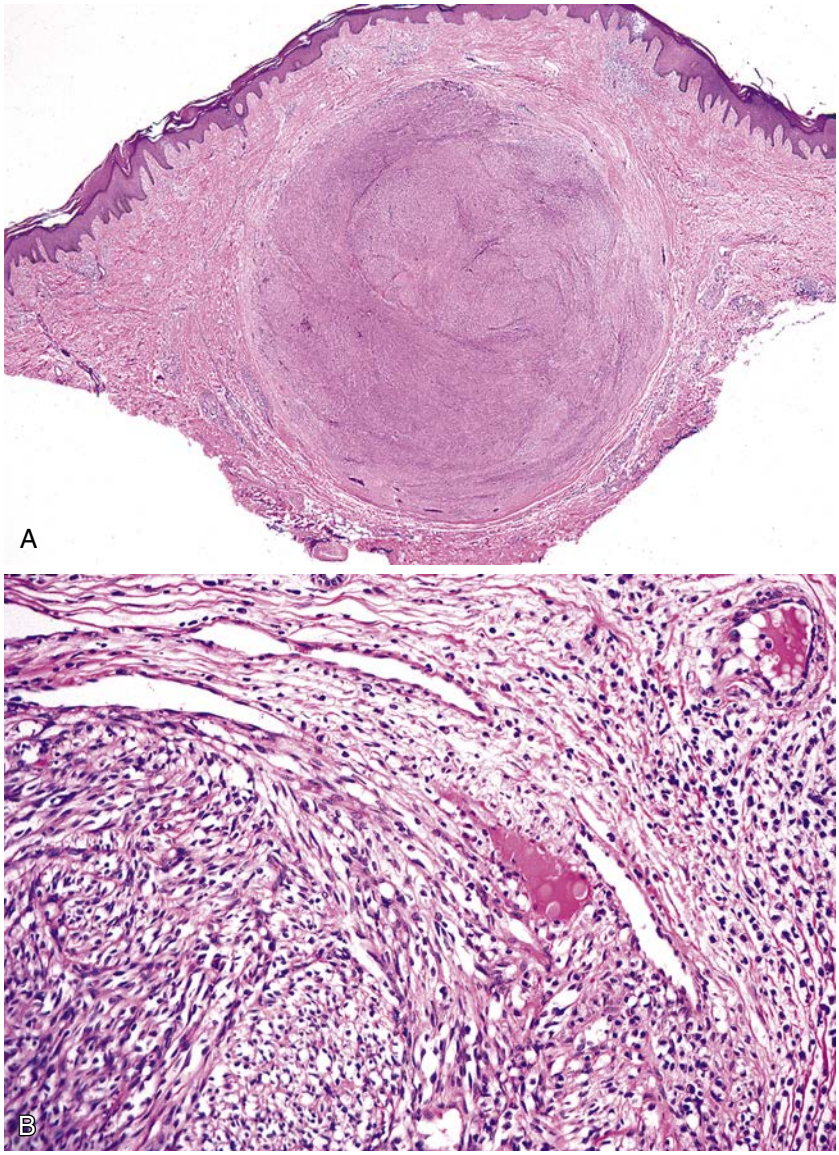


**Fig. 22.24** A, Well-established lesion of Kaposi sarcoma. B, Tumor nodule is circumscribed by lymphocytes and ectatic or crescentic vessels.

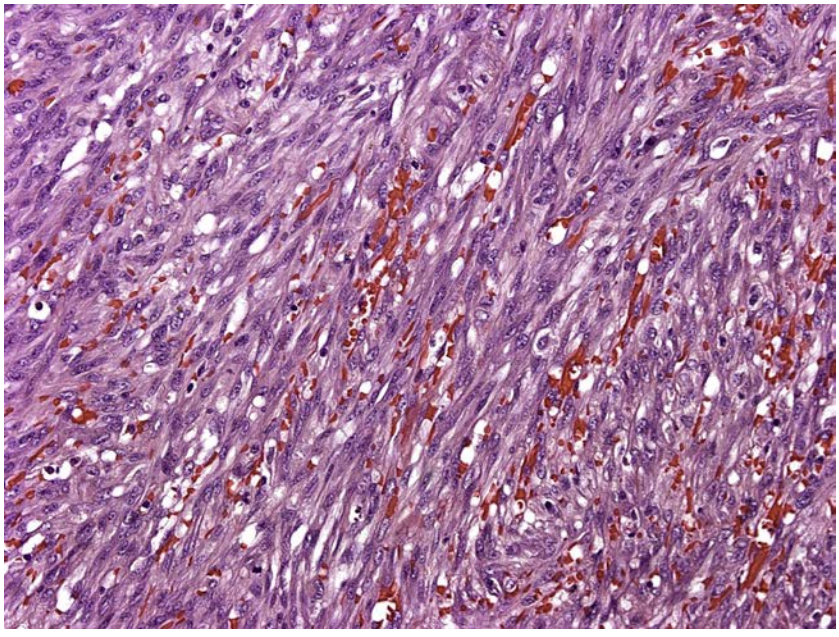

**Fig. 22.25** Kaposi sarcoma showing monomorphic spindle cells arranged in poorly defined fascicles. Cells are separated by slitlike vessels containing erythrocytes.

