David R. Crowe
Michael B. Morgan
Stephen C. Somach
Kara M. Trapp *Editors*

Deadly Dermatologic Diseases

Clinicopathologic
Atlas and Text

Second Edition

Springer

Deadly Dermatologic Diseases

Deadly Dermatologic Diseases
Clinicopathologic Atlas and Text

Second Edition

Editors

David R. Crowe

Michael B. Morgan

Stephen C. Somach

Kara M. Trapp

Springer

Editors
David R. Crowe, MD
Assistant Professor
Department of Dermatology
Case Western Reserve University
School of Medicine
Cleveland
OH
USA

Michael B. Morgan, MD
Director of Dermatopathology
Dermatology Specialists of Florida
Panama City
FL
USA

Staff Dermatopathologist
Advanced Dermatology and Cosmetic
Surgery
Clermont
FL
USA

Professor of Dermatology
Michigan State College of Medicine

Stephen C. Somach, MD
Associate Professor of Dermatology and
Pathology
MetroHealth Medical Center
Case Western Reserve University
School of Medicine
Cleveland
OH
USA

Kara M. Trapp, BA
Georgetown University School of Medicine
Washington
DC
USA

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.

<div align="right">

David R. Crowe, MD
Cleveland, OH, USA
Michael B. Morgan, MD
Panama City, FL, USA
Stephen C. Somach, MD
Cleveland, OH, USA
Kara M. Trapp, MD
Washington, DC, USA

</div>

Contents

Contributors

Katelynn Campbell, MD Department of Pathology, University of Arkansas, Little Rock, Arkansas, USA

Brianna Castillo, MD Department of Internal Medicine, University of South Florida College of Medicine, Tampa, FL, USA

Dylan Greeney, MD Department of Dermatology, William Beaumont College of Medicine, Rochester, MI, USA

David R. Crowe, MD Department of Dermatology, MetroHealth Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Michael Garone Jr, DO Department of Internal Medicine, Largo Medical Center, American Osteopathic College of Dermatology, Largo, FL, USA

Alexander Herbst, MD Department of Internal Medicine, Florida State University College of Medicine, Tallahassee, FL, USA

Jeff Kushner, DO Saint Joseph Mercy Health System, Howell, MI, USA

Kiran Mian, DO Department of Internal Medicine, Largo Medical Center, St. Joseph, MI, USA

Michael B. Morgan, MD Dermatopathology, Dermatology Specialists of Florida, Panama City, FL, USA

Advanced Dermatology and Cosmetic Surgery, Clermont, FL, USA

Dermatology Michigan State College of Medicine, Pathology University of South Florida, Tampa, FL, USA

Kaylan Pustover, DO Saint Joseph Mercy Health System, Howell, MI, USA

Ryan Schuering, DO Department of Internal Medicine, Largo Medical Center, Largo, FL, USA

Bruce R. Smoller University of Rochester Medical Center, Pathology and Laboratory Medicine, Rochester, NY, USA

Stephen Suah, MD Department of Internal Medicine, University of Florida College of Medicine, Gainesville, FL, USA

Stephen C. Somach, MD Dermatology and Pathology, MetroHealth Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Kara M. Trapp, BA Georgetown University School of Medicine, Washington, DC, USA

Nicole Vesely, MD Department of Internal Medicine, University of Florida College of Medicine, Gainesville, FL, USA

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

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
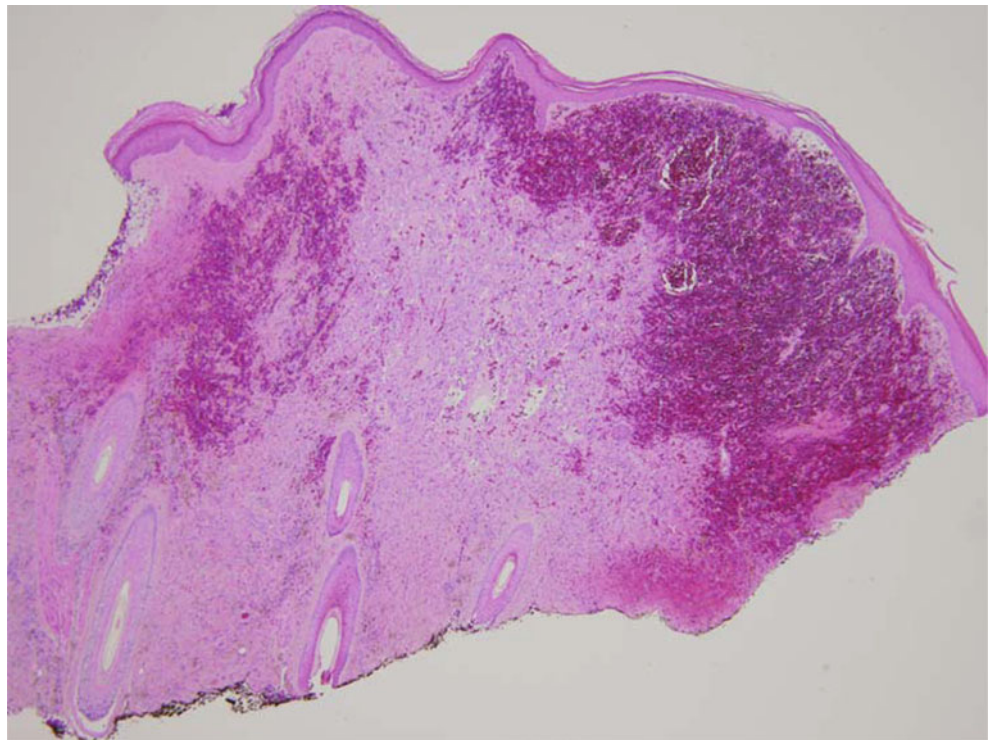
FIGURE 1.2. Low-power photomicrograph depicting diffuse dermal hemorrhage.
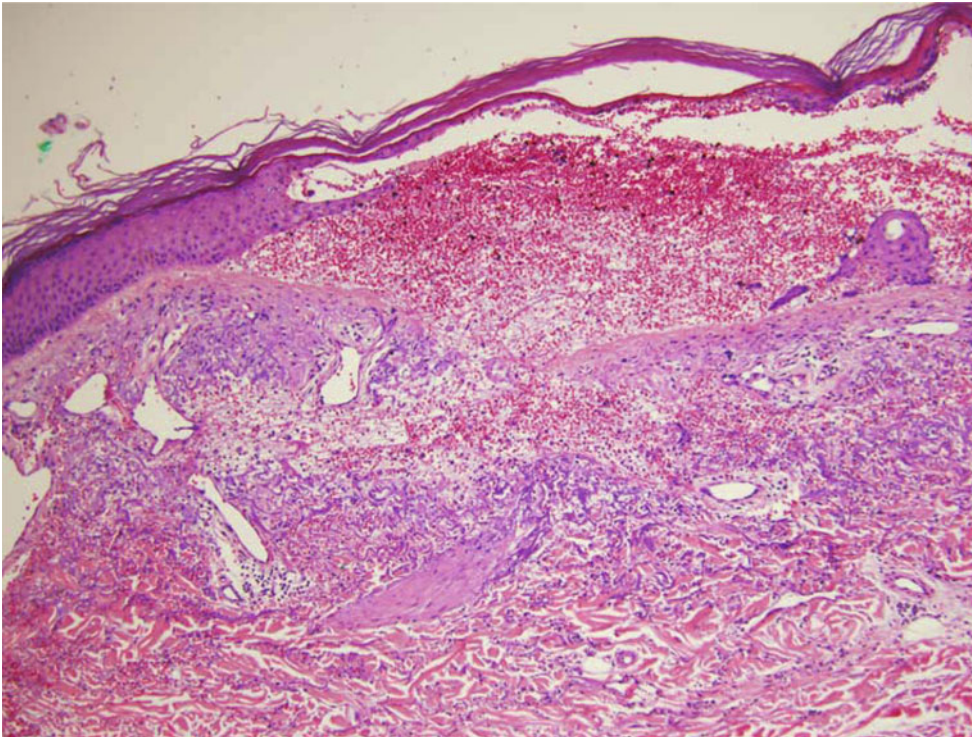
FIGURE 1.3. Medium-power photomicrograph depicting subtle proliferation of endothelial-lined dermal vascular channels.
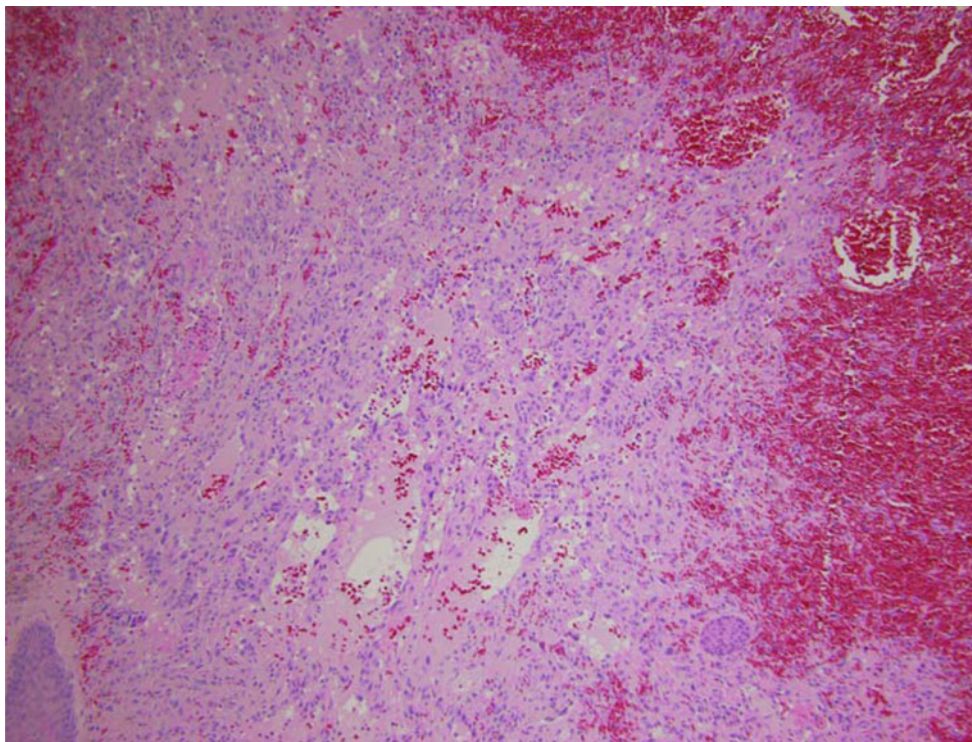
FIGURE 1.4. Medium-power photomicrograph depicting deeper dermis with gaping vascular channels lined by atypical hyperchromatic endothelial cells.

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.
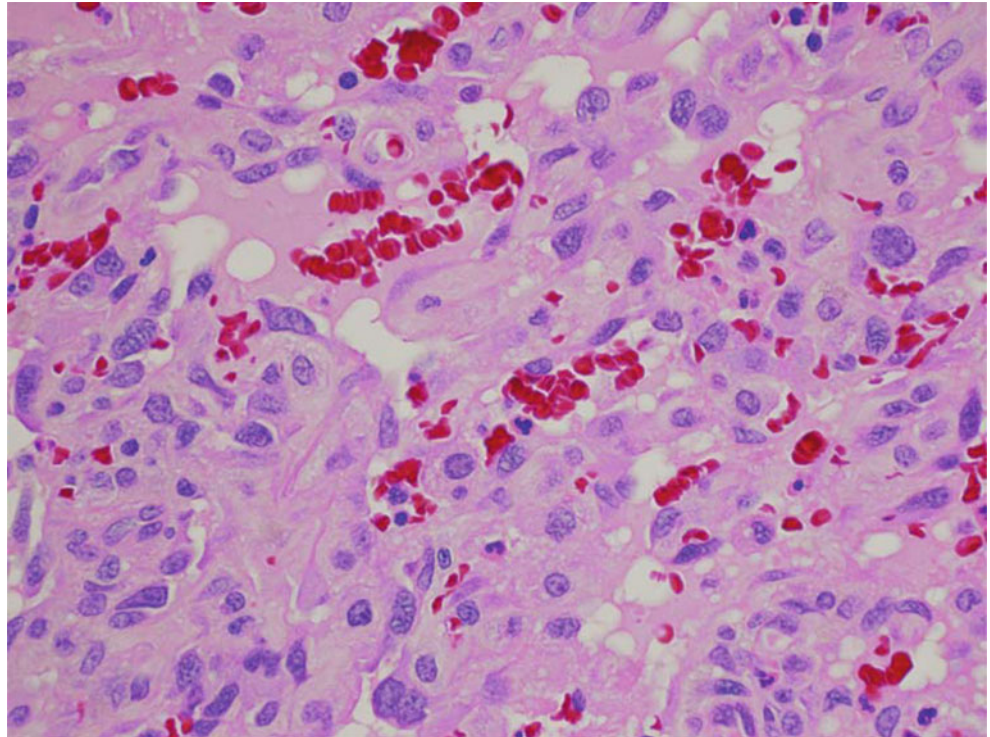
angioma (TA) and targetoid hemosiderotic hemangioma (THH), low-grade vascular tumors of intermediate prognosis such as epithelioid hemangioendothelioma (EHA) and Kaposi's sarcoma (KS), as well as malignant entities such as poorly differentiated carcinoma. THH consists of a superficial papillary dermal 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 intraop-*

erative 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

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 mm, 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 [9]. Due to the rarity of this tumor, there are no widely adopted standard protocols for therapy [9]. 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, paclitaxel, docetaxel, and vincristine, has been reported with varying success. The role of chemotherapy is not well defined and requires further investigation. Neoadjuvant chemotherapy may have a role in treating areas in which a wide margin excision is unobtainable [29]. Chemotherapy may help spare adnexal structures and the eye when the periorbital region is affected [29] or in few cases allow the avoidance of surgery all together, without decreasing disease-specific or overall survival rates. Even with the use of chemotherapeutic agents, recurrence remains problematic [29]. Recently, increasing evidence has grown for the potential value of paclitaxel in treating cAS and metastatic AS; this has caused a movement from the use of doxorubicin to paclitaxel [7, 39–41]. Multiple studies have shown paclitaxel to be efficacious when given on a low-dose weekly schedule [6, 7, 42]. Paclitaxel has also shown to be uniquely active in AS of the face and scalp [39, 41, 43]. Other studies have shown that response to paclitaxel may be short lived, only being efficacious for a few months before AS becomes resistant [44]. In metastatic AS, paclitaxel and doxorubicin have shown similar efficacy, leaving clinicians to choose treatment based on comorbidities of the particular patient. Other taxanes such as docetaxel have shown mixed results [44]. Studies from the Mayo Clinic and out of Europe have reported docetaxel to be rather ineffective in AS [45, 46].

Given that AS arises from endothelial cells of the vascular and lymphatics, antiangiogenic and anti-endothelial treatments have been suggested as a treatment option. Some drugs serving this pharmacologic action have been studied to include bevacizumab and sorafenib. In a phase II clinical trial, bevacizumab, which targets VEGF-A, was used alone to treat both metastatic and local advanced AS. Results were promising, as half of the patients had stable disease with a mean time to disease progression of 26 weeks [47]. Another phase II study is currently considering bevacizumab combined with other agents in the treatment of AS [48]. However it has been implicated that blocking VEGF-A alone is not adequate to stop disease. Drugs such as sorafenib, which inhibits KIT, FLT-3, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-B may serve a role in disease reduction and palliation [49, 50].

With current treatments disease control and survival remain poor. Further study of treatment modalities is necessary to fill the void in clinical knowledge regarding treatment modalities for AS. Anti-endothelial antibodies conjugated with cytotoxins and XRT radiosensitizers may serve a future role in AS treatment.

References

1. Cooper PH. Angiosarcomas of the skin. Semin Diagn Pathol. 1987;4(1):2–17.
2. Haustein UF. Angiosarcoma of the face and scalp. Int J Dermatol. 1991;30(12):851–6.
3. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol. 1998;22(6):683–97.
4. Albores-Saavedra J, et al. Cutaneous angiosarcoma. Analysis of 434 cases from the surveillance, epidemiology, and end results program, 1973–2007. Ann Diagn Pathol. 2011;15(2):93–7.
5. Antman KH, Eilber FR, Shiu MH. Soft tissue sarcomas: current trends in diagnosis and management. Curr Probl Cancer. 1989;13(6):337–67.
6. Fury MG, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005;11(3):241–7.
7. Penel N, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008;26(32):5269–74.
8. Aust MR, et al. Angiosarcomas of the head and neck: clinical and pathologic characteristics. Ann Otol Rhinol Laryngol. 1997;106(11):943–51.
9. Holden CA, Spittle MF, Jones EW. Angiosarcoma of the face and scalp, prognosis and treatment. Cancer. 1987;59(5):1046–57.
10. Mark RJ, et al. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer. 1996;77(11):2400–6.
11. Wanebo HJ, et al. Head and neck sarcoma: report of the head and neck sarcoma registry. Society of head and neck surgeons committee on research. Head Neck. 1992;14(1):1–7.
12. Weber RS, et al. Soft tissue sarcomas of the head and neck in adolescents and adults. Am J Surg. 1986;152(4):386–92.
13. Dettenborn T, et al. Prognostic features in angiosarcoma of the head and neck: a retrospective monocenter study. J Craniomaxillofac Surg. 2014;42(8):1623–8.
14. Morgan MB, et al. Cutaneous angiosarcoma: a case series with prognostic correlation. J Am Acad Dermatol. 2004;50(6):867–74.
15. Rouhani P, et al. Cutaneous soft tissue sarcoma incidence patterns in the U.S.: an analysis of 12,114 cases. Cancer. 2008;113(3):616–27.

16. Young RJ, et al. Angiosarcoma. Lancet Oncol. 2010;11(10):983–91.

17. Weiss SJ, Goldblum JR. Soft tissue tumors. St. Louis: C.V. Mosby Company; 2002.

18. Kacker C, et al. High frequency of MYC gene amplification is a common feature of radiation-induced sarcomas. Further results from EORTC STBSG TL 01/01. Genes Chromosomes Cancer. 2013;52(1):93–8.

19. Mitelman, F. Mitelman database of chromosome aberrations and gene fusions in cancer. 2014 [cited 2014 30 Nov 2014]; Available from: http://cgap.nci.nih.gov/Chromosomes/Mitelman.

20. Feller JK, Mahalingam M. c-myc and cutaneous vascular neoplasms. Am J Dermatopathol. 2013;35(3):364–9.

21. Manner J, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol. 2010;176(1):34–9.

22. Lee R, Saardi KM, Schwartz RA. Lymphedema-related angiogenic tumors and other malignancies. Clin Dermatol. 2014;32(5):616–20.

23. Lee RE, Micali G, Schwartz RA. Lymphedema. In: Treatment of skin disease: comprehensive therapeutic strategies. 4th ed. Philadelphia: Elsevier Limited; 2014. p. 423–4.

24. Duzgun S, et al. A cutaneous angiosarcoma arising from the rhinophyma. Kulak Burun Bogaz Ihtis Derg. 2013;23(6):344–7.

25. Lo Presti M, et al. Angiosarcoma mimicking rhinophyma. Dermatol Res Prac. 2010;2010:365173.

26. Leake J, et al. Angiosarcoma complicating xeroderma pigmentosum. Histopathology. 1992;21(2):179–81.

27. Ludolph-Hauser D, et al. Mast cells in an angiosarcoma complicating xeroderma pigmentosum in a 13-year-old girl. J Am Acad Dermatol. 2000;43(5 Pt 2):900–2.

28. Marcon I, et al. Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. Pediatr Hematol Oncol. 2004;21(1):23–6.

29. DeMartelaere SL, et al. Neoadjuvant chemotherapy-specific and overall treatment outcomes in patients with cutaneous angiosarcoma of the face with periorbital involvement. Head Neck. 2008;30(5):639–46.

30. Deyrup AT, et al. Sporadic cutaneous angiosarcomas: a proposal for risk stratification based on 69 cases. Am J Surg Pathol. 2008;32(1):72–7.

31. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer. 1981;48(8):1907–21.

32. Lydiatt WM, Shaha AR, Shah JP. Angiosarcoma of the head and neck. Am J Surg. 1994;168(5):451–4.

33. Cerroni L, et al. Angiosarcoma of the face and scalp. A case report with complete spontaneous regression. J Dermatol Surg Oncol. 1991;17(6):539–42.

34. Guadagnolo BA, et al. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. Head Neck. 2011;33(5):661–7.

35. Lahat G, et al. Angiosarcoma: clinical and molecular insights. Ann Surg. 2010;251(6):1098–106.

36. Penel N, et al. Prognostic factors for adult sarcomas of head and neck. Int J Oral Maxillofac Surg. 2008;37(5):428–32.

37. Pawlik TM, et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer. 2003;98(8):1716–26.

38. Perez MC, et al. Cutaneous angiosarcoma: a single-institution experience. Ann Surg Oncol. 2013;20(11):3391–7.

39. Casper ES, et al. Phase II trial of paclitaxel in patients with soft-tissue sarcoma. Cancer Invest. 1998;16(7):442–6.

40. Skubitz KM. A phase I study of ambulatory continuous infusion paclitaxel. Anticancer Drugs. 1997;8(9):823–8.

41. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer. 2005;104(2):361–6.

42. Italiano A, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer. 2012;118(13):3330–6.

43. Fata F, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86(10):2034–7.

44. Nagano T, et al. Docetaxel: a therapeutic option in the treatment of cutaneous angiosarcoma: report of 9 patients. Cancer. 2007;110(3):648–51.

45. Edmonson JH, et al. Phase II study of docetaxel in advanced soft tissue sarcomas. Am J Clin Oncol. 1996;19(6):574–6.

46. Verweij J, et al. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the european organization for research and treatment of cancer soft tissue and bone sarcoma group. J Clin Oncol. 2000;18(10):2081–6.

47. Agulnik M, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013;24(1):257–63.

48. De Yao JT, et al. Scalp angiosarcoma remission with bevacizumab and radiotherapy without surgery: a case report and review of the literature. Sarcoma. 2011;2011:160369.

49. Ono S, et al. Angiosarcoma of the scalp successfully treated with a single therapy of sorafenib. Arch Dermatol. 2012;148(6):683–5.

50. Wilhelm SM, et al. Preclinical overview of sorafenib, a multi-kinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008;7(10):3129–40.

2

Life-threatening Lymphomas and Leukemias with Prominent Cutaneous Involvement

2.1 Primary Cutaneous Gamma–Delta T-Cell Lymphoma

David R. Crowe

Primary cutaneous gamma–delta T-cell lymphoma (PCGDTCL) is a rare condition, the details of which have come into focus in dermatologic and oncologic literature in the last 25 years. The effector cell is an activated gamma–delta T cell with a cytotoxic phenotype. This entity represents 1 % of cutaneous T-cell lymphomas and 10 % of peripheral T-cell lymphomas. It is classified as a provisional entity in the category of peripheral T-cell lymphomas, unspecified by the World Health Organization and European Organisation for Research and Treatment of Cancer (WHO-EORTC) [1]. Unfortunately, those stricken with this disorder have a poor prognosis, with rapid progression of disease and average survival of 15 months [2].

Gamma–delta T cells compose 3–6 % of peripheral blood lymphocytes. They represent 30 % of splenic T cells and preferentially accumulate in the skin, mucosa, and the GI tract. They are markedly cytotoxic and phagocytic. They are thought to represent a bridge between antimicrobial and antitumor cells and are sometimes referred to as "natural T cells" given their likeness to natural killer cells in some respects. Target recognition of gamma–delta T cells is not restricted by MHC molecules (unlike their alpha–beta counterparts), but instead hone in on altered cellular homeostasis. In their natural state, they are strong tumor-infiltrating cells for multiple solid malignant neoplasms, causing lysis of autologous tumor cells. They are also strongly antiviral, particularly in HIV [3]. Gamma–delta T cells are generally not found to represent greater than 10 % of lymphocytic infiltrates of other inflammatory or neoplastic disorders of the skin [4]. Hepatosplenic T-cell lymphoma is another peripheral T-cell lymphoma characterized by malignant transformation of gamma–delta T-cells, often in the context of immunosuppression. Similar to PCGDTCL, it is rapidly progressive and unresponsive to chemotherapy [5]. Primary lymphomas of gamma–delta cell derivation can also arise in the intestines, thyroid, nasal mucosa, and respiratory tract.

Clinical findings are variable but are notable for certain trends. Age of occurrence is usually in the fifth to seventh decade of life, occurring with a 2:1 male predominance.

Clinical lesions are often extremity-predominant, most often found on the legs (75 %), although the torso is involved in 30 % of patients. Preferential involvement of the subcutis results in deep violaceous plaques resembling panniculitis which occurs in 60–70 % of patients. Presentation can, less commonly, resemble psoriasis or mycosis fungoides (MF) with more superficial histologic findings (20–30 % of cases). Ulceration is common regardless of clinical appearance (50 %) [2, 5–7].

Associated signs and symptoms of disease are important to note. Constitutional symptoms, including fevers, night sweats, and weight loss, can occur in more than half of patients. Lymphadenopathy and histologic lymph node involvement are uncommon, occurring in approximately 10 % of patients. Lactate dehydrogenase (LDH) was found to be elevated in 55 % of one large series of patients with PCGDTCL [6]. Hemophagocytic syndrome is rare but can cause pancytopenia and hasten death. The ability of gamma–delta T cells to suppress hematopoiesis (likely by elaboration of IFN-gamma) may worsen myelosuppression [8]. Central nervous syndrome involvement is another poor prognostic sign. This occurred in 6 % of a series of 53 patients, with variable presentation including blurred vision, diplopia due to cranial nerve palsy, Bell's palsy, dysarthria, and ataxia, depending on the site of involvement [6, 9]. Dissemination to the nasopharynx, intestine, thyroid, lung, breast, and testes can also occur. Primary and disseminated disease can be seen on positron emission tomography–computed tomography in 50 % of cases [6].

Despite differing clinical features, it is important to note that histopathologic infiltrates of lymphocytes in PCGDTCL can be epidermotropic, dermal, and/or subcutaneous in the same patient or the same clinical lesion. Individual lymphocytes are medium sized with slightly granular cytoplasm and nuclear pleomorphism. Typical cerebriform nuclei of mycosis fungoides are not present. Malignant lymphocytes are usually CD2+, CD3+, and CD7+, with positivity to markers of cytotoxicity (TIA-1, granzyme B, and perforin). Granzyme B positivity in particular may be a poor prognostic marker [6, 9]. While most cases of PCGDTCL are noted to be "double negative" for CD4 and CD8, some cases showing CD8 positivity have been noted. CD56 positivity is occasionally noted, usually with panniculitis-like clinical features or in patients with nasal mucosa infiltration. In comparison with alpha–beta

panniculitis-like T-cell lymphoma, PCGDTCL has more varied histology in terms of cellular morphology, with more superficial spread of tumor cells [2, 7]. Staining for Epstein–Barr virus (EBV) is usually negative, occurring in <8 % of cases [6]. Staining for T-cell receptor (TCR) gamma-1 is positive, and staining for T-cell receptor beta is not positive to a significant extent. Clonal rearrangement is observed for both TCR-gamma and TCR-delta.

Despite overall tendency toward poor prognosis in gamma–delta T-cell lymphoma, cases with indolent courses have been described. Among eight patients considered to have indolent disease, 88 % were female, none had hemophagocytic lymphohistiocytosis, 75 % had onset in the third to fifth decade of life, and although 43 % eventually died from their disease, response to therapy was favorable. Histopathology was notable for a trend toward mild lymphocyte atypia and the lack of findings of hemophagocytic cells. Otherwise, staining patterns were similar to those reported in typical cases of gamma–delta T-cell lymphoma, with negativity for CD4 and CD8 and positivity for cytolytic proteins [10].

Initial staging of disease should include full-skin examination, PET-CT scan, and bone marrow biopsy, in particular if pancytopenia is noted. Guidelines for TNM staging are easily accessible, and extent of disease on the skin (solitary, regional, generalized) as well as the presence of lymphadenopathy should be carefully documented [11]. Treatment strategies have included combination chemotherapy, interferon therapy, photochemotherapy, topical nitrogen mustard, and radiotherapy [12]. No consistently useful treatment options have emerged that will significantly prolong survival. Bexarotene has been advocated as an adjuvant treatment option in selected patients [13]. Some advocate for early prednisone treatment followed by doxorubicin-based combination chemotherapy (CHOP). Others note impressive response (92 % complete remission) to high-dose chemotherapy followed by stem cell transplant for a combination of patients with alpha–beta and (likely) gamma–delta T-cell lymphoma [14]. Rates of response are likely inflated, as multiple studies were performed prior to the clinicopathologic delineation between alpha–beta and gamma–delta lymphomas.

2.2   Hydroa Vacciniforme-Like Cutaneous T-Cell Lymphoma

David R. Crowe

Hydroa vacciniforme-like cutaneous T-cell lymphoma (HVCTCL) is a lymphoproliferative disorder which occurs predominantly in children and has a close relationship to chronic Epstein–Barr virus (EBV) infection and idiopathic hydroa vacciniforme (HV). Ruiz-Maldonado et al. described

14 children with a chronic condition which was referred to as "edematous, scarring vasculitic panniculitis" in 1995, which likely represented early descriptions of HVCTCL [15]. After more detailed analysis, HVCTCL was initially grouped with NK/T-cell lymphoma, nasal type, although more recently (2008) had been reclassified by the World Health Organization as an EBV-associated lymphoproliferative disorder of childhood in the broad category of peripheral T-cell lymphoma, unspecified [16]. Prognosis is variable. Some cases exhibit a chronic, relapsing and remitting, but ultimately indolent course. Other patients exhibit a rapid downward spiral to death within months of diagnosis.

Pathogenesis of both hydroa vacciniforme and HVCTCL is tied closely to the activity of EBV. EBV DNA is invariably found in the blood in those with both conditions, and RNA is found in the infiltrating lymphocytes and sometimes the keratinocytes of lesional skin. Evidence of EBV is occasionally found in other types of cutaneous lymphoproliferative conditions, including angiocentric CD56+ lymphomas and subcutaneous T-cell lymphomas in which hemophagocytosis is present [3, 9]. EBV-encoded gene products such as EBV-determined nuclear antigen-1 (EBNA-1) and latent membrane proteins (LMP-1 in particular) likely play a role in malignant transformation in EBV-associated T-cell lymphomas. These proteins are highly expressed in the "Latency II" pattern of gene expression and are also implicated in EBV-associated nasopharyngeal carcinoma in China and Hodgkin disease [17]. The infected and likely pathologic cell in most cases of HVCTCL is the CD8+ cytotoxic T cell. Cells of pathologic significance in severe mosquito-bite hypersensitivity and when both mosquito-bite hypersensitivity and HVCTCL are present are more likely to be NK cells [18].

Cutaneous findings are similar to severe cases of hydroa vacciniforme, and many believe the two disorders exist on a spectrum. Hydroa vacciniforme presents with vesiculobullous lesions occurring in sites of sun exposure, particularly the face, ears, and forearms. Lesions resolve with prominent cribriform scarring reminiscent of the remnants of vaccinia. Compared to HV, HVCTCL exhibits individual lesions which are persistent, ulcerative, and necrotic, with distribution in both sun-exposed and sun-protected sites. Transition of classic HV, to severe HV, to HVCTCL can take 2–10 years, although a stepwise progression is not always seen. Overt sun sensitivity does not accompany HVCTCL. Prominent facial edema, often involving the periorbital area and the lips, commonly accompanies lesions. Tendency for hypersensitivity to arthropod bites has been noted in many patients. Unlike HV, HVCTCL often worsens with age. Monoclonality of T-cell receptor gene rearrangement studies can be helpful in differentiating the two entities in borderline cases. Serum studies of EBV activity reveal findings of chronic active EBV infection, with high titers of viral capsid antigen IgG (VCA-IgG) in most patients [19].

The histologic epidermal findings are variable and nonspecific, often including features such as parakeratosis, spongiosis,

epidermotropic lymphocytes (rare), acanthosis, and necrosis. Dense diffuse lymphocytic infiltrates involving the dermis and occasionally the subcutis are a commonly found histologic feature. Nerves and adnexa are usually surrounded by neoplastic cells. Perivascular or intravascular angiotropism is almost always seen [20, 21]. A portion of the infiltrating lymphocytes are large in size with pleomorphic, medium-sized nuclei and multiple mitotic figures. Immunohistochemistry reveals universal staining for EBV RNA (EBER-1). Cell type is thought to be cytotoxic T cells, as most patients reveal CD3 and CD8+ cells, with alpha–beta T-cell receptors (TCR) being found much more commonly than gamma–delta receptors. CD56 positivity occurs in a minority of patients (in the absence of CD8) indicating NK-cell lineage. CD56 positivity was present in a group of four patients with relatively indolent disease course [19]. In a larger case series of 21 patients, 27 % were CD56+ and 70 % exhibited T-cell phenotype. Of those of T-cell lineage, 86 % showed alpha–beta TCR and 14 % showed gamma–delta TCR [22]. CD30 positivity in a large number of cells occurs with some frequency, more often when the primary infiltrating cell is CD56+. Markers of cytotoxicity including TIA-1, granzyme B, and perforin are usually positive [23]. High levels of Ki-67 expression can be a marker of poor prognosis [24].

Prognosis is guarded but can be quite variable. Combining the results of multiple case series, the mortality rate is approximately 50 %, although follow-up data is incomplete on many patients [15, 17–22, 24]. Cause of death can be related to either septicemia or hemophagocytic syndrome, although renal and respiratory insufficiencies were often contributing factors. It is also likely that mortality rate is inflated due to delayed diagnosis in more indolent cases, which are often carried as "severe HV" for years. Interestingly, patients with HVCTCL from the western hemisphere (Central and South America) seem to have a worse prognosis (approximately 50–60 % mortality) than those from India, China, or Japan (15–20 % mortality). Combination chemotherapy does not seem to improve survival for most patients, although immunomodulation with treatments such as thalidomide may result in partial control of disease [22]. The rarity of this condition makes any statement on treatment efficacy difficult to justify.

2.3 Primary Cutaneous Aggressive Epidermotropic CD8+ CTCL

Michael B. Morgan and Brianna Castillo

Primary cutaneous aggressive epidermotropic (PCAE) CD8-positive cutaneous T-cell lymphoma (CTCL), alternatively referred to as primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphoma, is a rare cutaneous variant of cutaneous T-cell lymphoma (CTCL). The World Health Organization and European Organisation for Research and Treatment of Cancer (WHO-EORTC) has recognized it as a provisional entity within the realm of primary cutaneous peripheral T-cell lymphomas.

According to the WHO-EORTC organizations, PCAE represents less than one percent of CTCL cases. Patients with this disease are predominantly elderly males but can be adults of either sex.

The typical clinical presentation of patients with PCAE consists of local or widely distributed erythematous papules, nodules, and tumors with central necrosis and ulceration, with a tendency for acral accentuation. Patients typically develop stigmata precipitously, unlike the indolent development of conventional CTCL/mycosis fungoides (MF). Despite the marked difference in initial clinical presentation, both forms of conventional CTCL may eventuate similarly to PCAE with late-stage multicentric plaques and tumors. Unlike the typical and predictable spread of conventional CTCL from the skin to the lymph nodes, PCAE often progress unpredictably and rapidly to the central nervous system, mucosa, lung, and testes without eventuating lymph nodal involvement. Rare additional manifestations that have been reported include pyogenic gangrenosum-like lesions, erythema marginatum-like lesions, and hemorrhagic and nonhemorrhagic bullae. Alternatively, PCAE can uncommonly present as acral accentuated superficial hyperkeratotic patches and plaques, similar to the aggressive form of pagetoid reticulosis, Ketron–Goodman type.

Histologically, the lesions of PCAE show marked epidermotropism of cytologically atypical lymphocytes with irregular enlarged hyperchromatic nuclei involving foci just beneath and within the basal keratinocyte layer or forming coalesced aggregates within the stratum malpighi (Pautrier's abscesses). These abscesses can be round, oval, or potentially irregular and often are more conspicuous than Pautrier's abscesses of epidermotropic stimulants such as pagetoid reticulosis. Like conventional CTCL, the atypical lymphocytes are often surrounded by intercellular edema producing an intercellular halo effect [25]. The latter feature is helpful in separating all forms of CTCL from reactive conditions that masquerade as such, including allergic contact dermatitis. Similar to all forms of cutaneous T-cell lymphoma is the single-cell scatter of atypical lymphocytes within the epithelium, alternatively referred to as pagetoid spread. In distinction, however this pagetoid scatter of atypical lymphocytes is often accompanied by necrotic keratinocytes within the epidermis, which can be acanthotic or atrophic, with occasional evidence of blister formation in PCAE. Dermal changes can provide an additional and important means of distinguishing this entity from other forms of CTCL including pagetoid reticulosis. Nodular or diffuse lymphocytic extension deep into the dermis as well as the subcutaneous fat may be

observed. Typical of this aggressive disease process is angioinvasion or angiocentricity and destruction of adnexal skin structures which would be an exceptional finding in conventional CTCL. Unlike other forms of angioinvasive T-cell lymphomas such as nasal and NK/T-cell lymphoma, epidermotropism is maintained in PCAE [26]. The subcutaneous fat extension as seen in this entity can be confused with subcutaneous panniculitis-like T-cell lymphoma (SPTCL); however, the latter entity typically shows characteristic rimming of adipocyte cells and the lack of epidermotropism not seen in PCAE [27].

The cells of PCAE are consistently positive for CD8 and negative for CD4 T-lymphocyte markers. In addition, these atypical cells are positive for conventional T-cell markers such as CD3 with lesser expression of CD5, CD2, and CD7, typical of both this entity and other forms of CTCL. Additional immunohistochemical markers that may differentiate this form of CTCL include immunopositivity to cytotoxic markers BF1, granzyme B, TIA-1, and CD45RA. Proliferative markers such as Ki-67 or PCNA would be increased in this in distinction to more indolent forms of conventional CTCL. B-cell markers such as CD20, CD45RO, and the natural killer and NK/T marker CD56 are typically negative. CD8 immunopositivity is not exclusive to PCAE as other forms of epidermotropic cutaneous T-cell lymphoproliferative disorders and includes (1) pagetoid reticulosis that typically shows immunopositivity to CD4 or dual immunopositivity with both CD4 and CD8, (2) the hypopigmented variant of CTCL that is more common in patients with skin of color and can be as often seen in childhood as with adults, (3) and a recently described provisional entity that presented with isolated ear or other facial lesions and pursued an indolent course [28].

The diagnosis of PCAE is based on a combination of clinical, histopathological, and immunophenotypic features. Given its aggressive nature, higher tendency to metastasize to extranodal sites, and poor prognosis of this disease, it is imperative to avoid delays in its diagnosis. For this reason, PCAE should be considered in the differential diagnosis of the more commonly suspected tumor stage of mycosis fungoides, which has very similar clinical and histopathological features, but runs a more indolent course. The two diseases can be virtually indistinguishable and difficult to differentiate. Therefore, immunophenotyping is invaluable in establishing a diagnosis.

