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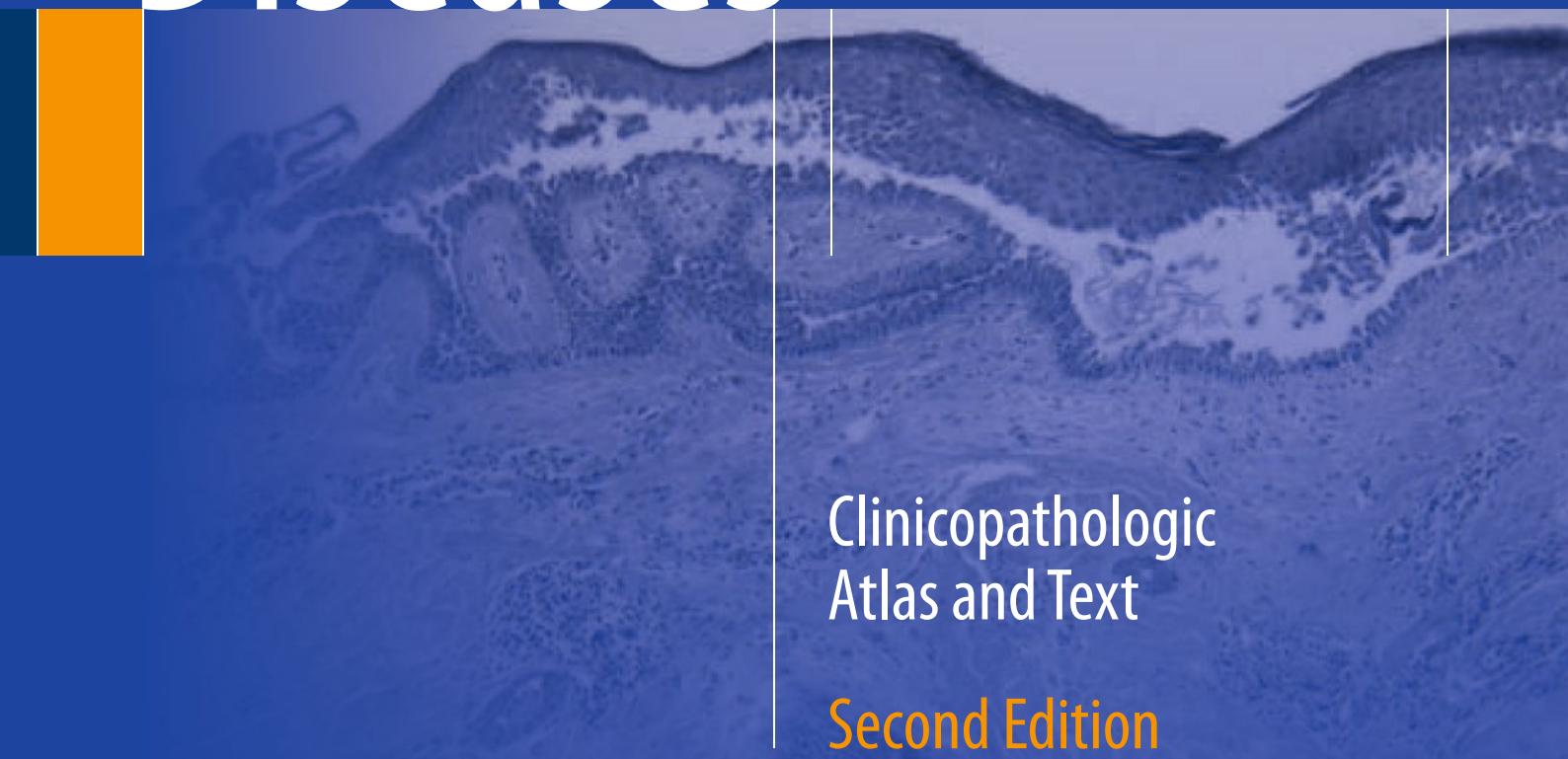
Deadly Dermatologic Diseases



Clinicopathologic Atlas and Text

Second Edition

Springer

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Preface

Primary dermatologic disease can result in significant morbidity and mortality, and the skin can also serve as a useful reflection of internal disease. This textbook is not meant to list and summarize all conditions of the skin which can result in death. Some are intentionally omitted, including melanoma and squamous cell carcinoma. Attempting to summarize these in a single chapter would be a disservice to the complexities of the subject and the abundant research which is present. We intend to broaden the knowledge of clinical identification, histopathology, and treatment of a group of fascinating, occasionally deadly diseases. We also attempt to clarify the story behind how these entities came to the attention of the medical community.