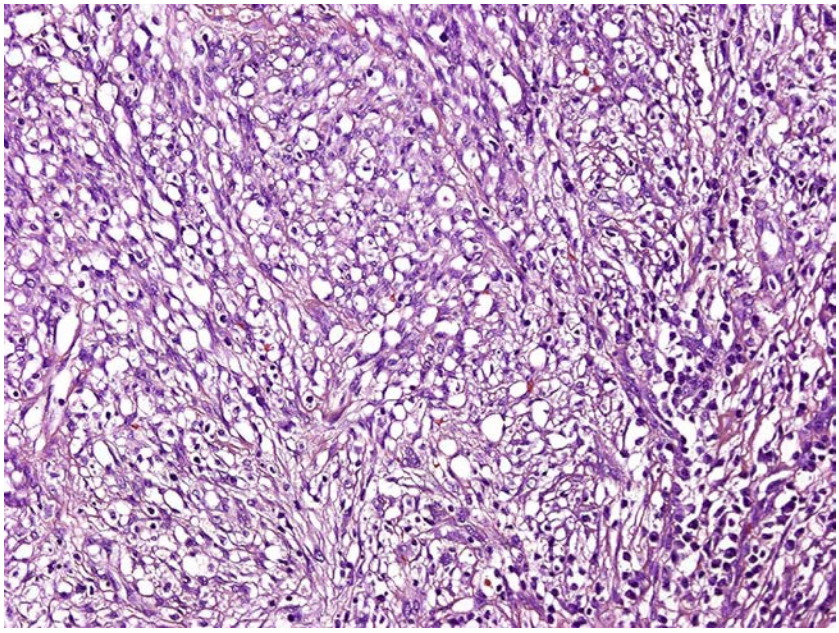

**Fig. 22.26** Transverse section through fascicle of Kaposi sarcoma showing sievelike pattern.

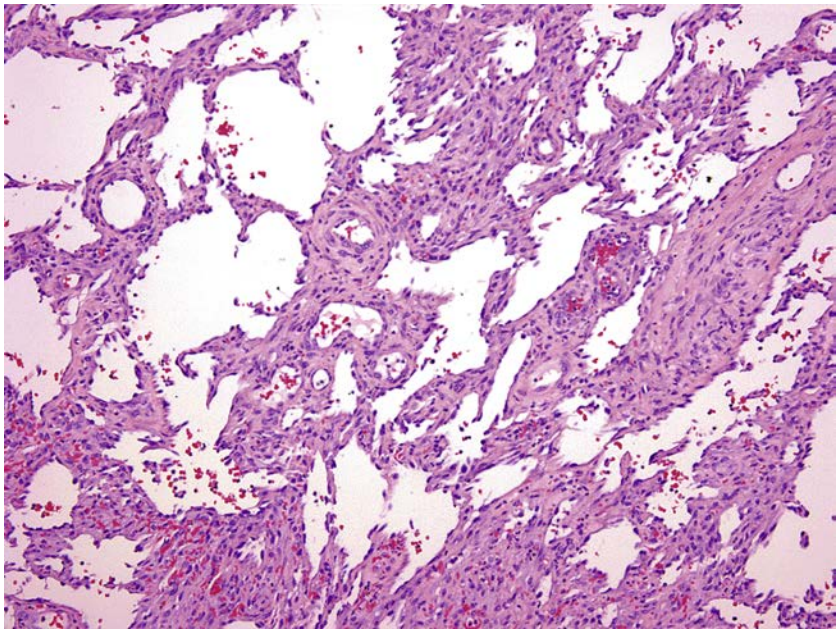

**Fig. 22.27** Kaposi sarcoma with lymphangioma-like areas.

lesion, KSHV infection is known to alter the pattern of endothelial marker expression. When infected with KSHV, vascular endothelial cells upregulate markers of lymphatic lineage; conversely, after infection, lymphatic endothelial cells shift in the direction of a vascular transcriptional profile. The ability of the virus to reprogram target cells explains the unusual pattern of marker expression in KS and why lineage assignment is problematic.[111]

## Differential Diagnosis

Recognizing the early changes of KS, especially in the AIDS patient, remained a difficult diagnostic problem but has been greatly simplified using immunostains for HHV8. The irregular infiltrative pattern of the endothelial cells in early lesions is more helpful for the diagnosis than the degree of cytologic atypia, although the changes may be virtually indistinguishable from those in a well-differentiated angiosarcoma. The well-advanced case may be confused with a **fibrosarcoma**. Features that distinguish a highly cellular form of KS from a fibrosarcoma include the presence of ectatic vessels and inflammatory cells at the periphery of the lesions, the more curvilinear fascicles, and the presence of hyaline globules.

HHV8 immunostaining has also proved to be valuable in discriminating KS from various mimics, although histologic features should never be ignored. **Arteriovenous malformations** occasionally give rise to cutaneous lesions that