Additional diagnostic adjuncts such as T-cell surface receptor clonal analysis fail to provide helpful information as clonal rearrangement of the most commonly rearranged (β) subunit of the T-cell receptor is typically positive in all forms of CTCL with the exception of the extremely uncommon γ/δ form of CTCL that typically lacks this rearrangement. PCR or serologic analysis of viral agents such as Epstein–Barr virus is negative in this and other forms of CTCL with the exception of NK/T lymphoma.

The rarity of this neoplasm and the lack of clinical trials render generalizations regarding therapeutic options difficult. However, case reports and a single series suggest that therapies including interferon alpha may actually worsen the disease and contribute to its rapid progression. Encouraging results have been reported with the combination of total skin electron beam irradiation and an oral retinoid as first-line therapy. However, long-term remission with this treatment has not been documented. Doxorubicin-based polychemotherapy regimens such as cyclophosphamide, doxorubicin, Oncovin, and prednisone (CHOP) are often used. There has also been some success with hyper-cyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) chemotherapy. Treatment failure unfortunately has been reported with all these regimens, a testament to its aggressive nature.

Primary cutaneous aggressive epidermotropic CD8+ CTCL has a very poor prognosis, with a median survival in the range of 22.5–32 months. This prognosis may be due to consequential delay in diagnosis due to limited awareness of the disease and the aggressive behavior of the disease itself, its poor response to treatment, and its high tendency for metastasis. Systemic involvement, angiocentricity, angioinvasion, and the expression of CD56, CD15, and CD2+/CD7- may be associated with an even poorer prognosis.

2.4 Sézary Syndrome

Michael B. Morgan and Brianna Castillo

Sézary syndrome (SS) is a rare and aggressive leukemic form of cutaneous T-cell lymphoma (CTCL)/mycosis fungoides MF that has classically been defined by the presence of erythroderma, lymphadenopathy, and atypical lymphocytes ("Sézary cells") in the lymph nodes, in the skin, and in circulation [29]. It most commonly arises de novo from a distinct subset of memory T cells than does mycosis fungoides (MF) but may rarely arise from preexisting MF [30]. The presence of large numbers of circulating Sézary cells distinguishes SS from other erythrodermic forms of CTCL.

SS is rare and accounts for a minority of CTCL, which itself represents 3.9 % of all non-Hodgkin's lymphoma. CTCL generally affects adults over the age of 60, and men are more commonly affected than women. In the United States, about 70 % of patients with SS are white, while blacks (14 %), Hispanics (9 %), and Asians (7 %) are affected less commonly.

Clinically, SS is characterized by intensely pruritic erythroderma. Erythroderma, which is an intense and widespread inflammatory reddening of the skin, may be associated with exfoliation, edema, and lichenification. Other common clinical features include lymphadenopathy, alopecia, palmo-

plantar hyperkeratosis, and onychodystrophy. The intense pruritus is often resistant to treatment, thereby resulting in significant morbidity.

The histologic changes seen in SS are variable and often nonspecific. 20–40 % of cases demonstrate confinement of the atypical lymphocytes within the epidermis (epidermotropism), but the most common finding is an infiltrate of atypical lymphocytes within the superficial dermal capillaries or situated in perivascular locales within the papillary dermis [31]. These atypical lymphocytes possess enlarged hyperchromatic nuclei similar to conventional CTCL yet in a minority of cases demonstrate exaggerated nuclear membrane ridges or convolutions, referred to as "cerebriform" nuclei. Clusters of these within the epidermis, known as Pautrier's microabscesses, are present in approximately half of the epidermotropic cases. Additional infiltrate of eosinophils and plasma cells may also be present. Although these findings are similar to those of patch-stage MF, psoriasiform acanthosis and Pautrier's microabscesses are more commonly seen in SS than MF. Edema is often present in early lesions and may gradually be replaced by fibrosis of the papillary dermis. As seen in other causes of erythroderma, the loss of superficial epithelium (stratum corneum) may be seen in the exfoliative stage of the disease along with dilated dermal capillaries possessing prominent endothelium.

Due to similarities between Sézary cells of SS and atypical cells present in some nonmalignant inflammatory skin diseases, immunophenotyping and determination of T-cell clonality is an integral part of the diagnosis and management of SS. The neoplastic cells are a mature T-helper phenotype and most often demonstrate the following immunophenotype: CD2+, CD3+, CD4+, CD5+, CD45RO+, and CD30−. Classically, the neoplastic cells have been considered to be CD7− and CD26−, although there can be CD7 variability even within a single patient. Additionally, the loss of CD2 and CD5 can be seen with disease progression, and the loss of these or other T-cell antigens such as CD3 or CD4 may be seen in two-thirds of patients with SS. The diagnostic picture is further complicated by reports of CD8+ variants of SS as well as the well-documented occurrence of CD7− and CD26− cells in benign inflammatory dermatoses. Despite these reports, expansion of the CD4+ population is a commonly cited criterion for the diagnosis of SS, and a CD26- subset exceeding 30 % of the CD4+ population is considered diagnostic of SS by some authors.

Although immunophenotyping can strengthen suspicion of SS in the appropriate clinical context, demonstration of the same dominant T-cell clone within the skin and circulation can confirm the diagnosis by helping to separate SS from benign dermatoses and possibly aid in monitoring treatment response. This is accomplished by detection of α/β or γ/δ T-cell receptor (TCR) gene

rearrangements with either Southern blot or polymerase chain reaction methods, the latter of which has demonstrated greater sensitivity and specificity.

An indispensable diagnostic adjunct in the confirmation of SS is flow cytometry (FC). FC allows for the determination of cellular size and binding of specific cell surface antibodies. The technology basically involves isolating the patient's white blood cells and eluting them in a single-cell fashion into chamber that interacts with a laser light producing scatter plots of cellular size (forward) and binding of cellular surface monoclonal antibodies (side) scatter. These scatter plots allow for the determination of clonal (similar)-sized populations of lymphocytes that can then be isolated and analyzed for the presence or absence of specific cell surface cluster designation (CD) lymphocyte markers (e.g., CD4, CD8).

Due to clinical and histological similarities, differentiating SS from other erythrodermic diseases is often difficult. Included in the differential are other malignant processes such as erythrodermic MF and adult T-cell leukemia/lymphoma (ATLL) and nonmalignant erythrodermic diseases such as psoriasis, pityriasis rubra pilaris, contact dermatitis, and atopic dermatitis. Less likely causes of erythroderma include graft-versus-host disease, drug reactions, Norwegian scabies, paraneoplastic erythroderma, and idiopathic erythroderma. Histologically, nondiagnostic findings such as spongiotic or psoriasiform acanthosis are common, while only a minority of cases demonstrate diagnostically specific findings such as epidermotropism of atypical lymphocytes and Pautrier's microabscesses. Examination of peripheral blood is therefore critical to arriving at a diagnosis but still must be interpreted with caution because many peripheral blood findings in SS are shared with benign erythrodermic dermatoses.

In the appropriate clinical context, the International Society for Cutaneous Lymphoma (ISCL) recommends that a diagnosis of SS be primarily based on the demonstration of one or more of the following:

Absolute Sézary cell count of 1000/μL or greater
Expanded CD4+ T-lymphocyte population, resulting in a CD4/CD8 ratio greater than ten
Loss of T-cell antigens such as CD2, CD3, CD4, CD5, CD7, and CD26
Molecular or cytogenetic demonstration of a dominant T-cell clone in the peripheral blood

Although these findings can significantly increase diagnostic confidence in patients with consistent skin histology, they should be interpreted with caution when skin histology is nonspecific. Elevation of the CD4/CD8 ratio, for example, may be seen in patients with benign inflammatory erythroderma. Additionally, some studies have demonstrated that peripheral blood T-cell clonality is more common in patients with benign erythroderma than in

patients with SS. Immunophenotyping and demonstration of T-cell clonality are therefore more diagnostically informative when findings are consistent between the skin and peripheral blood.

SS is a leukemic disease and therefore requires systemic treatment, but skin-directed therapies are often used as adjuvant therapy. Due to the immunosuppression that occurs in patients with SS, treatments are aimed not only at destruction of malignant T-cells but also at preservation and reconstruction of the immune system. Despite advances in the understanding of SS and the development of targeted therapies, prognosis remains poor without a demonstrable impact upon survival or consensus in terms of recommended therapy. The median survival is 2.5–5 years, and most authors maintain that treatment is primarily palliative with emphasis on maintenance of quality of life and immune function.

Extracorporeal photopheresis (ECP), either alone or in combination with other therapies, appears to be one of the most effective and well-tolerated therapies, but response rates vary widely. Overall response rates are approximately 35–75 %, and complete response rates are approximately 14–26 %. Response rates are reportedly increased by combination with immunostimulatory therapies such as IFN-α. The European Organisation for Research and Treatment of Cancer (EORTC) recommended first-line treatments which include ECP, IFN-α, denileukin diftitox (targets the IL-2α receptor expressed by some malignant T cells of CTCL), and chlorambucil plus prednisone [32]. Second-line therapies recommended by the EORTC include the retinoid bexarotene, multidrug chemotherapy regimens, targeted therapy with the anti-CD52 drug alemtuzumab, and methotrexate. Studies have also reported responses to histone deacetylase inhibitors such as vorinostat and romidepsin [33]. Hematopoietic stem cell transplantation shows high response rates, but relapses occur rapidly with autologous transplants, and allogenic transplants result in significant treatment-related mortality in approximately 30 % of patients.

2.5 Intravascular Large B-Cell Lymphoma

Stephen C. Somach

Intravascular large B-cell lymphoma is an aggressive systemic intravascular non-Hodgkin's lymphoma which was first reported as "angioendotheliomatosis proliferans systemisata" by Pfleger and Tappeiner in 1959. At that time it was suspected to be of endothelial origin [34]. Its true nature as a B-cell lymphoma was highlighted in the 1980s [35], and since then it has been classified as intravascular

large B-cell lymphoma (IVLBCL) by the WHO-EORTC classification of cutaneous lymphomas [1].

Patients with IVLBCL present with protean manifestations, which frequently results in delayed diagnosis, often postmortem. While there may be multi-organ involvement, unlike other lymphomas, circulating blood and lymph nodes are usually do not have detectable disease, and marrow involvement may not be seen. The disease more frequently manifests as nonspecific symptoms such as fever, weight loss, fatigue, and neurological and skin changes, which suggest a broad differential diagnosis, including infection and autoimmune diseases. There are two forms of the disease, often called "Asian" and "Western." The Asian presentation is characterized by high incidence of fever, hemophagocytosis, and hepatic, splenic, marrow, and pulmonary involvement, with anemia, thrombocytopenia, and elevated liver enzymes and bilirubin. The Western form has a high incidence of skin involvement and neurologic symptoms. Methodical review of Asian cases has revealed that those unassociated with hemophagocytosis have clinical characteristics which are not significantly different from Western cases, suggesting that future classification may include hemophagocytosis-associated IVLBCL and classical IVLBCL [36]. Some cases of IVLBCL arise in association with antecedent indolent lymphomas [37].

Cutaneous manifestations of IVLBCL include induration, erythema, violaceous plaques or nodules which may ulcerate, telangiectasia or superficial venous ectasia and congestion, and edema of the legs (Fig. 2.1) [38, 39]. Favored areas of involvement include the arms, thighs, legs, lower abdomen, breasts, and sub-mammary areas. In rare instances, the disease may present as a changing cutaneous hemangioma due to lymphomatous vascular congestion [40]. Neurologic symptoms are also varied and include altered mental status, seizures, tremor, gait disturbance, and localizing neurologic deficits [37].

Diagnosis of IVLBCL is usually made by observing lymphoma cells in small vessels of involved tissues. Given the high incidence of microscopic skin involvement, random skin biopsy has been advocated for diagnosis. When compared with bone marrow biopsy, skin biopsy detected 10 of 12 cases, and bone marrow biopsy detected only half. With the addition of the marrow smear and flow cytometry, 11 of 12 cases were detected [41]. The malignant cells are large lymphocytes displaying large nucleoli and expressing CD20 (Fig. 2.2). Some cells aberrantly express CD5. Many harbor cytogenetic abnormalities, but characteristic ones are not identified [37].

Not all intravascular lymphomas are B-cell lymphomas. There are rare NK- and T-cell lymphomas that may have an intravascular presentation. These are usually highly aggressive and tend to express cytotoxic markers and harbor Epstein–Barr virus. Skin presentations are common [42]. A rare form of aggressive intravascular lymphoma is

both HHV-8- and EBV-positive and partially expresses both T- and B-cell markers. Some of these patients are HIV-infected. It has been suggested that this represents a purely intravascular form of primary effusion lymphoma [43]. There is also a recently described intralymphatic CD30+ lymphoproliferative disease which may mimic IVLBCL microscopically, but unlike IVLBCL, this tends to be an indolent disease [44]. A case of intravascular CD30-positive atypical T-cell proliferation following trauma has been described, with a benign clinical course [45].

FIGURE 2.1. Diffuse induration of trunk with patchy erythema and prominent telangiectasia (Photo courtesy of Maren Locke, MD).

Prognosis in patients with IVLBCL is poor. Combination anthracycline-containing chemotherapy has been used with complete response rates of approximately 50 % and 2-year survival of just under 50 %. The addition of rituximab to these regimens has increased the complete response rate to 82 % and 2-year survival to 66 % in one study [46]. Given high rates of CNS involvement in IVLBCL, intrathecal methotrexate should be considered as an additional induction agent [47]. Autologous bone marrow transplantation has been undertaken in some cases of IVLBCL and may play a larger future role as consolidation therapy [47].

IVLBCL is a rare aggressive non-Hodgkin's lymphoma which may have a prominent cutaneous presentation. An awareness of this entity along with its manifestations can often secure the diagnosis with a simple skin biopsy.

2.6 Blastic Plasmacytoid Dendritic Cell Neoplasm

Stephen C. Somach

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a highly aggressive lymphoma/leukemia which most often presents with cutaneous involvement. Ambiguity and heterogeneity in cell surface markers have obscured the classification of this disease. It has been labeled in the past as blastic NK lymphoma, agranular CD4+ natural killer cell leukemia, blastic natural killer leukemia/lymphoma, and agranular CD4+/CD56+ hematodermic neoplasm. Its current classification was established in the WHO classification from 2008, in which it is listed under the category of acute myelogenous leukemia and related
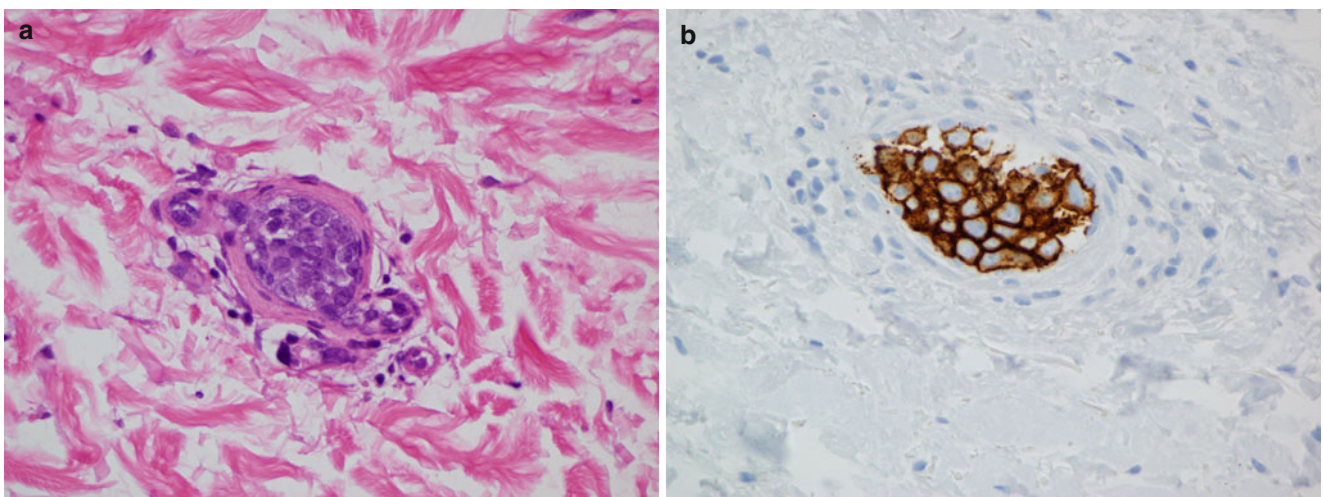
FIGURE 2.2. (**a**, **b** are side by side in one panel). Dermal vessels are congested with atypical lymphocytes with prominent nucleoli. These cells express CD20 (*right panel*).

precursor neoplasms [48]. The putative cell of origin is the plasmacytoid dendritic cell, a cell which may arise from either myeloid or lymphoid precursors. Gene expression profiling has established that lesional cells of BPDCN closely correspond to myeloid-derived resting plasmacytoid dendritic cells. However, they differ from this population in their overactivation of genes which may have relevance in malignant biologic behavior, including anti-apoptotic factor *BCL2*, cell cycle regulator *CCND1*, and interferon regulatory factor *IRF4* [49].

The large majority of patients with BPDCN have cutaneous presentations preceding or concurrent with leukemic dissemination. Skin disease commencing after systemic involvement is uncommon. In one series of 90 patients presenting with skin disease, there was an average age of 67 years with a male predominance. Children were occasionally affected. One-third of patients had no evidence of disease elsewhere at initial evaluation. Two-thirds had bone marrow, lymph node, or blood involvement. Systemic involvement is frequently manifested as cytopenias, particularly thrombocytopenia [48]. Approximately one-half of patients in the noted series presented with only one or two violaceous nodules. The pattern of presentation was nodule/s (73 %), violaceous "bruise-like" patches (12 %), or a combined morphology in 14 % (Fig. 2.3). Mucosal involvement was noted in 6 %. Central nervous system involvement is generally meningeal and may be seen in approximately 10 % of patients. It has been suggested that this may represent a harbor for malignant cells responsible for relapse after treatment. It was also noted that while the presentation with multiple cutaneous lesions was more likely to indicate systemic involvement at the time of diagnosis, the type of cutaneous presentation and even whether or not there was leukemic dissemination at presentation did not have a significant impact on prognosis [50]. An association with myeloid lineage is highlighted by the observation that 5–20 % of patients with BPDCN may develop or have a history of myeloid leukemia or myelodysplastic syndrome [51].

Diagnosis of BPDCN is most frequently made by skin biopsy, using morphology along with a typical immunohistochemical profile. Tumor cells are medium-sized blast-appearing cells with slightly irregular nuclear contours, fine chromatin, small nucleolus, and scant cytoplasm which is agranular (Fig. 2.4) [48, 51]. The epidermis is usually spared, and generally necrosis and vascular destruction are not seen. The subcutis is often involved [48]. Tumor cells frequently express CD4, CD56, CD123, TCL1, and CD303 (BDCA-2, or blood dendritic cell antigen-2, a maturation marker in plasmacytoid dendritic cells). Based upon a clinico-immunohistochemical study of 91 patients, it has been suggested that tumor labeling by four of these five markers secures the diagnosis of BPDCN. If only CD4, CD56, and CD123 are positive, it is important to evaluate for other myeloid marker expressions as these three may be expressed by some myeloid leukemias. In this series, the lack of CD4 and CD56 expression occurred occasionally, but in no case was expression of both lacking. Expression of CD303 and more prominent expression of Ki-67 correlated with better prognosis. It was suggested that those more mitotically active tumors as indicated by a higher level of Ki-67 expression may be more susceptible to antimitotic chemotherapy [52]. Two-thirds of tumors have an abnormal karyotype, and chromosomes 5, 9, 12, 13, and 15 are most affected [51]. Biallelic locus 9p21.3 deletion is associated with poor clinical outcome [53].

Combination chemotherapy for BPDCN has been used with limited success and generally associated with short-term remissions. In one multicenter Italian study, an acute lymphoid leukemia/lymphoma regimen resulted in higher complete remission and overall survival rate than that achieved with an acute myeloid leukemia-type regimen (median survival of 12.3 months versus 7.1 months). The addition of allogeneic hematopoietic stem cell transplantation increased median survival to 22.7 months [54]. Another study using high-dose chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplantation yielded overall survival rates at 4 years of 83 % for autologous versus 53 % for allogeneic stem cell transplantation [55]. This therapy appears to offer the best hope for longer-term survival in a disease which has been almost uniformly fatal. Recent gene profiling studies have revealed that the NF-kB pathway is activated in BPDCN. In this pathway, DNA-binding proteins translocate to the nucleus and activate genes associated with cell proliferation, adhesion, and migration, all features which likely contribute to malignant biologic behavior. Bortezomib is an antineoplastic proteasome inhibitor already in clinical use which is known to inhibit the NF-kB pathway. In vitro studies have shown a strong inhibitory effect on the *CAL-1* BPDCN cell line, suggesting that bortezomib may offer hope for targeted molecular therapy in patients with BPDCN [49].

Blastic plasmacytoid dendritic cell neoplasm is a rare highly aggressive hematopoietic neoplasm which frequently has an asymptomatic yet ominous presentation as localized or limited skin disease prior to a rapidly progressive leukemic phase which is frequently fatal. This is a disease likely to present to dermatologists and dermatopathologists and one that requires rapid diagnosis and institution of systemic therapy in an attempt to prolong survival.

FIGURE 2.3. Deeply erythematous and focally crusted indurated thick plaque (Photo courtesy of Maria Charif, MD).
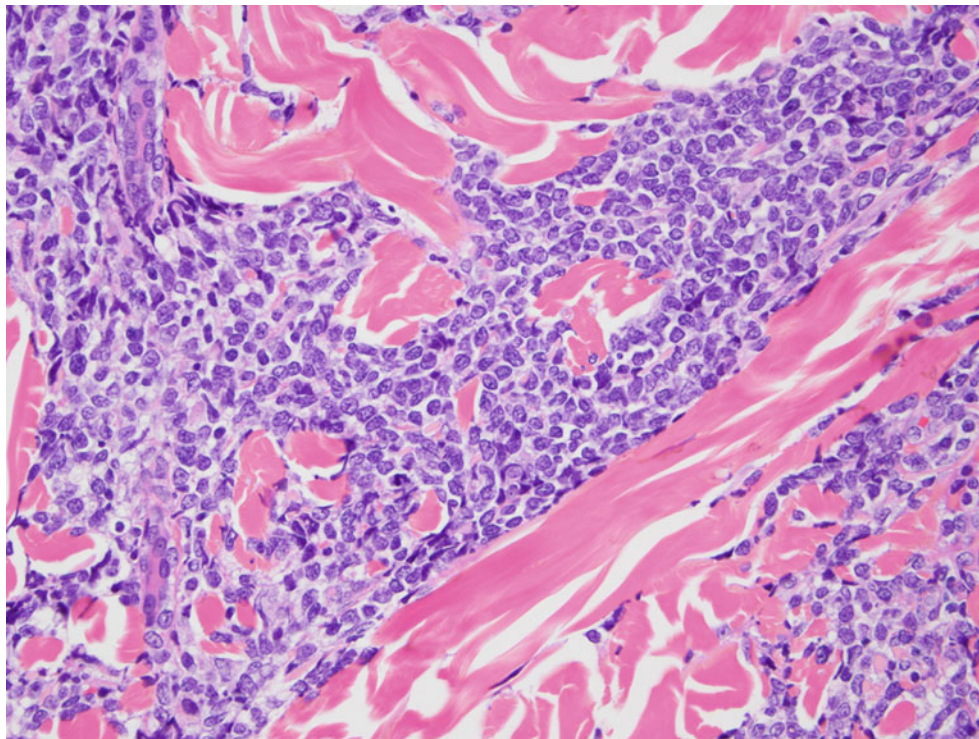
FIGURE 2.4. Dermal infiltrate of medium-sized blast-appearing cells with irregular nuclear contours.

References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
2. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM, Jaffe ES. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood. 2003;101:3407–12.
3. Malkovsky M, Fisch P, Wallace M, Sen A, Mejia G, Lewis PG, et al. Gamma/delta T cells: from bench to bedside. Clin Appl Immunol Rev. 2003;3:235–45.
4. Hocker TL, Wada DA, El-Azhaary R, Gibson LE. Expression of T-cell receptor-gamma delta in normal human skin,

inflammatory dermatoses and mycosis fungoides. J Cutan Pathol. 2012;39:419–24.

5. Tripodo C, Ianitto E, Florena AM, Pucillo CE, Piccaluga PP, Franco V, Pileri SA. Gamma-delta T-cell lymphomas. Nat Rev Clin Oncol. 2009;6:707–17.

6. Guitart K, Weisenburger DD, Subtil A, et al. Cutaneous gamma-delta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. Am J Surg Pathol. 2012;36:1656–65.

7. Toro JR, Beaty M, Sorbara L, et al. Gamma-delta T-cell lymphoma of the skin. Arch Dermatol. 2000;136:1024–32.

8. Wilhelm M, Meyer P, Batram C, Tony HP, Dummer R, Nestle E, Burg G, Wilms K. Gamma-delta receptor expressing T-cell clones from a cutaneous T-cell lymphoma suppress hematopoiesis. Ann Hematol. 1992;65:111–5.

9. Harrington L, Sokol L, Holdener S, Shao H, Zhang L. Cutaneous gamma-delta T-cell lymphoma with central nervous system involvement: report of a rarity with review of the literature. J Cutan Pathol. 2014;41:936–43.

10. Endly DC, Weenig RH, Peters MS, Viswanatha DS, Comfere NI. Indolent course of cutaneous gamma-delta T-cell lymphoma. J Cutan Pathol. 2013;30:896–902.

11. Kim YH, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(2):479–84.

12. Foppoli M, Ferreri AJM. Gamma-delta t-cell lymphomas. Eur J Haematol. 2015;94(3):206–18.

13. Mehta N, Wayne AS, Kim YH, et al. Bexarotene is active against subcutaneous panniculitis-like T-cell lymphoma in adult and pediatric populations. Clin Lymphoma Myeloma Leuk. 2012;12:20–5.

14. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer. 2004;101:1404–13.

15. Ruiz-Maldonado R, Millan-Parilla F, Orozco-Covarrubias ML, et al. Edematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential. J Am Acad Dermatol. 1995;32:378–81.

16. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T cell lymphoma. Blood. 2011;117(25):6756–67.

17. Iwatsuki K, Xu Z, Ohtsuka M, Kaneko F. Cutaneous lymphoproliferative disorders associated with Epstein-Barr virus infection: a clinical overview. J Dermatol Sci. 2000;22:191–5.

18. Kimura H, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood. 2012;119(3):673–86.

19. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. Pediatr Dermatol. 2010;27(5):463–9.

20. Sangueza M, Plaza JA. Hydroa vacciniforme-like cutaneous T-cell lymphoma: clinicopathologic and immunohistochemical study of 12 cases. JAAD. 2013;69(1):112–9.

21. Magana M, Massone C, Magana P, Cerroni L. Clinicopathologic features of hydroa vacciniforme-like lymphoma: a series of 9 patients. Am J Dermatopathol. 2015;38:20–5.

22. Quintanilla-Martinez L, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. Blood. 2013;122(18):3101–10.

23. Eminger LA, Hall LD, Hesterman KS, Heymann WR. Epstein-Barr virus, dermatologic associations and implications: part II. Associated lymphoproliferative disorders and solid tumors. J Am Acad Dermatol. 2015;72(1):21–34.

24. Rodriguez-Pinilla SM, et al. EBV-associated cutaneous NK/T-cell lymphoma: a review of a series of 14 cases from Peru in children and young adults. Am J Surg Pathol. 2010;34(12):1773–82.

25. Emilio B, Dario T, Vermeer MH, Meijer CJLM, Elvio A, Rein W. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. Am J Pathol. 1999;155:2.

26. Nofal A, Abdel-Mawla MY, Assaf M, Salah E. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. J Am Acad Dermatol. 2012;67(4):748–59.

27. Gormley RH, Hess SD, Anand D, Junkins-Hopkins J, Rook AH, Ki EJ. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. J Am Acad Dermatol. 2010;62(2):300–7.

28. Petrella T, Maubec E, Comillet-Lefeverbe P, et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? Am J Surg Pathol. 2007;31:1887–92.

29. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70(2):205.e201–216; quiz 221–202.

30. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part II. Prognosis, management, and future directions. J Am Acad Dermatol. 2014;70(2):223.e221–217; quiz 240–222.

31. Nagler AR, Samimi S, Schaffer A, Vittorio CC, Kim EJ, Rook AH. Peripheral blood findings in erythrodermic patients: importance for the differential diagnosis of Sezary syndrome. J Am Acad Dermatol. 2012;66(3):503–8.

32. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2006;42(8):1014–30.

33. Wieselthier JS, Koh HK. Sézary syndrome: diagnosis, prognosis, and critical review of treatment options. J Am Acad Dermatol. 1990;22(3):381–401.

34. Pfleger L, Tapperner J. Zur Kenntnis der systemisierten Endotheliomatose der cutanen Blutgefässe. Hautarzt. 1959;10:359–63.

35. Sheibani K, Battifora H, Winberg CD, et al. Further evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med. 1986;314:943–8.

36. Ferreri AJM, Dognini GP, Campo E, et al. Variations in clinical presentation, frequency of hemophagocytosis and clinical

behavior of intravascular lymphoma diagnosed in different geographical regions. Haematologica. 2007;92:486–92.

37. Shimada K, Kinoshita T, Naoe T, Nakamura S. Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol. 2009;10:895–902.

38. Ferreri AJM, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol. 2004;127:173–83.

39. Röglin J, Böer A. Skin manifestations of intravascular lymphoma mimic inflammatory diseases of the skin. Br J Dermatol. 2007;157:16–25.

40. Rubin MA, Cossman J, Freter CE, Azumi N. Intravascular large cell lymphoma coexisting within hemangiomas of the skin. Am J Surg Pathol. 1997;21:860–4.

41. Matsue K, Asada N, Odawara J, et al. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. Ann Hematol. 2011;90:417–21.

42. Cerroni L, Massone C, Kutzner J, Mentzel T, Umbert P, Kerl H. Intravascular large T-cell or KN-cell lymphoma: a rare variant of intravascular large cell lymphoma with frequent cytotoxic phenotype and association with Epstein-Barr virus infection. Am J Surg Pathol. 2008;32:891–8.

43. Crane GM, Ambinder RF, Shirley CM, et al. HHV-8 and EBV-positive intravascular lymphoma: an unusual presentation of extracavitary primary effusion lymphoma. Am J Surg Pathol. 2014;38:426–32.

44. Samols MA, Su A, Ra S, et al. Intralymphatic cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis: expanding the spectrum of CD30-positive lymphoproliferative disorders. Am J Sugg Pathol. 2014;38:1203–2111.

45. Baum CL, Stone MS, Liu V. Atypical intravascular CD30+ T-cell proliferation following trauma in a healthy 17-year-old male: first reported case of a potential diagnostic pitfall and literature review. J Cutan Pathol. 2009;36:350–4.

46. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL Study Group in Japan. J Clin Oncol. 2008;26:3189–95.

47. Kato K, Ohno Y, Kamimura T, et al. Long-term remission after high-dose chemotherapy followed by auto-SCT as consolidation for intravascular large B-cell lymphoma. Bone Marrow Transplant. 2014;49:1543–4.

48. Facchetti F, Jones DM, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: WHO classification of tumors of haematopoietic and lymphoid tissues. 4th ed. France: International Agency for Research on Cancer (IARC) Lyon; 2008. p. 145–7.

49. Sapienza MR, Fuligni F, Agnostinelli C, et al. Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF-kB pathway inhibition. Leukemia. 2014;28:1606–16.

50. Julia F, Petrella T, Beylot-Barry M, et al. Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients. Br J Dermatol. 2013;169:579–86.

51. Petrella T, Facchetti F. Tumoral aspects of plasmacytoid dendritic cells: what do we know in 2009? Autoimmunity. 2010;43:210–4.

52. Julia F, Dalle S, Duru G, et al. Blastic plasmacytoid dendritic cell neoplasms: clinico-immunohistochemical correlations in a series of 91 patients. Am J Surg Pathol. 2014;38:673–80.

53. Lucioni M, Novara F, Fiandrino G, et al. Twenty-one cases of blastic plasmacytoid dendritic cell neoplasm: focus on biallelic locus 9p21.3 deletion. Blood. 2011;118:4591–4.

54. Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica. 2013;98:239–46.

55. Aoki T, Suzuki R, Kuwatsuka Y, et al. Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. Blood. 2015;125:3559–62.

3
Langerhans Cell Histiocytosis

■	Synonyms:	Histiocytosis X, Langerhans cell granulomatosis, eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, self-healing reticulohistiocytosis, and Hashimoto-Pritzker syndrome
■	Etiology:	Unknown, a clonal or reactive expansion of Langerhans cells infiltrating various organs
■	Associations:	May coexist, precede, or follow the development of various solid tumors and hematopoietic malignancies
■	Clinical:	Polymorphous: red-brown purpuric scaly papules, lichenoid papules, purpura, vesicles, pustules, erosions, and ulcers of the head, neck, trunk, and mucosa, sometimes prominently involving intertriginous areas; may be solitary or extensive
■	Histology:	Superficial dermal mononuclear cells with abundant eosinophilic cytoplasm and lobulated and clefted nucleus often with "coffee bean" or reniform appearance; epidermotropism common
■	IHC:	Langerin+, CD 1a+, and S100+
■	Ultrastructure:	Deep nuclear cleaving, Birbeck granules (cytoplasmic linear tubular structures with inner serrations and terminal bulbous dilations, "tennis racquet-like")
■	Evaluation:	Radiographic skeletal survey, chest radiograph, CBC, blood chemistries, abdominal ultrasound, and urine specific gravity
■	Treatment:	Excision of solitary lesions and curettage of solitary bone lesions, with or without low-dose irradiation; for multifocal disease, observation or prednisone, vinblastine, or methotrexate
■	Prognosis:	Excellent for unifocal disease if no progression to multifocal disease within 2 years; multifocal disease is associated with limited mortality, primarily due to respiratory failure or cor pulmonale

Langerhans cell histiocytosis (LCH) refers to a collection of syndromes, characterized by infiltration of various tissues by Langerhans cells (LC). In 1941, Farber suggested that eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease all represent different manifestations of a single pathologic process, and in 1953, Lichtenstein used the term "histiocytosis X" to encompass these entities [1, 2]. Subsequent to the description of Birbeck granules as a specific ultrastructural marker for LC [3], the infiltrating cells of histiocytosis X were identified as LC. In 1987, the Clinical Writing Group of the Histiocyte Society proposed that *Langerhans cell histiocytosis* replaces the term *histiocytosis X* as more appropriate [4].

Paul Langerhans first observed the cell that bears his name in the epidermis in 1868. The function of the LC remained a mystery until recently. Langerhans cells are dendritic antigen-presenting cells that normally reside within squamous epithelium, peri-epithelial connective tissue, and lymphatics and in areas of lymph node. They are important in antigen processing that occurs in the development of contact dermatitis.

Studies to date suggest that LCH is a heterogeneous disease with an unclear etiology. A clonal expansion of Langerhans cells has been demonstrated in many cases [5, 6]. LCH was presumptively derived from epidermal LC, but gene profiling of LCH cells reveals a closer relationship with immature myeloid dendritic cells of the bone marrow than with LC of the skin, favoring origin from the bone marrow [7]. Recently, the oncogenic *BRAF* V600E mutation was found in over half of archived LCH specimens, supporting that LCH is a neoplastic disease [8]. It was subsequently found that approximately 50 % of LCH specimens with wild-type *BRAF* harbor *MAP2K1* mutations, yielding another mechanism for MAPK pathway activation. In this study, the mutations were mutually exclusive. The findings indicate an important role of oncogenic MAPK signaling in LCH [9]. *BRAF* V600E expression has also been found in bone marrow precursors in high-risk disease, but not in low-risk disease, leading to a hypothesis that LCH is an inflammatory myeloid neoplasia, with high-risk LCH resulting from somatic mutation in hematopoietic progenitors and low-risk disease resulting from somatic mutation in tissue-restricted precursors [10].

An analysis of pulmonary LCH found that the majority of nodules were not clonal, suggesting that some forms of the disorder may be reactive [11]. Cigarette smoking was suggested as a possible stimulus in some cases, and favoring a reactive process is the observation that many cases of pure pulmonary LCH will involute spontaneously with cessation of tobacco use [12]. Also supporting a reactive nature in some cases of LCH is the observation of a close pathological association of lesions of LCH with associated malignancies, particularly lymphomas and lung carcino-

mas [13]. Nodular collections of LC have also been observed in close association with lymph node-metastatic melanoma [14].

A possible infectious etiology of LCH has been explored, and no evidence of genomes for adenovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpesvirus-6, human immunodeficiency virus, human T-cell leukemia viruses, or parvovirus has been found [15]. A familial clustering has been reported, supporting a genetic factor in the development of the disease [16]. There is some epidemiologic evidence linking LCH to cigarette smoking, solvent exposure, family history of benign tumors, blood transfusions, and urinary tract infections during pregnancy. Cigarette smoking, in particular, has been linked to pulmonary LCH [17]. LCH has also been reported in association with malignant neoplasms [13, 18, 19]. Approximately two-thirds occur in association with lymphomas or leukemia and one-third, with solid tumors, most commonly lung carcinoma [13]. A clonal relationship between B-cell lymphoid malignancy and LCH has been found in some patients having both diseases [20]. Transdifferentiation has been suggested as an explanation of this phenomenon [20], but bidirectional differentiation from a common bone marrow precursor cell provides an alternative explanation.

Cutaneous lesions of LCH have a wide range of morphologies. These include papules or plaques that may be scaly or eroded, bullae, vesicles, ulcers, petechiae, or purpura (Figs. 3.1 and 3.2). The lesions may be solitary but in widespread disease tend to favor scalp and intertriginous areas, following an anatomic distribution similar to that of seborrheic dermatitis, which it may resemble. Solitary or

FIGURE 3.1. Coalescing *red-brown papules* with flexural accentuation.

FIGURE 3.2. Red-violaceous scaly papules with hemorrhagic crust.

multiple lesions of the external genitalia may also occur. Mucosal lesions may manifest as ulcers, gingivitis, bleeding, odontalgia, and dental hypermobility [21]. A variety of nail changes have been described, including onycholysis, subungual hyperkeratosis, hemorrhages, longitudinal grooving, subungual pustules, and paronychia [22].