There are slight changes from the original edition of *Deadly Dermatologic Diseases*. Several additional chapters were added. The format now includes 7 sections and 43 chapters. Each section contains etiologically similar conditions. Chapters includes clinical photographs and histopathologic photomicrographs which attempt to capture the essence of each condition. A summary including history, epidemiology, pathogenesis, clinical findings and histopathology are included, with treatment algorithms when appropriate.

Physicians and physician extenders from many disciplines will find this a useful reference, including primary care providers, dermatologists, dermatopathologists, and surgical pathologists. Medical students and residents in the above areas of medicine will also find this a captivating look into the complex world of medical dermatology, and the deadly conditions which we appreciate and despise.

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Part VII Vasculitis and Vasculopathic Disease

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Part I
Malignant Cutaneous Neoplasms

1 Angiosarcoma

▪ Synonyms:	Hemangiosarcoma, lymphangiosarcoma, malignant hemangioendothelioma
▪ Etiology:	Ultraviolet light, radiotherapy, lymphedema (Treves-Stewart syndrome), preexisting vascular malformations (Maffucci's syndrome)
▪ Associations:	Maffucci's syndrome, *BRCA 1 and BRCA 2 mutations*, *Klippel-Trenaunay*, *and neurofibromatosis type 1*
■ Clinical:	Rapidly expanding bruise-like patch *with indistinct borders*, erythematous papules, violaceous nodules, *may present with hemorrhage and ulceration if advanced*
■ Histology:	Ill-defined anastomosing dermal network of atypical endothelial-lined spaces (most common) or defined diffusely arranged aggregates of epithelioid or spindled cells
■ IHC repertoire:	CD-31 (most sensitive and specific), CD-34, *Ulex europaeus*, factor VIII
■ Staging:	None for cutaneous disease
■ Prognosis:	Overall 5-year *survival rate* 10 %, *resectable lesions localized to the skin have a 53.6 % 10-year survival rate*
■ Adverse variables:	Size 5 cm; depth of invasion 3.0 mm; mitotic rate 3 HPF; positive surgical margins, recurrence, and metastases; *age >50*; *tumor located on the scalp and neck*; *nonsolid growth pattern on histology*; *epithelioid histology*
■ Treatment:	WLE/XRT for localized disease, XRT for systemic disease, limited role for CTX

Angiosarcoma (AS), otherwise known as hemangiosarcoma, lymphangiosarcoma, or malignant hemangioendothelioma, is a malignant tumor derived from the endothelium that occurs in a variety of anatomic sites including the skin [1–3]. Sixty percent of cases arise within the skin or superficial soft tissues. *Anatomically the head and neck are most frequently involved* [4]. *These tumors derive from the vascular endothelium. T*he exact vascular origin is unknown and likely *originates* from both the blood vessels and lymphatics. AS is an extremely uncommon tumor, accounting for less than 1 % of all sarcomas [5]. With the exception of tumors that may arise in preexisting vascular lesions, AS predominantly afflicts the *elderly in their sixth decade of* life and is seen most often in men [4, 6, 7]. Males outnumber females by a ratio of approximately 2:1 *regarding AS involving the head and neck* [6, 8, 9]. *A recent retrospective review of 434 cutaneous AS* (*cAS*) *found only a slight male predisposition* [4]. *Below the clavicle* (*excluding AS of the breast*), *males and females exhibit nearly a 1:1 ratio* [6]. *AS has been shown to be preceded 26 % of the time by primary cancer of the breast* (*48.5 %*) *and prostate* (*14.75 %*) [4]. The etiology of AS is multifactorial and is influenced by the clinical setting. Fifty percent of cases occur on the head and neck *making AS responsible for 15 % of all head and neck cancer* [10–12]. Particularly the scalp of *elderly Caucasian men tends to be affected in which exposure to* ultraviolet light is thought to constitute an important risk factor [1, 13, 14]. *The scalp has been affected in up to 48 % of AS cases* [4, 15]. *AS arising in this clinical setting has been referred to as angiosarcoma sporadica* [16]. While tenable, investigators have argued that *cAS* remains an extremely uncommon tumor among individuals with