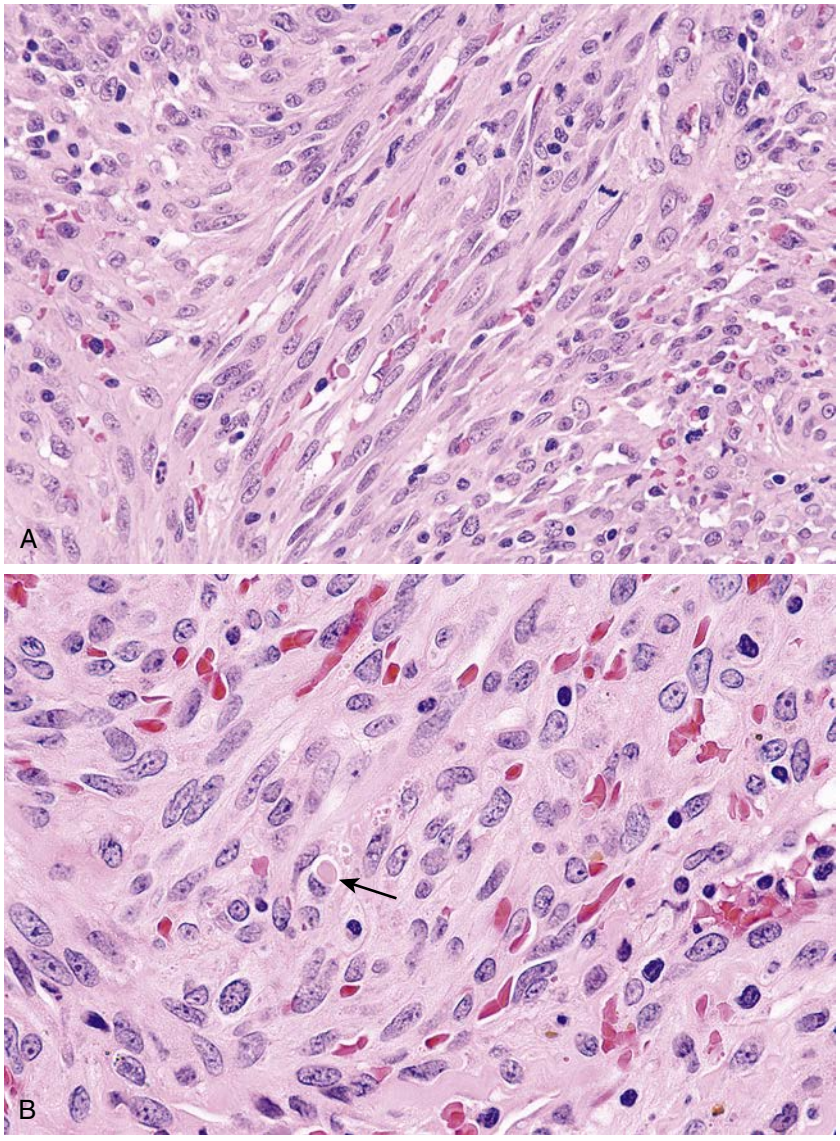


**Fig. 22.28** High-power view of Kaposi sarcoma showing mitoses (A) and hyaline globules (B).

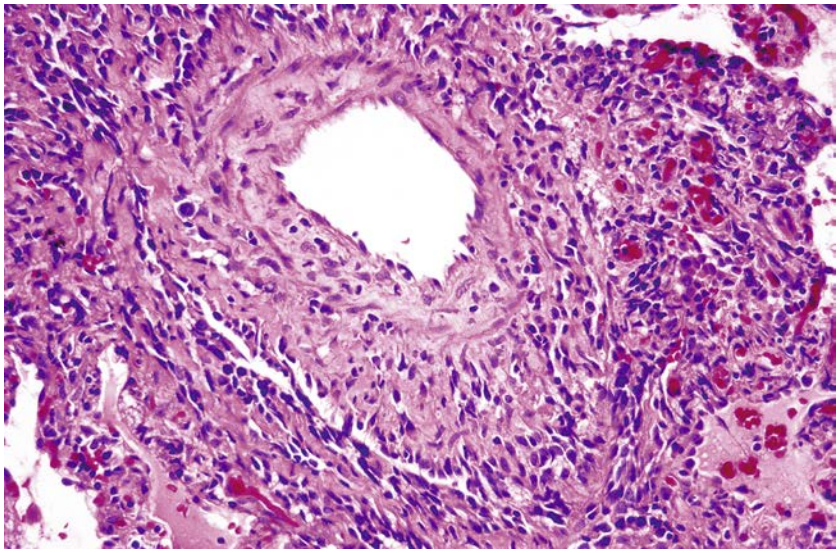

**Fig. 22.29** Kaposi sarcoma involving lung. Note permeation of septa and perivascular connective tissue.

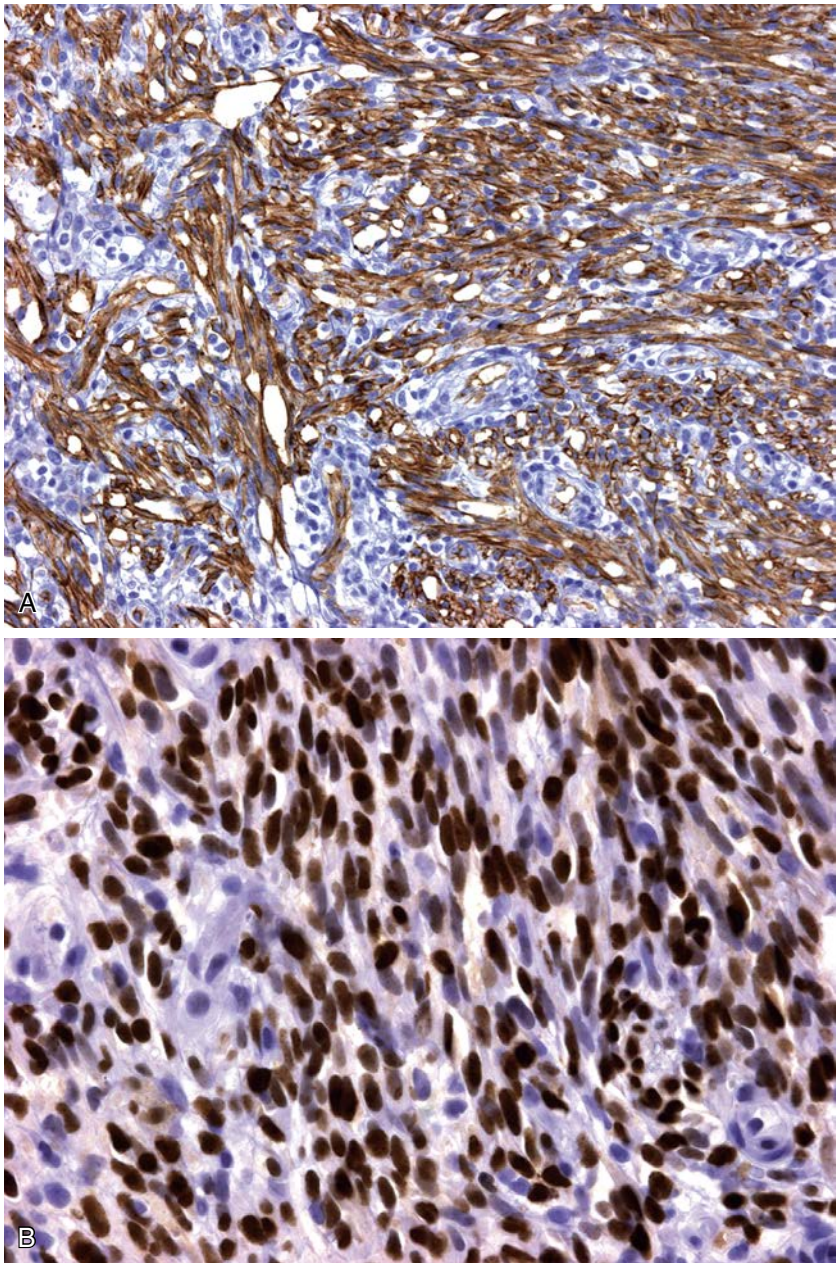


**Fig. 22.30** A, CD31 immunostaining of Kaposi sarcoma illustrating immunoreactivity of majority of spindled cells. B, Immunostaining for LANA-1 of KSHV decorates most nuclei within lesional cells of Kaposi sarcoma.

clinically duplicate the picture of KS; these lesions have been termed *pseudo-Kaposi sarcoma*. Histologically, these lesions consist of a proliferation of capillary-sized vessels occasionally surrounded by extravasated erythrocytes and hemosiderin. Frank spindling and formation of slitlike lumens are not seen. Arteriographic studies documenting an underlying arteriovenous malformation and the clinical findings of a bruit in the area of the lesions provide additional contrasting points.

**Spindle cell hemangiomas** are frequently confused with KS. The presence of cavernous vessels and epithelioid endothelial cells (not seen in KS) are important histologic features for distinguishing the two tumors. **Kaposiform hemangioendotheliomas** and closely related (if not identical) **tufted angiomas** also may mimic Kaposi sarcoma but occur in much younger patients, often show hyaline fibrosis, and lack HHV8 LANA-1 expression (see Chapter 20).

## Behavior and Treatment

The behavior of KS depends on interrelated factors such as the form of the disease, clinical stage, immunocompetence of the host, and presence or absence of opportunistic infections.

In the *classic* or chronic form of KS, which occurs in more immunocompetent individuals who present with limited cutaneous disease, disease-related mortality is 10% to 20%. Even in patients of this group who die of their disease, the duration