Biopsy specimens of LCH contain an infiltrate of LC, usually within the papillary and superficial reticular dermis, sometimes in greater density around adnexal structures [23], often demonstrating varying degrees of epitheliotropism (Fig. 3.3a, b). The individual cells are 10–12 μm, with eosinophilic cytoplasm and convoluted, sometimes reniform, nuclei. Small nucleoli may be apparent. Mitotic figures are uncommon. By contrast, foci of necrosis are common and correlate with the frequent clinical scenario of erosion and sometimes ulceration. LC are frequently admixed with eosinophils. Multinucleated cells and lipidized macrophages are seen in some lesions, but

there is no evidence that these are LC [18, 24]. Given overlapping morphology with other cells, additional confirmatory studies should be undertaken. These include immunohistochemical staining with antibodies to CD1a, displaying a membranous pattern [24]. LC are also labeled by antibodies to S100 and peanut agglutinin, but not by histiocytic markers such as muramidase or HAM56 [18]. Prior to the development of antibodies to CD1a, a specific diagnosis of LC required ultrastructural identification of Birbeck granules. Birbeck granules are linear cytoplasmic granules with interior serrations and occasional bulbous "tennis racquet-like" terminal dilations that are thought to arise from cell membrane and may show membrane connections. Their formation is known to be induced by a C-type lectin cell surface receptor, langerin. Langerin (CD207) is a more specific marker of LC than is CD1a and has been documented to be specific immunohistochemical marker of LC [25]. The role of langerin and Birbeck granules is unknown, but they do not appear to be necessary for principal LC functions [26]. Once Langerhans cell infiltration of the skin has been ascertained, clinicopathologic correlation remains important as Langerhans cell hyperplasia has also been described in scabies and lymphomatoid papulosis [27, 28].

Mucocutaneous involvement in LCH should be taken in the context of involvement of other organ systems. Combining the two largest single-center series, 67 % of LCH cases involve a single organ system, the bone being by far the most frequent [18, 19]. When looking at both single-system and multisystem disease, bone involvement occurs in 70 %, followed by pulmonary in 18 %, and mucocutaneous involvement in 16 %. Of those with mucocutaneous involvement, approximately one-fifth have disease limited to the skin [18]. Evaluation of data from the French
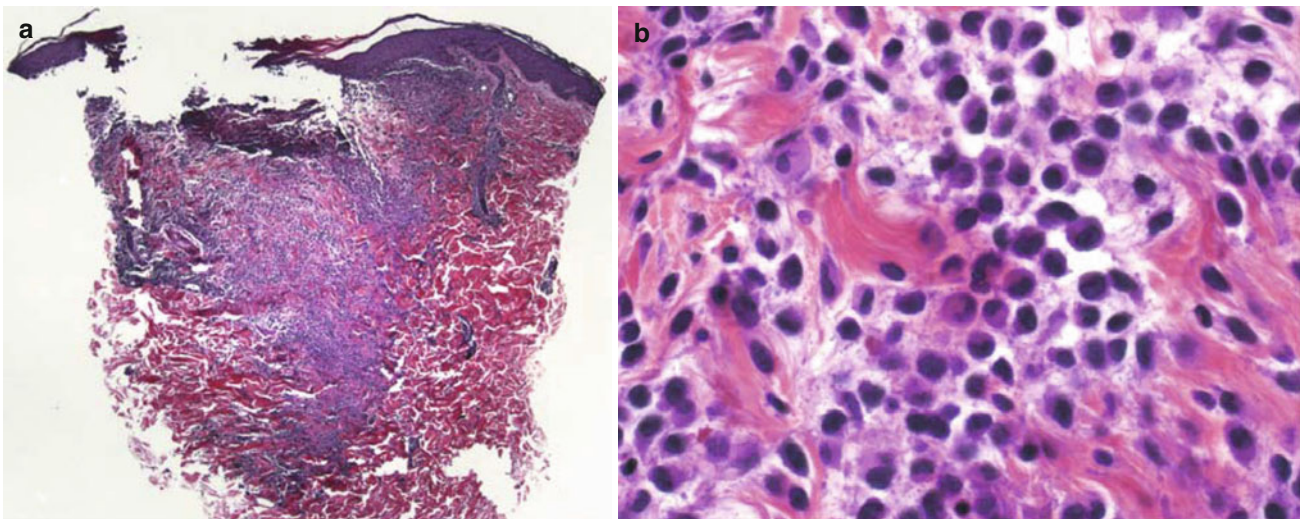
FIGURE 3.3. (**a**, **b**) Ulcerated papule with wedge-shaped and epitheliotropic infiltrate of Langerhans cells with amphophilic cytoplasm and eccentric reniform nuclei.

Langerhans Cell Histiocytosis Study Group, a pediatric population, and the adult cases from the International Registry of the Histiocyte Society suggests a greater incidence of pulmonary disease in adults (58 % versus 9 % in the pediatric population) [29, 30].

Having made a diagnosis of cutaneous Langerhans cell histiocytosis, it is important to perform an additional diagnostic evaluation for multisystem disease, as many cutaneous presentations are accompanied by other organ system involvements. One referral center reported a 40 % rate of systemic involvement in patients referred for purportedly skin-limited disease. In that cohort, those with isolated skin involvement rarely progressed to systemic disease [31]. Appropriate evaluation is directed by clinical symptoms and signs. General guidelines are suggested (after [32]).

3.1 Evaluation of the Patient Presenting with Cutaneous Langerhans Cell Histiocytosis

1. Thorough physical examination with attention to the lymph nodes, liver, and spleen
2. Skeletal radiograph survey (bone scan optional)
3. Chest radiograph
4. Random urine specific gravity and osmolality
5. Complete blood count with differential and platelets
6. Blood chemistry, including total protein, albumin, bilirubin, ALT, AST, and alkaline phosphatase
7. Coagulation studies, including INR/PT, APTT/PTT, and fibrinogen
8. Abdominal ultrasound with attention to the liver and spleen

Should no evidence of multifocal disease be present, close clinical follow-up in the first 2 years is advised since additional foci of disease are most likely to become apparent in that time period [18].

Prognosis in LCH is generally favorable. Large series have shown low mortality directly due to disease, the most frequent cause being respiratory failure associated with pulmonary disease [18, 19]. There may be considerable morbidity and mortality associated with treatment [18]. Deaths due to overwhelming LCH are exceptional. Long-term complications from the disease include pituitary dysfunction or diabetes insipidus, each occurring in approximately 25 % of patients, and a neurodegenerative syndrome occurring in approximately 10 % of patients with long-term follow-up [33].

Treatment for LCH is determined by the extent and type of organ system involvement. Isolated bone lesions are best treated with curettage. If the lesions are in critical weight-bearing bones, low-dose irradiation may be added. Systemic treatment most commonly consists of prednisone, followed by vinblastine, or methotrexate. It has been emphasized that doses associated with bone marrow depression or other toxicities are not generally required for a good therapeutic response [18]. 2-Chlorodeoxyadenosine and clofarabine are also effective agents in LCH [34, 35]. Lenalidomide and infliximab have been reported effective in multisystem disease in case reports [36, 37]. Vemurafenib, a mutant *BRAF* inhibitor, has been reported to be dramatically effective in a patient with refractory systemic disease harboring the *BRAF* V600E mutation [38]. Hematopoietic stem cell transplantation has been used in some cases of severe refractory LCH with complete remission, but death may occur from therapy [39].

Cutaneous LCH has been treated effectively with topical nitrogen mustard [40]. Additional therapeutic modalities for cutaneous and mucosal disease have included topical steroids [18], PUVA [41], narrowband UVB [42], topical imiquimod [43], thalidomide [44], and α-interferon [45]. Should disease resolution occur, clinical follow-up is advised because of potential for long-term complications, recurrence of disease, or the development of associated malignancy.

References

1. Farber S. The nature of "solitary or eosinophilic granuloma" of bone. Am J Pathol. 1941;17:625–9.
2. Lichtenstein L. Histiocytosis X, integration of eosinophilic granuloma of bone, Letterer-Siwe disease and Schuller-Christian disease as related manifestations of a single nosologic entity. Arch Pathol. 1953;56:84–102.
3. Birbeck MS, Breathnach AS, Everall JD. An electron microscopic study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo. J Invest Dermatol. 1961;31:51–64.
4. Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. Lancet. 1987;1:208–9.
5. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X): a clonal proliferative disease. N Engl J Med. 1994;331:154–60.
6. Yu RC, Chu C, Buluwela L, Chu AC. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet. 1994;343:767–8.
7. Allen CE, Li L, Peters TL, et al. Cell-specific gene expression in Langerhans cell histiocytosis lesions reveals a distinct profile compared with epidermal Langerhans cells. J Immunol. 2010;184:4557–67.
8. Badalian-Very G, Vergilio J, Degar BA, et al. Recurrent *BRAF* mutations in Langerhans cell histiocytosis. Blood. 2010;116:1919–23.
9. Brown NA, Furtado LV, Betz BL, et al. High prevalence of somatic *MAP2K1* mutations in *BRAF* V600E-negative Langerhans cell histiocytosis. Blood. 2014;124:1655–8.

10. Berres ML, Lim KPH, Peters T, et al. *BRAF-V600E* expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med. 2014;211:669–83.

11. Yousem SA, Colby TV, Chen YY, et al. Pulmonary Langerhans' cell histiocytosis: molecular analysis of clonality. Am J Surg Pathol. 2001;25:630–6.

12. Elia D, Torre O, Cassandro R, Caminati A, Harari S. Pulmonary Langerhans cell histiocytosis: a comprehensive analysis of 40 patients and literature review. Eur J Intern Med. 2015;26:351–6.

13. Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME. Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer. 1993;71:865–73.

14. Richmond I, Eyden BP, Banerjee SS. Intranodal Langerhans' cell histiocytosis associated with malignant melanoma. Histopathology. 1995;26:380–2.

15. McClain K, Jin H, Gresik V, Favara B. Langerhans cell histiocytosis: lack of viral etiology. Am J Hematol. 1994;47:16–20.

16. Arico M, Nichols K, Whitlock JA, et al. Familial clustering of Langerhans cell histiocytosis. Br J Haematol. 1999;107:883–8.

17. Hamre M, Hedberg J, Buckley J, et al. Langerhans cell histiocytosis: an exploratory epidemiologic study of 177 cases. Med Pediatr Oncol. 1997;28:92–7.

18. Lieberman PH, Jones CR, Steinman RM, et al. Langerhans cell (eosinophilic) granulomatosis. Am J Surg Pathol. 1996;20:519–52.

19. Howarth DM, Gilchrist GS, Mullan B, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer. 1999;85:2278–90.

20. West DS, Dogan A, Quint PS, et al. Clonally related follicular lymphomas and Langerhans cell neoplasms: expanding the spectrum of transdifferentiation. Am J Surg Pathol. 2013;37:978–86.

21. Madrigal-Martínez-Pereda C, Guerrero-Rodríguez V, Guisado-Moya B, Meniz-Garcia C. Langerhans cell histiocytosis; literature review and descriptive analysis of oral manifestations. Med Oral Patol Oral Cir Bucal. 2009;14:E222–8.

22. Mataix J, Betloch I, Lucas-Costa A, Pérez-Crespo M, Moscardó-Guilleme C. Nail changes in Langerhans cell histiocytosis; a possible marker of multisystem disease. Pediatr Dermatol. 2008;25:247–51.

23. Helm KF, Lookingbill DP, Marks JG. A clinical and pathologic study of histiocytosis X in adults. J Am Acad Dermatol. 1993;29:166–70.

24. Emile JF, Wechsler J, Brousse N, et al. Langerhans' cell histiocytosis: definitive diagnosis with the use of monoclonal antibody O10 on routinely paraffin-embedded samples. Am J Surg Pathol. 1995;19:636–41.

25. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. Am J Surg Pathol. 2008;32:615–9.

26. Kissenpfennig A, Ait-Yahia S, Clair-Moninot V, et al. Disruption of the langerin/CD207 gene abolishes Birbeck granules without a marked loss of Langerhans cell function. Mol Cell Biol. 2005;25:88–99.

27. Bhattacharjee P, Glusac EJ. Langerhans cell hyperplasia in scabies: a mimic of Langerhans cell histiocytosis. J Cutan Pathol. 2007;34:716–20.

28. Jokinen CH, Wolgamot GM, Wood BL, Olerud J, Argenyi ZB. Lymphomatoid papulosis with CD1a + dendritic cell hyperplasia, mimicking Langerhans cell histiocytosis. J Cutan Pathol. 2007;34:584–7.

29. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. Arch Dis Child. 1996;75:17–24.

30. Arico M, Girschikofsky M, Genereau T, et al. Langerhans cell histiocytosis in adults: report from the International Registry of the Histiocyte Society. Eur J Cancer. 2003;39:2341–8.

31. Simko SJ, Garmezy B, Abhyankar H, et al. Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr. 2014;165:990–6.

32. Minkov M, Grois N, McClain K, et al. Langerhans cell histiocytosis: Histiocyte Society evaluation and treatment guidelines. 2009. www.histiocytesociety.org/document?id=290.

33. Donadieu J, Rolon MA, Thomas C, et al. Endocrine involvement in pediatric-onset Langerhans' cell histiocytosis: a population-based study. J Pediatr. 2004;144:344–50.

34. Pardanani A, Phyliky RL, Li CY, Tefferi A. 2-Chlorodeoxyadenosine therapy for disseminated Langerhans cell histiocytosis. Mayo Clin Proc. 2003;78:301–6.

35. Simko SJ, Tran HD, Jones J, et al. Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma, and Rosai-Dorfman disease. Pediatr Blood Cancer. 2014;61:479–87.

36. Szturz P, Adam Z, Řehák Z, et al. Lenalidomide proved effective in multisystem Langerhans cell histiocytosis. Acta Oncol. 2012;51:412–5.

37. Clohan G, Barnett Y, Gibson J, Reddel SWR, Barnett MH. Langerhans cell histiocytosis with refractory central nervous system involvement responsive to infliximab. J Neurol Neurosurg Psychiatry. 2012;83:573–5.

38. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the *BRAF* V600E mutation. Blood. 2013;121:1495–500.

39. Akkari V, Donadieu J, Piguet C, et al. Hematopoietic stem cell transplantation in patients with severe Langerhans cell histiocytosis and hematological dysfunction: experience of the French Langerhans Cell Study Group. Bone Marrow Transplant. 2003;31:1097–103.

40. Sheehan MP, Atherton DJ, Broadbent V, et al. Topical nitrogen mustard: an effective treatment for cutaneous Langerhans' cell histiocytosis. J Pediatr. 1991;119:317–21.

41. Iwatsuki K, Tsugiki M, Yoshizawa N, Tagikawa M, Yamada M, Shamoto M. The effect of phototherapies on cutaneous lesions of histiocytosis X in the elderly. Cancer. 1986;57:1931–6.

42. Imafuku S, Shibata S, Tashiro A, Furue M. Cutaneous Langerhans cell histiocytosis in an elderly man successfully treated with narrowband ultraviolet B. Br J Dermatol. 2007;157:1267–304.

43. Taverna JA, Stefanato CM, Wax FD, Demierre MF. Adult cutaneous Langerhans cell histiocytosis responsive to topical imiquimod. J Am Acad Dermatol. 2006;54:911–3.

44. Thomas L, Ducros B, Secchi T, et al. Successful treatment of adult's Langerhans cell histiocytosis with thalidomide. Arch Dermatol. 1993;129:1261–4.

45. Kwong YL, Chan ACL, Chan TK. Widespread skin-limited Langerhans cell histiocytosis: complete remission with interferon α. J Am Acad Dermatol. 1997;36:628–9.

4
Leukemia Cutis

- ■ Synonyms: Cutaneous leukemia and extramedullary myeloid tumor
- ■ Associations: Systemic leukemia
- ■ Clinical: Variable: erythematous patches, papules, nodules, and hemorrhagic and purpuric lesions
- ■ Histology: Malignant hematopoietic precursor cells throughout the dermis: diffuse, perivascular, or nodular pattern
- ■ IHC repertoire: Lymphocyte surface markers and/or markers of specific granules useful if bone marrow biopsy is unavailable
- ■ Staging: Systemic work-up required
- ■ Prognosis: Poor, except for CLL
- ■ Adverse variables: Histologic subtype of high-grade leukemias
- ■ Treatment: No local therapy; systemic chemotherapy

Leukemia cutis (LC) is the infiltration of skin by malignant cells in the context of leukemia. Acute myelogenous leukemia (AML) is associated with leukemia cutis in approximately 4 % of cases overall, but certain subtypes have higher rates of LC. Acute myelomonocytic leukemia (FAB classification) represented the majority (56 %) in one large case series [1]. Abnormalities of chromosome 8 on molecular studies were more common in patients with AML and leukemia cutis (36 %) than in patients with AML without leukemia cutis (2.8 %) [2]. In cases which have associated coagulopathy, hemorrhagic lesions may be present. Leukemia cutis prior to bone marrow involvement in AML is exceptional (0.01 % of total cases, 0.1 % of leukemia cutis cases). Relapse of skin disease prior to bone marrow involvement is more common but is still quite rare. In a large series of AML patients, additional extramedullary leukemic spread, particularly meningeal disease, were present in 90 and 33 % of patients with leukemia cutis, respectively [1]. "Congenital" leukemia refers to that which presents within 1 month of birth and is usually of myeloid lineage, usually FAB class M4 or M5. Leukemia cutis in congenital leukemia occurs in 25–30 % of affected infants, often in those with high tumor burden and hepatosplenomegaly [3].

Leukemia cutis may occur in acute lymphoblastic leukemia (ALL), although it is quite uncommon. Overall, the incidence of leukemia cutis in ALL is approximately 3 %. Chronic myelogenous leukemia (CML) is associated with leukemia cutis in 0–4 % of cases [4]. Chronic lymphocytic leukemia (CLL) generally progresses to leukemia cutis at a later stage of disease, although does not necessarily represent a poor prognostic sign. About 4–27 % of patients with CLL are affected with leukemia cutis. The higher rate of leukemia cutis likely reflects high prevalence and indolent nature of CLL. Mature T-cell leukemias such as HTLV-associated adult T-cell leukemia (HTLV-associated ATL, 40–70 %) and T-cell prolymphocytic leukemia (T-PLL, 25–30 %) have higher rates of skin involvement [5, 6]. "Aleukemic" leukemia cutis refers to leukemia cutis presenting prior to bone marrow or peripheral blood involvement with the absence of systemic symptoms of leukemia. This variant represents less than 10 % of leukemia cutis cases overall, is more common in AML, and is often widespread with papulonodular or morbilliform morphology both reported [7, 8]. The occurrence of leukemia cutis in myelodysplastic syndrome may herald progression to overt leukemia [9].

Clinical appearance and distribution are usually not specific for leukemia type (Figs. 4.1 and 4.2). Smooth papules, plaques, and nodules, with variable consistency (soft, rubbery, firm), arise with equal incidence on the head, extremities, or trunk but are uncommon on the palms, soles, and oral mucosa. Color varies widely and red, brown, yellowish, bluish gray, and skin-colored nodules have been reported. The occurrence of cutaneous lesions near sites of prior

FIGURE 4.1. Multiple discrete and coalescing violaceous nodules of leukemia cutis.

FIGURE 4.2. Single violaceous nodule with surrounding purpura.

trauma or inflammation is common [10]. Less commonly, lesions are small and widely disseminated, imparting an exanthematous or erythrodermic appearance. The course of skin findings can reflect the biologic nature of the underlying myeloproliferative disorder. Acute leukemia often manifests with rapidly growing, potentially ulcerative skin lesions. CLL's indolent nature is reflected in slowly growing or seemingly unchanging skin lesions. The scalp, upper trunk, face, and upper extremities are slightly favored in the distribution of cutaneous lesions of CLL [11], occasionally presenting with intense facial erythema. T-PLL also presents with facial erythema and swelling, with clinical lesions often having a purpuric quality due to RBC extravasation [12]. HTLV-associated ATL lesions are polymorphous in morphology but are always multiple and usually generalized in distribution. The size of individual lesions can also reflect the biologic nature of the underlying disease, with larger nodular or tumoral lesions seen more frequently in acute or lymphomatous presentations [13]. Gingival hyperplasia and oral mucosal infiltration by leukemic cells are more common in acute myelogenous leukemia, in particular the myelomonocytic type [14]. Chloroma, otherwise known as myelosarcoma, is also more common in AML and is more common in children. Large, firm red-brown nodules or plaques occur in variable locations of the skin, lymph nodes, and gastrointestinal tract, and gross pathological examination reveals green color when cut, due to high content of peroxidase in myeloid cells [15].

Histologic appearance varies depending on the type of associated leukemia (Figs. 4.3 and 4.4). Acute lymphoblastic
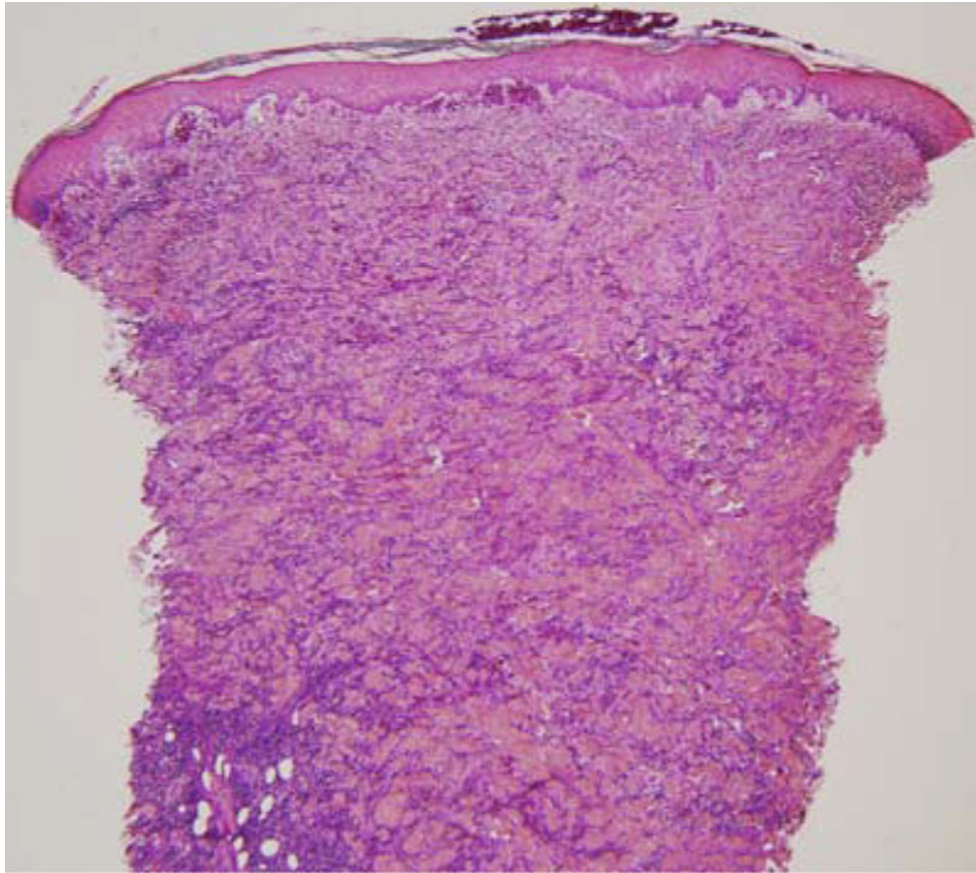
FIGURE 4.3. Leukemia cutis, low power. Dense diffuse dermal infiltrate with Grenz zone.

leukemia histopathology shows a dense diffuse or nodular infiltrate of medium to large blastic cells with vesicular nuclei extending throughout the dermis and into the subcutaneous fat, with intermingled mitotic figures and individual cell necrosis. Acute myelogenous leukemia findings in the skin vary based on the type of cell found on bone marrow examination, but the infiltrate is again nodular or diffuse and fills the entire dermis. The cellular infiltrate in chronic myelogenous leukemia can be similarly dense and diffuse, although can be more subtle and perivascular on occasion. Multiple mitoses and necroses of individual cells often are present. Chronic lymphocytic leukemia has three patterns: patchy perivascular/periadnexal, nodular/diffuse, and band-like, and the cellular infiltrate consists of small unremarkable lymphocytes with the absence of variability in size and shape [16]. Neoplastic lymphocytes can also be found infiltrating the dermis surrounding keratinocyte neoplasms in CLL [17, 18]. Generally, the pattern and appearance of cells histologically in the absence of immunohistochemical staining should not be relied upon for accurate characterization of leukemia type, as findings are largely nonspecific.

Immunohistochemical stains can be performed on the skin in the absence of the availability of bone mar-row pathologic specimens. Useful initial stains include myeloperoxidase and lysozyme to differentiate myeloid (+ for both) from lymphoproliferative (often − for both) disorders. Among myeloid leukemias, AML and CML cells are often CD117 + and CD34 + and CD68−. Acute myelomonocytic and acute monocytic leukemia cells are often CD56 +, CD68 +, CD117 −, and CD 34−. Among lymphoproliferative disorders, TdT and CD10 positivity indicates an immature lymphocyte population, while negativity indicates a mature B- or T-cell leukemia. B-cell ALL is PAX-5+ and CD79a+, while T-cell ALL usually stains positive for CD1a, cytoplasmic CD3, CD4, and CD8 (with CD79a negativity). B-cell CLL usually stain positive for Cd5, CD19, CD20, and CD23, which is negative for cyclin D1. A-TLL stains positive for CD3, CD4, and CD25 but is usually negative for CD8. T-PLL stains positive for CD3, CD4, CD7, CD45RO, and TCL-1, but staining is variable for CD8.

The treatment of patients with leukemia cutis is dependent on the type of associated leukemia. Leukemic infiltration of the skin is generally a poor prognostic sign, with overall mortality of 88 % after 1 year [19]. Exceptions to this occur in the setting of CLL, as survival with and
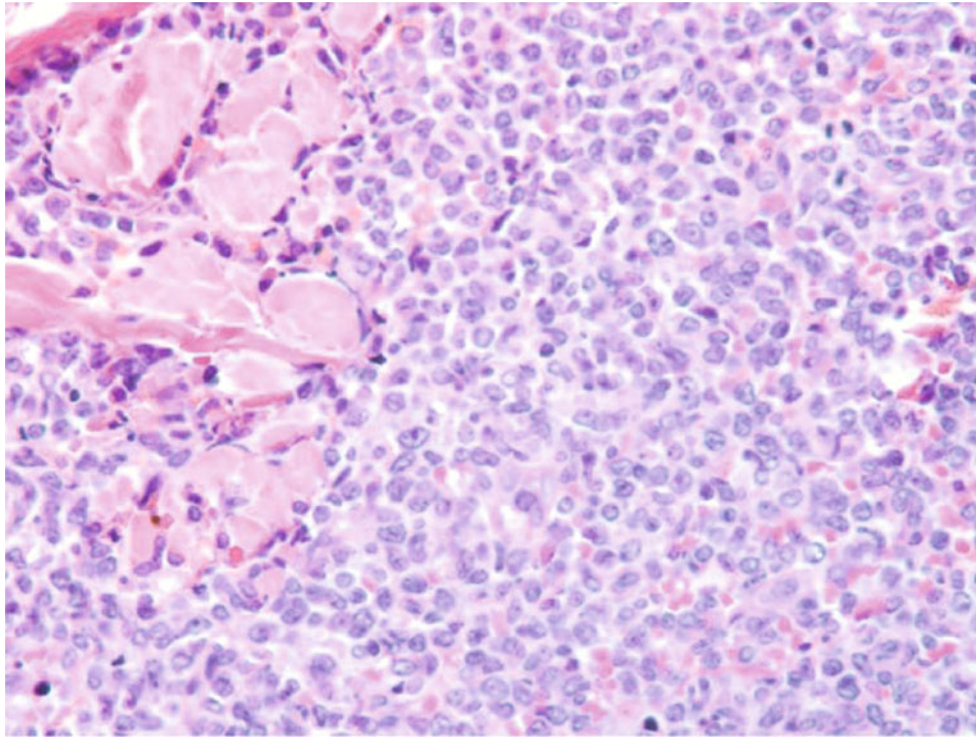
FIGURE 4.4. Leukemia cutis, high power. Large atypical cells with vesicular nuclei and surrounding myeloid precursors.

without skin involvement can be similar in some patient groups, in particular B-cell CLL. Congenital leukemia with and without leukemia cutis also follows a similar clinical course without differences in prognosis (although outlook overall is grim) [20].

References

1. Baer MR, Barcos M, Farrell H, Raza A, Preisler HD. Acute myelogenous leukemia with leukemia cutis: eighteen cases seen between 1969 and 1986. Cancer. 1969;1989:2192–200.
2. Agis H, Weltermann A, Fornatsch C, et al. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. Ann Hematol. 2002;81:90–5.
3. Bresters D, Reus AC, Veerman AJ, et al. Congenital leukemia: the Dutch experience and review of the literature. Br J Haematol. 2002;117:513–24.
4. Su WPD. Clinical, histopathologic, and immunohistochemical correlations in leukemia cutis. Semin Dermatol. 1994;13:223–30.
5. Buechner SA, Li CY, Su WP. Leukemia cutis: a histopathologic study of 42 cases. Am J Dermatopathol. 1985;7:109–19.
6. Mallett RB, Matutes E, Catovsky D, et al. Cutaneous infiltration in T-cell prolymphocytic leukemia. Br J Dermatol. 1995;132:263–6.
7. Tomasini C, Quaglino P, Nocelli M, et al. "Aleukemic" granulomatous leukemia cutis. Am J Dermatopathol. 1998;20:417–21.
8. Hejmadi RK, Thompson D, Shah F, Naresh KN. Cutaneous presentation of aleukemic monoblastic leukemia cutis – a case report and review of literature with focus on immunohistochemistry. J Cutan Pathol. 2008;35:46–9.
9. Longacre TA, Smoller BR. Leukemia cutis. Analysis of 50 biopsy-proven cases with an emphasis on occurrence in myelodysplastic syndromes. Am J Clin Pathol. 1993;100(3):276–84.
10. Paydas S, Zorludemir S. Leukemia cutis and leukemic vasculitis. Br J Dermatol. 2000;143:773–9.
11. Bonvalet D, Foldes C, Civatte J. Cutaneous manifestations in chronic lymphocytic leukemia. J Dermatol Surg Oncol. 1984;10:278–82.
12. Magro CM, Morrison CD, Heerema N, et al. T-cell prolymphocytic leukemia: an aggressive T cell malignancy with frequent cutaneous tropism. J Am Acad Dermatol. 2006;55:467–77.
13. Bittencourt AL. Oliveira, Maria de Fátima Paim de Cutaneous manifestations associated with HTLV-1 infection. Int J Derm. 2010;49(10):1099–110.
14. Kaddu S, Zenahlik P, Beham-Schmid C, Ceroni L. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. J Am Acad Dermatol. 1999;40:966–78.
15. Kleo JM, Welch JS, Nguyen TT, Hurley MY, Kreisel FH, Hassan A, Lind AC, Frater JL. State of the art in myeloid sarcoma. Int J Lab Hematol. 2011;33(6):555–65.
16. Cerroni L, Zenahlik P, Hofler G, Kaddu S, Smolle J, Helmut K. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol. 1996;20(8):1000–10.

17. Smoller BR, Warnke RA. Cutaneous infiltrate of chronic lymphocytic leukemia and relationship to primary cutaneous epithelial neoplasms. J Cutan Pathol. 1998;25:160–4.

18. Walther BS, Gibbons G, Chan EF, Ziselman E, Rothfleisch JE, Willard RJ, Baldassano MF. Leukemia cutis (involving chronic lymphocytic leukemia) within excisional specimens: a series of 6 cases. Am J Dermatopathol. 2009;31(2):162–5.

19. Su WPD, Buechner SA, Li CY. Clinicopathologic correlations in leukemia cutis. J Am Acad Dermatol. 1984;11(1):121–8.

20. Zhang IH, Zane LT, Braun BS, et al. Congenital leukemia cutis with subsequent development of leukemia. J Am Acad Dermatol. 2006;54(2 suppl):S22–7.

5
Mast Cell Disease: Urticaria Pigmentosa

■	Synonyms:	Urticaria pigmentosa, telangiectasia macularis eruptiva perstans, mastocytoma, and mastocytosis
■	Etiology:	Point mutation of c-kit at codon 816
■	Associations:	Nausea vomiting, diarrhea, syncope, mast cell leukemia, and other hematologic malignancies
■	Clinical:	Papules or nodules with or without associated hyperpigmentation and telangiectasia; positive Darier's sign
■	Histology:	Increased dermal mast cells perivascular or as tumor nodules, basilar hyperpigmentation, and vascular ectasia
■	IHC repertoire:	CD117 (c-kit) and tryptase-positive mast cell
■	Staging:	Bone marrow involvement conveys poor prognosis
■	Prognosis:	Varies with subtype of disease; benign in children
■	Adverse variables:	Bone marrow involvement
■	Treatment:	Chemotherapy including interferon alpha if bone marrow involvement; topical steroids close; clinical follow-up in patients with adult-onset disease

Nettleship and Tay first described urticaria pigmentosa in 1869 [1]. It was not until 1949 that Ellis described increased numbers of mast cells in several organs, demonstrating the systemic involvement of mastocytosis [2].

Most cases of urticaria pigmentosa are caused by a point mutation of the proto-oncogene c-kit at codon 816. C-kit functions as a transmembrane protein and is involved in signaling cell division when bound to mast cell growth factor. Mutations in the 816 position result in abnormal proliferation of mast cells [3].

Cutaneous mast cell disease has several different manifestations. It can present during the neonatal period or throughout life. Different age populations generally develop different clinical manifestations and different associated conditions. It is the systemic form of mastocytosis in adults that has the most potentially severe complications. It has been estimated that from 15 to 50 % of patients with adult-onset mast cell disease will have systemic involvement [4, 5]. However, for the sake of completeness, the other variants of this disease spectrum will also be considered. Urticaria pigmentosa is the global term for all conditions that are characterized by increased numbers of mast cells within the dermis. There is no gender predilection.

Mast cell disease in childhood is only rarely associated with systemic disease (less than 2 % of the time in one series). About one-third of all patients with mast cell disease are less than 15 years old [6]. The disease resolves spontaneously in 2–3 years in the vast majority of these patients, by adolescence in virtually all. Children with mast cell disease often have single or a few large, nodular lesions called mastocytomas (Fig. 5.1). These most commonly appear within the first 3 years of life. These lesions urticate easily with stroking (Darier's sign). Bullous lesions may be present due to extensive papillary dermal edema secondary to histamine release from mast cells. Vesicles do not generally occur as part of cutaneous mast cell disease in patients older than 10 years of age. Rarely, children with diffuse mast cell disease may present with erythroderma (Fig. 5.2). Despite the absence of systemic disease, these children are at risk for hypotension, shock, and even death.

Adults with mast cell disease are more likely to present with a widely scattered macular eruption. Individual lesions are often red brown or hyperpigmented. The lesions are randomly distributed and generalized but are accentuated on the chest. Petechiae and ecchymoses may occur. Depending upon the mast cell burden within each lesion, an

Figure 5.1. Erythematous/tan plaque of mastocytosis in a child.
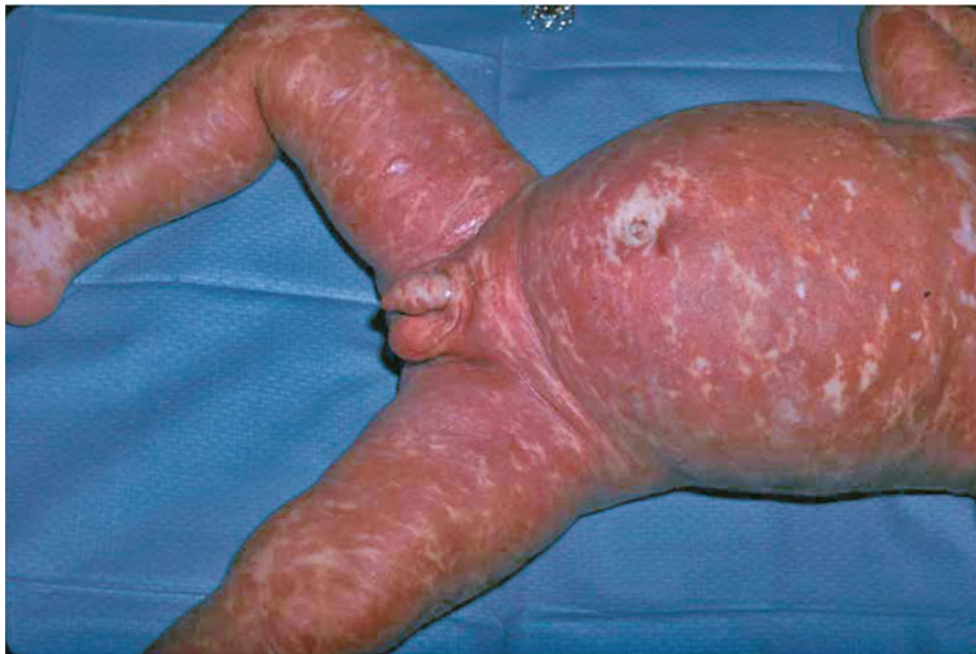
Figure 5.2. Erythroderma with islands of sparing and hepatosplenomegaly associated with parenchymal organ infiltration in systemic mastocytosis.

urticarial reaction can be elicited by gently stroking these lesions. Pruritus is the most common symptom. Less commonly, nausea, vomiting, diarrhea, and abdominal pain may be reported. These symptoms occur in patients with limited cutaneous disease as frequently as those with systemic involvement. One type of adult-onset form of the disease is known as telangiectasia macularis eruptiva perstans (TMEP). In this variant, abundant hyperpigmented 2–6-mm macules are present on the back and chest in concert with telangiectasias. Pruritus and urtication are not common. It is currently not possible to distinguish adult patients with disease limited to the skin from those with systemic disease based purely on the cutaneous disease. There is no difference in the age of presentation between those with and without systemic involvement. The mean age of presentation

is in the fourth decade. Systemic disease presents much later, often with as much as 20 years separating these findings from the initial cutaneous presentation [6]. Patients with systemic disease may remain alive with persistent disease for many years or may succumb to their illness.