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excessive ultraviolet light exposure and that other sun-prone anatomic sites are rarely afflicted by AS [17]. In reconciling these contradictions, it has been recently hypothesized that factors unique to these anatomic locations might exist that predispose to its development. These factors might include the vascular density of the scalp or the anastomotic arrangement of the vessels in these areas. Unusual vascular arrangements or density might also combine with ultraviolet light or thermal (heat) effect potentiating oncogenesis [14]. Ionizing radiation in the form of radiotherapy is a recognized risk factor for these tumors particularly involving the anterior chest wall of women who have undergone treatment for breast cancer [10]. *AS arising in areas subjected to ionizing radiation and lymphedema differ biologically to AS sporatica in that myc oncogenes are overexpressed* [18, 19]. *Florescent in situ hybridization testing to determine myc expression can be helpful in determining if AS is a primary or secondary cancer, as primary AS will not display abhorrent myc expression* [20, 21]. Lymphedematous extremities, particularly resulting from radical mastectomy for breast cancer, predispose to AS. Known as the Treves-Stewart syndrome, named after the surgeons who described this association among six patients in 1948, *AS presenting within the setting of lymphedema has now been reported in no less than 400 cases. The permissive environment for the development of AS may result from the lack of adequate lymphatic function compromising immune response and the increase in vascular collaterals. High levels of VEGF and other growth factors commonly found in lymphedematous areas may play a permissive role* [22]. *First-line treatment options include physical therapy and compression where applicable* [23]. Other causes of chronic lymphedema, including congenital lymphedema, and complications resulting from long-standing filariasis infection may eventuate in this tumor as well. *Treatment of lymphedema may prevent the occurrence of malignancy and therefore should be treated straightaway. Rhinophyma, which is thought to be caused by microlymphatic dysfunction, has also been a setting in which AS has presented* [22, 24, 25]. Preexisting vascular lesions, including arteriovenous malformations, have been described in conjunction with this neoplasm. Interestingly, most of these cases have been described in children. AS has also been rarely described following foreign body implantation, *xeroderma pigmentosum*, and in sites of recurring herpes zoster infection [26–28]. *Familial syndromes associated with AS include neurofibromatosis type 1, BRCA 1 and BRCA 2 mutations, Maffucci's syndrome, and Klippel-Trenaunay syndrome* [16]. Unlike identical tumors occurring in the viscera, there is no established association of cutaneous lesions with toxin exposure including thorotrast, arsenic, polyvinyl chloride, or anabolic steroids. *Arsenic exposure resulting in the development of primary AS of the periorbital area was reported in a single case in the literature* [29].

The clinical presentation is varied and dependent upon the various risk factor(s). Some lesions may appear benign or resemble infectious or inflammatory pathology. *This variable presentation can delay proper initial diagnosis and treatment. Delay in diagnosis contributes to the overall poor prognosis of AS. AS masquerading as rosacea, rhinophyma, isolated eyelid edema, scarring alopecia, and chronic episodic facial edema can lead to misdiagnosis* [14, 30]. Among the most common entities cited in the differential diagnosis are lymphoma and metastatic carcinoma. The classic presentation associated with ultraviolet exposure is of a rapidly centripetally expanding brown-to-erythematous patch situated on the forehead or scalp (Fig. 1.1) [31]. In time, the lesion is capable of producing an ulcerated *and potentially bloody* erythematous-to-violaceous plaque or nodule. Later, there is a tendency to develop a centrifugal pattern of tumor satellites [32, 33]. *Skip lesions can make determining the area of cutaneous involvement difficult to appreciate upon inspection* [29, 34]. Although the scalp and face are most commonly afflicted, *the ears, the neck, and the upper* trunk may be involved as well. Lesions attributed to antecedent