**TABLE 22.5 Revised AIDS Clinical Trials Group Staging Classification for Kaposi Sarcoma (KS)**

| | Good Risk (0; All of Following) | Poor Risk (1; Any of Following) |
|---|---|---|
| Tumor (T) | Confined to skin and/or lymph nodes | Tumor-associated edema or ulceration; extensive oral KS; gastrointestinal KS; KS in other nonnodal visceral locations |
| Immune system (I; not included if HIV sensitive to HAART)* | CD4 cells >150 μL | CD4 cells <150 μL |
| Systemic illness (S) | No history of opportunistic infection or thrush; no "B" symptoms (unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea) persistent >2 wk; performance status >70 (Karnofsky) | History of opportunistic infections and/or thrush; "B" symptoms present; performance status <70; other HIV-related illness (e.g., lymphoma) |

*CD4 cutoff of 200 μL previously proposed has been revised to 150 μL.
*AIDS,* Acquired immunodeficiency syndrome; *HAART,* highly active antiretroviral therapy; *HIV,* human immunodeficiency virus.
Data from Krown SE et al. AIDS-related Kaposi sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. *J Clin Oncol.* 1997;15:3085; and Nasti G et al. AIDS-related Kaposi sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group staging system in the HAART era—the Italian Cooperative Group on AIDS and Tumors and the Italian cohort of patients naïve from antiretrovirals. *J Clin Oncol.* 2003;21:2876.

of the disease is 8 to 10 years, although an additional 25% of patients die of a second malignancy. Local therapy consisting of cryotherapy, intralesional injections, and radiation therapy is usually sufficient for limited mucocutaneous disease. Surgery is used principally to provide diagnostic biopsy material before therapy.

