Deadly Dermatologic Diseases
Deadly Dermatologic Diseases
Clinicopathologic Atlas and Text

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Foreword by Mark Allen Everett, MD

CD-ROM INCLUDED
To my parents, James and Glenda, who were first to inculcate an enduring fascination with books and their contents.

MBM

I would like to dedicate this work to my always loving and supportive family, Gabey, Jason, and Laura, without whom none of this would be worth doing.

BRS

This effort to highlight life-threatening skin diseases is made in the spirit of the dermatology training I received at MetroHealth Medical Center (formerly Cleveland Metropolitan General Hospital). This was a department of faculty members never seeking national recognition, but dedicated to outstanding training in medical dermatology. The department was headed by Dr. Jerome Pomeranz and given much of its energy by the tireless teaching of the residency director, Dr. Bryan Davis, who instilled his enthusiasm and passion for dermatology into scores of dermatologists who have received their training in the department. Another prominent member of this department to whom I owe thanks is the late Dr. Richard Belcher, whose personal photographs are included in this book. I would also like to thank my colleagues, Drs. Christine Jaworsky and Arlene Rosenberg, for reviewing the manuscript and providing valuable suggestions and my colleague and good friend, Dr. Michael Morgan, for giving me the opportunity to participate in this project.

I would like to dedicate this work to my parents, Roberta Fox Somach and Dr. Fredric Somach, for countless gifts, especially a love of teaching, music, and medicine.

SCS
Foreword

Almost exactly ten years ago, two young physicians joined me at the University of Oklahoma for the study of dermatopathology: Stephen C. Somach, a brilliant dermatologist-scholar from Cleveland, who was also a highly accomplished cellist, and Michael B. Morgan, an effervescent, newly minted pathologist from Florida, who was brimming with energy, curiosity, and zeal and was also sporting water skis and a red Porsche! Bruce R. Smoller, whose impressive erudition is universally acknowledged, I met during a Residency Review committee visit to Stanford some fifteen years ago. Each of these men has made original contributions to the dermatopathology literature as well as to patient care in the clinical setting. Their publications have broadened our understanding of the biologic behavior of pigmented lesions, cutaneous lymphomas, vascular lesions, and soft tissue tumors. It is indeed a pleasure to welcome their volume, Deadly Dermatologic Diseases, a unique and stimulating outcome of their enthusiastic collaboration.

Deadly Dermatologic Diseases discusses a wide variety of entities—neoplastic, vascular, infectious, metabolic—each of which may eventuate in death of the patient. In addition, numerous tumors and dermatoses frequently associated with internal malignancies are reviewed. High-quality histologic photomicrographs and clinical pictures accompany many of the discussions. A unique initial summary page facilitates the reading of each presentation. Recent relevant genetic and biochemical findings in every chapter were particularly helpful to this reader. Finally, the detailed reviews of immunohistochemistry presented with each entity are highly practical. This volume is a welcome addition to the library of practicing dermatologists and pathologists.

Mark Allen Everett, MD
Regents’ Professor Emeritus
Dermatology and Pathology
Preface

The last thing one settles in writing a book is what one should put in first.
—Blaise Pascal, 1654

Dermatology textbooks exist in abundance. They include classics, such as Lever’s Histopathology of the Skin, which have gone through several editions, as well as a burgeoning number of newer titles. They have served practitioners of pathology and dermatology well. However, the diagnosis and treatment of deadly dermatologic disorders remains a relatively unexamined topic. In Deadly Dermatologic Diseases, we have attempted to address this void in the literature. A wide variety of dermatologic entities are capable of directly leading to or are associated with serious medical consequences, including death. Because entities present in a variety of clinical and pathologic guises or represent emerging pathogens (such as anthrax or smallpox), it is important that clinicians and pathologists are apprised of and able to quickly recognize and treat these important public health concerns. This book is comprised of disorders capable of causing the death of the patient.