In adults with cutaneous mast cell disease, hepatosplenomegaly is often seen in addition to the macular, hyperpigmented eruption. Lymph node involvement is not uncommon. Osteoblastic lesions can be detected with radiographs. The bone marrow is the most frequently involved extracutaneous site. Eosinophilia is present in 15 % of all patients with systemic disease. In these patients, pancytopenia may be present, and a bone marrow biopsy and aspiration is necessary to eliminate the presence of mastocytosis or leukemia (mast cell leukemia or
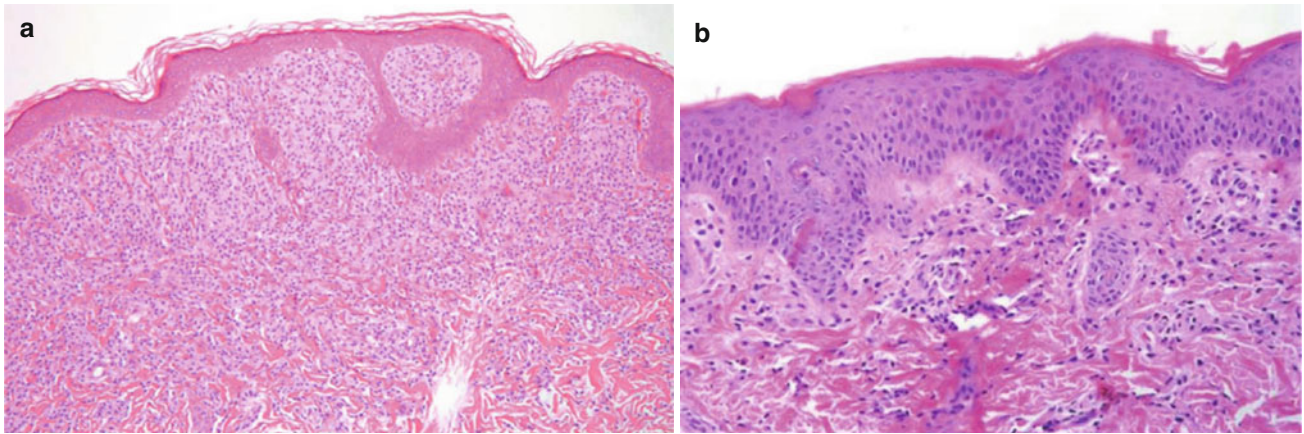
FIGURE 5.3. (**a**) Low-power photomicrograph depicting superficial dermal infiltrate of mastocytosis. (**b**) Low-power photomicrograph depicting superficial dermal infiltrate of mastocytosis in adult TMEP.
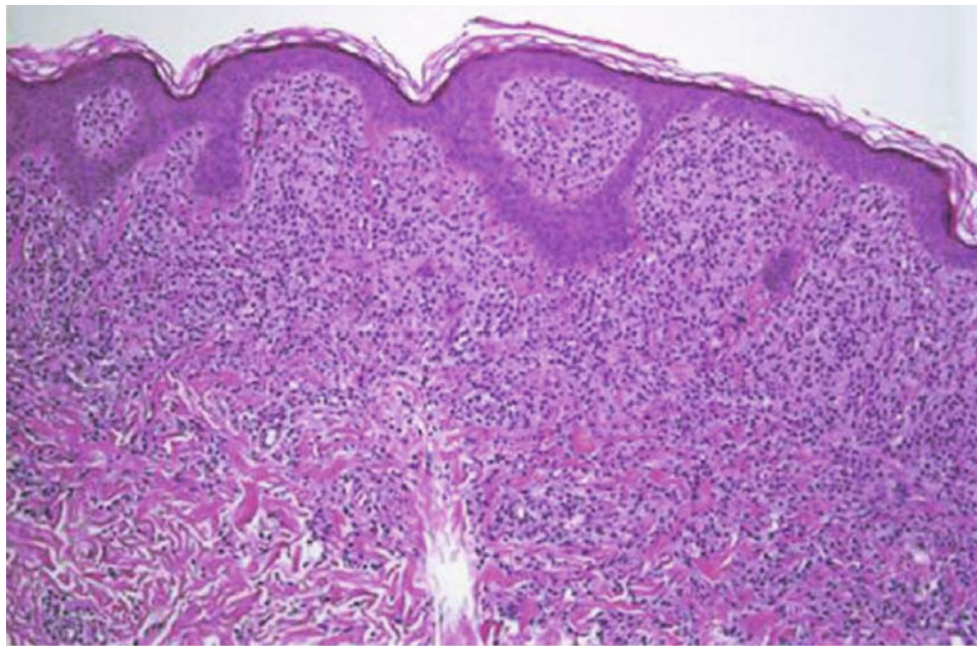
FIGURE 5.4. Medium-power photomicrograph depicting uniform population of epithelioid cells within the superficial dermis.

chronic myelogenous leukemia). Leukemia is reported to develop in 4–5% of patients with systemic mastocytosis [7]. Involvement of the gastrointestinal tract has been reported but is very uncommon. Increased serum tryptase and increased urinary levels of *t*-methyl histamine may also be detected in these patients [8].

The histologic findings in child-onset mast cell disease include a very dense dermal infiltrate of mast cells, often filling the entire dermis and extending into the subcutaneous fat. In some cases, prominent papillary dermal edema leads to a subepidermal bulla, correlating with the blisters encountered clinically.

The histologic findings in adult-onset mast cell disease fall into two general categories. Mast cells may be distributed diffusely or in a perivascular pattern (Fig. 5.3a, b).

Neither pattern is predictive of systemic involvement, though the superficial perivascular pattern is more common [6]. The number of perivascular mast cells varies widely but in most cases is relatively slight, with only a minimal increase in cellularity over physiologic levels. Morphometric point counting has suggested that while the absolute numbers may be small, there is a nine- to 160-fold increase in numbers of mast cells in these cases compared with normal patients [9]. Dense diffuse infiltrates within the papillary dermis are encountered less commonly (Fig. 5.4).

In these cases, prominent nuclear atypia and the presence of nucleoli and multinucleation may be present; however, these findings do not associate invariably with systemic involvement. Mitotic activity is rare in all cases of mast cell disease (Fig. 5.5).
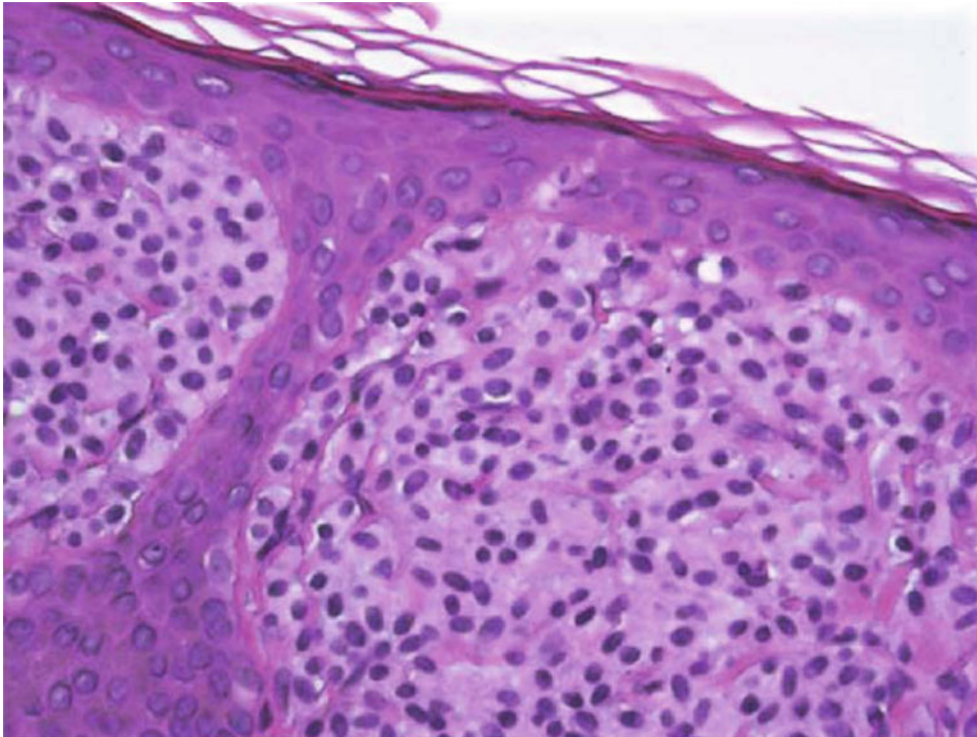
FIGURE 5.5. High-power photomicrograph depicting uniform population of rounded cells possessing oval nuclei with amphophilic staining cytoplasm.
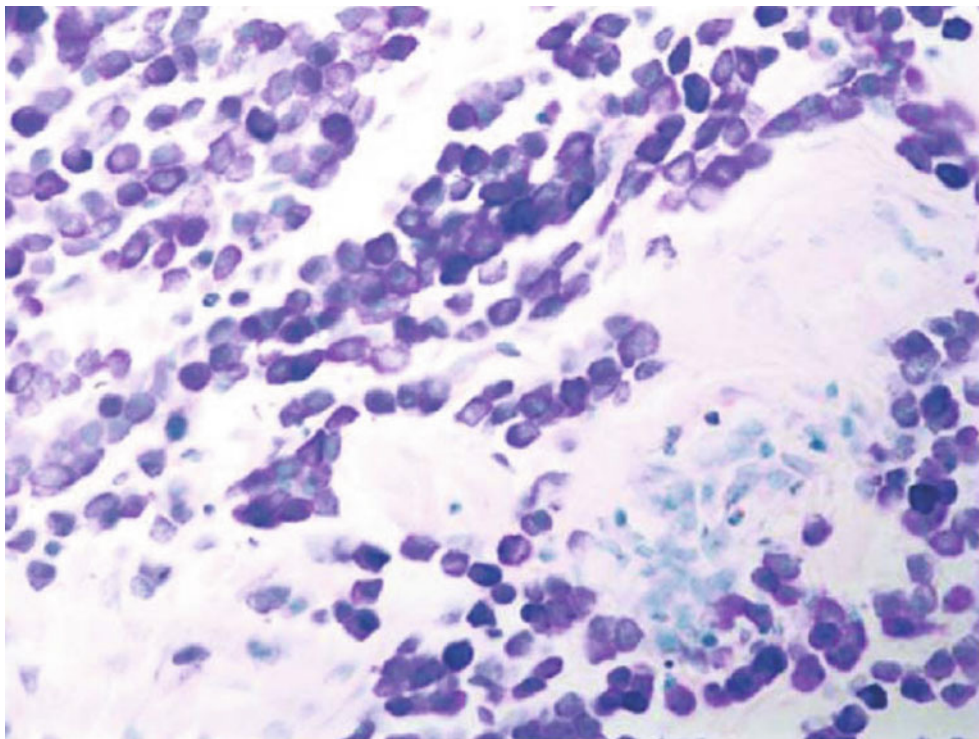
FIGURE 5.6. Giemsa stains reveal metachromatic staining of cytoplasmic granules within mast cells.

In one study, electron microscopy suggested that mast cells from patients with systemic disease are larger and have more cytoplasm and larger cytoplasmic granules [10]. In biopsies from both patterns, an admixture of lymphocytes and eosinophils is present within the dermis. In more subtle cases, mast cell numbers can be better assessed with special stains such as toluidine blue or Giemsa stains or more specifically, staining with CD117 (c-kit) or mast cell tryptase (Fig. 5.6).

Bone marrow involvement with mast cell disease may be very focal, and a negative biopsy does not guarantee limited cutaneous disease [6]. Conversely, skin involvement is not present in all cases of systemic mast cell disease [11, 12].

Treatment options vary with the extent of disease. Cutaneous lesions can be watched or treated with topical steroids or even surgical excision of limited lesions. More extensive disease requires topical steroids, antihistamines, chemotherapy, interferon, and ultraviolet light therapy. None of these options are entirely effective.

References

1. Nettleship E, Tay W. Rare forms of urticaria. Br Med J. 1869; 2:323–30.
2. Ellis JM. Urticaria pigmentosa; a report of a case with autopsy. Arch Pathol (Chic). 1949;48(5):426–35.
3. Akin C. Molecular diagnosis of mast cell disorders: a paper from the 2005 William Beaumont Hospital Symposium on Molecular Pathology. J Mol Diagn. 2006;8(4):412–9.
4. Caplan RM. The natural course of urticaria pigmentosa. Arch Dermatol. 1983;87:146–57.
5. Ridell B, Olafsson JH, Roupe G, Swolin B, Granerus G, Rodjer S, Enerback L. The bone marrow in urticaria pigmentosas and systemic mastocytosis. Arch Dermatol. 1986;122: 422–7.
6. Travis WD, Li C-Y, Su WPD. Adult-onset urticaria pigmentosa and systemic mast cell disease. Am J Clin Pathol. 1985;84:710–4.
7. DiBacco RS, DeLeo VA. Mastocytosis and the mast cell. J Am Acad Dermatol. 1982;7:709–22.
8. Asmis LM, Cirardet C. Systemic mast-cell disease (mastocytosis): letter to the editor. N Eng J Med. 2002;346:174.
9. Kaspar CS, Freeman RG, Tharp MD. Diagnosis of mastocytosis subsets using a morphometric point counting technique. Arch Dermatol. 1987;123:1017–21.
10. Soter NA. The skin in mastocytosis. J Invest Dermatol. 1991;96:32S–9.
11. Mutter RD, Tannenbaum M, Ultmann JE. Systemic mast cell disease. Ann Intern Med. 1963;59:887–906.
12. Roberts II LJ, Fields JP, Oates JA. Mastocytosis without urticaria pigmentosa: a frequently unrecognized cause of recurrent syncope. Trans Assoc Am Physicians. 1982;85:36–41.

6
Merkel Cell Carcinoma

■ Synonyms:	Trabecular carcinoma of the skin, primary small cell carcinoma of the skin, cutaneous APUDoma
■ Etiology:	Ultraviolet light, chromosome 1 abnormalities, p53, bcl-2, c-kit receptor, Merkel cell polyomavirus
■ Associations:	Aging, immunosuppression, other cutaneous and visceral malignancies
■ Clinical:	Painless, solitary rapidly growing nodule on exposed cutaneous site
■ Histology:	Diffuse or aggregated dermal nests of small blue cells, numerous mitoses
■ IHC repertoire:	CK-20 (+), synaptophysin (+), NSE (+), NFP (+), S-100 (+/−), Melan-A (−), CK-7 (−), CD-45 (−), TTF-1 (−), LCA (−), HMB45 (−)
■ Staging:	I = localized disease, II = I and regional node(s) (+), III = extranodal metastases
■ Prognosis:	Overall 5-year ∼60 % survival
■ Adverse variables:	Male, head location, mitoses >10/HPF, vascular permeation, (+) lymph nodes
■ Treatment:	I, II = WLE/XRT/ELND, III = XRT/CTX/*HPF* high-power fields, *WLE* wide local excision, *XRT* X-ray radiotherapy, *CTX* chemotherapy

Merkel cell carcinoma (MCC) was first described by Toker [1] in 1972 as trabecular carcinoma of the skin. It is also known as neuroendocrine carcinoma of the skin, cutaneous APUDoma, and primary small cell carcinoma of the skin with endocrine differentiation. Merkel cell carcinoma is an uncommon and aggressive non-melanoma cutaneous neoplasm. Friedrich Merkel first discovered the Merkel cell in 1875. It is a large, clear, usually round or oval cell found in the basal layer of the epidermis. It is found in close association with terminal axons and is joined to keratinocytes. They are found in highest concentrations in acral skin, namely, the fingertips and nasal tip, as well as glabrous skin, hairy skin, and mucous membranes. The function of Merkel cells is thought to be that of a slowly adapting mechanoreceptor [2]. The origin of Merkel cell carcinoma is controversial as well. It may arise from epidermal Merkel cells, dermal neuroendocrine cells, or poorly differentiated epidermal stem cells.

The exact etiology of this tumor is unknown, although the recent discovery of the Merkel cell polyomavirus (MCV) in 2008 lends new information in the causality of this neoplasm [3]. It was demonstrated that MCV was present in about 80 % of MCC [3]. This information, combined with the increased prevalence of MCC in elderly and immunocompromised individuals, is highly supportive of an infectious etiology of MCC. Studies demonstrate that the MCV encodes a tumor antigen, which targets several tumor suppressor proteins (viz., p53 and Rb) in humans, thus providing the opportunity for tumor growth [3–9]. Indeed MCV tumor antigen expression was found exclusively in tumor cells, further supporting its role as a direct viral carcinogen [8].

Merkel cell carcinoma is located primarily on the head and neck areas that commonly receive actinic damage. Hence, it is thought that UV radiation may play a role in the development of these tumors. One study by Demetriou

et al. demonstrated the enhancement of the development of cancer in patients who had both extensive UV exposure and MCV positivity [10]. The study revealed that the tumor antigen expressed by MCV was mutated by UV light. This mutated T antigen was then shown to decrease the amount of XPC protein, a protein normally responsible for initially recognizing solar-induced DNA damage. Thus the initial mechanism by which the body begins to repair solar damage was inhibited, leaving the way open for carcinogenesis. However, there have been many reports of tumors arising in non-sun-exposed regions as well, and thus other factors must play a role.

While MCV seems a promising development in understanding the etiology of Merkel cell carcinoma, there are still cases arising in seronegative individuals. Such cases are being studied and a number of tumor suppressor genes are being investigated as causes of tumorigenesis. One study compared MCV-positive and MCV-negative individuals and demonstrated an inactivation of tumor suppressor RB protein by tumor antigens in MCV-positive individuals and a complete lack of expression of the RB protein in MCV-negative individuals [11, 12]. This study suggests that the loss of activity of the RB protein, however it is brought about, may be integral in the development of MCC. Other genes implicated in tumors with little-to-no MCV viral expression are c-kit, KIT, and p53, which demonstrate increased expression [12, 13]. Changes in chromosome 1 have been frequently identified in MCC, thus lending to the hypothesis that there may be a genetic predisposition in certain individuals to develop this tumor [3].

Merkel cell carcinoma is a very rare neuroendocrine cutaneous neoplasm, with a prevalence of 0.6 cases per 100,000 people [14]. However, the number of cases is on the rise with approximately 1600 new cases reported annually in the USA. This increase is partly due to increased awareness and improved diagnostic techniques, most notably the introduction of cytokeratin 20 immunostaining [15]. It is most common in elderly individuals as well as the immunosuppressed. The incidence of MCC is approximately 11–13-fold higher in AIDS patients and 5–10-fold higher in patients with solid organ transplants [16]. The association of MCC with UV exposure largely explains the clinical distribution of this neoplasm. Merkel cell carcinoma is primarily located on the head and neck (44–50 %, 20 % of which arise in the periocular region), followed by the extremities (40–44 %). There is a notable asymmetry that reveals more neoplasms in these UV-exposed locations to be on the left side of the body due to increased UV exposure on the left while driving automobiles [17]. In areas hidden from the sun like the trunk (8 %) and the buttocks (9 %), the distribution is symmetrical [16]. This tumor occurs primarily in Caucasians, with a few case reports in African Americans and Polynesians. The average age at diagnosis is 76.2 years for women and 73.6 years for men,

with cases in children being exceedingly rare [18]. The ratio of men to women varies among different reports, with some citing equal incidence of occurrence among both sexes, some reporting a slightly higher incidence in men (1.5:1), and others finding a slightly higher incidence in women. Merkel cell carcinoma has also been reported to arise in patients with other neoplasms, at a frequency higher than expected by chance alone [16]. These include squamous cell carcinoma, basal cell carcinoma, and Bowen's disease. Other internal malignancies that have been documented to be associated with MCC are Hodgkin's lymphoma, breast carcinoma, endometrial carcinoma, colon carcinoma, prostate cancer, ovarian cancer, bladder transitional cell carcinoma, squamous cell carcinoma of the larynx, B-cell lymphoma, and chronic lymphocytic leukemia (CLL). Immunosuppressed patients have been found to be at an increased risk for many malignancies, including Merkel cell carcinoma. Immunosuppressed individuals tend to have tumors that behave more aggressively than those seen in the general population [16, 19].

Merkel cell carcinoma can present in many different ways, but is most often a solitary, painless, pink to reddish-blue or brown dome-shaped nodule or plaque on sun-exposed skin of elderly individuals (Fig. 6.1). The lesion may sometimes ulcerate and can range in size from 0.2 to 5.0 cm, with the largest lesion reported as 23.0 cm in greatest diameter [20, 21].

Merkel cell carcinoma is composed of small, monomorphic, basophilic tumor cells with round to oval-shaped nuclei and scanty cytoplasm. The nuclei have finely granular dispersed chromatin, and nucleoli are absent or few in number. The nuclear-to-cytoplasmic ratio is high, as is as the mitotic rate, and pyknotic nuclei and apoptotic bodies may be present. The tumor cells occupy the dermis and may extend into the subcutaneous fat (Figs. 6.2 and 6.3). The epidermis is generally spared, but there are reports of epidermotropism or "pagetoid" spread. In these instances, MCC may mimic melanoma, mammary and extramammary Paget's disease, mycosis fungoides, pagetoid Bowen's disease, and intraepidermal epithelioma [8, 9]. The association of Merkel cell carcinoma with the aforementioned tumors, and its propensity to develop both squamous and eccrine differentiation, supports a link between MCC and the epithelium. A dense lymphocytic infiltrate is typically present within and surrounding the tumor. There may be involvement of the dermal lymphatics and blood vessels. Merkel cell carcinoma has been classified into three histologic subtypes. The intermediate cell type is considered the most common variant of MCC, seen in approximately 80 % of all Merkel cell carcinomas. It displays a solid, diffuse pattern made up of cells that are less compact, with focal areas of necrosis. Mitotic figures are conspicuous. There is a lymphocytic infiltrate within and around the tumor. The second histologic variant described by

FIGURE 6.1. Erythematous glistening papule of Merkel cell carcinoma.
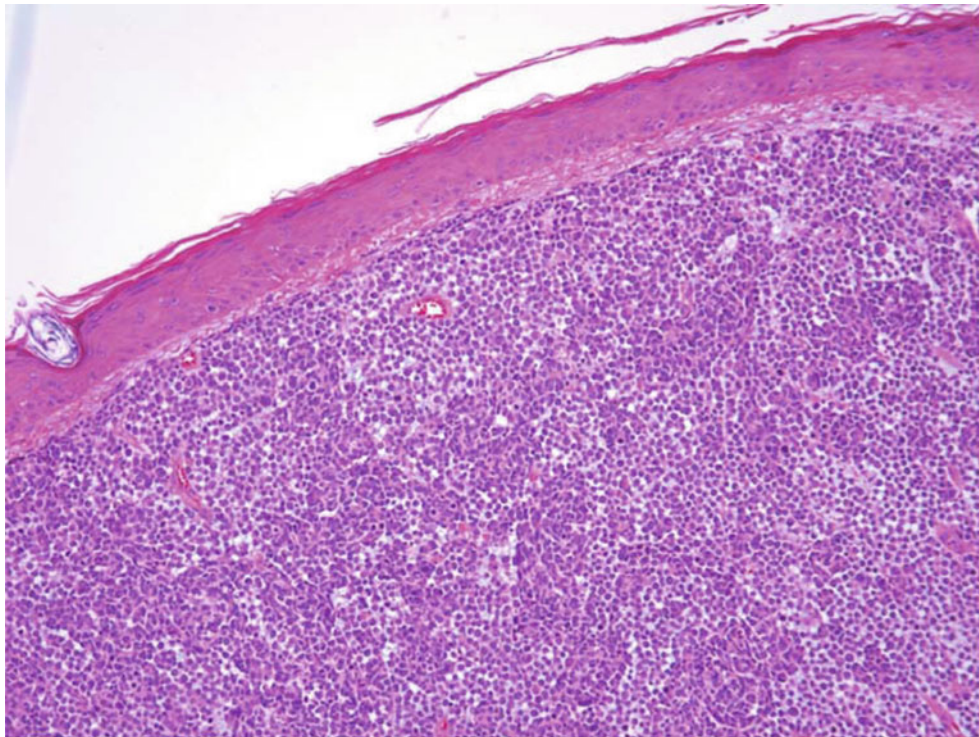
FIGURE 6.2. Low-power photomicrograph depicting diffuse dermal permeation by neoplastic cells.
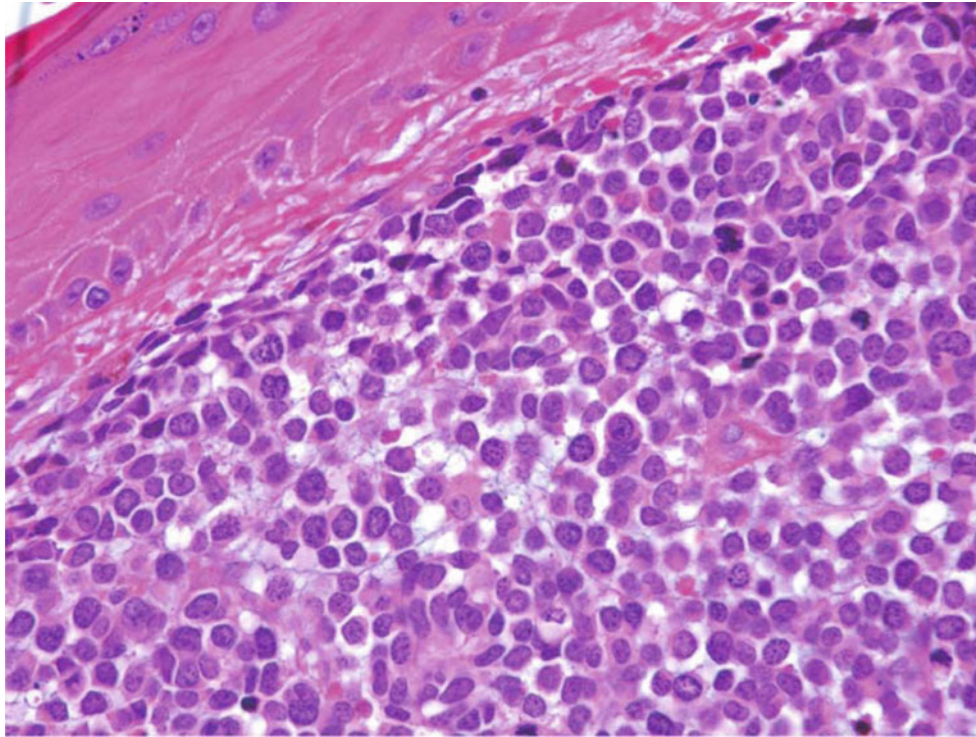
FIGURE 6.3. High-power photomicrograph depicting small blue cells containing speckled nuclear chromatin. Note scattered mitotic figures.

Gould et al., the small cell variant, is composed of solid sheets and clusters of cells in the dermis, lacks glandular differentiation, and often has areas of necrosis. The trabecular pattern, considered to be the least common pattern, is characterized by round to polygonal cells arranged in organoid clusters and trabeculae, which may occasionally exhibit gland-like formations. This classification scheme arranged by Gould et al. is comprehensive; however, many tumors are composed of cells of different sizes and patterns, and not all tumors will fit exactly into one subtype. A triad of findings suggested to be virtually pathognomonic of MCC includes vesicular nuclei with small nucleoli, abundant mitoses, and apoptosis. The differential diagnosis includes other poorly differentiated small cell tumors. These include small cell carcinoma of the lung (oat cell carcinoma), cutaneous large cell lymphomas, neuroblastoma, metastatic carcinoid, amelanotic melanoma, sweat gland carcinoma, medullary carcinoma of the thyroid, Langerhans cell histiocytoses, plasmacytoma, Ewing's sarcoma, leukemias, and anaplastic carcinoma.

The definitive diagnosis of Merkel cell carcinoma requires the use of immunohistochemistry. The armamentarium of immunohistochemical stains that may be useful in diagnosing MCC is vast, and controversy exists as to which markers are best suited for this purpose. Anti-cytokeratin antibodies are the most sensitive markers for MCC, with various studies citing up to 100 % positive reactivity to anti-keratin antibodies to low molecular weight

cytokeratins (Fig. 6.4). A perinuclear dot-like pattern of positivity is characteristic for MCC and is a feature generally not observed in SCC [10–12]. Keratin reactivity favors the diagnosis of MCC and excludes melanoma and lymphoma. Diagnoses that MCC cannot be differentiated from with these markers include carcinoid and metastatic small cell lung cancer. Positive reactivity with anti-CK 8, 18, 19, and 20 also supports an epithelial-derived component of MCC. Among the anti-cytokeratin markers, most studies suggest that anti-CK 20 is highly specific for MCC and is thought to be a strong predictor of MCC when determining the diagnosis of small cell carcinomas. The newest marker used in identifying Merkel cell carcinomas is thyroid transcription factor 1 (TTF-1). It is a nuclear transcription factor expressed in thyroid and lung epithelial cells. TTF-1 belongs to a family of transcription factors that are expressed in the thyroid, lung, and certain regions of the brain. This marker is also found in pulmonary carcinomas, reacting with 72.5 % of adenocarcinomas, 83–100 % of small cell carcinomas, 100 % of atypical carcinoid tumors, and 75 % of neuroendocrine carcinomas. It is not, however, expressed at all in MCC. TTF-1 is a sensitive and specific marker for small cell lung carcinoma, and CK 20 is a sensitive but not 100 % specific marker for MCC. Thus, with the above information, it appears that a combination of TTF-1 and anti-CK 20 should provide the best sensitivity and specificity when needing to distinguish MCC from other small cell carcinomas.
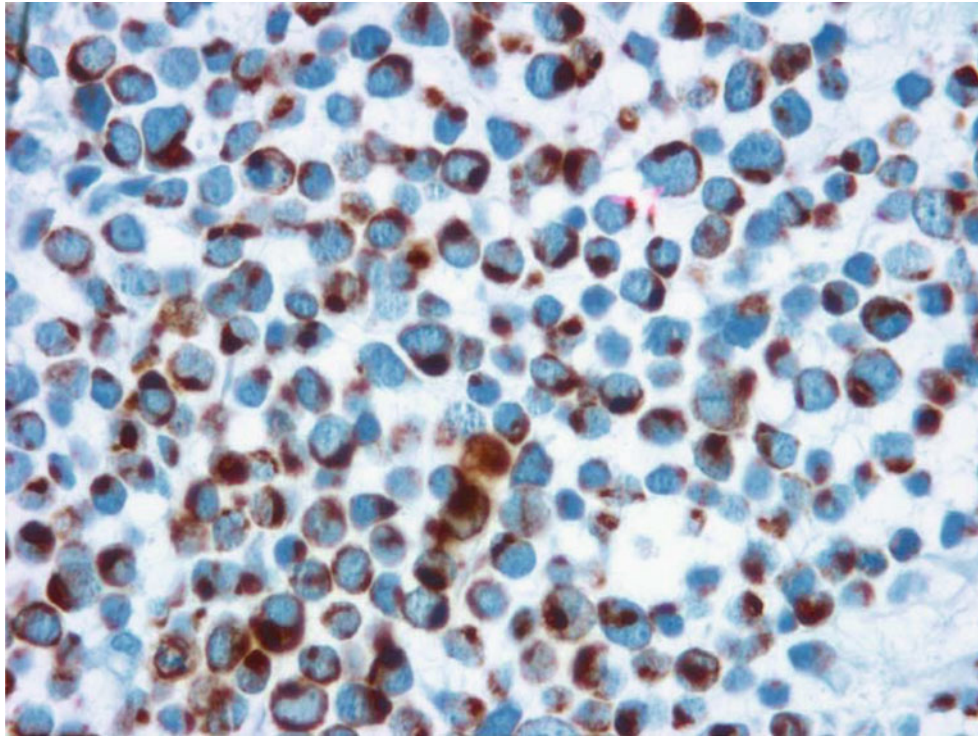
FIGURE 6.4. Dot-like paranuclear immunostaining with cytokeratin 20 in Merkel cell carcinoma.

Staging, based on the extent of local and systemic disease, is important in guiding treatment as well as determining prognosis. Stage I disease is a local disease without lymph node or systemic involvement. Stage II disease refers to regional lymph node disease without evidence of systemic spread. Stage III refers to metastatic disease.

Merkel cell carcinoma is a very aggressive malignancy in which metastatic disease is not uncommon. The 5-year survival rate of MCC patients is 64%, 39%, and 18% for primary tumors, lymph node metastases (and/or local recurrences), and distant metastases, respectively [6, 22]. It is considered to be the deadliest skin cancer, with a higher fatality rate than melanoma. Factors that have been found to be relevant to prognosis include tumor size and location, the sex and age of the patient, the stage of disease, and histologic characteristics. Tumors on the head and neck, and especially the lip, have the worst prognosis, followed by lesions on the trunk and extremities. Male sex has been reported to portend a worse prognosis, while age at diagnosis has been controversial. Histologic features associated with a poor prognosis include a mitotic rate of >10 per high-power field, small cell size, depth of invasion, infiltrative growth pattern, and evidence of vascular or lymphatic involvement [23].

Merkel cell carcinoma has been considered to follow a course similar to that of an intermediate or thick melanoma, but with a worse prognosis. Local recurrence usually occurs within 4 months of excision of the primary tumor and is not uncommon, occurring in 20–44% of cases, with few reports citing up to 70%. Regional nodal metastases have been reported to occur in 31–80% of MCC; however, only 12–31% of these cases are present at the initial presentation. They are more common in tumors of the head and neck, and most nodal metastases are discovered within 7–24 months of initial treatment. Nodal involvement is a significant prognostic indicator, with a 5-year survival rate of 48% for patients with nodal disease, as compared to 88% for those without nodal involvement. Distant metastases indicate a very poor prognosis and are the most important predictor of survival. They are found in 1/3 to 2/3 of patients with MCC, but are rarely present at initial presentation. The most common sites are lymph nodes, followed by the liver, bone, brain, lung, skin, and GI tract. Distant metastases are diagnosed at a mean time of 18 months after initial diagnosis. The mortality rate of patients with systemic metastases ranges from 67 to 74%, with death usually occurring within 6 months of detection of the metastases. Spontaneous regression is a rare phenomenon that has been noted to occur in some cases of Merkel cell carcinoma. As of 2002, ten cases in the literature have been reported.

Early diagnosis and treatment are essential due to the aggressiveness of MCC and its propensity for local recurrence and metastases. The principles of treatment for Merkel cell carcinoma are as follows: for localized disease, surgical excision is the standard of care, usually followed by adjuvant radiotherapy. Sentinel lymph node biopsy is recommended due to the propensity for metastasis. Patients who are node negative require no further surgical therapy. For those with nodal disease and metastasis che-

motherapy, using similar regimens as small cell carcinoma of the lung is recommended [22–25]. The following are recommendations based on each stage of disease [22–25]. Stage I and II (localized) disease should be treated with surgical excision, using wide local excision with 2–3-cm margins, dissecting to the fascia. Excision may be followed by sentinel lymph node biopsy and possible lymph node dissection when appropriate. Postoperative radiation may also be considered. Mohs micrographic surgery may also be used at this stage when feasible. The use of chemotherapy at this stage is not well defined and requires further investigation. Stage III (regional) disease requires wide local excision plus lymph node dissection if feasible, or optionally radiation therapy to primary nodal regions is recommended. The use of adjuvant chemotherapy is controversial but may be considered in higher-risk patients. Stage IV (distant) disease ultimately requires palliative care; however, surgery, chemotherapy, and radiotherapy may be used.

References

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972;105:107–10.
2. Nakatani M, Maksimovic S, Baba Y, Lumpkin EA. Mechanotransduction in epidermal Merkel cells. Pflug Arch Eur J Phy. 2014;467(1):101–8. http://www.ncbi.nlm.nih.gov/pubmed/25053537.
3. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319(5866):1096–100. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2740911/.
4. Di Paulo NC. Recognition of human oncogenic viruses by host pattern-recognition receptors. Front Immunol. 2014;5:353. http://www.ncbi.nlm.nih.gov/pubmed/25101093.
5. Hughes MP, Hardee ME, Cornelius LA, Hutchins LF, Becker JC, Gao L. Merkel cell carcinoma: epidemiology, target and therapy. Curr Dermatol Rep. 2014;3(1):46–53. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3931972/.
6. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat Rev Cancer. 2010;10(12):878–89. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3718018/#R34.
7. Erstad DJ, Jr JC. Mutational analysis of Merkel cell carcinoma. Cancers (Basel). 2014;6(4):2116–36. http://www.ncbi.nlm.nih.gov/pubmed/25329450.
8. Shuda M, et al. Human Merkel cell polyomavirus infection MCV T antigen expression in Merkel cell carcinoma, lymphoid tissues and lymphoid tumors. Int J Cancer. 2009;125:1243–9.
9. Cheng J, et al. Merkel Cell polyomavirus large T antigen has growth promoting and inhibitory activities. J Virology 2013; 87(11):6118–126.
10. Demetriou SK, Ona-Vu K, Sullivan EM, Dong TK, Hsu S, Oh DH. Defective DNA repair and cell cycle arrest in cells expressing Merkel cell polyomavirus T antigen. Int J Cancer. 2012;131(8):1818–27. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3352966/.
11. Harms PW, et al. Distinct gene expression profiles of viral- and non-viral associated Merkel cell carcinoma revealed by transcriptome analysis. J Invest Dermatol. 2013;133(4):936–45. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597750/.
12. Bhatia K, Goedert JJ, Modali R, Preiss L, Ayers LW. Increased p53 expression in MCV – cases. Int J Cancer. 2010;126(9):2240–6.
13. Waltari M, Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Association of Merkel cell polyomavirus infection with tumor p53, KIT, stem cell factor, PDGFR-alpha and survival in Merkel cell carcinoma. Int J Cancer. 2011;129(3):619–28. http://www.ncbi.nlm.nih.gov/pubmed/20949558/.
14. Afanasiev OK, et al. Merkel polyomavirus-specific T cells fluctuate with Merkel cell carcinoma burden and express therapeutically targetable PD-1 and Tim-3 exhaustion markers. Clin Cancer Res. 2013;19(19):5351–60. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790865/.
15. Shailender B, Afanasiev O, Nghiem P. Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer. Curr Oncol Rep. 2011;13(6):488–97. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112947/.
16. Becker JC. Merkel cell carcinoma. Ann Oncol. 2010;21(7):81–5. http://annonc.oxfordjournals.org/content/21/suppl_7/vii81.long.
17. Koljonen V, Kluger N, Sihto H, Böhling T. Lateral distribution of Merkel cell carcinoma in a nationwide cohort. J Eur Acad Dermatol Venereol. 2013;27(7):884–8. http://www.ncbi.nlm.nih.gov/pubmed/22741742.
18. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010;37(1):20–7. http://www.ncbi.nlm.nih.gov/pubmed/19638070/.
19. Marek L, Grzanka A, Chmielowska E, Jankowski M, Schwartz R, Czajkowsk R. Merkel cell carcinoma: an illustrative case and review. Postepy Dermatol Alergol. 2014;31(5):325–8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221346/.
20. Hapcic K, Panchal J, Stewart J, Levine N. Giant Merkel cell carcinoma involving the upper extremity. Dermatol Surg. 2001;27(5):493–4. http://www.ncbi.nlm.nih.gov/pubmed/11359501.
21. Poulsen M. Merkel cell carcinoma of skin: diagnosis and management strategies. Drugs Aging. 2005;22:219–29.
22. Paulson KG, Iyer JG, Byrd DR, Nghiem P. Pathologic nodal evaluation is increasingly commonly performed for patients with Merkel cell carcinoma. J Am Acad Dermatol. 2013;69(4):653–4. http://www.ncbi.nlm.nih.gov/pubmed/24034376/.
23. Tai P. A practical update of surgical management of Merkel cell carcinoma of the skin. ISRN Surg. 2013;2013:850797. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3570924/.
24. Miller SJ, et al. Merkel cell carcinoma. J Natl Compr Canc Netw. 2009;7(3):322–32. http://www.ncbi.nlm.nih.gov/pubmed/19401064/.
25. Tai P. Merkel cell cancer: update on biology and treatment. Curr Opin Oncol. 2008;20(2):196–200. http://www.ncbi.nlm.nih.gov/pubmed/18300770.
26. Cirillo F, Vismarra M, Cafaro I, Martinotti M. Merkel cell carcinoma: a retrospective study on 48 cases and review of literature. J Oncol. 2012;749030:9 pages. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3449125/.