Before ART, the mortality among AIDS-associated KS patients approached 90%. Effective ART now not only prevents the development of KS lesions but also is responsible for substantial disease regression in AIDS patients.[98] It is now recommended that patients with AIDS-associated KS receive ART and that those with advanced symptomatic disease receive chemotherapy as well. To accurately evaluate the efficacy of various drug combinations, the AIDS Clinical Trials Group Oncology Committee has devised specific definitions of *clinical response* along with a staging system unique for AIDS-related KS.[113,114] This staging system replaces traditional ones and encompasses a number of parameters, including extent of tumor (T), status of the immune system (I), and severity of the illness (S) (Table 22.5). *Good risk* is designated with subscript 0 following the criteria and *poor risk* with 1. In the pre-ART era, poor risk in any category denoted poor risk overall. With ART, the CD4 level does not seem to provide additional prognostic information. Therefore, two risk groups are currently recognized: *good* (T0S0, T1S0, T0S1) and *poor* (T1S1). In resource-rich countries, ART has been estimated to reduce the incidence of KS by 33% to 95%.[115] A wide variety of chemotherapeutic agents have been used for treatment of KS, with varying efficacy; newer agents targeting angiogenic and signaling pathways have shown some value in early clinical trials.[116]

## REFERENCES


1. Breiteneder-Geleff S, Soleiman A, Kowalski H. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. *Am J Pathol.* 1999;154:385.
2. Deyrup AT, Miettinen M, North PE, et al. Angiosarcomas arising in the viscera and soft tissue of children and young adults: a clinicopathologic study of 15 cases. *Am J Surg Pathol.* 2009;33:264.
3. Deyrup AT, Miettinen M, North PE, et al. Pediatric cutaneous angiosarcomas: a clinicopathologic study of 10 cases. *Am J Surg Pathol.* 2011;35:70.
4. Lahat G, Dhuka AR, Hallevi H, et al. Angiosarcoma: clinical and molecular insights. *Ann Surg.* 2010;251:1098.
5. Schreiber H, Barry FM, Russell WC, et al. Stewart-Treves syndrome: a lethal complication of postmastectomy lymphedema and regional immune deficiency. *Arch Surg.* 1979;114:82.
6. Bessis D, Sotto A, Roubert P, et al. Endothelin-secreting angiosarcoma occurring at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient. *Br J Dermatol.* 1998;138:361.
7. Wehrli BM, Janzen DL, Shokeir O, et al. Epithelioid angiosarcoma arising in a surgically constructed arteriovenous fistula: a rare complication of chronic immunosuppression in the setting of renal transplantation. *Am J Surg Pathol.* 1998;22:1154.
8. Chanyaputhipong J, Hock DL, Sebastian MG. Disseminated angiosarcoma of the dialysis fistula in 2 patients without kidney transplants. *Am J Kidney Dis.* 2011;57:917.
9. Qureshi YA, Strauss DC, Thway K, et al. Angiosarcoma developing in a nonfunctioning arteriovenous fistula post-renal transplant. *J Surg Oncol.* 2010;101:520.
10. Jennings TA, Peterson L, Axiotis CA, et al. Angiosarcoma associated with foreign body material: a report of three cases. *Cancer.* 1988;62:2436.
11. Folpe AL, Johnston CA, Weiss SW. Cutaneous angiosarcoma arising in a gouty tophus: report of a unique case and a review of foreign material–associated angiosarcoma. *Am J Dermatopathol.* 2000;22:418.
12. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. *Am J Surg Pathol.* 1998;22:683.
13. Fletcher CD, Beham A, Bekir S, et al. Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm. *Am J Surg Pathol.* 1991;15:915.
14. Brown RW, Tornos C, Evans HL. Angiosarcoma arising from malignant schwannoma in a patient with neurofibromatosis. *Cancer.* 1992;70:1141.
15. Chaudhuri B, Ronan SG, Manaligod JR. Angiosarcoma arising in a plexiform neurofibroma. *Cancer.* 1980;46:605.
16. Meis JM, Kindblom LG, Enzinger FM. Angiosarcoma arising in von Recklinghausen's disease (NF1): report of five additional cases. *Mod Pathol.* 1994;7:8A.