The book is organized in four sections dealing with dermatologic diseases: serious cutaneous malignancies, including merkel cell carcinoma and paraneoplastic syndromes such as paraneoplastic pemphigus; life-threatening and/or emerging infectious pathogens, including anthrax and smallpox; endocrinologic disorders such as calciphylaxis; and, lastly, inborn errors of metabolism or life-threatening genodermatoses, such as ataxia telangiectasia. Each section of the book is organized alphabetically for easy reference. Approximately 50 disease states are discussed with accompanying full-color clinical and microscopic photographs. Each entity contains clinical photographs accompanied by photomicrographs detailing the diagnostic features of each case. Subsections detailing the demographic attributes, etiology, pathogenesis, clinical presentation, pathologic features, diagnostic adjuncts, treatment, and prognosis with a current bibliography of each disease state presented in a succinct bullet-style manner. Although comprehensive by design, this textbook is by no means exhaustive in scope. Several entities rarely capable of causing death or that are extremely uncommon have not been included due to space constraints.

This book should become a shelf reference work for primary care clinicians, including general practitioners and internists, dermatologists, and pathologists, who are responsible for the diagnosis of skin biopsy specimens. The book might also serve as a potential study source for dermatology and pathology residents preparing for board examinations and dermatopathologists in training.

Michael B. Morgan, MD
Bruce R. Smoller, MD
Stephen C. Somach, MD
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Part I
Malignant Cutaneous Neoplasms
Angiosarcoma (AS), otherwise known as hemangiosarcoma, lymphangiosarcoma, or malignant hemangioendothelioma, is a malignant tumor derived from 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. Although these tumors derive from the vascular endothelium, the exact vascular origin is unknown and likely derives from both the blood vessels and lymphatics.

AS is an extremely uncommon tumor, accounting for less than 1% of all sarcomas (4). With the exception of tumors that may arise in preexisting vascular lesions, AS predominantly afflicts the elderly and is seen more commonly in men. Males outnumber females by a ratio of approximately 2:1. Most patients described have been Caucasian. The etiology of AS is multifactorial and is influenced by the clinical setting. Fifty percent of cases occur on the head and neck and in particular the scalp of elderly men where ultraviolet light is thought to constitute an important risk factor. While tenable, investigators have argued that CA remains an extremely uncommon tumor among individuals with excessive ultraviolet light exposure and that other sun-prone anatomic sites are rarely afflicted by AS (5). 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. 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 (6). 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, this condition has been reported in over 300 patients to date. Other causes of chronic lymphedema, including congenital lymphedema, and complications resulting from long-standing filariasis
infection may eventuate in this tumor as well. Preexisting vascular lesions, including arteriovenous malformations, and hemangiomas including the Mafucci syndrome 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 and in sites of recurring herpes zoster infection. Unlike identical tumors occurring in the viscera, there is no known association of cutaneous lesions with toxin exposure including Thoratras, arsenic, polyvinyl chloride, or anabolic steroids.

The clinical presentation is varied and dependent upon the various risk factor(s). The classic presentation associated with ultraviolet exposure is of a rapidly centripetally expanding brown-to-erythematous patch situated on the forehead or scalp (Figure 1.1) (7). In time, the lesion is capable of producing an ulcerated erythematous-to-violaceous plaque or nodule. Later, there is a tendency to develop a centrifugal pattern of tumor satellites (8,9). Among the most common entities cited in the differential diagnosis are lymphoma and metastatic carcinoma. Although the scalp and face are most commonly afflicted, the ears, neck, and upper trunk may be involved as well. Lesions attributed to antecedent 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 typical of longstanding 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 (5). The vascular channels diffusely ramify throughout the dermis, forming an anastomosing network of endothelial lined vascular spaces (Figures 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 (Figures 1.4 and 1.5). The endothelial 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. Although early lesions are confined to the dermis, well-developed lesions may extend laterally over a large expanse of dermis as well as 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 (6). 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
1. Angiosarcoma

**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.

Various markers that include CD-31, CD-34, Ulex europaeus, Factor VIII, CD-31 is regarded as the most specific marker for endothelial derivation with Ulex europaeus as the most sensitive (4). An important pitfall to consider is that approximately one-third of cases stain with keratin antibodies, prompting consideration for carcinoma.

Important entities to consider in the histologic differential diagnosis include benign entities such as the tufted 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 hobnail-lined 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 char-

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

**FIGURE 1.5.** High power photomicrograph depicting cytologic detail of vascular channels lined by atypical endothelial cells.
1. Angiosarcoma

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. Because of its predilection for multifocality and inapparent spread, complete surgical resection is often unattainable. Overall prognosis is poor, with reported 5-year survival rates of 10%–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. Histologic appearance, tumor grade, demographic factors such as age and gender, anatomic location, and clinical setting, do not influence prognosis (10). The diameter of the lesion at the time of initial diagnosis is the most important factor in influencing survival. Lesions of less than 5 centimeters have a better prognosis (5). 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 favorable attributes recently shown to influence survival include average tumor mitotic rate of less than 3 per microscopic high power field, a tumor depth of less than 3 millimeters, and absence of recurrence and metastases.