7
Cutaneous Metastasis

■ Synonyms:	Cutaneous metastatic neoplasm, Sister Mary Joseph nodule
■ Etiology:	Hematogenous or lymphatic spread of primary tumor to umbilical skin, rarely direct extension/satellitosis; may also arise within remnant structures
■ Associations:	Primary malignancies (most commonly gastrointestinal and genitourinary); cancer family syndromes (e.g., hereditary breast ovarian cancer syndrome BRCA1/2, Muir-Torre)
■ Clinical:	Nodule, occasionally ulcerated, scalp most common site; rarely pulsatile in association with metastatic renal cell carcinoma; diffuse cutaneous skin color changes with diffuse cutaneous melanosis; diffuse cyanosis with metastatic carcinoid syndrome
■ Histology:	Most commonly adenocarcinoma in the dermis, lymphatic/vascular permeation, pyramidal orientation, foreign appearance, poor tumor differentiation, no connection with the epithelium
■ IHC repertoire:	Cytokeratins 7/20, carcinoembryonic antigen, p63, TTF-1
■ Staging:	Implies widespread metastatic disease
■ Prognosis:	Less than 1-year survival in most cases
■ Adverse variables:	None (ovarian primary may be associated with slightly better prognosis)
■ Treatment:	Surgery, chemotherapy, biologics

Cutaneous metastases occur in approximately 10 % of all cancer patients. The frequencies of cutaneous metastases correlate directly with the frequencies of primary malignancies. In women, breast carcinoma is the most common tumor to spread to the skin, followed by large intestine, melanoma, lung, and ovary. In men, primary tumors from the lung most commonly involve the skin, followed by tumors of the large intestine, melanoma, and squamous cell carcinomas of the oral cavity [1]. Metastases can affect any part of the body, with a disproportionate number involving the scalp (presumably due to increased circulatory volume). Overall, skin metastases represent the presenting sign of underlying malignancy in about 8 % of these patients [2]. In addition to cutaneous metastasis, additional dermatologic manifestations may occur with metastatic cancers. Diffuse cutaneous pigmentary alterations such as melanosis can occur in accord with metastatic melanoma. Cyanotic to erythodermatous skin can occur in association with malignant carcinoid syndrome due to metastatic carcinoid tumors.

An example of a well-known but uncommon presentation of a cutaneous metastasis is the Sister Mary Joseph nodule. In 1854, Baluff first described umbilical metastases; however, it wasn't until 1928 that Sister Mary Joseph, the head surgical nurse of Dr. William James Mayo, recognized the association between intra-abdominal malignancy and umbilical metastasis [3]. The term "Sister Mary Joseph nodule" was first mentioned by Hamilton Bailey in his 11th edition of "Demonstrations of Physical Signs in Clinical Surgery" in 1949 [4]. The term is commonly used to describe a malignant umbilical cancer associated with advanced-stage intra-abdominal and gynecological malignancy demonstrating a poor prognosis.

The pathogenesis of umbilical metastasis is not entirely elucidated; however, mechanisms of spread to the umbilicus from an intra-abdominal source include direct

TABLE 7.1. Percentage of cases of umbilical metastasis in relation to site of the primary tumor.

Site of primary tumor	% of cases of umbilical metastasis
Stomach	28
Pancreas	15
Sigmoid colon	10
Ovary	10
Endometrium	3
Cecum	3
Transverse colon	3
Penis	3
Cervix	3
Appendix	3
Liver	3

FIGURE 7.1. (a) Periumbilical nodule seen in Sister Mary Joseph nodule. (b) Gross specimen removed from the umbilicus.

hematogenous spread, transperitoneal spread via lymphatics, or through remnant embryological structures including the falciform ligament, medical umbilical ligament, or a remnant of the umbilical duct [4].

Umbilical metastases involve from 5 to 10 % of tumors involving the abdomen and may be the presenting sign of an internal malignancy in up to 45 % of cases. In one study, 57 % of tumor nodules located in the umbilicus were benign [5]. Neoplasms originating in the gastrointestinal tract account for the great majority of the metastatic processes (Table 7.1) [1]. Other primary neoplasms with umbilical metastases have been reported less commonly. These include adenocarcinomas of the gallbladder [6], renal cell carcinoma [7], and lymphoma [8].

Umbilical metastases most commonly present as firm nodules. A less common presentation is that of an indurated plaque. These growths rarely ulcerate and are not usually painful or tender. Hyperkeratosis is seen in some cases, but is unusual in this location (Fig. 7.1a, b). The tumor nodule with dermal sclerosis is apparent on the cut specimen. They are more common in women, in part due to the contribution of ovarian carcinomas to this clinical presentation [9].

Breast cancer represents the most common cancer in women when excluding non-melanoma skin cancer; recognition of cutaneous metastasis of breast carcinoma remains an important diagnostic aim of the physician in order to facilitate treatment of the systemic spread of the cancer (Fig. 7.2a, b). Types of metastatic cutaneous breast cancers include inflammatory breast carcinoma (also known as carcinoma erysipeloides), peau d'orange, telangiectatic, en cuirasse, and alopecia neoplastica. Inflammatory breast carcinoma presents with erythematous, edematous, indurated, warm patches or plaques with well-defined borders. Peau d'orange refers to a dimpled orange peel appearance of the breast caused by lymphedema resultant from tumor infiltrate within the dermal lymphatics. Telangiectatic metastatic carcinoma presents
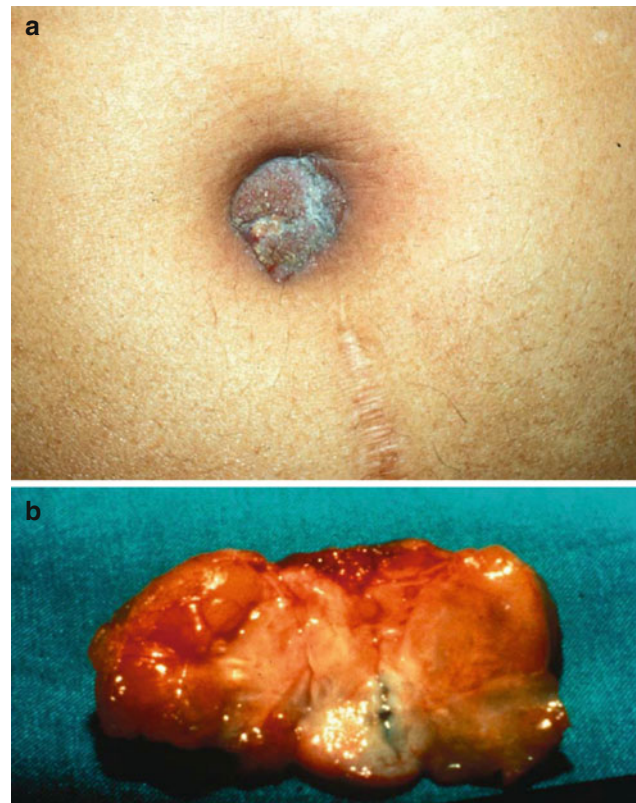
with purple papulovesicles on an erythematous base resulting from dilated blood vessels. Breast cancer en cuirasse is a rare cutaneous metastasis that presents with scattered, elevated, indurated nodules or plaques on an erythematous base. A common clinical pattern of cutaneous metastasis of breast cancer is alopecia neoplastica, a condition characterized by indurated circular plaques or patches of painless, nonpruritic, cicatricial alopecia on the scalp.

Lung cancer may present with erythema gyratum repens, a paraneoplastic rash characterized by erythematous plaques in concentric bands arranged in parallel rings lined by scale that often presents several months before the primary cancer is diagnosed. Additional dermatologic manifestations of common cancers include nodules underneath the skin in Trousseau's syndrome associated most notably with pancreatic cancer; cyanosis in accord with carcinoid syndrome from colorectal cancer; the acute onset of multiple seborrheic keratoses, termed the Leser-Trélat sign, in association with gastrointestinal carcinomas; thickening of the palms and soles, termed palmoplantar keratoderma (also Howel-Evans syndrome) in association with esophageal

FIGURE 7.2. (**a**, **b**) Clinical examples of metastatic breast carcinoma.

cancer; and paraneoplastic dermatomyositis from gyneco-logic malignancy. Rare dermatologic manifestations include diffuse pigmentation associated with melanoma termed diffuse cutaneous melanosis; painful, erythematous nodules, plaques, or papules accompanied by fever and peripheral neutrophilia in Sweet's syndrome; and cutaneous leiomyomas and uterine leiomyomas associated with renal cell carcinoma in Reed's syndrome.

The histologic features of the cutaneous metastasis vary with the origin of the primary lesion; however, several characteristics are observed in most cases including a foreign histologic appearance, vascular or lymphatic permeation, pyramidal orientation, and no connection to the epithelium. In about 75–90 % of SMJ nodule cases, the primary tumor is an adenocarcinoma, and the resulting SMJ nodule has the histologic features of adenocarcinoma [5, 9]. Glandular structures course throughout the dermis, often surrounded by desmoplastic stroma. The histologic features recapitulate the features of the primary tumor to different degrees. Metastases from colon carcinomas may demonstrate tall columnar epithelial lining to the glandular structures and may produce mucin. Ovarian metastases may be characterized by mucinous or serous type of glandular epithelia. In all cases, the better-differentiated neoplasms will recapitulate their sites of origin closely, while the less-differentiated ones are undifferentiated adenocarcinomas that may be difficult to further classify (Figs. 7.3, 7.4, 7.5, and 7.6).

Immunostains with antibodies directed against cytokeratins 7 and 20, carcinoembryonic antigen (CEA), and estrogens and progesterones may be helpful in further characterizing cutaneous metastases. Colon carcinomas often express cytokeratin 20 and CEA, but only rarely

strongly express cytokeratin 7. Pancreatic tumors are negative for cytokeratins 7 and 20 and do not contain estrogen or progesterone receptors. Breast, lung, and gastric neoplasms frequently express cytokeratin 7 and are often negative for cytokeratin 20. Melanoma, esophageal, and hematologic neoplasms are negative for cytokeratins 7 and 20, whereas renal, ovarian, and uterine neoplasms are positive for both cytokeratins 7 and 20. Biliary duct carcinomas may also strongly express both cytokeratins 7 and 20 [9]. Additional markers include p63 and TTF-1. Primary cutaneous adnexal carcinomas express p63, whereas metastatic adnexal adenocarcinomas to the skin are negative for p63. Lung cancers commonly express TTF-1; thus, TTF1 positivity demonstrates the tumor is of lung origin.

The appearance of cutaneous metastases portends an ominous prognosis. Surgery and chemotherapy for Sister Mary Joseph nodules have been used with some success, but in most cases, the patient succumbs to widespread metastatic disease within a year of diagnosing the umbilical nodule [10]. Patients with primary ovarian carcinomas involving the umbilicus may have a slightly better prognosis than those with metastases from other sites [11]. Biologic agents also demonstrate utility in the treatment of metastatic cancers such as metastatic melanoma and metastatic breast cancer. It is important to note that while cutaneous metastases may be treated for cosmetic purposes, the prognosis of the patient is largely contingent upon the characteristics of the primary malignancy.

The clinical, histologic, and immunohistochemical findings of the aforementioned syndromes associated with common neoplasms demonstrating cutaneous metastasis or dermatologic manifestations are described (Table 7.2).
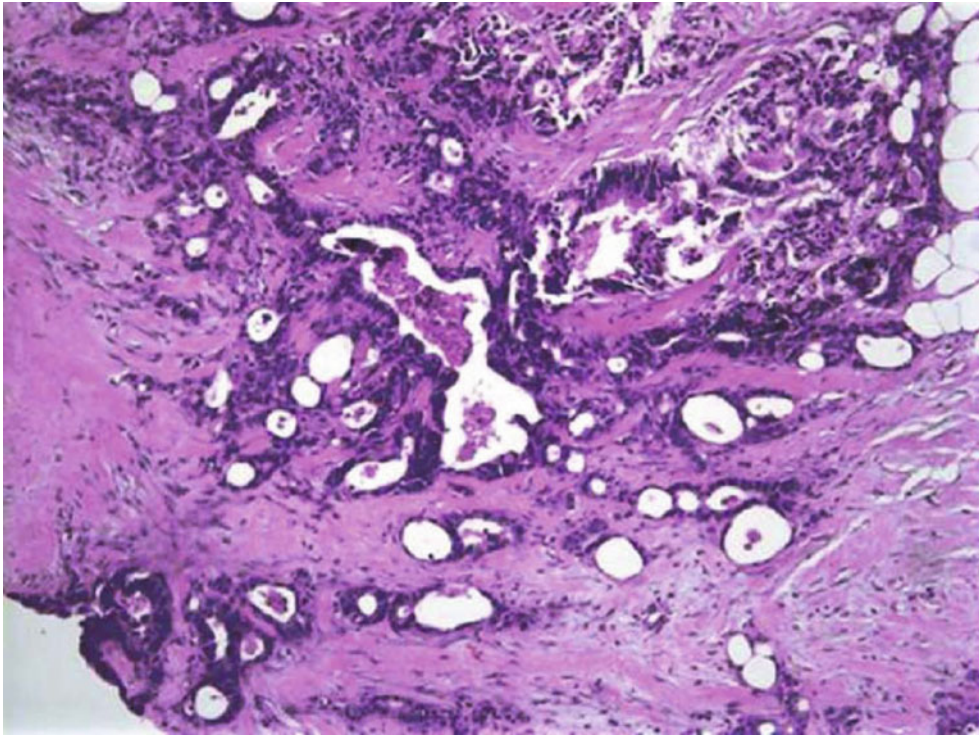
Figure 7.3. Medium-power photomicrograph depicting metastatic colon cancer. Note ductular structures embedded in dense (desmoplastic) collagenous stroma.
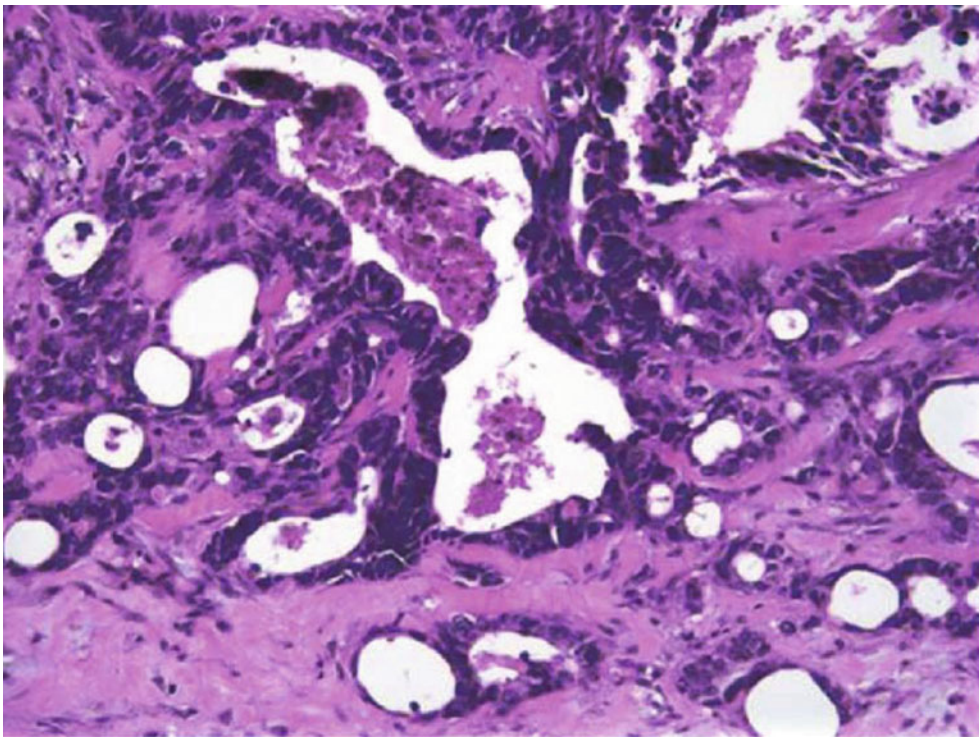
Figure 7.4. High-power photomicrograph depicting glands with columnar lining and inspissated luminal secretions.
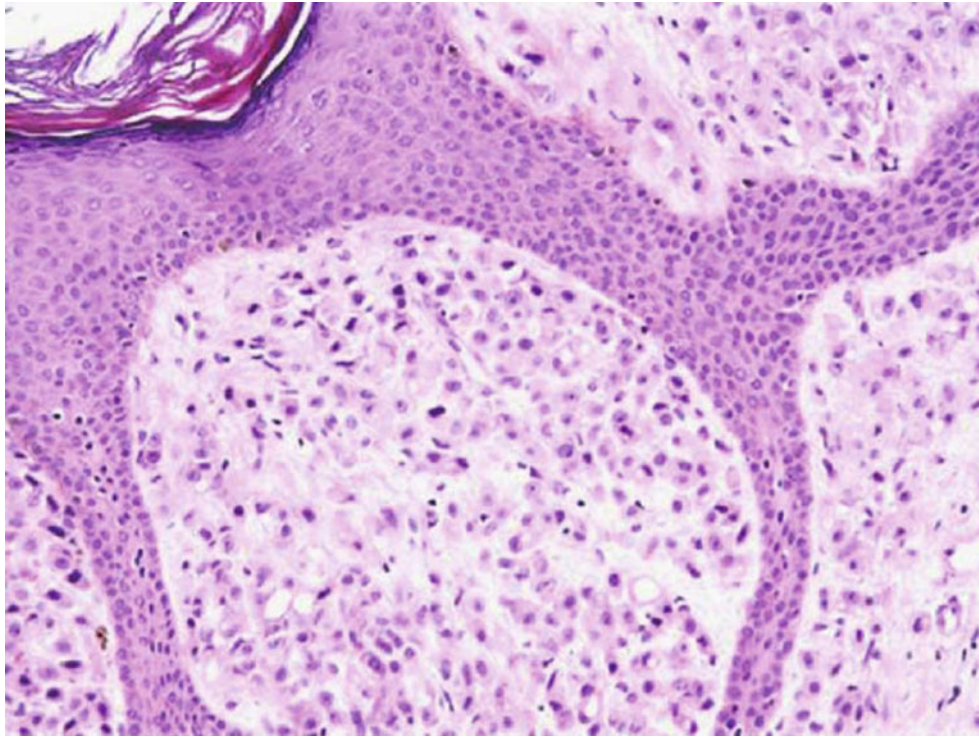
Figure 7.5. Medium-power photomicrograph depicting metastatic gastric carcinoma. Note characteristic signet rings.
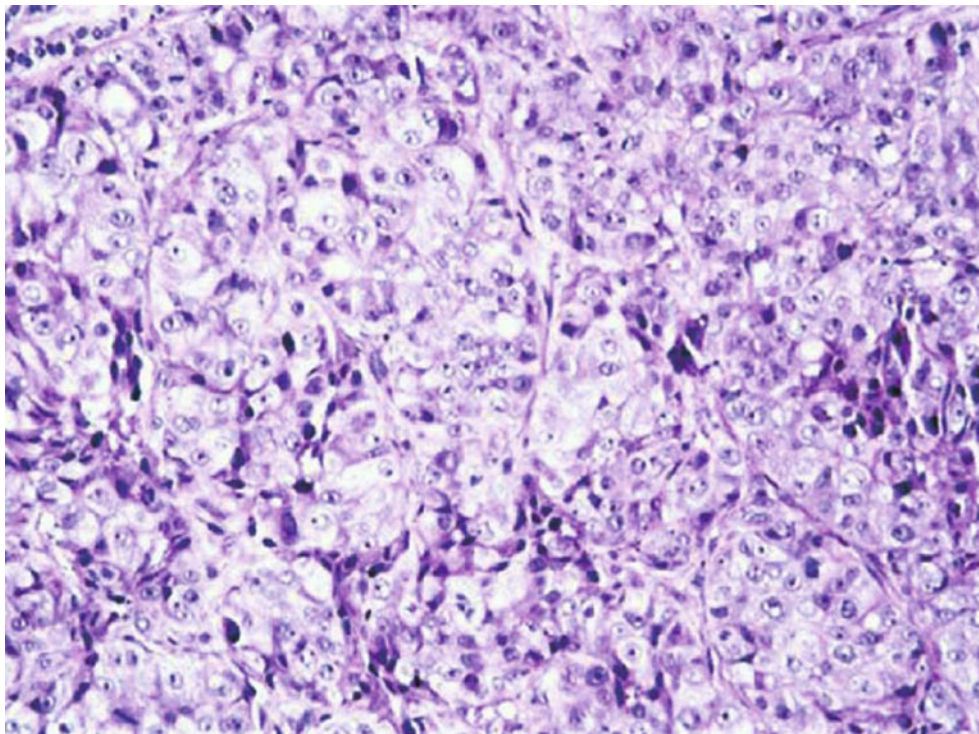
Figure 7.6. This undifferentiated neoplasm is a metastasis from the prostate, identified by staining with prostate-specific antigen.

TABLE 7.2 Syndromes associated with common cancers with cutaneous metastasis or dermatologic manifestations

Primary cancer	Breast	Lung	Pancreatic	Melanoma	Colorectal	Esophageal	Gastric	Uterus/ovary	Hematologic	Kidney
Syndrome	Inflammatory En cuirasse Peau d'orange Telangiectatic Alopecia neoplastica	Erythema gyratum repens	Trousseau's syndrome	Diffuse cutaneous melanosis	Carcinoid syndrome Leser-Trélat sign	Howel-Evans syndrome	SMJ nodule	Dermatomyositis	Sweet's syndrome (acute febrile neutrophilic dermatosis)	Reed's syndrome; hereditary leiomyomatosis and renal cell carcinoma
Clinical	Inflammatory– erythema, edema, and warmth of the skin overlying the breast En cuirasse – elevated, indurated nodules or plaques Peau d'orange – erythematous, thickened skin with an orange skin appearance; dimpling and nipple retraction may be observed Telangiectatic – purple papulovesicles on an erythematous base with pruritus Alopecia neoplastica – solitary or multiple plaques or patches with painless, nonpruritic alopecia	Paraneoplastic rash with wavy, erythematous, concentric bands arranged in parallel rings lined by an edge of scale described as "woody grained" [12]	Spontaneous, recurrent, or migratory venous thromboses; arterial emboli from nonbacterial thrombotic endocarditis	Diffuse skin and mucosal darkening	Carcinoid – dermatologic findings may include flushing, cyanosis, rosacea, features of pellagra, and scleroderma [13] Leser-Trélat sign – acute onset of multiple seborrheic keratoses	Thickening of the skin of the palms and soles with pruritus and fissures	Variously colored, firm nodule located at the umbilicus	Erythematous papules and plaques on the metacarpophalangeal and interphalangeal joints (Gottron's papules). Violaceous eruption and edema of the upper eyelids (heliotrope rash). Confluent, macular erythema on the anterior neck and chest (Shawl sign)	Painful, edematous, erythematous plaques, papules, or nodules	Painful, multiple, firm, skin- or pink-colored papules or nodules

Histology	Inflammatory – neoplastic cells within dilated blood vessels; a perivascular lymphocytic and plasmacytic infiltrate is often present En cuirasse – fibrosis with neoplastic cells Peau d'orange – neoplastic cells within dermal lymphatics Telangiectatic – neoplastic cells and erythrocytes in aggregates; dilated blood vessels in the papillary dermis are observed Alopecia neoplastica – infiltrated neoplastic cells surrounding hair follicles	Nonspecific histology including acanthosis, mild hyperkeratosis, spongiosis, and focal parakeratosis within the epidermis and superficial dermal tissues A monocytic, histiocytic, or lymphocytic perivascular infiltrate in the superficial plexus may be observed	Neoplastic cells surrounded by fibrous stroma at the primary site; veins with fibrinous thrombi; inflammatory infiltrate in the vessel wall	Dermal melanin pigment in the extracellular connective tissue, histiocytes, fibroblasts, and endothelial cells Epidermal melanocyte hyperplasia [14]	Carcinoid – nests of neuroendocrine cells demonstrating round nuclei, "salt and pepper" chromatin and moderate clear cytoplasm Leser-Trélat – histopathologic exam of skin specimens demonstrating seborrheic keratosis	Palmar and plantar keratoderma, exaggerated rete ridges	Histologic features are similar to the primary cancer	Epidermal atrophy, hyperkeratosis, mild perivascular lymphocytic infiltrate, telangiectasia, basal layer vacuolization [15]	Diffuse mature neutrophilic infiltrate in the upper dermis [16]	Cutaneous leiomyomas are poorly circumscribed lesions composed of interlaced bundles of smooth muscle fibers and collagen bundles in the dermis, with extension into subcutaneous tissues Uterine leiomyomas demonstrate whirled bundles of smooth muscle cells with elongated nuclei Renal cell carcinoma (most commonly type II papillary seen with HLRCC) demonstrates large cells with abundant cytoplasm and high-grade owl eye nuclei [17]
IHC	CK 7 positive CK 20 negative	CK 7 positive CK 20 negative TTF-1 positivity with cancer of lung origin	CK 7 negative CK 20 negative	CK 7 negative CK 20 negative	CK 7 negative CK 20 positive	CK 7 negative CK 20 negative	CK 7 positive CK 20 negative p63 negativity with adnexal adeno-carcinoma metastatic to the skin	CK 7 positive CK 20 positive	CK 7 negative CK 20 negative	CK 7 positive CK 20 negative

References

1. Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol. 1995;33:161–82.

2. Lookingbill DP, Spangleer N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol. 1993;29:228–36.

3. Menzies S, Chotirmall SH, Wilson G, O'Riordan D. Sister Mary Joseph nodule. BMJ Case Rep. 2015;2015. doi:10.1136/bcr-2014-206808.

4. Dar IH, Kamili MA, Dar SH, Kuchaai FA. Sister Mary Joseph nodule-a case report with review of literature. J Res Med Sci. 2009;14(6):385–7.

5. Steck WD, Helwig EB. Tumors of the umbilicus. Cancer. 1965;18:907–15.

6. Cosentini T, Tempesta R, Gentile F, Colavita N. Sister Mary Joseph nodule secondary to gallbladder carcinoma. Radiol Med (Torino). 2003;105:391–4.

7. Chen P, Middlebrook MR, Goldman SM, Sandler CM. Sister Mary Joseph nodule from metastatic renal cell carcinoma. J Comput Assist Tomogr. 1998;22:756–7.

8. Dornier C, Reichert-Penetrat S, Barbaud A, Kaisse W, Schmutz JL. Lymphoma presenting as Sister Mary-Joseph's nodule. Ann Dermatol Venereol. 2000;127:732–4.

9. Cabibi D, Licata A, Barresi E, Craxi A, Aragona F. Expression of cytokeratin 7 and 20 in pathological conditions of the bile tract. Pathol Res Pract. 2003;199:65–70.

10. Touraud JP, Lentz N, Dutrone Y, Mercier E, Sagot P, Lambert D. Umbilical cutaneous metastasis (or Sister Mary Joseph's nodule) disclosing an ovarian adenocarcinoma. Gynecol Obstet Fertil. 2000;28:719–21.

11. Majmudar B, Wiskind AK, Croft BN, Dudley AG. The Sister (Mary) Joseph nodule: its significance in gynecology. Gynecol Oncol. 1991;40:152–9.

12. Gore M, Winters ME. Erythema gyratum repens: a rare paraneoplastic rash. West J Emerg Med. 2011;12(4):556–8. doi:10.5811/westjem.2010.11.2090.

13. Bell HK, Poston GJ, Vora J, Wilson NJ. Cutaneous manifestations of the malignant carcinoid syndrome. Br J Dermatol. 2005;152(1):71–5.

14. Bohm M, Schiller M, Nashan D, Stadler R, Luger TA, Metze D. Diffuse melanosis arising from metastatic melanoma: pathogenetic function of elevated melanocyte peptide growth factors. J Am Acad Dermatol. 2001;44(5):747–54. doi:S0190-9622(01)51712-0 [pii].

15. Nakanishi K, Cualing H, Husseinzadeh N. Dermatomyositis as a presenting symptom of ovarian cancer. Obstet Gynecol. 1999;94(5 Pt 2):836–8.

16. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007;2:34.

17. Choudhary S, McLeod M, Torchia D, Romanelli P. Multiple cutaneous and uterine leiomyomatosis syndrome: a review. J Clin Aesthet Dermatol. 2013;6(4):16–21.

8

Paget's Disease

■	Synonyms:	Extramammary Paget's disease and mammary Paget's disease
■	Etiology:	Ductular extension of carcinoma from the breast, genitourinary system, gastrointestinal tract, or apocrine glands and in situ malignant transformation
■	Associations:	Underlying adenocarcinoma of the breast (mammary) or genitourinary or gastrointestinal carcinoma (extramammary) or primary appendageal adenocarcinoma
■	Clinical:	Scaly, erythematous patch on the nipple (mammary) or anogenital region (extramammary Paget's)
■	Histology:	Large, atypical cells at all levels of the epidermis
■	IHC repertoire:	Cytokeratin 7, CEA, and EMA
■	Staging:	Essential to workup for underlying adenocarcinoma
■	Prognosis:	Excellent if no underlying carcinoma; poor if internal carcinoma is present
■	Adverse variables:	Dermal invasion by neoplastic cells; association with underlying malignancy
■	Treatment:	Surgery (topical chemotherapy, radiation)

Mammary Paget's disease was first described by Sir James Paget in 1874 [1]. Mammary Paget's disease is an uncommon condition, representing about 1–4.3 % of all breast cancers [2]. Extramammary Paget's disease was first described by Radcliffe Crocker in 1889 [3].

There are currently two theories that postulate the development of Paget's disease. The epidermotropic (ductal) theory holds that the Paget cells are duct cancer cells that have migrated along the basement membrane of the underlying ducts to the epidermis of the nipple [4]. The second theory, in situ malignant transformation or degeneration from existing cells, postulates that the Paget cell is a malignant keratinocyte in situ; thus, this theory defines Paget's disease as an in situ carcinoma without underlying cancer of the breast [5].

Mammary Paget's disease and extramammary Paget's disease represent two clinical conditions with potentially serious consequences for the patient. Mammary Paget's disease is associated with underlying carcinoma of the breast in virtually all cases. Exact incidence numbers vary, but with meticulous serial sections of major ducts entering into the nipple, foci of ductular carcinoma are identified in most cases [6]. The disease has the same epidemiologic characteristics as breast carcinoma, independent of the presence of Paget's disease. It is most frequently encountered in middle-aged to elderly women, and it may be unilateral or bilateral. Mammary Paget's disease presents as an erythematous, scaling patch on the nipple (Fig. 8.1).

The clinical differential diagnosis usually includes squamous cell carcinoma in situ and, most commonly, eczematous processes.

Extramammary Paget's disease has an identical appearance but is located in areas with abundant apocrine glands (Fig. 8.2).

The most frequently involved site is the anogenital region, though cases have been reported in the axillae and within the external auditory canal. Extramammary Paget's disease is slightly more common in women and is more frequent in elderly patients [7]. The relationship between underlying carcinomas is less strong with extramammary Paget's disease. Incidence estimates range from 0 to 54 % of cases, depending upon series [8]. In approximately 25 % of these cases, the underlying tumor appears to arise from apocrine or (less commonly) eccrine glands [9]. 10–15 % of these cases have underlying tumors of the genitourinary

Figure 8.1. Scaly eruption centered on the nipple in Paget's disease.

Figure 8.2. The anogenital region is a frequent site of involvement with extramammary Paget's disease.

or gastrointestinal tracts [7]. Cases of extramammary Paget's disease involving the anogenital region seem to have a higher association with underlying carcinoma.

The histologic features of Paget's disease of the nipple and extramammary Paget's disease are identical except for site-specific anatomic variations. Large cells with abundant pale cytoplasm are present at all levels of the affected epidermis (Fig. 8.3).

The atypical cells may display vesicular nuclei, and nucleoli are often visible, though not usually as prominent as those seen in melanoma cells (Fig. 8.4).

There is no tendency for nest formation by the atypical cells. In some cases, intracytoplasmic vacuoles may be present, suggesting early ductular differentiation. This finding can be accentuated with the use of a periodic acid-Schiff stain that demonstrates cytoplasmic acidic mucopolysac-

charides. The background epidermis is often acanthotic and spongiotic, with overlying parakeratosis.

The histologic differential diagnosis includes entities characterized by individual, atypical intraepidermal cells. The major differential possibilities include malignant melanoma and squamous cell carcinoma in situ. In most cases, it is useful to make this distinction with the use of immunostains. Melanoma cells strongly express S100 protein, an antigen that is occasionally expressed weakly and focally by Paget's disease cells (especially when they are ductular breast carcinoma cells). Squamous cell carcinoma expresses some pan-cytokeratin markers, as do the cells in Paget's disease. The most useful distinguishing markers are cytokeratin 7 (Fig. 8.5), which is expressed by neither the cells in malignant melanoma nor those in squamous cell carcinoma in situ, and epithelial membrane antigen (EMA), which has a similar staining profile (Fig. 8.6).

CAM5.2 and carcinoembryonic antigen (CEA) have also been used with good success in establishing the diagnosis. The use of an antibody panel using the reagents suggested makes the distinction between these entities very straightforward in most cases. It should be noted, however, that melanoma is not usually in the clinical differential diagnosis of this process.

In cases of extramammary Paget's disease, the neoplastic cells within the epidermis may represent upward extension of malignant transformation of cutaneous appendages (i.e., apocrine or eccrine structures). In these cases, similar-appearing tumor cells are apparent within the glandular apparatus. In more advanced cases, the same tumor cells may violate the basement membrane, invading the dermis. Lymphatic involvement has also been reported. This portends a significantly worse prognosis [10]. In other cases of extramammary Paget's disease, the tumor cells represent upward extension of underlying tumors arising within the genitourinary system (most commonly, bladder) or gastrointestinal tract (most commonly, colon). In these cases, invasion of the dermis denotes a more aggressive neoplasm, but careful histologic evaluation of the primary tumor is necessary for determining accurate prognostic data.