17. Morphopoulos GD, Banerjee SS, Ali HH, et al. Malignant peripheral nerve sheath tumour with vascular differentiation: a report of four cases. *Histopathology*. 1996;28:401.
18. Trassard M, LeDoussal V, Bui BN, et al. Angiosarcoma arising in a solitary schwannoma (neurilemoma) of the sciatic nerve. *Am J Surg Pathol*. 1996;20:1412.
19. Ulbright TM, Clark SA, Einhorn LH. Angiosarcoma associated with germ cell tumors. *Hum Pathol*. 1985;16:268.
20. Tallini G, Price FV, Carcangiu ML. Epithelioid angiosarcoma arising in uterine leiomyomas. *Am J Clin Pathol*. 1993;100:514.
21. Dunkel IJ, Gerald WL, Rosenfield NS, et al. Outcome of patients with history of bilateral retinoblastoma treated for a second malignancy: the Memorial Sloan Kettering experience. *Med Pediatr Oncol*. 1998;30:59.
22. Leake J, Sheehan MP, Rampling D, et al. Angiosarcoma complicating xeroderma pigmentosum. *Histopathology*. 1992;21:179.
23. Tso CY, Sommer A, Hamoudi AB. Aicardi syndrome, metastatic angiosarcoma of the leg, and scalp lipoma. *Am J Med Genet*. 1993;45:594.
24. Przygodski RM, Finkelstein SD, Keohayong P, et al. Sporadic and Thorotrast-induced angiosarcoma of the liver manifest frequent and multiple point mutations in K-ras-2. *Lab Invest*. 1997;76:153.
25. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. *Cancer Res*. 2009;69:7175.
26. Manner J, Radiwimmer B, Hohenberger P, et al. *MYC* high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. *Am J Pathol*. 2010;176:34.
27. Guo T, Zhang L, Chang NE, et al. Consistent *MYC* and *FLT4* gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. *Genes Chromosomes Cancer*. 2011;50:25.
28. Mentzel T, Schildhaus HU, Palmedo G, et al. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by *MYC* amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathologic, immunohistochemical and molecular analysis of 66 cases. *Mod Pathol*. 2012;25(1):75.
29. Behjati S, Tarpey PS, Sheldon H, et al. Recurrent *PTPRB* and *PLCG1* mutations in angiosarcoma. *Nat Genet*. 2014;46(4):376–379.
30. Huang SC, Zhang L, Sung YS, et al. Recurrent *CIC* gene abnormalities in angiosarcomas: a molecular study of 120 cases with concurrent investigation of *PLCG1, KDR, MYC,* and *FLT4* gene alterations. *Am J Surg Pathol*. 2016;40(5):645–655.
31. Yoshida A, Goto K, Kodaira M, et al. *CIC*-rearranged sarcomas: a study of 20 cases and comparisons with Ewing sarcomas. *Am J Surg Pathol*. 2016;40(3):313–323.
32. Bullen R, Larson PO, Landeck AE, et al. Angiosarcoma of the head and neck managed by a combination of multiple biopsies to determine tumor margin and radiation therapy: report of three cases and review of the literature. *Dermatol Surg*. 1998;24:1105.
33. Tatsas AD, Keedy VL, Florell SR, et al. Foam cell angiosarcoma: a rare and deceptively bland variant of cutaneous angiosarcoma. *J Cutan Pathol*. 2010;37:901.
34. Folpe AL, Chand EM, Goldblum J, et al. Expression of Fli-1, a nuclear transcription factor, distinguishes vascular neoplasm from potential mimics. *Am J Surg Pathol*. 2001;25:1061.
35. Rossi S, Orvieto E, Furlanetto A, et al. Utility of the immunohistochemical detection of Fli-1 expression in round cell and vascular neoplasm using a monoclonal antibody. *Mod Pathol*. 2004;17:547.
36. Miettinen M, Wang AG, Paetau A, et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. *Am J Surg Pathol*. 2011;35:432.
37. Machado I, Santonja C, Huerta V, et al. Unusual neuroendocrine differentiation in a small round cell angiosarcoma: a potential histologic mimicker of superficial Ewing sarcoma. *Am J Dermatopathol*. 2018;40(9):671–675.
38. Tessier Cloutier B, Costa FD, Tazelaar HD, Folpe AL. Aberrant expression of neuroendocrine markers in angiosarcoma: a potential diagnostic pitfall. *Hum Pathol*. 2014;45(8):1618–1624.
39. Shon W, Sukov WR, Jenkins SM, Folpe AL. *MYC* amplification and overexpression in primary cutaneous angiosarcoma: a fluorescence in-situ hybridization and immunohistochemical study. *Mod Pathol*. 2014;27(4):509–515.
40. Ginter PS, Mosquera JM, MacDonald TY, et al. Diagnostic utility of *MYC* amplification and anti-MYC immunohistochemistry in atypical vascular lesions, primary or radiation-induced mammary angiosarcomas, and primary angiosarcomas of other sites. *Hum Pathol*. 2014;45(4):709–716.
41. Requena C, Rubio L, Lavernia J, et al. Immunohistochemical and fluorescence in situ hybridization analysis of MYC in a series of 17 cutaneous angiosarcomas: a single-center study. *Am J Dermatopathol*. 2018;40(5):349–354.
42. Pawlik TM, Paulino AF, McGinn CJ, et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. *Cancer*. 2003;98:1716.
43. Deyrup AT, McKenney JK, Tighiouari M, et al. Sporadic cutaneous angiosarcomas: a proposal for risk stratification based on 69 cases. *Am J Surg Pathol*. 2008;32:72.
44. Holden CA, Spittle MF, Jones EW. Angiosarcoma of the face and scalp: prognosis and treatment. *Cancer*. 1987;59:1046.
45. Fury MG, Antonescu CR, Van Zee KF, et al. A 14-year retrospective review of angiosarcomas: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. *Cancer J*. 2005;11:241.
46. Albores-Saavedra J, Schwartz AM, Henson DE, et al. Cutaneous angiosarcoma: analysis of 434 cases from the Surveillance, Epidemiology and End Results Program, 1973–2007. *Ann Diagn Pathol*. 2011;15:93.
47. Mark RJ, Poen JC, Tran LM, et al. Angiosarcoma: a report of 67 patients and a review of the literature. *Cancer*. 1996;77:2400.
48. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of 44 cases. *Cancer*. 1981;48:1907.
49. Morgan MB, Swann M, Somach S, et al. Cutaneous angiosarcoma: a case series with prognostic correlation. *J Am Acad Dermatol*. 2004;50:867.
50. Fayette J, Martin E, Piperno-Neumann S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. *Ann Oncol*. 2007;2030.
51. Bacchi CE, Silva TR, Zambrano E, et al. Epithelioid angiosarcoma of the skin: a study of 18 cases with emphasis on its clinicopathologic spectrum and unusual morphologic features. *Am J Surg Pathol*. 2010;34:1334.
52. Suchak R, Thway K, Zelger B, et al. Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs. *Am J Surg Pathol*. 2011;35:60.
53. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema. *Cancer*. 1949;1:64.