Patients need clinical examination every 3 months for the first year following diagnosis to detect early recurrence. Lymph node survey and imaging studies including CT or MRI of the head and neck should be considered at these time intervals as well (11). Due to the rarity of this tumor, there are no widely adopted standard protocols for therapy (11). Localized disease is generally treated with wide local excision or in combination with radiotherapy if the anatomic site and health status of the patient permits. Those who cannot tolerate surgery can be palliated with radiotherapy. Most radiation protocols employ fractionalized megavoltage dosing of between 180 and 300 centigray per day for a total of between 3000 and 7000 centigray. Systemic disease can also be palliated with radiotherapy. The use of various chemotherapeutic agents, including methotrexate, doxorubicin, cyclophosphamide, and vincristine, has been reported with varying success. The role of chemotherapy is not well defined and requires further investigation. Future developments include the use of anti-angiogenic drugs, anti-endothelial antibodies conjugated with cytotoxins, and XRT radiosensitizers.

References

Cutaneous B-cell lymphoma is not a single disease, but rather a family of neoplastic processes characterized by a proliferation of malignant B lymphocytes. These lymphomas may arise de novo on the skin (primary cutaneous B-cell lymphoma) or spread to the skin as part of a systemic disease (secondary cutaneous B-cell lymphoma). It is not possible to make this distinction based purely on histologic findings, and a systemic work-up is required in all of these patients in order to determine the extent of disease. The prognosis is greatly altered depending upon this extent. As subtypes of lymphoma correlate with clinical correlation, histologic findings, and prognosis, several of the most prevalent subtypes will be described individually.

**Marginal Zone Lymphoma (Immunocytoma)**

Marginal zone lymphoma (MZL) is reported to be the most common B-cell lymphoma that occurs in the skin. This type of lymphoma may be closely related to mucosa-associated lymphoid tissue (MALT) lymphomas. There is a slight male predominance and the mean age of onset is approximately 50 years (1). The usual presentation is that of one or several red-brown papules or nodules, most commonly on the upper extremities or head and neck (Figure 2.1).

Histologic findings include diffuse infiltrates of lymphocytes within the dermis and subcutaneous fat. A Grenz zone is present in most cases (Figure 2.2).

The lymphocytes are often admixed with scattered plasma cells and plasmacytoid cells, which provide a clue to the diagnosis (Figure 2.3).

In more than 75% of cases, reactive germinal centers may be present, often masking the diagnosis (1). Areas containing a relatively monomorphic infiltrate of plasmacytoid lymphocytes constitute the neoplastic population. These marginal zones may demonstrate pallor at lowest magnification. This is often quite subtle, especially in early lesions. Rare eosinophils are occasionally present, further complicating the diagnosis.

Lymphocyte immunophenotyping is helpful in making the diagnosis, but the findings may be subtle. The neoplastic lymphocytes express both CD79a and CD20 and fail to express T cell markers. Light chain restriction can be detected in areas with neoplastic cells in some cases, though in others, the tumor cells fail to produce any light chains (2). In most cases of MZL, there is a brisk reactive
2. Cutaneous B-Cell Lymphoma

FIGURE 2.1. Erythematous nodule located at hairline biopsy showed marginal zone lymphoma.

T cell infiltrate that may obscure the diagnostic population.

The differential diagnosis mainly includes a reactive lymphoid hyperplasia. The presence of reactive germinal centers and plasma cells makes this distinction especially difficult. The presence of abundant plasmacytoid cells within greatly expanded interfollicular regions favors MZL, but this is not always apparent. In many cases, immunostains are helpful in detecting subtle light chain restrictions that reveal a clonal population not apparent with routine sections. Gene rearrangement studies are best reserved for cases in which there is a high degree of suspicion for lymphoma and when routine sections and immunostains are not helpful in arriving at a firm diagnosis (see Table 2.1).

The prognosis for patients with MZL is excellent. Aggressive chemotherapy is not necessary. Local excision and/or radiotherapy have been used with a great deal of success. The five-year survival rate is >95%.