Paget's disease (mammary and extramammary) is treated with locally destructive therapy. Complete surgical excision is usually the first line of treatment for suitable candidates. Prior to excision, a staging workup is performed in order to isolate any underlying malignancies. In Paget's disease of the nipple, the underlying ductular tissue is removed, as a minimum, in most cases in order to identify any associated breast carcinoma. In extramammary Paget's disease, screening procedures are initiated prior to the surgical procedure. For patients who are not candidates for surgery, radiation and topical chemotherapeutic agents have been used with some success.
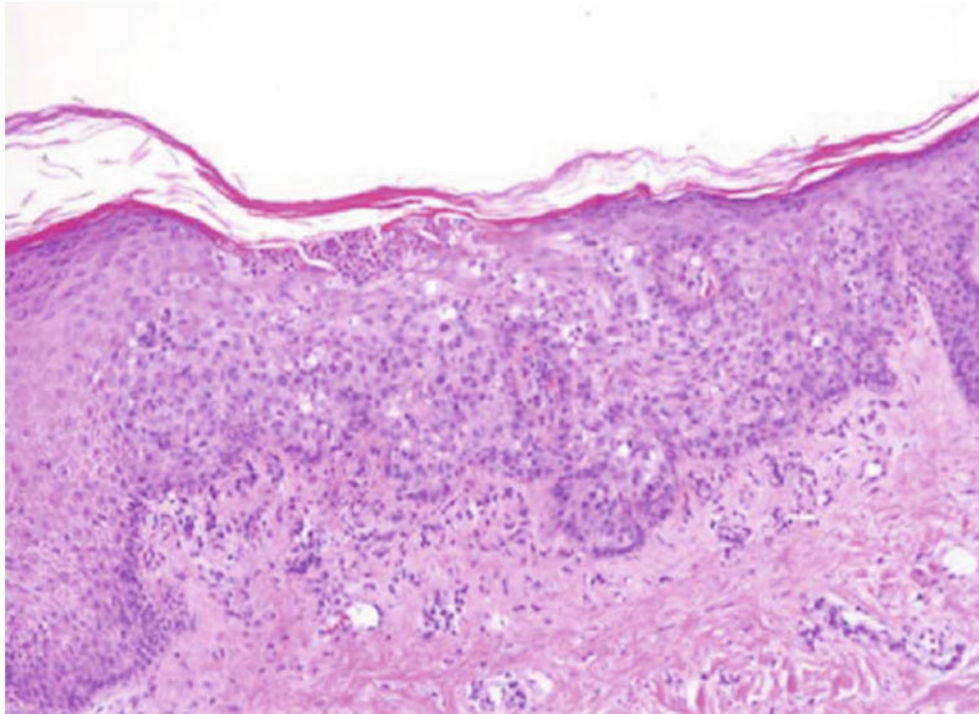
FIGURE 8.3. Medium-power photomicrograph depicting scattered atypical clear cells and Paget's cells occupying all levels of the epithelium.
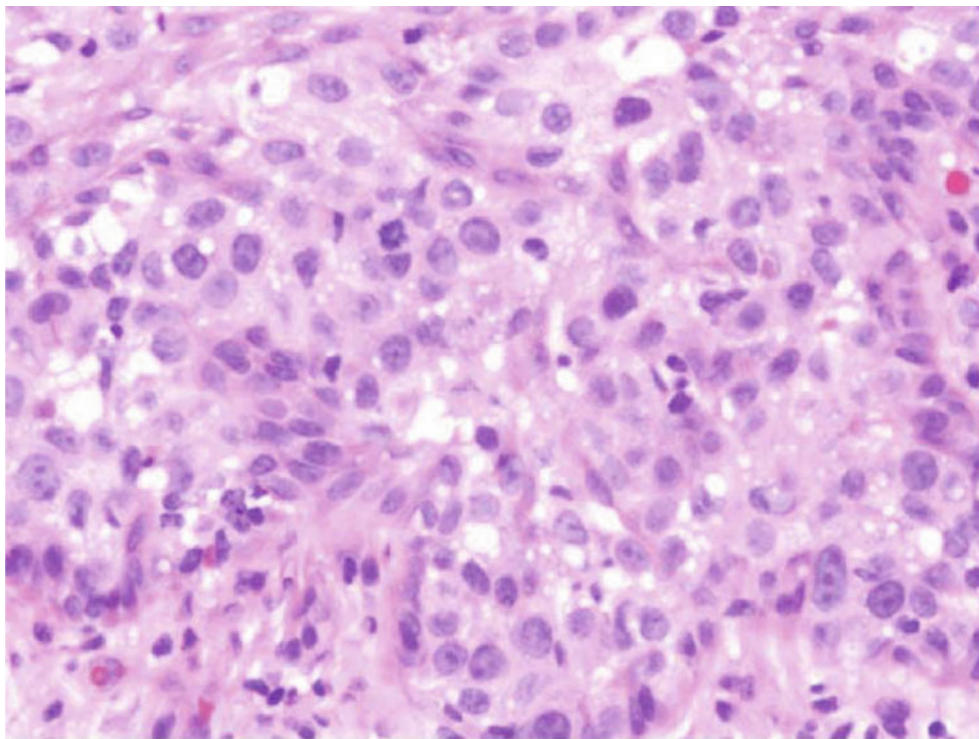
FIGURE. 8.4. The neoplastic cells in Paget's disease have vesicular nuclei with prominent nucleoli.
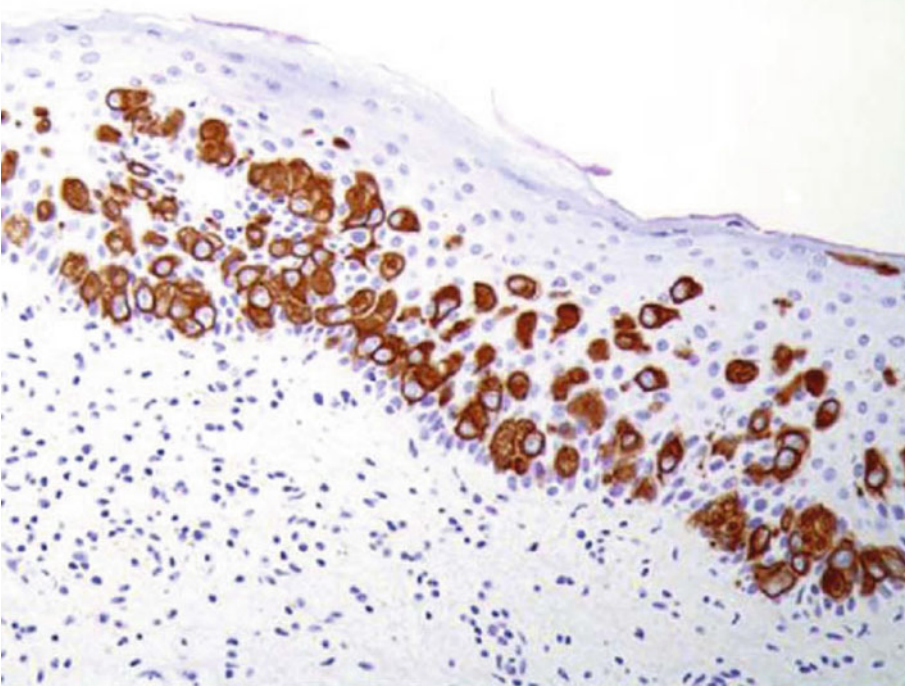
Figure 8.5. Cytokeratin 7 is strongly expressed by intraepithelial neoplastic cells, but not by the background keratinocytes within the epidermis.
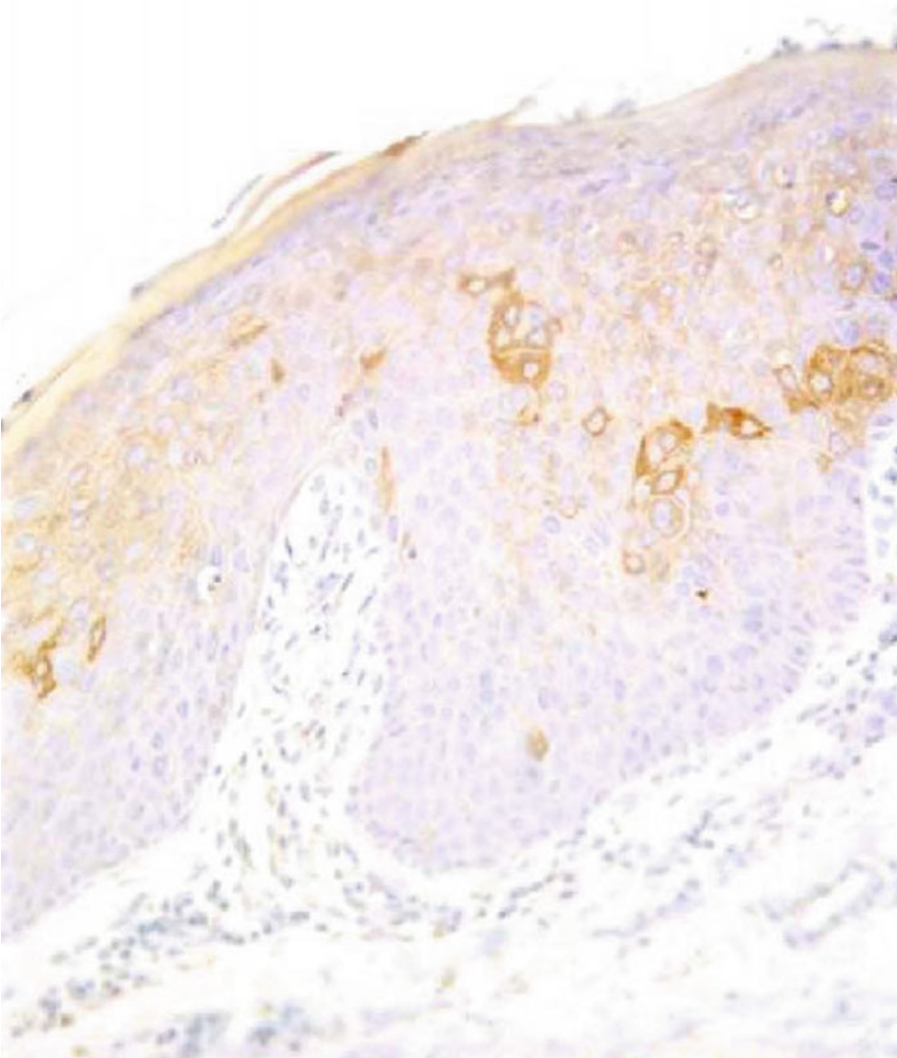
Figure 8.6. Epithelial membrane antigen is expressed by tumor cells in Paget's disease, but not by the background keratinocytes within the epithelium.

References

1. Classic articles in colonic and rectal surgery: Sir James Paget, 1814–1899, on disease of the mammary areola preceding cancer of the mammary gland. Dis Colon Rectum. 1980;23(4):280–1.

2. Günhan-Bilgen I, Oktay A. Paget's disease of the breast: clinical, mammographic, sonographic and pathologic findings in 52 cases. Eur J Radiol. 2006;60(2):256–63.

3. Crocker HR. Paget's disease, affecting the scrotum and penis. Trans Pathol Soc Lond. 1889;40:187–91.

4. Muir R. The pathogenesis of paget's disease of the nipple and associated lesions. Br J Surg. 1935;22(88):728–37.

5. Lagios MD, Westdahl PR, Rose MR, Concannon S. Paget's disease of the nipple. Alternative management in cases without or with minimal extent of underlying breast carcinoma. Cancer. 1984;54(3):545–51.

6. Ashikari R, Park K, Huvos AG, Urban JA. Paget's disease of the breast. Cancer. 1970;26:680–5.

7. Lee SC, Roth LM, Ehrlich C, Hall JA. Extramammary Paget's disease of the vulva: a clinicopathology study of 13 cases. Cancer. 1977;39:2540–9.

8. Chand JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. J Am Acad Dermatol. 1985;13:1009–14.

9. Piura B, Zirkin HJ. Vulvar Paget's disease with an underlying sweat gland adenocarcinoma. J Dermatol Surg Oncol. 1988;14:533–7.

10. Murata Y, Kumano K, Tani M. Underpants pattern erythema: a previously unrecognized cutaneous manifestation of extramammary Paget's disease of the genitalia with advanced metastatic spread. J Am Acad Dermatol. 1999;40:949–56.

9

Kaposi Sarcoma

■ Synonyms:	Granuloma multiplex hemorrhagicum and idiopathic multiple pigmented sarcomas
■ Etiology:	Vascular hyperproliferation induced by human herpesvirus-8
■ Associations:	HIV/AIDS, Mediterranean and Eastern European origin, and MSM
■ Clinical:	Violaceous patches, plaques, and tumor nodules
■ Histology:	Clusters of dermal slit-like vascular spaces and variable spindle cell predominance depending on stage of disease
■ IHC:	LNA1 of HHV-8
■ Prognosis:	Good if disease is limited and HIV/AIDS is treated appropriately
■ Treatment:	Antiretrovirals and destructive treatments; combination chemotherapy for extensive disease

Moritz Kaposi originally gathered five patients with "idiopathic multiple pigmented sarcomas of the skin," described them in detail, and published his data in 1872 [1]. This entity, subsequently known as Kaposi sarcoma, has become a complicated neoplastic disease with multiple clinical subtypes, which are neither pigmented nor idiopathic. Differences in genetic background and immunologic status create a variety of cutaneous and systemic manifestations which vary from indolent to frighteningly aggressive biologic behavior.

There are currently four subtypes of Kaposi sarcoma (KS), the first of which was described by Kaposi himself. Older men of Mediterranean and Eastern European origin develop multiple vascular neoplasms on the lower extremities, generally with indolent behavior, which in this subtype is deemed "classic." "Endemic" Kaposi sarcoma refers to that which occurs mainly in sub-Saharan Africa, in patients without immune dysfunction. Endemic KS can be both indolent or aggressive and involves the extremities (similar to classic KS). The aggressive subtype often occurs in young children and can present with widespread visceral and lymph node involvement. "Latrogenic" KS occurs in those who are immunosuppressed, often for long periods of time, often in the context of transplant-associated immunosuppression. Lastly, the most recently described type is "epidemic" KS, associated also with immunosuppression, this

time from the devastating effects of the human immunodeficiency virus (HIV).

Through the history of the study of Kaposi sarcoma from 1872 to the late twentieth century, an unexplained phenomenon was contemplated in relation to the seemingly restricted nature of the geographic location, ethnic group, and immune status of the vast majority of patients. The link between virus and malignancy was first described to skeptics in the scientific community by Peyton Rous and the Rous sarcoma virus in chickens in 1910 [2]. The first carcinogenic virus in humans, Epstein-Barr virus, was found to be associated with Burkitt lymphoma in 1958 [3]. After hepatitis B virus was found to be associated with hepatocellular carcinoma, it became clear that the virus could be a carcinogen. Epidemiologic patterns of viral induction of malignancy included isolation of cancer cases to specific geographic areas and ethnic groups, as well as association with immunosuppression. Given its relative lack of morbidity and relatively low incidence, research in the area of the spectral KS virus was slow.

A surge of aggressive Kaposi sarcoma cases related to immunosuppression from the horrifying first years of the HIV epidemic brought the disease back into the crosshairs of the scientific community [4]. It became the stigmatizing purple emblem of the epidemic, particularly in gay men with advanced disease. Patients presented with KS patches,
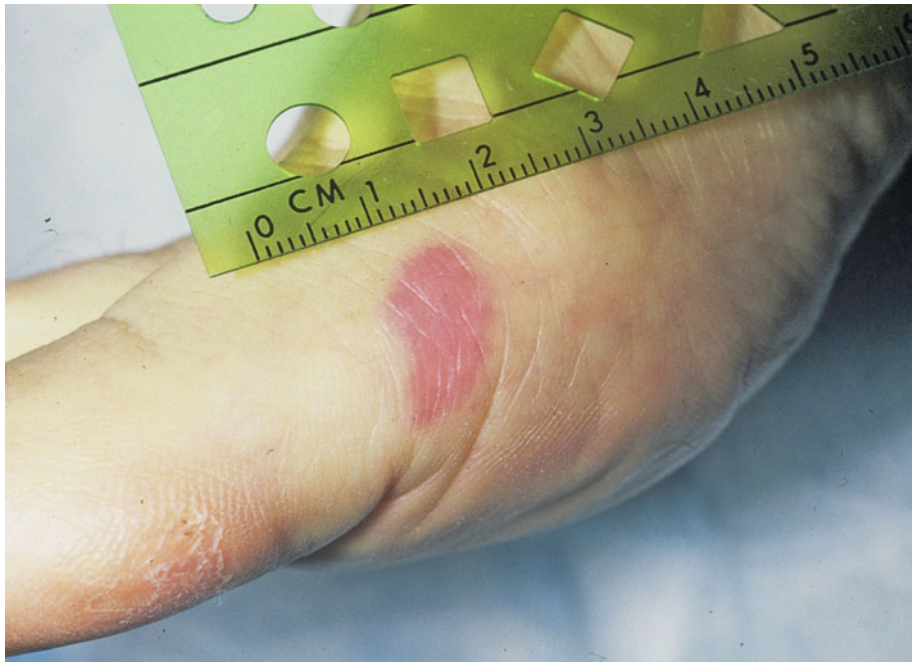
FIGURE 9.1. Kaposi sarcoma: violaceous smooth well-defined patch on the foot.

nodules, and tumors widespread throughout the skin, lungs, and gastrointestinal tract, a nearly unrecognizable version of the disease, with high morbidity and mortality. Mercifully, as treatment for HIV/AIDS improved and CD4 counts across the country began to rise, cases of aggressive KS began to drop.

Finally, in 1994 the virus which would eventually prove to be causative in all cases of Kaposi sarcoma was discovered by Chang and colleagues [5]. This virus was dubbed human herpesvirus-8 (HHV-8) and has also been found to be associated with Castleman disease and primary effusion lymphoma. Determination of rates of asymptomatic carrier status for HHV-8 further bolstered scientific data regarding association with KS. Most countries with low rates of KS, such as the USA and Southeast Asia, have rates of HHV-8 infection less than 5 %. Areas of "classic" KS, most commonly in Eastern Europe and countries bordering the Mediterranean Sea, had rates of HHV-8 antibodies as high as 20 %. Even these elevated numbers pale in comparison with those in Sub-Saharan African, where HHV-8 infection rates rise higher than 50 %, and the rates of uncontrolled HIV in some countries in this area result in 89 % of all cases of KS [6]. Other patients with high incidence of disease, such as men who have sex with men (MSM), also have a higher rate of carriage of HHV-8 and higher rates of KS even in the absence of HIV infection. HHV-8 antibody positivity is much more common in men, as is the case with all subtypes of KS.

The *pathogenesis* of induction of Kaposi sarcoma involves induction of aberrant differentiation, inflammation, and angiogenesis via HHV-8, which latently infects endothelial cells. Endothelial cells gradually transition to spindle cells with mesenchymal markers in addition to markers of blood and lymphatic endothelium. As the disease process progresses, proliferative capacity of infected cells increases, in part due to nuclear latency proteins, which both inhibit tumor suppressor p53 and ensure passing of the viral genome to daughter cells. HHV-8 is also able to induce an exuberant, yet ineffective, Th2 inflammatory response and inhibit the Th1 T-cell response to avoid immune surveillance. The capacity for invasion and migration of KS cells is brought about by induction of unstable, haphazard angiogenesis induced by HHV-8 viral proteins, mediated by induction or secretion of pro-angiogenic cytokines. The line between frank malignant transformation and viral induction of differentiation, angiogenesis, and invasion of a variety of tissues becomes quite unclear in widespread Kaposi sarcoma [7].

The *cutaneous morphology* of KS is similar regardless of subtype, although the extent of disease and propensity for more advanced lesion type vary widely based on clinical circumstances. Early lesions can be subtle and somewhat ill-defined, although color usually is helpful for diagnosis, ranging from blue, to violaceous, to brown depending on the age, depth, and degree of hemosiderin deposition (Fig. 9.1). Lesions partially blanch, given the underlying rudimentary

vascular structures which are characteristic of disease. In more established lesions, a violaceous color and lesional elevation become more prominent features, with sizes ranging from a few millimeters to plaques several centimeters in diameter (Fig. 9.2). Although classic and endemic KS is usually confined to the arms and legs, other subtypes are less bound by constraints of a "usual" distribution, which makes diagnosis slightly more difficult. More advanced lesions can become quite large, confluent on extremities, and hemorrhagic (Fig. 9.3). When the limbs are involved, lymphedema is often also present, especially in African endemic KS [8].

Internal disease can be present with or without cutaneous disease, although possible sites of involvement are numerous. The mucosal surfaces (in particular the soft palate), the gastrointestinal tract, and the lungs are relatively common places where KS can be found, with the latter two imparting substantial morbidity. Extensive disease can invade any organ or tissue. Lymph node involvement and small intestinal disease can be substantial in African endemic KS. Substantial lymph node enlargement can also signal associated multicentric Castleman disease.

Histopathology mirrors clinical morphology in many ways, with early lesions which are nonspecific and difficult to diagnose and late lesions in which the differential diagnosis becomes much more limited. Patch and plaque KS displays papillary dermal clusters of well-differentiated endothelial cells which can appear quite innocuous at low-power microscopy, similar to clusters of perivascular lymphocytes. Primitive vascular structures with barely discernible lumina can occasionally be spotted. Adnexa or normal blood vessels can occasionally be surrounded and "trapped" by these attempts at blood vessel formation, the so-called "promontory sign". These findings are quite subtle and can be overlooked in patch KS (Fig. 9.4) and are more recognizable in plaque KS (Fig. 9.5). Other changes which are more obvious are a spindled tumor cell morphology with tapered hyperchromatic nuclei and a surrounding lymphohistiocytic infiltrate. Monoclonal antibodies to the latent nuclear antigen-1 (LNA1) of HHV-8 will highlight endothelial cells in all cases [9], and proper clinical suspicion for KS will often lead to requests for immunohistochemistry. Nodular KS has more specific histopathology, and differential diagnosis shifts to benign and malignant vascular tumors. Cells form into more circumscribed nodules, with a predominantly spindled morphology, with intervening thin vascular spaces with occasional red blood cells within (Fig. 9.6). Mitotic figures become more numerous, although cellular atypia is usually unimpressive. Histologic differential diagnosis of nodular KS includes spindle cell hemangioma, hobnail hemangioma, tufted angioma, and well-differentiated angiosarcoma.
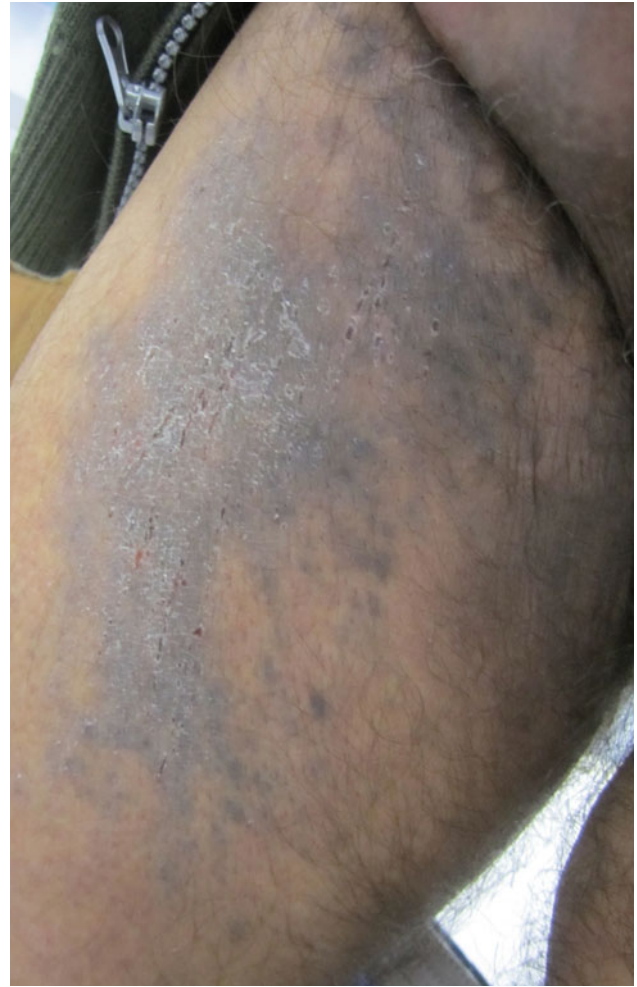
FIGURE 9.2. Kaposi sarcoma: indurated violaceous papules and nodules coalescing into a plaque of the inner thigh.

FIGURE 9.3. Kaposi sarcoma: multiple widespread violaceous papules and plaques in a patient with HIV/AIDS and multicentric Castleman disease.
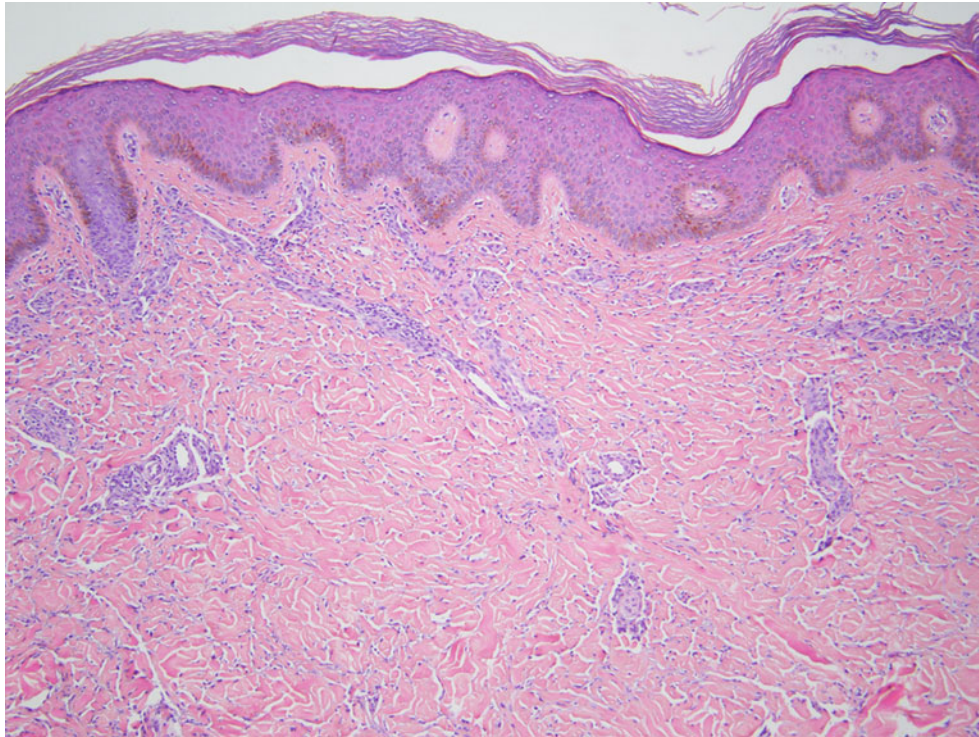
FIGURE 9.4. Kaposi sarcoma, patch, 4× magnification: vascular ectasia with dissecting interstitial spindle cell proliferation.
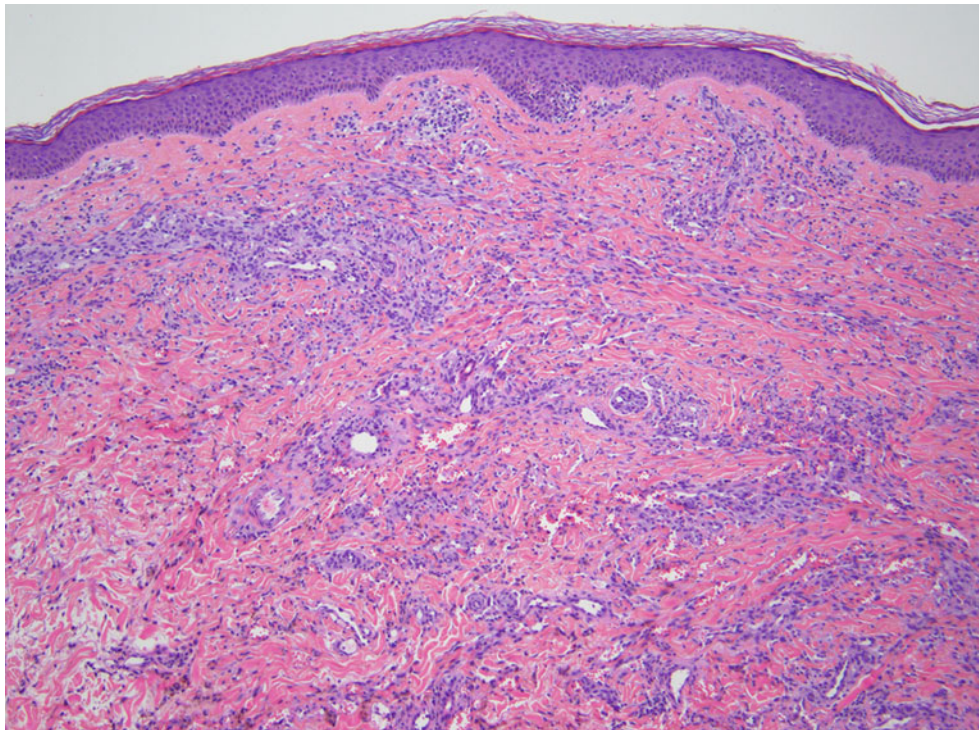
FIGURE 9.5. Kaposi sarcoma, plaque, 4× magnification: coalescence of spindle cells to form vague fascicles, with stromal hemorrhage and cleft formation.
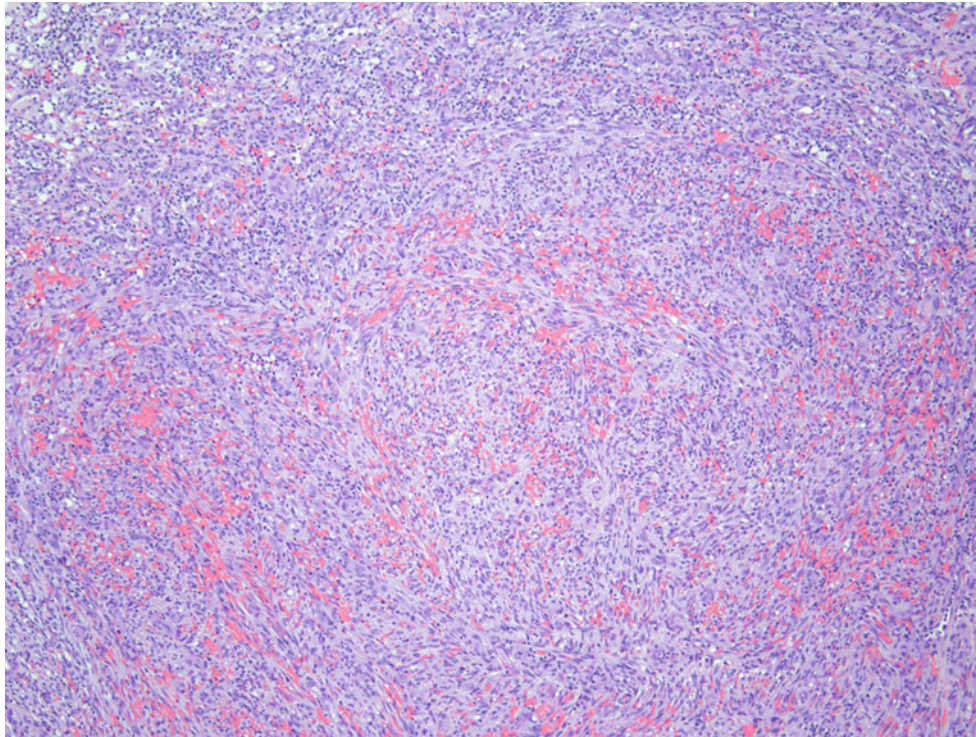
FIGURE 9.6. Kaposi sarcoma, tumor, 20× magnification: solid aggregates of spindled and epithelioid cells with abortive vascular spaces and prominent stromal hemorrhage.

TABLE 9.1. AIDS clinical trial group staging classification [11]

Characteristics	Good risk (low risk)	Poor risk (high risk)
Tumor	Confined to the skin and/or lymph nodes and/or minimal oral disease (non-nodular disease of palate only)	Tumor-associated edema, ulcers, extensive oral KS, gastrointestinal KS, other non-nodal visceral KS
Immune status	CD4 count > 200	CD4 count <200
Systemic illness	No prior opportunistic infection, thrush, or B symptoms, performance status > 70 % (Karnofsky)	Prior opportunistic infection, thrush, B symptoms, performance status <70 %, other HIV-related illnesses (neurologic symptoms, lymphoma)

Good risk all of the symptoms listed
Poor risk at least one of the symptoms listed
B symptoms fever, night sweats, diarrhea persisting >2 weeks, unintentional loss of >10 % body weight

*Treatment* varies depending on subtype as well. When immunosuppression in any form is causative of disease, improvement in immune status will often lead to partial or complete remission of KS. Chemotherapy is reserved for advanced or rapidly progressive disease and includes treatment with vinblastine, dacarbazine, doxorubicin, or bleomycin. Pegylated liposomal doxorubicin in monotherapy has been shown to be a more effective (45 % response rate) and less toxic treatment than doxorubicin-bleomycin-vincristine combination chemotherapy for AIDS patients with advanced KS [10]. The use of the AIDS clinical trial group staging classification has been helpful in the standardization of disease severity and response to treatment (Table 9.1) [11].

Of more interest to the practicing dermatologist is the treatment of localized disease. Limited cutaneous KS is defined as fewer than ten cutaneous lesions in the absence of visceral involvement or tumor-associated lymphedema. Simple excision or radiotherapy of single or clustered lesions can be curative, with radiotherapy in particular resulting in cure rates exceeding 90 % [12]. Cryotherapy with liquid nitrogen has been used with some success, with a response rate of 70 % among AIDS patients with localized KS, although lesions often recurred after a few months [13]. Alitretinoin 0.1 % gel has been studied with relatively well-designed trials demonstrating 37 % complete and partial response after 12 weeks of twice-daily treatment with alitretinoin vs 7 % complete and partial

response to placebo. Other studies have shown similar, somewhat underwhelming response rates [14, 15]. Intralesional and systemic interferon, imiquimod cream, nicotine patches, and photodynamic therapy have been shown to have very limited success. The lack of an adequate method of classification of severity of skin disease, and outcome measures of treatment, has hindered treatment research efforts.

References

1. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. Arch Dermatol Syph. 1872;4(2):265–73.
2. Rous P. A sarcoma of the fowl transmissible by an agent separable from the tumor cells. J Exp Med. 1911;13(4):397–411.
3. Burkitt D. A sarcoma involving the jaws in African children. Br J Surg. 1958;46(197):218–23.
4. Hymes KB, et al. Kaposi's sarcoma in homosexual men- a report of eight cases. Lancet. 1981;2(8247):598–600.
5. Chang Y, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266:1865–9.
6. De Sanjose S, et al. Geographic variation in the prevalence of Kaposi sarcoma-associated herpesvirus and risk factors for transmission. J Infect Dis. 2009;199:1449–56.
7. Gramolelli S, Schulz TF. The role of Kaposi sarcoma-associated herpesvirus in the pathogenesis of Kaposi sarcoma. J Pathol. 2015;235:368–80.
8. Stein ME, et al. Endemic African Kaposi's sarcoma: clinical and therapeutic implications: 10-year experience in the Johannesburg Hospital (1980–1990). Oncology. 1994;51:63–9.
9. Cheuk W, Wong KO, Wong CS, et al. Immunostaining for human herpesvirus 8 latent nuclear antigen-1 helps distinguish Kaposi's sarcoma from its mimics. Am J Clin Pathol. 2004;31:26.
10. Northfelt DW, Dezube BJ, Thomes JA, et al. Pegylated liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. Am Soc Clin Oncol. 1998;16(7):2445–51.
11. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol. 1989;7(9):1201–7.
12. Caccialanza M, Marca S, Piccinno R, Eulisse G. Radiotherapy of classic and human immunodeficiency virus-related Kaposi's sarcoma: results in 1482 lesions. J Eur Acad Dermatol Venereol. 2008;22(3):297–302.
13. Tappero JW, et al. Cryotherapy for cutaneous Kaposi's sarcoma (KS) associated with acquired immune deficiency syndrome (AIDS): a phase II trial. Acquir Immune Defic Syndr. 1991;4:839–46.
14. Bodsworth NJ, et al. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Am J Clin Dermatol. 2001;2:77–87.
15. Duvic M, et al. Topical treatment of cutaneous lesions of acquired immunodeficiency syndrome-related Kaposi sarcoma using alitretinoin gel: results of phase 1 and 2 trials. Arch Dermatol. 2000;146(12):1461–9.

Part II
Hereditary Cancer-Predisposition Syndromes and Paraneoplastic Disorders

10

Muir-Torre Syndrome

■ Synonyms:	None
■ Etiology:	Mutations in MLH1 and/or MSH2
■ Associations:	Visceral malignancies (mainly gastrointestinal)
■ Clinical:	Asymptomatic yellow papule/nodule
■ Histology:	Lobules of sebocytes surrounded by basaloid keratinocytes
■ IHC repertoire:	EMA+
■ Staging:	N/A
■ Prognosis:	100 % benign
■ Adverse variable:	Visceral malignancies
■ Treatment:	Careful screening

Sebaceous adenomas are benign adnexal tumors that have no malignant potential. They are of no clinical significance in isolation but may be indicators of internal malignancy when occurring as part of the Muir-Torre syndrome. Sebaceous adenomas grow as exophytic, yellowish papules and nodules. In most cases, these lesions are less than 1 cm in diameter [1]. While they may occur at any body site, they are most common on the face. They usually appear in middle age. Ulceration is not a common feature.

Muir and Torre independently described the syndrome in 1967; Muir reported on the occurrence of multiple internal malignancies in association with a keratoacanthoma [2]; Torre reported multiple internal malignancies in association with cutaneous sebaceous neoplasms [3]. Bakker et al. reported an additional case in 1971 who surmised that these three cases may represent a syndrome [4]. Muir-Torre syndrome is inherited in an autosomal dominant manner [5]. It has a high degree of penetrance and variable expression. The syndrome is twice as common in men as in women. It usually manifests in middle age, with the sixth decade the most common time of onset. In some studies, as many as 61 % of afflicted families will have a family history of visceral malignancy [6]. The syndrome is defined as the presence of at least one sebaceous neoplasm (excluding sebaceous hyperplasia and nevus sebaceous of Jadassohn) or keratoacanthoma with sebaceous differentiation and one visceral cancer. Alternatively, a patient

with multiple keratoacanthomas, multiple visceral malignancies, and a family history of Muir-Torre syndrome can be so classified [5]. In most cases, however, multiple cutaneous neoplasms are present (Fig. 10.1). In one review, the cutaneous tumors preceded the development of the visceral cancers in 22 % of cases, occurred concurrently in an additional 6 %, and presented after the internal malignancy in 56 %. No temporal relationship was established in the other cases [7].

An inherited mutation of the mismatch DNA repair gene MSH2 has been reported in many patients with Muir-Torre syndrome [8]. Others have reported germline mutations in the MLH1 mismatch repair gene [9].

Sebaceous adenomas may occur as part of the Muir-Torre syndrome. Multiple sebaceous neoplasms, keratoacanthomas, and visceral carcinomas characterize this syndrome (Table 10.1) [5]. The sebaceous tumors include sebaceous adenomas, epitheliomas, sebaceomas, and sebaceous carcinomas. Most investigators do not include sebaceous hyperplasia as a criterion for the syndrome, as the vast majority of these lesions are unrelated to a systemic process. The cutaneous neoplasms tend to be indolent. Even the sebaceous carcinomas, which can behave aggressively when isolated, do not usually metastasize in patients with the Muir-Torre syndrome. Keratoacanthomas also occur most frequently outside of the syndrome but, when multiple, may suggest visceral malignancy. Gastrointestinal

Figure 10.1. Multiple tan umbilicated papules representing sebaceous adenoma and sebaceous hyperplasia in patient with Muir-Torre syndrome.

Table 10.1. Tumors associated with Muir-Torre syndrome (expressed as percentage of affected patients)

Tumor	Percentage of patients with MTS
Sebaceous adenoma	>90
Sebaceous carcinoma	24
Other sebaceous neoplasms	
Keratoacanthoma	22
Colonic polyps	48
2–3 Visceral neoplasms	37
>3 Visceral neoplasms	10

Table 10.2. Visceral tumors associated with Muir-Torre syndrome (expressed as percentage of total tumors)

Colonic adenocarcinoma	50
Genitourinary carcinoma	24
Breast	5
Non-Hodgkin's lymphoma	2
Head and neck squamous cell carcinoma	3.9
Small intestinal adenocarcinoma	3.9
Lung carcinoma	1.5

and, more specifically, colonic adenocarcinomas are the most common visceral malignancies experienced by patients with the Muir-Torre syndrome (Table 10.2). The colonic adenocarcinomas occur a decade earlier than in the general population and are more frequently located proximal to the splenic flexure. They tend to behave in a relatively indolent fashion.

Sebaceous adenomas are neoplasms that are centered in the mid-reticular dermis. In some cases, they arise from the follicular epithelium that is connected to the epidermis, while in other cases, the epidermal connection may not be apparent. Lobules of mature sebocytes with abundant clear cytoplasm are surrounded by a collarette of more basaloid-appearing cells. The basal layer palisades around the outside of the lobules, and the cells within demonstrate progressive maturation as they move toward the middle of the lobules (Fig. 10.2a, b). Mitoses may be seen in small numbers, but no atypical forms are present. Cytologic atypia is minimal and necrosis is not a common feature.

Sebaceous epitheliomas differ from sebaceous adenomas in having a larger percentage of basaloid cells and smaller percentage of mature sebocytes (Fig. 10.3). Some investigators believe these to be indistinguishable from basal cell carcinomas with sebaceous differentiation. There is some overlap between sebaceous epithelioma and the more recently described tumor known as sebaceoma [10]. The distinction from sebaceous adenoma is academic, as the prognosis for each of these neoplasms is invariably benign.

Sebaceous carcinomas are most prevalent, arising from the meibomian glands in the eyelids. However, they can occur in any hair-bearing body site. Eyelid lesions occur primarily in elderly patients, whereas extraocular neoplasms are more common in middle-aged men. Sebaceous carcinomas unassociated with the Muir-Torre syndrome have a relatively high rate of metastasis, but this appears to be much lower when occurring in conjunction with the syndrome. These tumors demonstrate the characteristics of malignant neoplasms (Fig. 10.4a, b). They are characterized by cells with greatly increased nucleus: cytoplasm ratios, high mitotic activity, abundant individual cell necrosis, and marked nuclear pleomorphism. Sebaceous differentiation may be difficult to detect. Immunostains with epithelial membrane antigen (EMA) may be helpful in isolating the intracytoplasmic microvesiculation frequently seen in sebocytic differentiation.