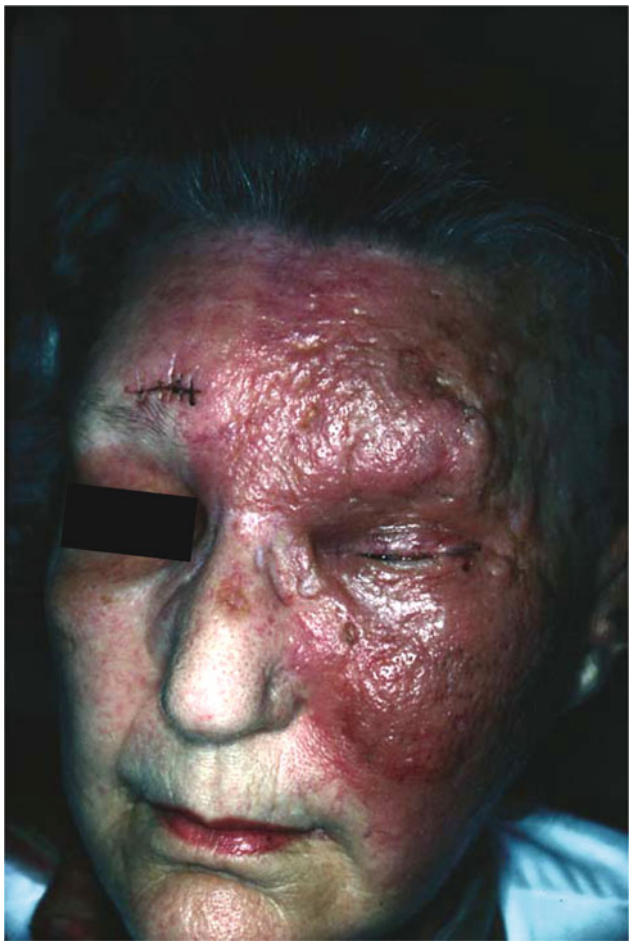

Figure 1.1. Violaceous plaque of angiosarcoma.

radiotherapy consist of rapidly growing papules and nodules classically located on the chest wall of women with a history of irradiated breast carcinoma. Radiotherapy-associated tumors may, however, arise in either sex and within the radiation field of a variety of anatomic sites. Most tumors arise following a 10-year or greater latent period. AS arising within a lymphedematous extremity is generally heralded by the development of a rapidly enlarging papule/nodule superimposed upon the brawny induration, *which is typical* of long-standing lymphedema. Most lesions develop an average of 10 years following surgery. Lesions associated with congenital lymphedema generally occur in younger patients who have experienced lymphedema for greater than 20 years. AS associated with preexisting vascular lesion(s) is characterized by rapid eccentric growth and epidermal ulceration.

The histologic attributes of this lesion are varied. The most common pathologic alteration consists of a subtle increase in vascularity detected in the superficial and mid-dermis [17]. The vascular channels diffusely ramify throughout the dermis, forming an anastomosing network of endothelial-lined vascular spaces (Figs. 1.2 and 1.3). The vascular channels may consist of sinusoids with parallel sides or gaping cavernous spaces. The vascular spaces are lined by a population of cuboidal to hobnailed cells possessing enlarged and hyperchromatic nuclei (Figs. 1.4 and 1.5). *One study reported statistical significance between histological examinations showing greater than 80% solid growth and better survival* [29]. The endothelium may stratify forming papillations. The intervening stroma often contains plasma cells and neutrophils as well as hemosiderin pigment. The tumor periphery is often bounded by a fringe of dilated and otherwise normal-appearing vascular spaces. Less common histologic presentations include a nested or diffusely arranged population of either spindled or enlarged epithelioid cells. In the latter setting, striking cellular pleomorphism may rarely be encountered. *Epithelioid histology has been reported to be associated with decreased disease-specific survival* [30, 35]. Although early lesions are confined to the dermis, well-developed lesions may extend laterally over a large expanse of dermis as well as invade deep into the subcutaneous fat and soft tissues. Microscopic extension of tumor is commonly seen well beyond what is deemed to be the clinical boundary of tumor.

Special techniques that may be employed in confirmation of the diagnosis include electron microscopy and, increasingly, immunohistochemistry [10]. Ultrastructural features of endothelial derivation include the presence of prominent external laminae, pinocytotic vesicles, and specialized endothelial organelles termed Weibel-Palade bodies. These attributes are more commonly observed in well-differentiated and epithelioid tumors. Immunohistochemistry has become an indispensable diagnostic adjunct, particularly in the evaluation of poorly differentiated tumors and in the epithelioid variant. Among the various markers that include CD-31, CD-34, *Ulex europaeus*, and factor VIII, CD-31 is regarded as the most specific marker for endothelial derivation with