**Follicular Cell Lymphoma**

Follicular cell lymphoma (FCL) occurs with approximately the same frequency as does MZL, but has a tendency to involve the head and neck, rather than the upper extremities. There is a slight female predominance for patients with FCL and these tumors occur most commonly in middle-aged adults (3). The most common presentation is that of one or several papules or nodules. There may be some clustering of lesions.

The histologic changes in FCL can be separated into several histologic patterns. Similar to the subtypes seen in node-based FCL, the neoplastic infiltrate can involve the dermis diffusely or with a tendency to form neoplastic follicles (Figure 2.4).

The neoplastic follicles can be distinguished from reactive germinal centers based upon the lack of surrounding mantle zone, absence of tingible-body macrophages, and uniformity of the follicular cells. The cells may be small or
large, round or cleaved, similar to the appearances described in the nodal counterparts to this family of lymphomas. More commonly, however, FCL does not demonstrate a follicular growth pattern. Rather, the most common appearance is that of a diffuse, dense infiltrate of a uniform population of lymphocytes coursing though the dermis and the subcutaneous fat. There is no tendency for involvement of the epidermis or appendageal epithelium, and a Grenz zone may be present. Plasma cells and eosinophils are usually not present in FCL (Figures 2.5 and 2.6).

Table 2.1.

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<td>Expansion of interfollicular regions with abundant plasmacytoid lymphocytes</td>
<td>Neoplastic follicles devoid of histiocytes or diffuse uniform population of lymphocytes throughout dermis</td>
<td>Markedly atypical lymphocytes with abundant mitoses and necrosis</td>
<td>Large, atypical cells largely confined to within lymphatic vessels</td>
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<td>Many CD79a+ cells in interfollicular regions; often light chain restriction</td>
<td>Large areas of CD79a+ cells; frequent light chain restriction</td>
<td>Sheets of CD79a+ cells; occasionally fail to express lymphocyte surface antigens</td>
<td>Intravascular CD79+ lymphocytes</td>
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<tr>
<td>Positive in some cases; early cases often negative</td>
<td>Positive for clonal population in most cases</td>
<td>Positive for clonal population in most cases</td>
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Figure 2.3. Abundant plasma cells and plasmacytoid lymphocytes are present in MZL in the interfollicular regions.
FIGURE 2.4. Low power photomicrograph depicting nodular lymphoid infiltrate of FCL.

FIGURE 2.5. FCL with a diffuse dermal disposition. Note sparing or Grenz zone.
Immunostains reveal the infiltrating lymphocytes to express CD79a and CD20. Most T cell markers are negative, but coexpression with CD43 has been described in FCC. Light chain restriction is found in some cases, but lack of any light chain production is also common in primary cutaneous FCL. Bcl-2, a good marker for node-based FCL, is seen only in a minority of cases of primary cutaneous FCL; further, as this marker is constitutively expressed by T lymphocytes, interpretation may be difficult in dermal infiltrates.

The major differential diagnosis includes cutaneous lymphoid hyperplasia. The presence of histiocytes, plasma cells, and eosinophils favors a reactive process, as does heterogeneity in the size and shape of the lymphocytes. In many cases, immunostains are helpful in demonstrating large sheets of B lymphocytes. The presence of significant numbers of B lymphocytes in the skin in any pattern other than confined to a reactive germinal center is concerning for lymphoma.

As is the case with MZL, patients with primary cutaneous FCL have an excellent prognosis and aggressive systemic chemotherapy is not required. The five-year survival rate exceeds 95%.

Large Cell Lymphoma of the Leg

This is a controversial form of B-cell lymphoma that involves the legs of elderly patients. Some investigators believe this subtype of lymphoma to be a variant of FCL. Others cite differences in histologic pattern and overall survival in supporting the contention that this should be considered a separate subtype of lymphoma.

The clinical presentation is that of one or several large erythematous to violaceous nodules with occasional ulceration in a linear distribution on a lower extremity. Bilateral involvement occurs in some cases, but rarely do tumor nodules extend beyond the lower extremities at the time of initial presentation. This subtype of lymphoma may be more common in women.

The histologic appearance is that of a diffuse infiltrate of large, atypical cells filling the entire papillary and reticular dermis. There is no tendency for involvement of the epidermis and a Grenz zone may be present. The tumor cells are large, with vesicular nuclei, occasional nucleoli, and abundant cytoplasm. Mitotic activity may be brisk, and individual cell necrosis is common.