Keratoacanthoma is a controversial entity that is considered by many to represent a rapidly growing yet indolent variant of cutaneous squamous cell carcinoma [11]. The discussion of the etiology of these neoplasms is outside the purview of this volume. The histologic features of keratoacanthoma are best detected at low magnification. These tumors demonstrate a cup-shaped, invaginated growth pattern. The central dell is filled with abundant keratin that
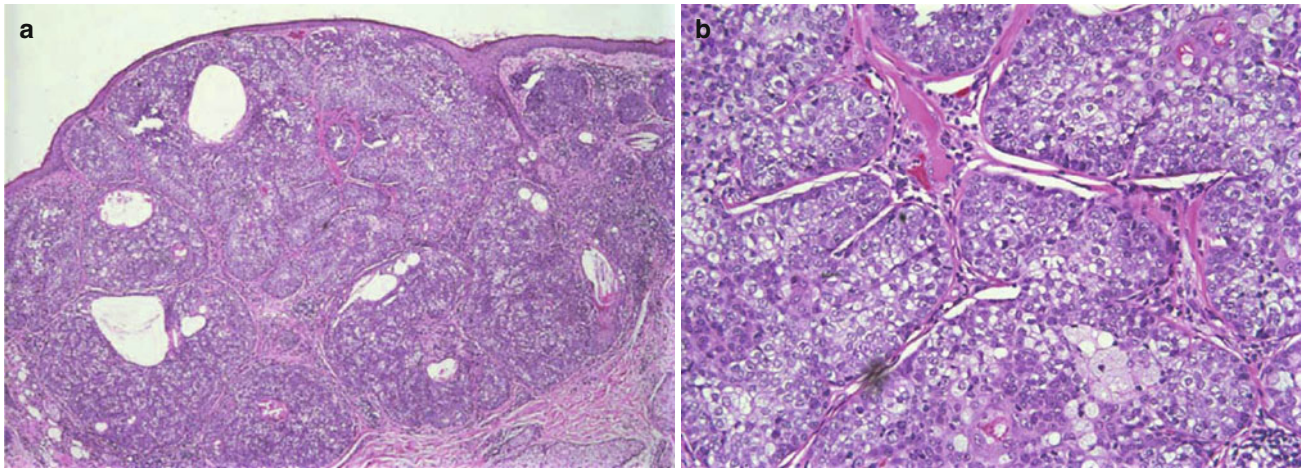
FIGURE 10.2. (**a**) Low-power photomicrograph depicting lobular architecture of sebaceous adenoma. (**b**) High-power photomicrograph depicting lobules of sebocytes. Note the central mature sebocytes with clear foamy cytoplasm and more immature basaloid cells at periphery.
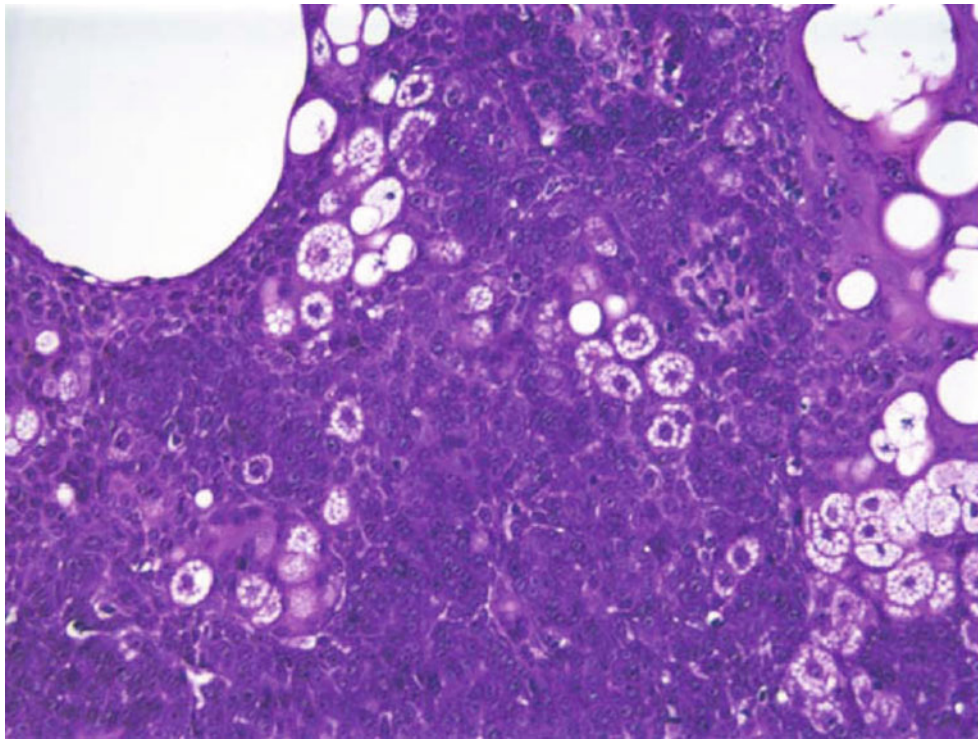
FIGURE 10.3. Predominance of basaloid cells in sebaceous epithelioma.

is often orthokeratotic. Beneath the invagination, sheets of keratinocytes with abundant, often pale-staining cytoplasm extend into the dermis. These cells may demonstrate nuclear atypia, pleomorphism, and a high mitotic rate (Fig. 10.5a, b). In many cases, there is a brisk underlying host response, and in resolving lesions, dermal fibrosis may signify the regressing phase of the lesion.

Distinction between keratoacanthoma and other types of cutaneous squamous cell carcinoma is not always possible.
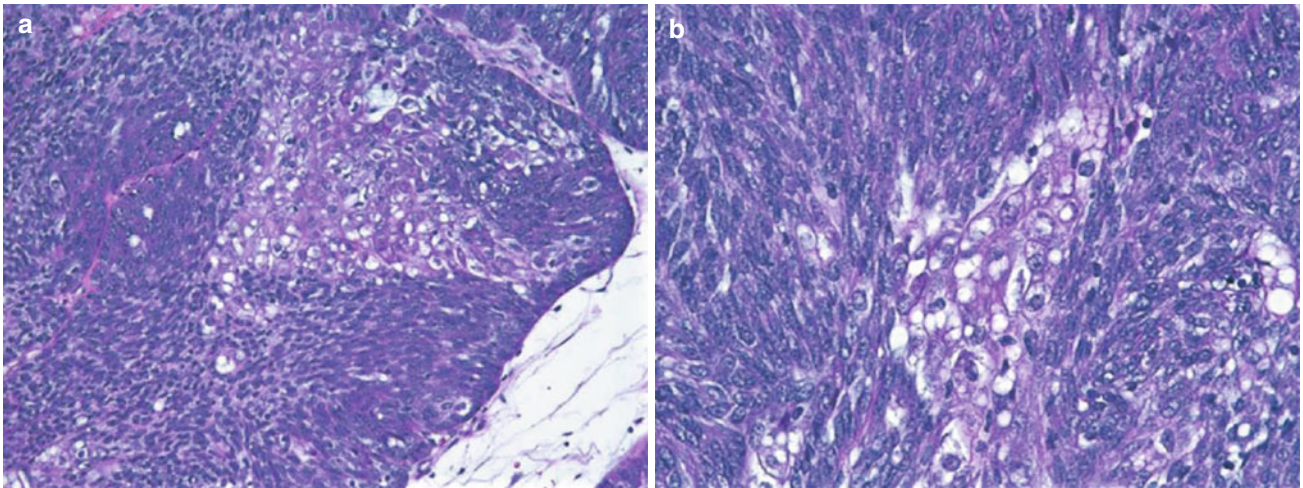
FIGURE 10.4. (**a**) Medium-power photomicrograph of sebaceous carcinoma. Note the predominance of basaloid cells and the cellularity of the neoplasm. (**b**) High-power photomicrograph depicting the close apposition of the cells producing the cellularity of sebaceous carcinoma. Note the hyperchromatic nuclei of sebaceous carcinoma.
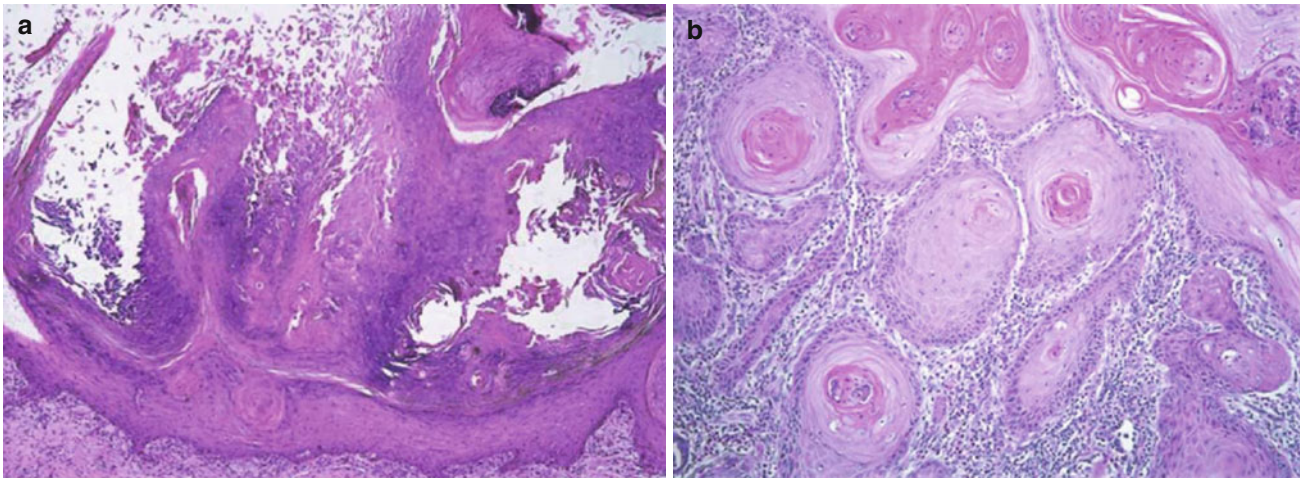
FIGURE 10.5. (**a**) Low-power photomicrograph depicting the cup-shaped architecture of keratoacanthoma. (**b**) Medium-power photomicrograph depicting the irregular infiltrating islands of neoplastic keratinocytes typical of invasive well-differentiated squamous cell carcinoma.

References

1. Rulon DB, Helwig EB. Cutaneous sebaceous neoplasms. Cancer. 1974;33:82–102.
2. Muir EG, Bell AJ, Barlow KA. Multiple primary carcinomata of the colon, duodenum, and larynx associated with kerato-acanthomata of the face. Br J Surg. 1967;54(3):191–5.
3. Torre D. Multiple sebaceous tumors. Arch Dermatol. 1968;98(5):549–51.
4. Bakker PM, Tjon A, Joe SS. Multiple sebaceous gland tumours, with multiple tumours of internal organs. A new syndrome? Dermatologica. 1971;142(1):50–7.
5. Schartz RA. The Muir-Torre syndrome: a 25-year retrospective. J Am Acad Dermatol. 1995;33:90–104.
6. Cohen PR, Kohn SR, Kurzrock R. Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. Am J Med. 1991;90:606–13.
7. Akhtar S, Oza KK, Khan SA, Wright J. Muir-Torre syndrome: case report of a patient with concurrent jejunal and ureteral cancer and a review of the literature. J Am Acad Dermatol. 1999;41:681–6.
8. Nystrom-Lahti M, Parsons R, Sistonen P, Pylkkanen L, Aaltonen LA, Leach FS, Hamilton SR, Watson P, Bronsen E, Fusar R, et al. Mismatch repair genes on chromosomes 2p

and 3p account for a major share of hereditary nonpolyposis colorectal cancer families evaluable by linkage. Am J Hum Genet. 1994;55:659–65.

9. Mathiak M, Rutten A, Mangold E, Fischer H-P, Ruzicka T, Friedl W, Propping P, Kruse R. Loss of DNA mismatch repair proteins in skin tumors from patients with Muir-Torre syndrome and MSH2 or MLH1 germline mutations: establishment of immunohistochemical analysis as a screening test. Am J Surg Pathol. 2002;26:338–43.

10. Troy JL, Ackerman AB. Sebaceoma. A distinctive benign neoplasm of adnexal epithelium differentiating toward sebaceous cells. Am J Dermatopathol. 1984;6:7–13.

11. Hodek E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. Am J Dermatopathol. 1993;15:332–42.

11 Birt-Hogg-Dubé Syndrome

■ Synonyms:	None
■ Etiology:	Mutation in the folliculin gene and chromosome 17p11.2
■ Associations:	Fibrofolliculomas, trichodiscomas, acrochordons, angiofibromas, pulmonary cysts with spontaneous pneumothorax, renal carcinoma, and colorectal carcinoma in some kindreds
■ Clinical:	Skin-colored papules of the face, neck, ears, and upper trunk, with intertriginous soft papules
■ Histology:	Trichodiscoma—interfollicular ovoid nodule with spindled cells in loose fibrillary stroma Fibrofolliculoma—central follicle with extension of irregular epithelial strands into surrounding well-defined cellular fibrous stroma
■ IHC:	CD34+ and S100−
■ Evaluation:	Molecular genetic testing, renal MRI, and high-resolution chest CT
■ Treatment:	Early tumor excision and laser resurfacing of facial lesions for cosmetic improvement
■ Prognosis:	Excellent with early diagnosis and vigilant monitoring

In 1977, Birt, Hogg, and Dubé described a kindred of 70 individuals, some of whom presented with small skin-colored papules, predominantly of the face. These developed in early adulthood and were noted to be inherited in a dominant pattern [1]. The histomorphology of the papules was described as "abnormal hair follicles with epithelial strands extending out from the infundibulum of the hair follicle into a hyperplastic mantle of specialized fibrous tissue." The authors applied the term *fibrofolliculoma* to these lesions. Also described in these patients were trichodiscomas and acrochordons. Trichodiscoma is a benign tumor of perifollicular mesenchyme. It is thought to represent a proliferation of the *haarscheibe* (hair disk), a perifollicular "richly vascularized dermal pad covered with thick epidermis containing Merkel cells and supplied by a thick myelinated nerve the branches of which end at the lower epidermal surface and on the blood vessels of the dermal pad" [2]. It is composed of a dermal interfollicular proliferation of spindle cells in a loose connective tissue matrix with varying amounts of mucin. It may have an orientation parallel to the skin surface. The *haarscheibe* is

thought to represent a mechanoreceptor in animal skin. Its significance in humans is uncertain. The acrochordons reported in the original description of the syndrome were reported to have histologic findings typical of acrochordons [1]. However, a subsequent study suggests that they have pathologic features of fibrofolliculoma and trichodiscoma [3]. Some patients have also been found to have facial lesions indistinguishable from angiofibroma [4].

The original kindred described by Birt, Hogg, and Dubé had several individuals who developed hereditary medullary carcinoma of the thyroid. This tumor susceptibility was apparently inherited from an individual without the syndrome. Subsequent series have confirmed that medullary thyroid carcinoma is not a part of the syndrome. However, benign thyroid nodules and cysts have been more recently described in some Birt-Hogg-Dubé syndrome (BHDS) families, and rare cases of thyroid carcinoma have occurred [4, 5]. While there were no other internal manifestations of the syndrome in the original report, there have been subsequent descriptions of renal tumors [6]. These include hybrid tumors with features of chromophobe

carcinoma and oncocytoma, chromophobe carcinoma, oncocytoma, clear cell renal cell carcinoma, and, rarely, papillary carcinoma [7]. Eighty-eight percent of BHDS patients have lung cysts on computed tomography (CT) and almost 40 % develop spontaneous pneumothorax [4]. CT imaging may suggest the diagnosis because unlike the blebs in smoking-related lung disease, which tend to occur in the upper lobes, cysts related to BHDS tend to occur in the lower lobes, bilaterally, and in relation to interlobular septa and pulmonary vasculature [8]. Additional entities uncommonly associated with BHDS include collagenoma [9], lipoma [10], angiolipoma [10], oral fibroma [11], parathyroid adenoma [10] including oncocytoma [12], melanoma including desmoplastic and choroidal [13], epidermal cysts [5], rhabdomyoma, basal cell carcinoma, sebaceous hyperplasia, squamous cell carcinoma, leiomyoma, cutaneous leiomyosarcoma, dermatofibrosarcoma protuberans [4], cutaneous neural tumors [14], neuroendocrine carcinoma [15], and flecked chorioretinopathy [16]. Colorectal carcinoma occurs in some BHDS families, but not at an early age, suggesting that early age screening is not warranted. The familial occurrence suggests that some mutations may predispose to the disease [17].

The Birt-Hogg-Dubé (BHD) gene has been mapped to chromosome 17p11.2 [18, 19]. It encodes a novel protein, folliculin (FLCN), which is highly conserved across species [20]. Mutations in the BHD gene result in the formation of a truncated protein. FLCN is a tumor suppressor which inhibits AMPK function. AMPK activation induces autophagy, inhibits apoptosis, and counteracts cellular stresses, all of which can predispose to tumorigenesis. Loss FLCN function allows AMPK activation, resulting in the loss of tumor suppression [21]. Based on studies in a rat model of inherited renal carcinoma, a germline mutation is likely transmitted as a heterozygote, with the homozygous form being lethal in fetal life. A "second hit" in the normal gene copy is required for tumorigenesis. This second hit causes loss of heterozygosity. In this scenario, only the abnormal gene product is expressed, and there is a loss of expression of the normal gene copy. This causes a lack of production of a functional protein product that would aid in tumor suppression. The second hit can be caused by a somatic mutation in the normal gene copy, which would result in loss of the normal gene product [22]. Alternatively, expression of the normal gene copy may be suppressed by methylation of the gene promoter region. Somatic inactivation of the BHD gene in sporadic renal cell carcinoma and colorectal carcinoma has been reported, implicating its role in the development of a subset of these tumors [23]. A deletion in exon 4 of the BHD gene causes primary spontaneous pneumothorax without other features of BHD syndrome [24].

Fibrofolliculomas (FF) and trichodiscomas (TD) of Birt-Hogg-Dubé syndrome usually develop in early adulthood. These patients present with small skin-colored or white papules that have a predilection for the face, neck, ears, and upper trunk (Fig. 11.1a, b). Acrochordons typically develop in intertriginous areas. The clinical differential diagnosis of the facial papules includes trichoepithelioma, angiofibroma, trichilemmoma, basaloid follicular hamartoma, and syringoma. There are several clinical features that may help distinguish these entities (Table 11.1), but histopathologic evaluation is required for definitive diagnosis.

Trichodiscoma is an ovoid superficial dermal nodule filling an interfollicular space (Fig. 11.2). There is generally epidermal flattening, with interwoven fascicles of fibrillar collagen with spindled cells in a loose stroma that contains varying amounts of mucin and vascularity. Fibrofolliculoma may contain a similar mesenchymal component but has a central distorted follicle from which thin epithelial strands extend in a sometimes retiform configuration, invested within a well-defined cellular fibrous stroma with spindled cells (Fig. 11.3). Much of the spindle cell component of both lesions is highlighted by antibodies to CD34, supporting perifollicular mesenchyme as the histogenic origin of both lesions [25]. The histomorphology of fibrofolliculoma is specific, but that of trichodiscoma is not. The differential diagnosis includes neurofibroma, to which it may show considerable similarity. Neurofibroma and trichodiscoma both display immunoreactivity with antibodies to CD34, but elements of neurofibroma will also label with antibodies to S100 protein. Clinical presentation also helps distinguish these two entities.

Once the diagnosis of multiple fibrofolliculomas and trichodiscomas has been made, a workup for underlying disease is mandatory, particularly because of the association of the syndrome with renal carcinoma. A suggested evaluation is given in Table 11.2 (after Toro, *GeneReviews*).

Management of Birt-Hogg-Dubé syndrome is aimed at early detection and treatment of tumors and pneumothorax. Treatment of cutaneous lesions is principally of cosmetic importance. Laser skin resurfacing of the face may result in significant improvement in appearance [26]. Renal tumors tend to be indolent, and most are multifocal. For that reason, nephron-sparing surgery to remove expanding tumors is generally recommended to preserve renal function [4].

Birt-Hogg-Dubé syndrome is a cancer-susceptibility syndrome that is of particular importance because of the potential for early recognition based on typical cutaneous findings. The benefits of diagnosis may be lifesaving not only for the index patient but also for the entire kindreds.

Figure 11.1. (**a**, **b**) Trichodiscomas and fibrofolliculomas: dome-shaped skin-colored papules.

Table 11.1. Clinical differential diagnosis of facial papules

Distribution	Onset	Associated features/syndrome	
Trichodiscoma, fibrofolliculoma	Diffuse involvement of the face, may have extrafacial involvement	Adulthood	*Birt-Hogg-Dubé syndrome* ± oral papules
Syringoma	Periocular prominence	Adulthood	Yellow hue
Basaloid follicular hamartoma	Diffuse involvement of the face, may have extrafacial involvement	Variable	± Pigment, comedones, ± alopecia
Angiofibroma	Central face	Childhood	Tuberous sclerosis
			Red hue, periungual fibromas, Shagreen patch
			Some BHDS patients
Trichoepithelioma	Central face	Adolescence	Skin-colored, varied lesion size
Trichilemmoma	Nose, cheeks	Adulthood	Cowden syndrome
			Tendency for epidermal change, cobblestone mucosa, acral keratoses
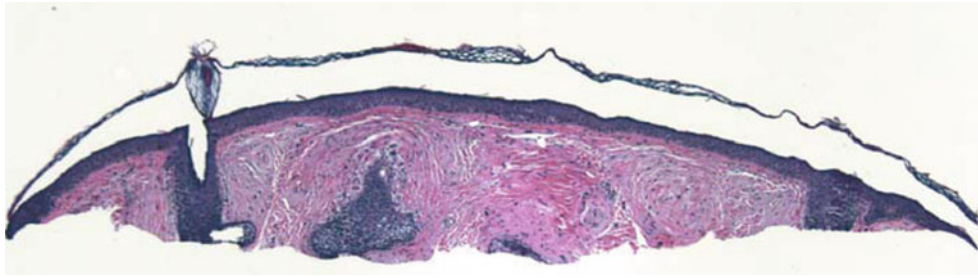
Figure 11.2. Trichodiscoma: periadnexal collagen is arranged in lamellae, with spindle cells and increased mucin.
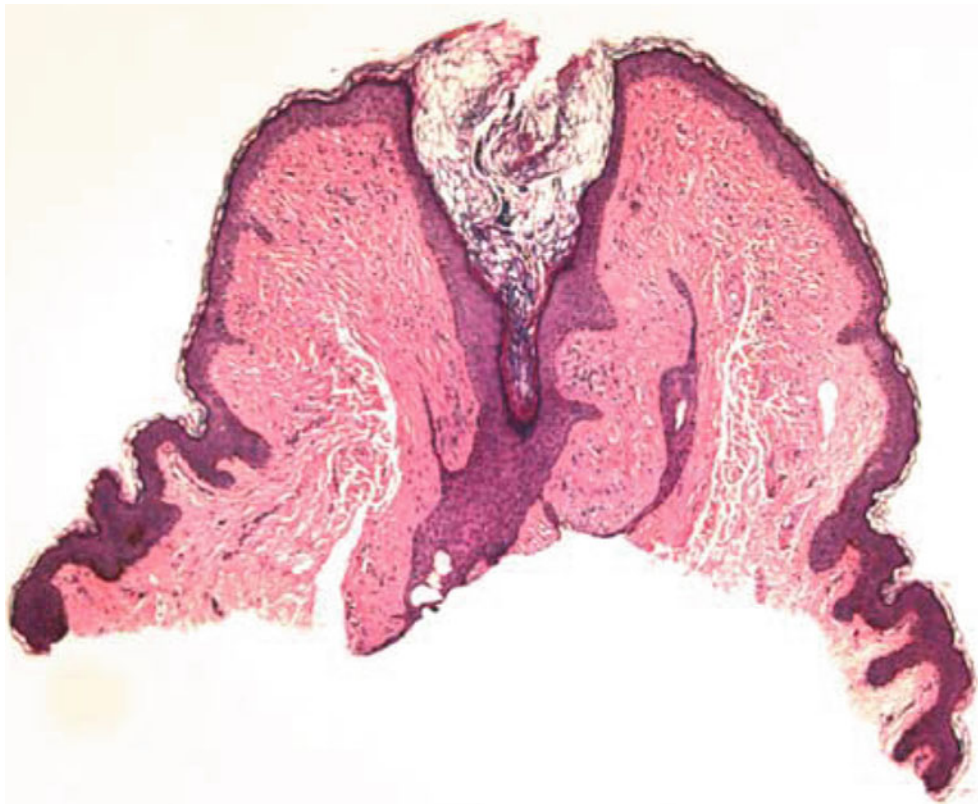
Figure 11.3. Fibrofolliculoma, perifollicular dense collagen within which are embedded thin follicular epithelial strands.

Table 11.2. Evaluation/management of the patient with Birt-Hogg-Dubé syndrome

1. Molecular genetic testing for those suspected of having the disease
2. Serial renal magnetic resonance imaging (MRI) of those with disease or CT with contrast if MRI is contraindicated. Periodic imaging for those with renal tumors <3 cm, surgical evaluation for those with renal tumors >3 cm
3. High-resolution chest CT to evaluate for pulmonary cysts
4. Lower gastrointestinal tract evaluation for polyps/carcinoma age appropriate or as otherwise warranted based on family history
5. Molecular genetic testing for at-risk relatives without disease manifestations to decrease number of screening procedures. If confirmed, proceed with screening as above
6. Avoidance of smoking, radiation, and high ambient pressures
7. Routine melanoma screening

References

1. Birt AR, Hogg GR, Dubé J. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol. 1977;113:1674–7.

2. Pinkus H, Coskey R, Burgess GH. Trichodiscoma: a benign tumor related to haarscheibe (hair disk). J Invest Dermatol. 1974;63:212–8.

3. De la Torre C, Ocampo C, Doval IG, Losada A, Cruces MJ. Acrochordons are not a component of the Birt-Hogg-Dubé syndrome: does this syndrome exist? Case reports and review of the literature. Am J Dermatopathol. 1999;21:369–74.

4. Toro JR, Wei M-H, Glenn GM. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008;45:321–31.

5. Kluger N, Giraud S, Coupier I, et al. Birt-Hogg-Dubé syndrome: clinical and genetic studies of 10 French families. Br J Dermatol. 2010;162:527–37.

6. Toro JR, Glenn G, Duray P, et al. Birt-Hogg-Dubé syndrome: a novel marker for kidney neoplasia. Arch Dermatol. 1999;135:1195–202.

7. Pavlovich CP, Walther MM, Eyler RA, et al. Renal tumors in the Birt-Hogg-Dubé syndrome. Am J Surg Pathol. 2002;26:1542–52.

8. Dal Sasso AA, Belém LC, Zanetti G, et al. Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary involvement. Respir Med. 2015;109:289–96.

9. Weintraub R, Pinkus H. Multiple fibrofolliculomas (Birt-Hogg-Dubé) associated with a large connective tissue nevus. J Cutan Pathol. 1977;4:289–99.

10. Chung JY, Ramos-Caro FA, Beers B, Ford MJ, Flowers F. Multiple lipomas, angiolipomas, and parathyroid adenomas in a patient with Birt-Hogg-Dubé syndrome. Int J Dermatol. 1996;35:365–7.

11. Nadershahi NA, Wescott WB, Egbert B. Birt-Hogg-Dubé syndrome: a review and presentation of the first case with oral lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;83:496–500.

12. Liu V, Kwan T, Page EH. Parotid oncocytoma in the Birt-Hogg-Dubé syndrome. J Am Acad Dermatol. 2000;43:1120–2.

13. Toro JR. Birt-Hogg-Dubé syndrome. 2006 Feb 27 [Updated 2014 Aug 7]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 1993–2015. http://www.ncbi.nlm.nih.gov/books/NBK1522/.

14. Vincent A, Farley M, Chan E, James WD. Birt-Hogg-Dubé syndrome: two patients with neural tissue tumors. J Am Acad Dermatol. 2003;49:717–9.

15. Claessens T, Weppler SA, van Geel M, et al. Neuroendocrine carcinoma in a patient with Birt-Hogg-Dubé syndrome. Nat Rev Urol. 2010;7:583–7.

16. Walter P, Kirchhof B, Korge B, Heimann K. Flecked chorioretinopathy associated with Birt-Hogg-Dubé syndrome. Graefes Arch Clin Exp Ophthalmol. 1997;235:359–61.

17. Nahorski MS, Lim DHK, Martin L, et al. Investigation of the Birt-Hogg-Dubé tumour suppressor gene (FLCN) in familial and sporadic colorectal cancer. J Med Genet. 2010;47:385–90.

18. Khoo SK, Bradley M, Wong FK, Hedblad MA, Nordenskjold M, Teh BT. Birt-Hogg-Dubé syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. Oncogene. 2001;20:5239–42.

19. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg Dubé syndrome: a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. Am J Hum Genet. 2001;69:876–82.

20. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. Cancer Cell. 2002;2:157–64.

21. Possik E, Jalali Z, Nouët Y, et al. Folliculin regulates Ampk-dependent autophagy and metabolic stress survival. PLoS Genet. 2014;10(4):e1004273. doi:10.1371/journal.pgen.1004273. eCollection 2014.

22. Okimoto K, Sakurai J, Kobayashi T, et al. A germ-line insertion in the Birt-Hogg-Dubé (BHD) gene gives rise to the Nihon rat model of inherited renal cancer. Proc Nat Acad Sci U S A. 2004;101:2023–7.

23. da Silva NF, Gentle D, Hesson LB, Morton DG, Latif F, Maher ER. Analysis of the Birt-Hogg-Dubé (BHD) tumour suppressor gene in sporadic renal cell carcinoma and colorectal cancer. J Med Genet. 2003;40:820–4.

24. Painter JN, Tapanainen H, Somer M, Tukiainen P, Aittomaki K. A 4-bp deletion in the Birt-Hogg-Dubé gene (FLCN) causes dominantly inherited spontaneous pneumothorax. Am J Hum Genet. 2005;76:522–7.

25. Collins GL, Somach S, Morgan MB. Histomorphologic and immunophenotypic analysis of fibrofolliculomas and trichodiscomas in Birt-Hogg-Dubé syndrome and sporadic disease. J Cutan Pathol. 2002;29:529–33.

26. Jacob CI, Dover JS. Birt-Hogg-Dubé syndrome: treatment of cutaneous manifestations with laser skin resurfacing. Arch Dermatol. 2001;137:98–9.

12
Cowden Syndrome

■ Synonyms:	None
■ Etiology:	pTEN mutation
■ Associations:	Multiple hamartomas, keratoacanthomas, and neoplasms
■ Clinical:	Hyperkeratotic folliculocentric papules
■ Histology:	Proliferations of pale staining keratinocytes from the epidermis
■ IHC repertoire:	N/A
■ Staging:	N/A
■ Prognosis:	100 % survival
■ Adverse variables:	Visceral neoplasms
■ Treatment:	Careful screening

Trichilemmomas are benign epidermal neoplasms that may serve as an indicator of underlying malignancy. Trichilemmomas appear, largely on the head and neck, as exophytic, small, hyperkeratotic papules (Fig. 12.1). There is no particular gender predilection and they usually arise during the second decade. When occurring as isolated lesions, these tumors are invariably benign and are of no clinical significance.

Multiple trichilemmomas may occur as part of the multiple hamartoma or Cowden syndrome [1]; this syndrome was first described in 1963 by Lloyd and Dennis. This syndrome has an autosomal dominant inheritance pattern [2] and is associated with mutations in the pTEN gene located at 10q22–23 [3]. Table 12.1 summarizes the systemic conditions associated with the syndrome [4–7]. These patients develop many hamartomatous lesions, fibrocystic changes in the breast, and breast and thyroid carcinomas. The neoplastic proliferations tend to be relatively indolent and confer a good prognosis for afflicted patients. The gastrointestinal polyps do not appear to harbor malignant potential. There are isolated reports of many other neoplasms occurring in patients with the syndrome [8].

Cowden syndrome displays other cutaneous manifestations. These include cobblestone-like fibromas on the tongue and within the oral mucosa, sclerotic fibromas [9], lipomas, and hyperkeratotic plaques on the dorsa of the hands. While less common and less specific than trichilemmomas, these other processes can also be valuable clues in establishing the diagnosis.

A set of operational diagnostic criteria for Cowden syndrome was proposed by the International Cowden Consortium in 2000; the criteria were adapted by the US-based National Comprehensive Cancer Network Genetics/High Risk Cancer Surveillance Panel [10]. Pathognomic criteria include facial trichilemmomas, acral keratoses, papillomatous papules, and mucosal lesions. Major criteria include thyroid cancer, breast cancer, endometrial cancer, macrocephaly, and Lhermitte-Duclos disease. Minor criteria include other thyroid lesions, genitourinary cancers, gastrointestinal hamartomas, lipomas, fibromas, mental retardation, and fibrocystic disease of the breast. Operational diagnosis in an individual includes mucocutaneous lesions alone if (a) there are six or more facial papules (three or more must be trichilemmoma), (b) cutaneous facial papules and oral mucosal papillomatoses, (c) oral mucosal papillomatoses and acral keratoses, or (d) palmoplantar keratoses. Additional operational diagnosis includes two major criteria, one of which must be macrocephaly or Lhermitte-Duclos disease; one major and three minor criteria; or four minor criteria. Operational diagnosis in a family with one individual being diagnostic for Cowden syndrome includes one or more pathognomic criteria, one major criterion with or without minor criteria, or two minor criteria [10].

Figure 12.1. Multiple skin-toned papules distributed on the face of a patient with Cowden syndrome.

Table 12.1. Cowden syndrome

Abnormality	Incidence (percentage) in patients with Cowden syndrome
Breast carcinoma	25–36
Fibrocystic changes of breast	53
Thyroid adenomas	68
Follicular carcinoma, thyroid	3
Gastrointestinal polyps and fibromas	35–60
Lipoma	31
Neuroma	5
Angioid streaks, eyes	13
Acanthosis nigricans	11
Enlarged head circumference	70–80
Adenocarcinoma, uterus	6
Trichilemmomas	>80
Bone cysts	
Hepatic hamartomas	
Meningiomas	
Retinal gliomas	
Sclerotic fibromas	76
Oral cobblestone fibromas	>50
Palmoplantar hyperkeratoses	>50
Hemangioma	18

Trichilemmomas have a characteristic histologic appearance. Keratinocytes proliferate down from the surface of the epidermis as an expansile plaque (Fig. 12.2). There are frequently overlying parakeratosis, focal diminution of the granular layer, and clumped keratohyalin granules in other sections of the epidermis. In some cases, a central hair follicle may be present. The keratinocytes within the tumor have abundant, pale staining cytoplasm, resembling the appearance of the outer root sheath of follicular epithelium (Fig. 12.3). The bottom of the lesion may have a lobulated configuration. Inward turning rete ridges may be seen at the periphery of the lesion. One characteristic finding is the presence of a thickened, PASD-positive basement membrane immediately beneath the intraepidermal proliferation (Fig. 12.4). This membrane is refractile. Squamous eddies are present. Some authors have contended that these lesions represent human papillomavirus infections involving hair follicles, but the scientific evidence for that position is lacking [11, 12].

Desmoplastic trichilemmoma is a histologic variant that may be confused with squamous cell carcinoma or basal cell carcinoma on microscopic examination. The overall architecture of the lesion is preserved; however, in the center of the growth, islands of proliferating keratinocytes are separated by a desmoplastic stromal response, mimicking an invasive growth pattern. Mitoses may be present. Careful attention to the overall growth pattern should prevent misdiagnosis.

There is a very rare malignant variant known as trichilemmal carcinoma. This neoplasm invades the dermis and is characterized by abundant mitoses, including atypical variants, zonal necrosis, and marked cytologic atypia.