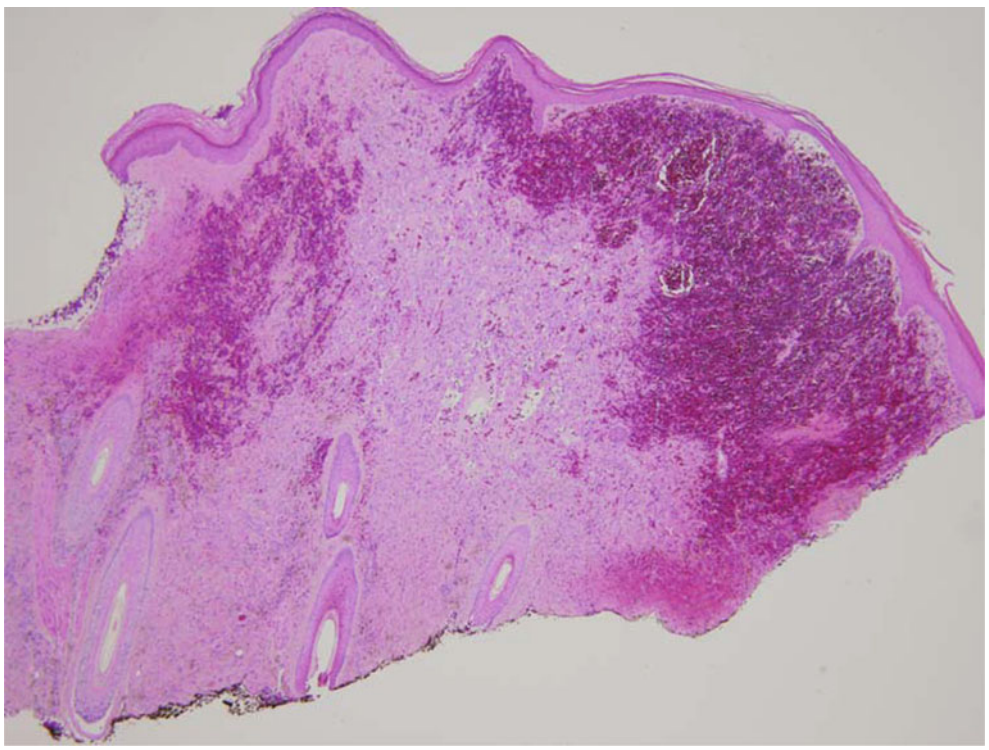

Figure 1.2. Low-power photomicrograph depicting diffuse dermal hemorrhage.

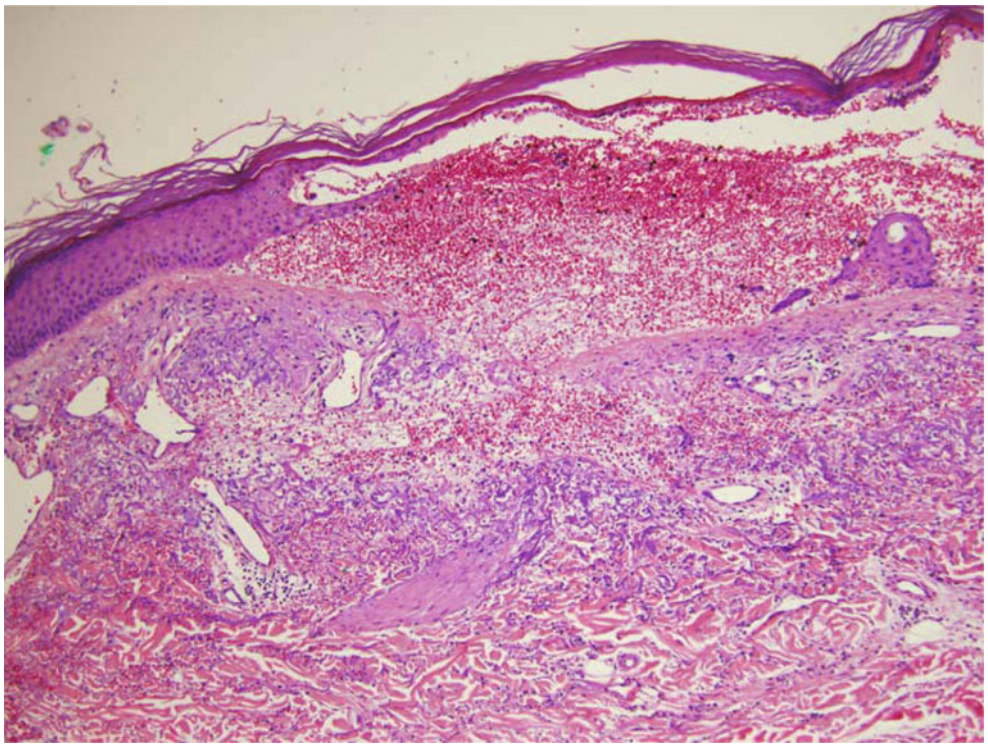

Figure 1.3. Medium-power photomicrograph depicting subtle proliferation of endothelial-lined dermal vascular channels.