54. Shon W, Ida CM, Boland-Froemming JM, et al. Cutaneous angiosarcoma arising in massive localized lymphedema of the morbidly obese: a report of five cases and review of the literature. *J Cutan Pathol*. 2011;38:560.
55. Woodward AH, Ivins JC, Soule EH. Lymphangiosarcoma. *Cancer*. 1981;48:1674.
56. Harker D, Jennings M, McDonough P, et al. *MYC* amplification in angiosarcomas arising in the setting of chronic lymphedema of morbid obesity. *J Cutan Pathol*. 2017;44(1):15–19.
57. Udager AM, Ishikawa MK, Lucas DR, et al. MYC immunohistochemistry in angiosarcoma and atypical vascular lesions: practical considerations based on a single institutional experience. *Pathology*. 2016;48(7):697–704.
58. Steingaszner LC, Enzinger FM, Taylor HB. Hemangiosarcoma of the breast. *Cancer*. 1965;18:352.
59. Hodgson NC, Bowen-Wells C, Moffat F, et al. Angiosarcoma of the breast: a review of 70 cases. *Am J Clin Oncol*. 2007;30:570.
60. Luini A, Gatti G, Diaz J, et al. Angiosarcoma of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat*. 2002;105:81.
61. Sher T, Hennessy BT, Valero V, et al. Primary angiosarcomas of the breast. *Cancer*. 2007;110:173.
62. Nascimento AF, Raut CP, Fletcher CD. Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. *Am J Surg Pathol*. 2008;32:1896.
63. Rosen PP, Kimmel M, Ernsberger D. Mammary angiosarcoma: the prognostic significance of tumor differentiation. *Cancer*. 1988;62:2145.
64. Fraga-Guedes C, André S, Mastropasqua MG, et al. Angiosarcoma and atypical vascular lesions of the breast: diagnostic and prognostic role of *MYC* gene amplification and protein expression. *Breast Cancer Res Treat*. 2015;151(1):131–140.
65. Laé M, Lebel A, Hamel-Viard F, et al. Can c-Myc amplification reliably discriminate postradiation from primary angiosarcoma of the breast? *Cancer Radiother*. 2015;19(3):168–174.
66. Marchal C, Weber B, de Lafontan B. Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French comprehensive cancer centers. *Int J Radiat Oncol Biol Phys*. 1999;44:113.
67. Fodor J, Orosz Z, Szabo E, et al. Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature. *J Am Acad Dermatol*. 2006;54:499.
68. Billings SD, McKenney JK, Folpe AL, et al. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. *Am J Surg Pathol*. 2004;28:781.
69. Seinen JM, Styring E, Verstappen V, et al. Radiation-associated angiosarcoma after breast cancer: high recurrence rate and poor survival despite surgical treatment with R0 resection. *Ann Surg Oncol*. 2012;19(8):2700–2706.
70. Morgan EA, Kozono DE, Wang Q, et al. Cutaneous radiation-associated angiosarcoma of the breast: poor prognosis in a rare secondary malignancy. *Ann Surg Oncol*. 2012;19(12):3801–3808.
71. Albores-Saavedra J, Schwartz AM, Henson DE, et al. Cutaneous angiosarcoma: analysis of 434 cases from the Surveillance, Epidemiology, and End Results Program, 1973–2007. *Ann Diagn Pathol*. 2011;15(2):93–97.
72. Patel SH, Hayden RE, Hinni ML, et al. Angiosarcoma of the scalp and face: the Mayo Clinic experience. *JAMA Otolaryngol Head Neck Surg*. 2015;141(4):335–340.
73. Reference deleted in proofs.
74. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. *Ann Surg Oncol*. 2013;20(4):1267–1274.
75. Mendenhall WM, Mendenhall CM, Werning JW, et al. Cutaneous angiosarcoma. *Am J Clin Oncol*. 2006;29:524.
76. Abraham JA, Hornicek FJ, Kaufman AM, et al. Treatment and outcome of 82 patients with angiosarcoma. *Ann Surg Oncol*. 2007;14:1953.
77. Young RJ, Brown NJ, Reed MW, et al. Angiosarcoma. *Lancet Oncol*. 2010;11:983.
78. Miki Y, Tada T, Kamo R, et al. Single institutional experience of the treatment of angiosarcoma of the face and scalp. *Br J Radiol*. 2013;86(1030):20130439.
79. Fujisawa Y, Yoshino K, Kadono T, et al. Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. *Br J Dermatol*. 2014;171(6):1493–1500.
80. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II trial from the French Sarcoma Group (GSF/GETO). *Oncologist*. 2012;17(2):260–266.
81. Shimizu A, Kaira K, Okubo Y, et al. Positive PD-L1 expression predicts worse outcome in cutaneous angiosarcoma. *J Glob Oncol*. 2016;3(4):360–369.
82. Young RJ, Woll PJ, Staton CA, et al. Vascular-targeted agents for the treatment of angiosarcoma. *Cancer Chemother Pharmacol*. 2014;73(2):259–270.
83. Sener SF, Milos S, Feldman JL, et al. The spectrum of vascular lesions in the mammary skin including angiosarcoma after breast conservation treatment for breast cancer. *J Am Coll Surg*. 2001;193:22.
84. Requena L, Kutzner H, Mentzel T, et al. Benign vascular proliferations in irradiated skin. *Am J Surg Pathol*. 2002;26:328.
85. Brenn T, Fletcher CD. Radiation-associated cutaneous atypical vascular lesions and angiosarcoma: clinicopathologic analysis of 42 cases. *Am J Surg Pathol*. 2005;29:983.
86. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. *Histopathology*. 2006;48:106.
87. Patton KT, Deyrup AT, Weiss SW. Atypical vascular lesions after surgery and radiation of the breast: a clinicopathologic study of 32 cases analyzing histologic heterogeneity and association with angiosarcoma. *Am J Surg Pathol*. 2008;32:943.
88. Fineberg S, Rosen PP. Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. *Am J Clin Pathol*. 1994;102:7.
89. Fernandez AP, Sun Y, Tubbs RR, et al. FISH for *MYC* amplification and anti-MYC immunohistochemistry: useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. *J Cutan Pathol*. 2012;39:234.
90. Reference deleted in proofs.
91. Gengler C, Coindre JM, Leroux A, et al. Vascular proliferation of the skin after radiation therapy for breast cancer: clinicopathologic analysis of a series in favor of a benign process: a study from the French Sarcoma Group. *Cancer*. 2007;109:1584.
92. Santi R, Cetica V, Franchi A, et al. Tumour suppressor gene *TP53* mutations in atypical vascular lesion of breast skin following radiotherapy. *Histopathology*. 2011;58:455.
93. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. *Arch Dermatol Syph*. 1872;4:265.

94. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi sarcoma. *Science*. 1994;266:1865.
95. Dourmishev L, Dourmishev AL, Paleri D, et al. Molecular genetics of Kaposi sarcoma–associated herpesvirus (human herpesvirus 8) epidemiology and pathogenesis. *Microbiol Mol Biol Rev*. 2003;67:175.
96. Pantanwitz L, Dezube BJ. Advances in the pathobiology and treatment of Kaposi sarcoma. *Curr Opin Oncol*. 2004;16:443.
97. Flore O, Rafii S, Ely S, et al. Transformation of primary human endothelial cells by Kaposi sarcoma–associated herpes virus. *Nature*. 1998;394:588.
98. Uldrick TS, Whitby D. Update on KSHV epidemiology, Kaposi sarcoma pathogenesis, and treatment of Kaposi sarcoma. *Cancer Lett*. 2011;305:150.
99. Masood R, Cai J, Zheng T, et al. Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma. *Proc Natl Acad Sci USA*. 1997;94:979.
100. Bluefarb SM. *Kaposi Sarcoma*. Springfield, IL: Charles C Thomas; 1966.
101. Cossu S, Satta R, Cottoni F, et al. Lymphangioma-like variant of Kaposi sarcoma: clinicopathologic study of seven cases with review of the literature. *Am J Dermatopathol*. 1997;19:16.
102. Cheuk WW, Wong KO, Wong SC, et al. Immunostaining for human herpesvirus 8 latent nuclear antigen-1 helps distinguish Kaposi sarcoma from its mimickers. *Am J Clin Pathol*. 2004;121:335.
103. Patel RM, Goldblum JR, His ED. Immunohistochemical detection of human herpesvirus-8 latent nuclear antigen-1 is useful in the diagnosis of Kaposi sarcoma. *Mod Pathol*. 2004;17:456.
104. Hammock L, Reisenauer A, Wang W, et al. Latency associated nuclear antigen expression and human herpesvirus 8 polymerase chain reaction in the evaluation of Kaposi sarcoma and other vascular tumors in HIV positive patients. *Mod Pathol*. 2005;18:463.
105. Folpe AL, Chand EM, Goldblum JR, Weiss SW. Expression of Fli-1, a nuclear transcription factor, distinguishes vascular neoplasms from potential mimics. *Am J Surg Pathol*. 2001;25(8):1061–1066.
106. Miettinen M, Wang ZF, Paetau A, et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. *Am J Surg Pathol*. 2011;35(3):432–441.
107. Weninger W, Partanen TA, Breiteneder-Geleff S, et al. Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi sarcoma tumor cells. *Lab Invest*. 1999;79:243.
108. Folpe AL, Veikkola T, Valtola R, et al. Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. *Mod Pathol*. 2000;13:180.
109. Kahn HJ, Bailey D, Marks A. Monoclonal antibody D2-40, a new marker of lymphatic endothelium, reacts with Kaposi sarcoma and a subset of angiosarcomas. *Mod Pathol*. 2002;15:434.
110. Fukunaga M. Expression of D2-40 in lymphatic endothelium of normal tissues and in vascular tumors. *Histopathology*. 2005;46:396.
111. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to the human biology and medicine. *J Clin Invest*. 2010;120:939.
112. McNutt NS, Fletcher V, Conant MA. Early lesions of Kaposi sarcoma in homosexual men: an ultrastructural comparison with other vascular proliferations in the skin. *Am J Pathol*. 1983;111:62.
113. Krown SE, Testa MA, Huang J. AIDS-related Kaposi sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. *J Clin Oncol*. 1997;15:3085.
114. Nasti G, Talamini R, Antinori A, et al. AIDS-related Kaposi sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group staging system in the HAART era—the Italian Cooperative Group on AIDS and Tumors and the Italian cohort of patients naïve from antiretrovirals. *J Clin Oncol*. 2003;21:2876.
115. Semeere AS, Busakhala N, Martin JN. Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-rich and resource-limited settings. *Curr Opin Oncol*. 2012;24(5):522–530.
116. La Ferla L, Pinzone MR, Nunnari G, et al. Kaposi's sarcoma in HIV-positive patients: the state of art in the HAART-era. *Eur Rev Med Pharmacol Sci*. 2013;17(17):2354–2365.