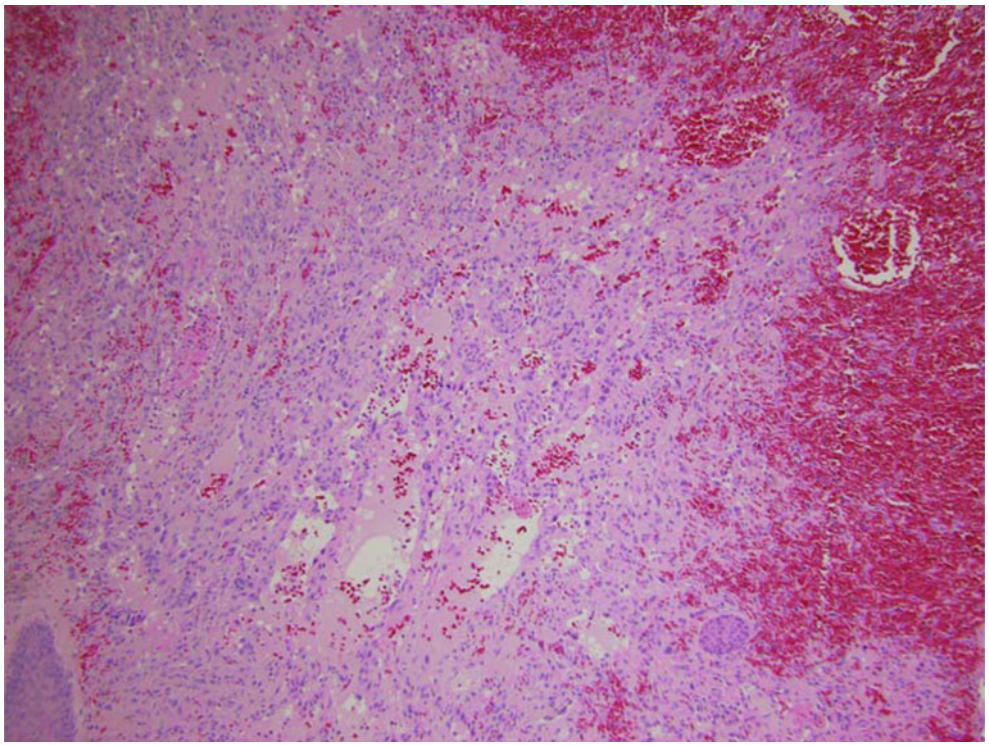

Figure 1.4. Medium-power photomicrograph depicting deeper dermis with gaping vascular channels lined by atypical hyperchromatic endothelial cells.

Ulex europaeus as the most sensitive [5]. An important pitfall to consider is that approximately one-third of cases stain with keratin antibodies, prompting consideration for carcinoma. *Overexpression of VEGF-A and VEGF-C along with p-AKT, p-4EBP1, and CIF4E has been reported in the literature* [35].

Important entities to consider in the histologic differential diagnosis include benign entities such as the tufted

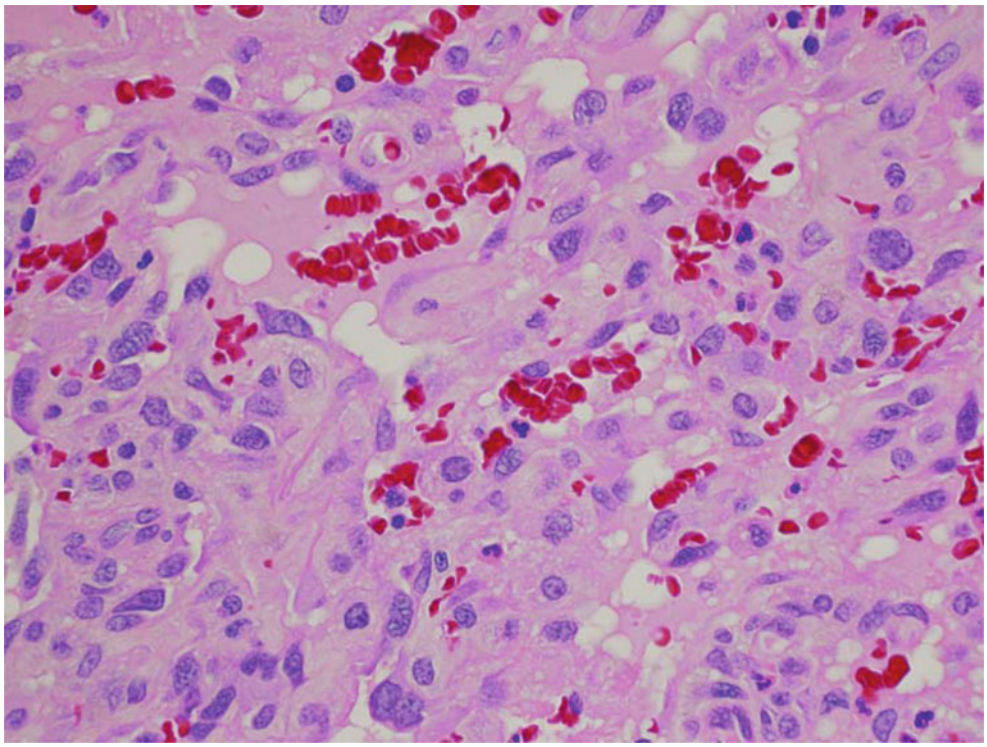

Figure 1.5. High-power photomicrograph depicting cytologic detail of vascular channels lined by atypical endothelial cells.

angioma (TA) and targetoid hemosiderotic hemangioma (THH), low-grade vascular tumors of intermediate prognosis such as epithelioid hemangioendothelioma (EHA) and Kaposi's sarcoma (KS), as well as malignant entities such as poorly differentiated carcinoma. THH consists of a superficial papillary dermal central focus of *hobnailed* vascular spaces and surrounding progressively inconspicuous and attenuated vascular channels. TA consists of discrete nests or tufts of epithelioid endothelia situated throughout the dermis. Endothelial atypia and/or extensive dermal or subcutaneous fat extension are not seen in these lesions. EHA is an uncommon tumor comprised of dermal and subcutaneous nests, strands, and diffusely arranged epithelioid cells often possessing intracytoplasmic lumina that contain erythrocytes. KS consists of a diffusely spindled cell population that characteristically forms slit-like vascular spaces and is punctuated by plasma cells and extracellular hyaline globules. Metastatic and poorly differentiated carcinoma may closely simulate AS. Epithelial connection, intercellular bridges, and glandular formation favor carcinoma. Difficult cases may require immunohistochemical characterization. Carcinomas should not stain with antibodies to CD-31.

AS is an aggressive tumor. It tends to recur locally, later metastasizing despite aggressive multimodal therapy. *Wide surgical excision if possible is the most successful treatment option* [6, 36]. *However, because of the predilection for multifocality and unapparent spread, complete surgical resection is often unattainable* [9, 37, 38]. *Oftentimes even if intraoperative frozen section reports negative margins, permanent sections will often visualize involvement* [37]. *Given that AS tends to be present beyond surgical margins, radiotherapy (RT) is also often performed following surgery as an additional measure. Combined surgical and RT improves local control, disease-specific survival, and overall survival* [34]. Overall prognosis is poor, with reported 5-year survival rates of 10–35 %. *Disease-specific survival has been reported at 53.6 % following complete excision* [35]. Usual metastatic sites are the skin, lung, lymph nodes, spleen, liver, and bone. The development of metastases is ominous, as most patients eventually succumb to their disease. Metastases and recurrences usually develop within 2 years of diagnosis. *Given the high rate of recurrence, better prognostic indicators to guide treatment and options for treatment are needed* [35]. *Tumor grade, demographic factors such as age and gender, anatomic location, and clinical setting do not influence prognosis* [14]. The diameter of the lesion at the time of initial diagnosis is the most important factor in influencing survival. *Lesions of less than 5 cm have a better prognosis* [35, 38] *although recently published retrospective studies report contrary results regarding size as a significant prognostic factor* [4, 6, 13]. *Size has been indicated to be a potentially unreliable factor estimating survival due to precise measurements being difficult to obtain given the growth patterns of AS* [4]. Generally, smaller tumors are more accessible to treatment with surgery. Other potential factors responsible for this observation include shorter clinical duration and limited vascular access with the attendant risk of metastases. Other