Sclerotic fibroma, also known as storiform collagenoma and plywood fibroma, grows as nodular dermal proliferations. The epidermis is often atrophic, with effacement of rete ridges (Fig. 12.5). Within the dermis, there is a sparse proliferation of spindle-shaped cells that grow in a storiform pattern. Dense, keloidal collagen is present between these cells in a pattern that has been described as resembling plywood (Fig. 12.6). The exact nature of this process and the dermal cells is not fully established. Some investigators believe these lesions represent end-stage lesions of dermatofibromas [13], while others maintain that they represent de novo growths [14]. Sclerotic fibromas may occur as sporadic lesions unassociated with Cowden syndrome [15].
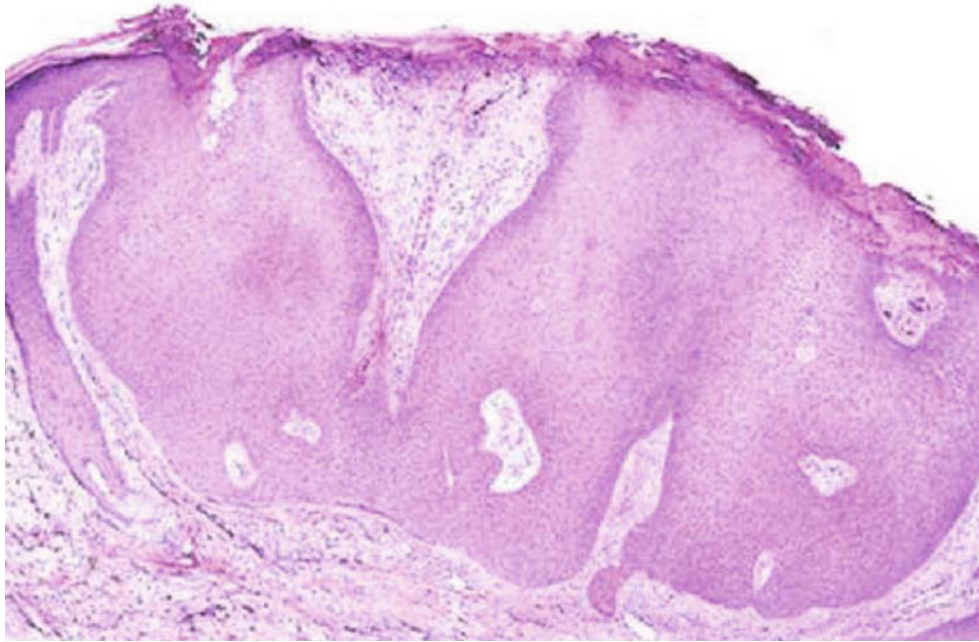
Figure 12.2. Low-power photomicrograph depicting platelike growth of the epithelium observed in trichilemmoma.
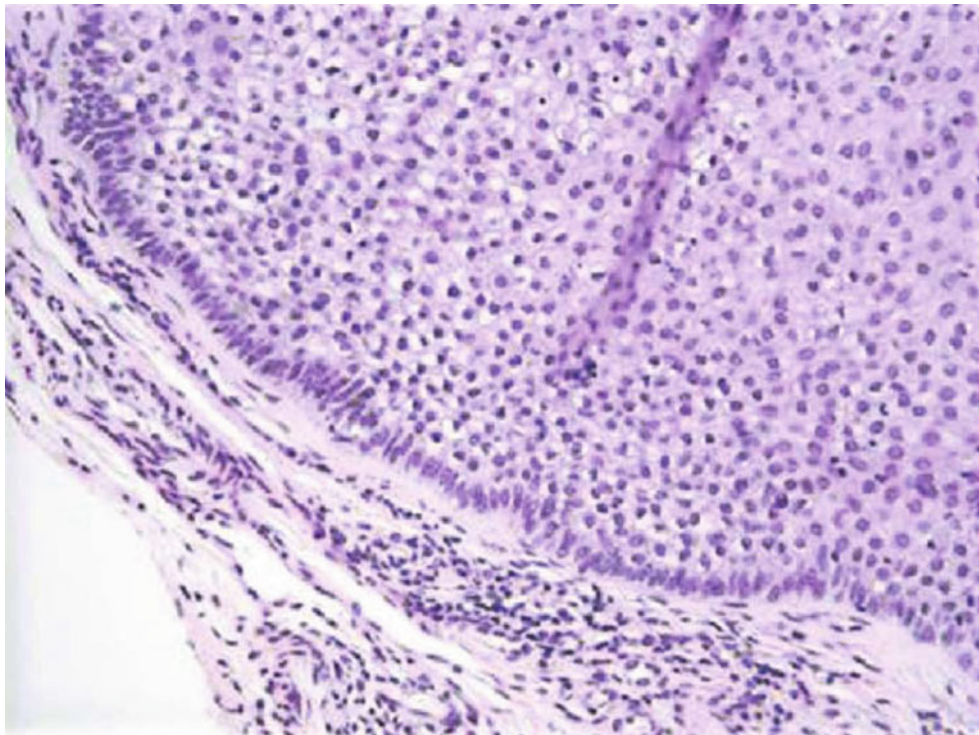
Figure 12.3. High-power photomicrograph depicting pale staining keratinocytes with basilar palisading resembling the outer root sheath of the follicle.
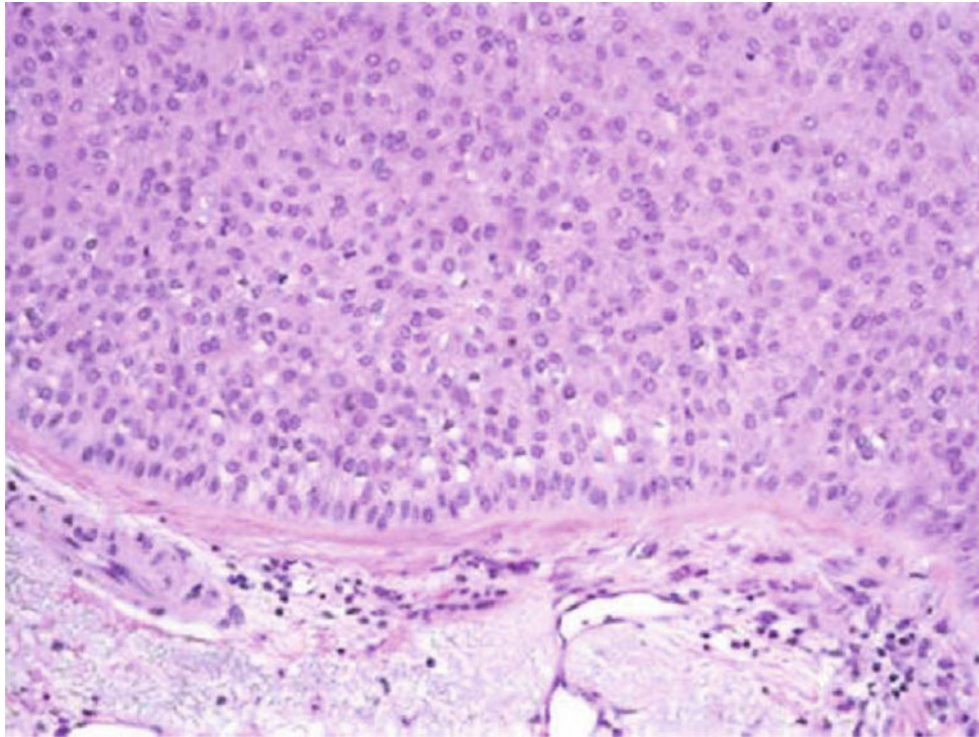
Figure 12.4. High-power photomicrograph depicting the prominent eosinophilic basement membrane surrounding the tumor periphery.
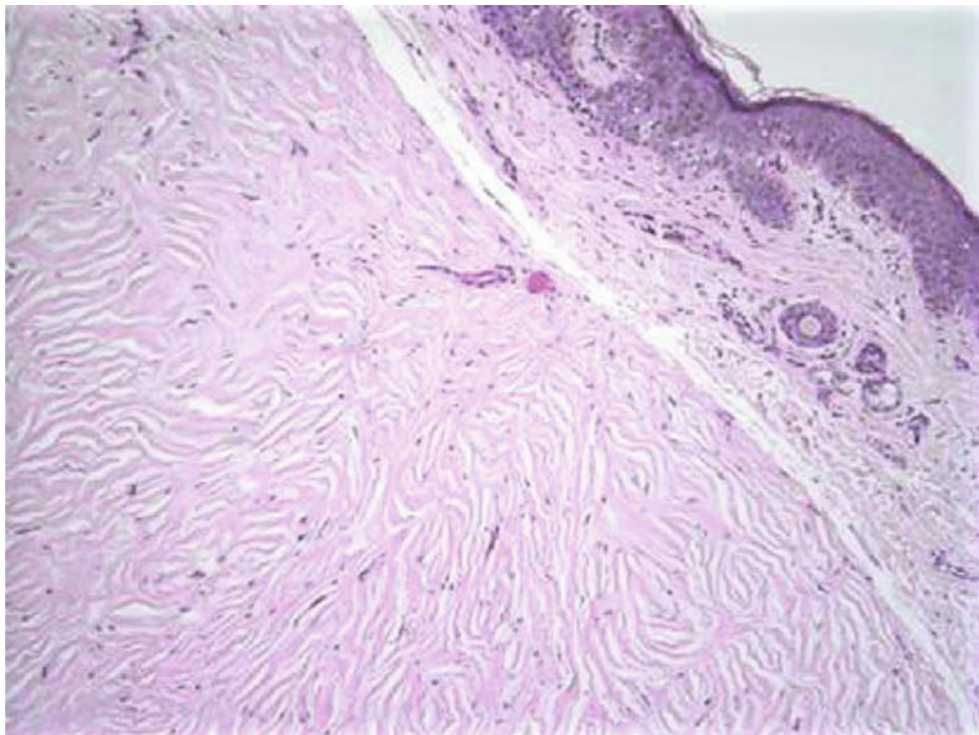
Figure 12.5. Low-power photomicrograph depicting well-circumscribed laminated appearance of sclerotic fibroma.

Figure 12.6. High-power detail of the sclerotic fibroma.

References

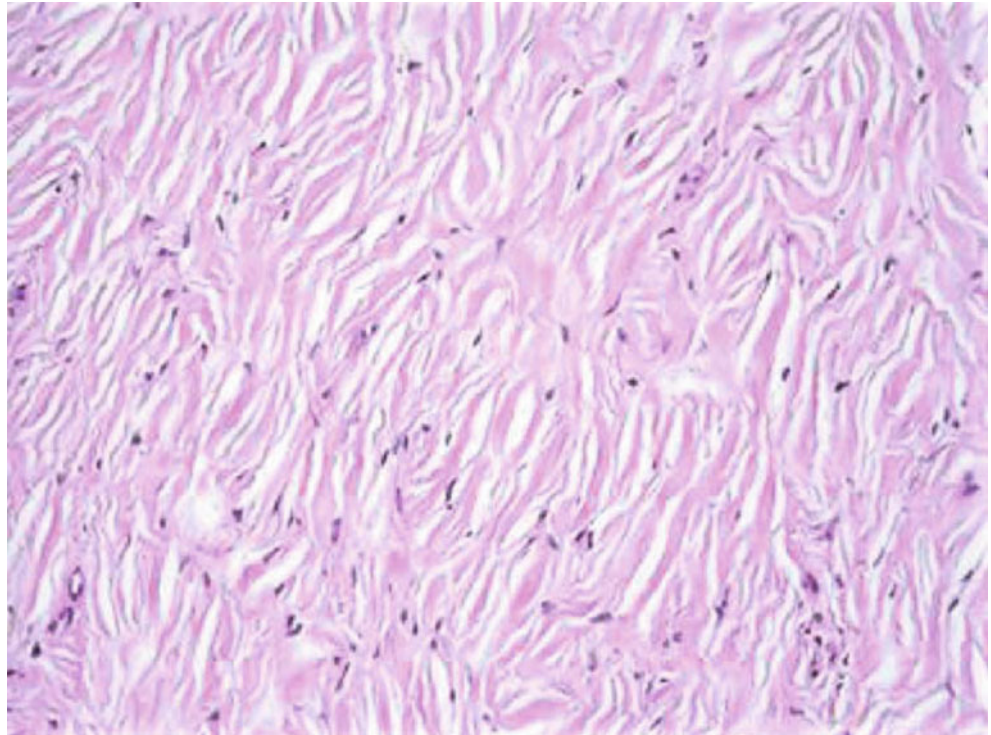1. Lloyd KM, Dennis M. Cowden's disease: a possible new symptom complex with multiple system involvement. Ann Intern Med. 1963;58:136–42.
2. Barax CN, Lebwohl M, Phelps RG. Multiple hamartoma syndrome. J Am Acad Dermatol. 1987;17:342–6.
3. Eng C. Genetics of Cowden syndrome: through the looking glass of oncology. Int J Oncol. 1998;12:701–10.
4. Starink TM, van derVeen JPW, Arwert F, de Waal LP, de Langer GG, Gille JJ, Eriksson AW. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet. 1986;29: 222–33.
5. Elston DM, James WD, Rodman OG, Graham GF. Multiple hamartoma syndrome (Cowden's disease) associated with non-Hodgkin's lymphoma. Arch Dermatol. 1986;122: 572–5.
6. Starink TM. Cowden's disease: an analysis of fourteen new cases. J Am Acad Dermatol. 1984;11:1127–41.
7. Salem OS, Steck WD. Cowden's disease (multiple hamartoma syndrome). J Am Acad Dermatol. 1983;8:686–95.
8. Mallory SB. Cowden syndrome (multiple hamartoma syndrome). Dermatol Clin. 1995;13:27–31.
9. Weary PE, Gorlin RJ, Gentry WC, Comer JE, Greer KE. Multiple hamartoma syndrome (Cowden's disease). Arch Dermatol. 1972;106:682–90.
10. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37(11):828–30.
11. Starink TM, Meijer CJLM, Brownstein MH. The cutaneous pathology of Cowden's disease: new findings. J Cutan Pathol. 1985;12:83–93.
12. Johnson BL, Kramer EM, Lavker RM. The keratotic tumors of Cowden's disease: an electron microscopic study. J Cutan Pathol. 1987;14:291–8.
13. Pujol RM, de Castro F, Schroeter AL, Su WPD. Solitary sclerotic fibroma of the skin: a sclerotic dermatofibroma? Am J Dermatopathol. 1996;18:620–4.
14. McCalmont TH. Sclerotic fibroma: a fossil no longer. J Cutan Pathol. 1994;21:82–5.
15. Requena L, Gutierrez J, Sanchez YE. Multiple sclerotic fibromas of the skin: a cutaneous marker of Cowden's disease. J Cutan Pathol. 1991;19:346–51.

13
Gardner Syndrome

▪	Synonyms:	Familial adenomatous polyposis (FAP) and adenomatous polyposis coli (APC)
▪	Etiology:	Mutation in adenomatous polyposis coli (*APC*) gene, chromosome 5q21-q22
▪	Associations:	Gastrointestinal tract adenomas and carcinoma, cutaneous cysts, fibromas, desmoids, and osteomas
▪	Histology:	Epithelial cysts with pilomatrical differentiation and fibrous nodules
▪	Evaluation:	Ophthalmologic examination, panoramic dental radiographs, GI tract evaluation, thyroid imaging, and possible *APC* gene mutation evaluation
▪	Treatment:	Prophylactic colectomy and periodic monitoring of upper GI tract and other organ systems for malignancy
▪	Prognosis:	Good, with early detection and intervention

Gardner syndrome is a variant of familial adenomatous polyposis, an autosomal dominant disease characterized by multiple adenomatous polyps of the colon that inevitably transform into adenocarcinoma, usually by the fifth decade. Some cases are the result of spontaneous mutations. In 1951, Gardner described a familial adenomatous polyposis kindred with extracolonic manifestations, including bone tumors and soft "cyst-like" surface tumors [1]. Interestingly, the cutaneous lesions were not characterized in that report because one family member had expired shortly after having a cutaneous lesion removed, and others in the family were afraid they would meet the same fate if their lesions were removed.

Gardner syndrome (GS) was initially viewed as a distinct variant of familial adenomatous polyposis (FAP). However, it became clear that within a given kindred, there is highly variable expression of extracolonic manifestations. Some patients express prominent extracolonic manifestations, and others express only gastrointestinal tract disease. The notion that GS and FAP are a single disease is supported by genetic studies that have localized germline mutations in FAP families to chromosome 5q21-q22, within the adenomatous polyposis coli (*APC*) gene [2–4]. In a given kindred, the identical mutation may be associated with pure colonic disease or colonic disease with prominent extracolonic manifestations, implicating other genetic or environmental factors in disease expression [4]. In one large kindred, there was a strong correlation of slow acetylators with extracolonic manifestations, but this has not been studied in other families [5]. Somatic mutations in this same gene have been implicated as the cause of some cases of sporadic colon cancer [4].

The *APC* gene encodes a protein complex that functions as a tumor suppressor by its interactions with β-catenin, a component of the adherens junctions at the plasma membrane. β-catenin also has an unbound soluble form that can act as a transcription factor with T-cell factor in the nucleus. This complex induces the expression of genes such as *c*-Myc, *cyclin* D1, and matrix metalloproteinase 7, which are involved in cell proliferation, migration, and metastasis. APC protein inhibits this process by phosphorylating β-catenin in the cytoplasm, precipitating its degradation. In the nucleus, it blocks β-catenin-induced transcriptional activity and aids in its removal from the nucleus. Once in the cytoplasm, β-catenin may be broken down or utilized at the adherens junctions [6]. Thus, the effect of *APC* gene mutations is the cellular accumulation of β-catenin, with its resultant proliferative and tumorigenic effects. β-catenin stabilizing mutations have been implicated in some cases of colon cancer and cutaneous tumors with pilomatrical differentiation [7].

β-catenin's resistance to breakdown in these cases results in the same cellular accumulation of the protein as occurs in *APC* mutations.

FAP patients will usually develop tubular adenomas of the colon in the second and third decade, and most will develop carcinomas by the fifth decade if not treated by prophylactic colectomy. FAP is generally divided into three severity categories: profuse or aggressive polyposis (early onset and extreme numbers of polyps), classic FAP, and attenuated FAP which has milder manifestations. These have characteristic mutational regions on the *APC* gene [3]. FAP accounts for fewer than 1 % of cases of colon cancer, but implications of diagnosis and early treatment in affected kindreds are profound [8]. Expression of extracolonic manifestations may allow for early diagnosis of FAP, potentially resulting in life-saving intervention. Given the highly variable expression of the disease within individuals, it is important to have an awareness of the spectrum of its features.

Ocular manifestations are present in a high percentage of FAP patients. They consist of round or oval pigmented patches of the retina, referred to as *congenital hypertrophy of the retinal pigment epithelium* (CHRPE). These are probably choristomas or hamartomas [9]. CHRPE is found in up to 90 % of FAP patients and is bilateral in 78 %. It should be noted that this finding is not specific. Similar unilateral lesions are found in one-third of control patients and bilateral lesions in 5 % [10]. Large or bilateral lesions are predictors of disease in the right clinical setting. Evaluation for CHRPE is particularly useful because such lesions are likely congenital, whereas other manifestations of the disease may not develop until adulthood.

Cutaneous manifestations of FAP help to define Gardner syndrome. These include epithelial cysts and fibromas (Fig. 13.1). Cutaneous cysts are usually multiple, and most

FIGURE 13.1. Follicular infundibular cyst with pilomatrical differentiation, a pretibial erythematous and violaceous cystic nodule.

occur on the scalp and face. Many begin to develop before puberty. While some cysts have no distinctive features, a study of cysts from a large kindred of Gardner syndrome patients revealed foci of pilomatrical differentiation in 63 % of lesions (Fig. 13.2a, b). Pilomatrical cells are those cells of the hair follicle that differentiate into the keratinizing cells that form the hair shaft. While the finding is of unknown specificity, such differentiation was not found in any of 100 randomly selected cysts [11]. Multiple pilomatricomas may also be a cutaneous marker of Gardner syndrome [12]. Nuchal-type fibroma is a deep-seated fibrous
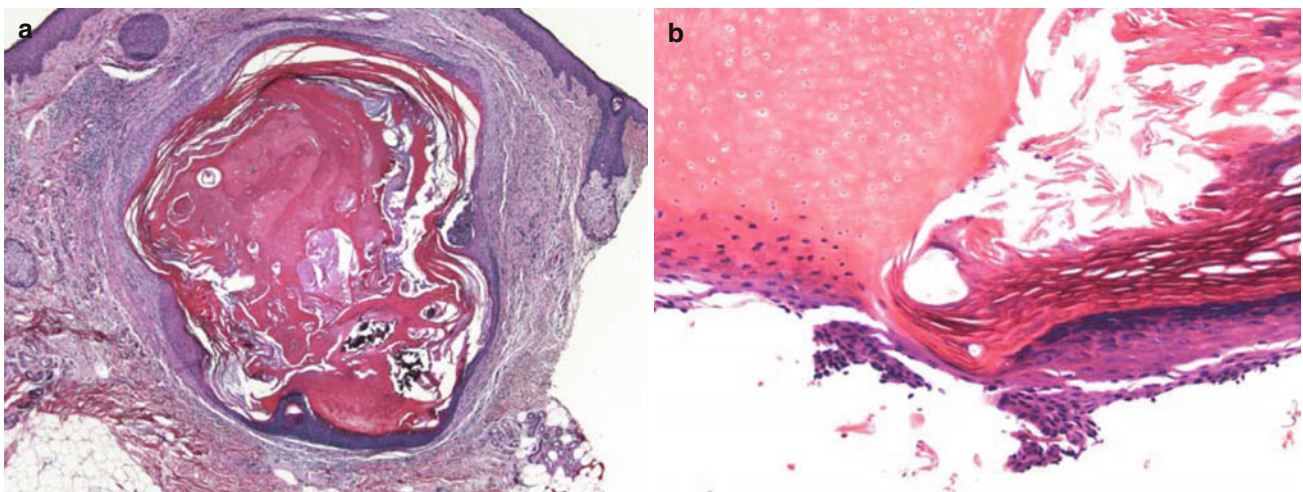
FIGURE 13.2. (**a**, **b**) Dermal cyst with follicular infundibular (*right on high-power panel*) and matrical (*left on high-power panel*) differentiation.

tumor, usually of the posterior neck, which may be associated with Gardner syndrome or, more commonly, diabetes mellitus. Tumors are composed of thick bundles of hypocellular collagen, which may entrap adipose tissue, and display traumatic neuroma-like areas (Fig. 13.3). A sparse population of CD34+ spindled cells is present [13, 14]. Similar lesions have been described at other anatomic sites in younger patients with GS, as early as 3 months of age. The back and paraspinal regions are most common. In some, it represented the initial presentation of the disease. It has been suggested that these Gardner fibromas have subtle differences from nuchal-type fibromas based upon a more "formless" pattern of collagen and the lack of neuroma-like areas, as well as nuclear β-catenin immunohistochemical staining in over half of lesions [15]. The differences in clinical presentation lend support to the idea of Gardner fibroma as a separate entity. Gardner fibromas may recur as desmoid fibromatosis, a myofibroblastic proliferation also known to occur in GS patients, suggesting that they may represent precursor lesions [14]. Some patients with Gardner syndrome have oral and cutaneous fibromas that do not display the typical features of Gardner fibroma, suggesting that GS should be regarded as being associated with a spectrum of benign fibrous lesions [16].

Desmoid fibromatosis, a benign-appearing myofibroblastic proliferation that may display a locally invasive growth pattern, occurs in approximately 10 % of individuals with FAP [9]. Microscopically, lesions have dense collagen with keloidal and myxoid change, vascular ectasia, and muscular hyperplasia of small arteries (Fig. 13.4). Both sporadic and Gardner-associated desmoids have increased nuclear β-catenin immunohistochemical staining. That seen in sporadic desmoids is due to mutations in the β-catenin gene and in Gardner-associated desmoids, nuclear accumulation of β-catenin as a result of the abnormal APC protein [15].
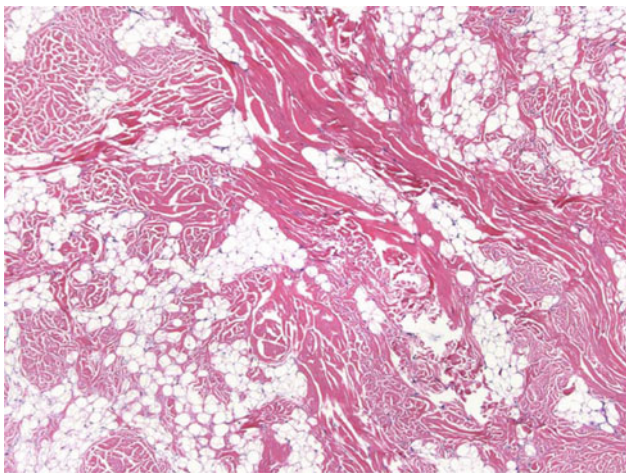
Abdominal cavity involvement, referred to as intra-abdominal fibromatosis, and abdominal wall involvement are the most common sites of involvement. Desmoids may be induced by pregnancy, oral contraceptives, or surgical procedures. Intra-abdominal fibromatosis occurs in the mesentery and in other peritoneal sites. Approximately 15 % of those with intra-abdominal fibromatosis have Gardner syndrome, and most of that group have their disease induced by prior abdominal surgery, most commonly colectomy. Some have coexistent abdominal wall involvement [17]. While desmoids do not have metastatic potential, their locally aggressive and destructive growth is an important cause of morbidity and mortality in those with FAP [3].

Other extracolonic manifestations of FAP are numerous. The association of brain tumors with FAP was originally described as Turcot syndrome, but like Gardner syndrome, mutations within the *APC* gene will result in this phenotype. The noncutaneous extracolonic manifestations of FAP are summarized in Table 13.1. Of these, osteomatous jaw change is worthy of special mention, because it may have early onset and be fairly prevalent among those with APC mutations. This makes panoramic dental radiographs a worthwhile screening tool [18].

Cutaneous presentations of the Gardner syndrome variant of FAP usually consist of multiple cysts or perhaps fibromas, nuchal-type or other, in childhood or early adulthood. Histopathologic evaluation of cysts is important because a finding of pilomatrical differentiation in such lesions should prompt evaluation for FAP. Family history may reveal FAP, but the lack of a history does not exclude the disease, as 25 % of cases may represent spontaneous mutations. Evaluation in childhood should begin with ophthalmologic evaluation for pigmented retinal lesions and panoramic dental radiographs or computed tomography for osteomatous change or other dental abnormalities.

Figure 13.3. Gardner fibroma, dense collagen bundles admixed with adipose tissue.
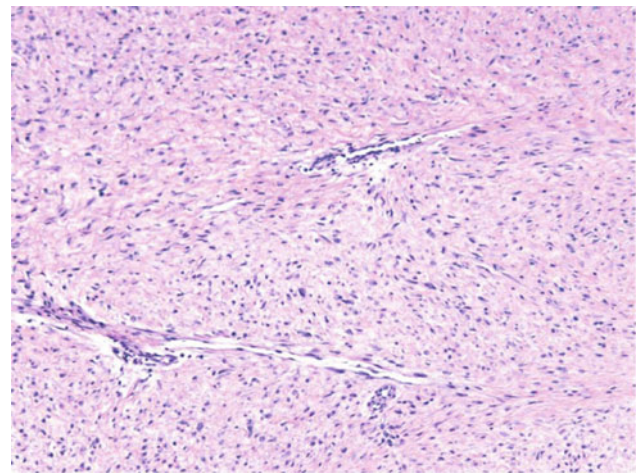
Figure 13.4. Desmoid fibromatosis, myofibroblastic spindle cell proliferation admixed with collagen and blood vessels.

Table 13.1. Noncutaneous extracolonic manifestations of FAP

1. *Dento-maxillary*—osteomas, diffuse osteomatous change, odontomas, dentigerous cysts, impacted teeth, hypercementosis, supernumerary teeth, fused or long roots
2. *Ocular*—congenital hypertrophy of the retinal pigment epithelium (CHRPE)
3. *Central nervous system tumors* (Turcot syndrome)—cerebellar medulloblastoma (most common), glioblastoma, craniopharyngioma
4. *Gastrointestinal tract*—duodenal and gastric polyps, periampullary adenoma and carcinoma (may cause obstructive pancreatitis), intra-abdominal fibromatosis
5. *Bone*—osteomas (facial or long bones)
6. *Other malignancy*—thyroid papillary carcinoma, hepatoblastoma, liposarcoma, osteosarcoma, testicular, renal

Genetic testing for *APC* mutations may be undertaken by sequencing all 15 coding exons of the *APC* gene, which will detect greater than 85 % of mutations. If sequencing fails to detect a mutation, then evaluation for large gene rearrangements using multiplex ligation-dependent probe amplification (MLPA), Southern blot, or real-time quantitative PCR analysis is likely to detect the remaining 10–15 % [3].

The treatment of FAP consists of prophylactic colectomy as the incidence of carcinoma otherwise approaches 100 % in the fifth decade. Screening recommendations of the American Society of Clinical Oncology include screening colonoscopy of affected family members every 1–2 years beginning at age 10–11 years for those with classic FAP and for those with attenuated FAP, screening colonoscopy every 2 years beginning at age 18–20. Surgery should be undertaken at the point at which there are large numbers of polyps or the polyps begin to show high-grade dysplasia. Gastroduodenal adenoma screening should begin once colorectal polyposis is established or at age 25–30 years, whichever occurs first [19].

Polyps have been shown to partially regress with sulindac and celecoxib therapy, but they recur upon cessation of treatment. As this treatment does not prevent the development of colorectal carcinoma, its role, if any, is limited to postponing surgery or controlling local recurrences after surgery [3]. Even with total colectomy, periodic evaluation of the upper gastrointestinal tract is indicated because of a 10–12 % estimated lifetime risk of developing duodenal or ampullary carcinomas [8]. Thyroid screening by ultrasound has been advocated due to the occurrence of thyroid nodules in approximately 50 % of FAP patients, with an incidence of papillary carcinoma of almost 10 % [20]. The onset of abdominal pain or gastrointestinal tract bleeding should prompt consideration of upper gastrointestinal tract tumors, obstructive pancreatitis due to periampullary tumors, or abdominal fibromatosis.

The Gardner syndrome variant of familial adenomatous polyposis is characterized by the presence of extracolonic manifestations, particularly cutaneous cysts and fibromas. The development of these markers early in life may herald the development of colonic polyposis and subsequent carcinoma, allowing for early diagnosis and potentially lifesaving intervention for the patient and other affected family members.

References

1. Gardner EJ. A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Am J Hum Genet. 1951;3:167–76.
2. Bodmer WF, Bailey CJ, Bodmer J, et al. Localisation of the gene for familial adenomatous polyposis on chromosome 5. Nature. 1987;328:614–6.
3. Leoz ML, Carballal S, Moreira L, Ocaña T, Balaguer F. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. Appl Clin Genet. 2015;8:95–107.
4. Nishisho I, Nakamura Y, Miyoshi Y, et al. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science. 1991;253:665–9.
5. Scott RJ, Taeschner W, Heinimann K, et al. Association of extracolonic manifestations of familial adenomatous polyposis with acetylation phenotype in a large FAP kindred. Eur J Hum Genet. 1997;5:43–9.
6. Hildesheim J, Salvador JM, Hollander MC, Fornace Jr AJ. CK2- and PKA-regulated APC and β-catenin cellular localization is dependent on p38 MAPK. J Biol Chem. 2005; 280:17221–6.
7. Chan EF, Gat U, McNiff JM, Fuchs E. A common human skin tumour is caused by activating mutations in beta-catenin. Nat Genet. 1999;21:410–3.
8. Burt RW, Bishop DT, Cannon-Albright L, et al. Population genetics of colon cancer. Cancer. 1991;70:1719–22.
9. Foulkes WD. A tale of four syndromes: familial adenomatous polyposis, Gardner syndrome, attenuated APC and Turcot syndrome. Q J Med. 1995;88:853–63.
10. Traboulsi EI, Krush AJ, Gardner EF, et al. Prevalence and importance of pigmented ocular fundus lesions in Gardner's syndrome. N Engl J Med. 1987;316:661–7.
11. Cooper PH, Fechner RE. Pilomatricoma-like changes in epidermal cysts of Gardner's syndrome. J Am Acad Dermatol. 1983;8:639–44.
12. Pujol RM, Casanova JM, Egido R, Pujol J, de Moragas JM. Multiple familial pilomatricomas: a cutaneous marker for Gardner syndrome? Pediatr Dermatol. 1995;12:331–5.
13. Michal M, Fetsch JF, Hes O, Miettinen M. Nuchal-type fibroma: a clinicopathologic study of 52 cases. Cancer. 1999; 85:156–63.
14. Wehrli BM, Weiss SW, Yandow S, Coffin CM. Gardner-associated fibromas (GAF) in young patients. Am J Surg Pathol. 2001;25:645–51.
15. Coffin CM, Hornick JL, Zhou H, Fletcher CDM. Gardner fibroma: a clinicopathologic and immunohistochemical analysis

of 45 patients with 57 fibromas. Am J Surg Pathol. 2007;31:410–6.

16. Michal M, Boudova L, Mukensnabi P. Gardner's syndrome associated fibromas. Pathol Int. 2004;54:523–6.

17. Burke AP, Sobin LH, Shekitka KM, Federspiel BH, Helwig EB. Intra-abdominal fibromatosis: a pathologic analysis of 130 tumors with comparison of clinical subgroups. Am J Surg Pathol. 1990;14:335–41.

18. Utsunomiya J, Nakamura T. The occult osteomatous changes in the mandible in patients with familial polyposis coli. Br J Surg. 1975;62:45–51.

19. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol. 2015;33:209–17.

20. Feng X, Milas M, O'Malley M, et al. Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. Thyroid. 2015;25:325–32.

14
Multiple Cutaneous Leiomyomas

■	Synonyms:	Multiple cutaneous and uterine leiomyomatosis (MCUL) syndrome Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome Reed syndrome
■	Etiology:	Mutation in fumarate hydratase gene, mapped to chromosome 1q42.3–q43
■	Associations:	Uterine leiomyomas and rarely leiomyosarcomas and renal carcinoma
■	Clinical:	Red-brown indurated papules, sometimes clustered or in linear array
■	Histology:	Reticular dermal fascicular tumor with cigar-shaped nuclei, amphophilic vacuolated cytoplasm, and rare mitotic figures
■	IHC:	Smooth muscle actin+ and desmin+
■	Evaluation:	Renal imaging and genetic testing for fumarate hydratase mutation and function
■	Treatment:	Surgical management of underlying tumors, excision of painful cutaneous tumors, or pharmacologic pain management
■	Prognosis:	Excellent with early detection of underlying malignancy

Cutaneous leiomyomas are uncommon tumors that arise from arrector pili (pilar leiomyoma), genital smooth muscle (genital leiomyoma), or vascular smooth muscle (angioleiomyoma). Angioleiomyomas are histologically distinct and are not known to occur as multiple lesions. Most pilar leiomyomas occur singly but can occur as multiple lesions. As multiple lesions, they may occur in association with uterine leiomyomas and, rarely, leiomyosarcomas, in the multiple cutaneous and uterine leiomyomatosis (MCUL) syndrome. More recently, cutaneous and uterine leiomyomas have been reported to occur in association with renal cell carcinoma in the hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome [1]. MCUL and HLRCC likely represent part of a spectrum of one disease. A relationship between cutaneous leiomyomas and uterine leiomyomas was highlighted by Reed et al., and because of that, HLRCC is sometimes referred to as the Reed syndrome [2]. This syndrome is transmitted in an autosomal dominant pattern, with variable penetrance. The implicated gene encodes fumarate hydratase (FH), an enzyme in the Krebs cycle that maps to chromosome 1q42.3–q43 [3]. Fumarate hydratase (FH) is distributed predominantly within the mitochondria but also within the cytosol of mammalian cells. In the cytosol, FH is involved in the purine nucleotide cycle. In the mitochondria, it catalyzes the reversible hydration of fumarate into malate as part of the Krebs cycle. The previous step in the Krebs cycle is the conversion of succinate to fumarate by succinate dehydrogenase. Succinate dehydrogenase mutations are also associated with a cancer predisposition, specifically pheochromocytoma and paraganglioma [4]. Deficient FH function induces cellular pseudohypoxia as a result of the Krebs cycle dysfunction, a state which likely promotes tumorigenesis [5].

There is a spectrum of fumarate hydratase gene defects described in different clinical settings, but the type of defect does not appear to correlate with disparate clinical manifestations [6]. Fumarate hydratase mutations cause MCUL syndrome, HLRCC syndrome, and autosomal recessive FH deficiency, which manifests as severe developmental delay and death in childhood. Autosomal recessive FH

deficiency does not appear to be associated with the development of malignancy. However, short life expectancy may not allow for its expression. Some parents of FH-deficient children develop leiomyomas as may be expected in the heterozygous state [3]. In HLRCC and MCUL, the development of cutaneous and uterine leiomyomas and renal cell cancer occurs with one mutant allele and one wild-type (normal) allele. Tumor development requires a "second hit," as suggested in Knudson's theory of tumorigenesis. Loss of expression of the wild-type allele may occur by loss of heterozygosity or second mutation in the previously normal allele. Loss of heterozygosity at the genetic locus for these syndromes is known to occur in the cutaneous and uterine leiomyomas and renal cell carcinomas in patients with the syndrome, supporting a role for FH in tumor suppression [7]. Mutations of the FH gene are rare in sporadic uterine leiomyomas and not found in sporadic uterine leiomyosarcomas. Therefore, the gene does not play a major role in the development of sporadic uterine smooth muscle tumors [8].

Cutaneous leiomyomas occur in approximately 80 % of patients with HLRCC, and of those patients presenting with leiomyomas, 85 % have FH mutations [9, 10]. Leiomyomas are red-brown dome-shaped papules, from several millimeters to approximately 1 cm in diameter (Fig. 14.1) [9]. When they are multiple, they may be clustered, may form a linear array, or may occur in a more disseminated pattern [11]. Solitary lesions usually occur on the extremities, and multiple lesions may occur on either the trunk or extremities. Pain is commonly reported and may be precipitated by cold or pressure. The discomfort is described as sharp, burning, or throbbing [12]. The differential diagnosis is wide for solitary lesions and for multiple lesions may include such disparate entities as segmental neurofibromatosis, foreign body granuloma, dermatofibrosarcoma protuberans, and sarcoidosis.

Histopathology reveals a reticular dermal tumor composed of fascicles of smooth muscle bundles, with cigar-shaped nuclei and eosinophilic to amphophilic vacuolated cytoplasm (Fig. 14.2a, b). Tumor cells are highlighted by antibodies to smooth muscle actin and desmin. In one series, 55 % of these tumors had epidermal hyperplasia, and 10 % had focal infiltration of the fat. Twenty-eight percent had mitotic figures, but these were usually sparse. No recurrences were seen in the mitotically active lesions. A nodular, more circumscribed architecture appears to correlate with the presence of multiple lesions [12]. Leiomyomas associated with HLRCC may display atypical features, and rare cases of leiomyosarcoma have been described [9, 13]. A recent case of isolated cutaneous leiomyosarcoma in a patient with a germline FH mutation, a family history of renal cancer, and no cutaneous leiomyomas has been described, suggesting that assessment of FH activity in this clinical setting should be considered [14].

Figure 14.1. Clustered erythematous papules and small nodules of the calf (Photo courtesy of Cleveland Clinic Foundation, Department of Dermatology).

Renal carcinomas occurring in association with FH deficiency occur in approximately 15 % of affected individuals [9]. The mutation type does not correlate with renal carcinoma risk [11]. Renal carcinomas are most commonly papillary, some with tubular features. The most characteristic feature of HLRCC renal tumors is that of a large nucleus with an inclusion-like orangiophilic or eosinophilic nucleolus, surrounded by a clear halo. HLRCC renal tumors tend to behave aggressively and have a poor prognosis [15].

Multiple leiomyomas are not exclusively a manifestation of fumarate hydratase deficiency. They have also been reported to occur in patients with chronic lymphocytic leukemia [16] and HIV infection [17]. An association of leiomyosarcomas and leiomyomas with HIV infection and other forms of immunosuppression is well established and is known to be induced by Epstein-Barr virus (EBV) infection. In these tumors, EBV genomes are detectable within tumor cells by in situ hybridization [18].
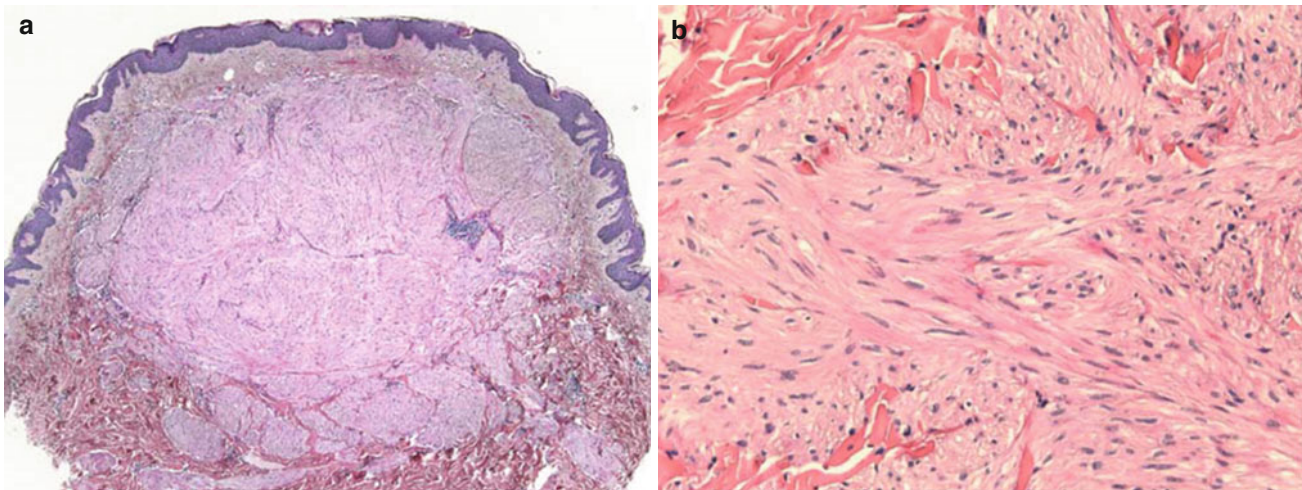
Figure 14.2. (**a**, **b**) Dermal tumor composed of fascicles of smooth muscle cells with vacuolated cytoplasm and blunt-ended nuclei.

Management of multiple leiomyomas is primarily surgical. Excision of symptomatic lesions may be warranted. Nifedipine, injected botulinum toxin, and oral doxazosin have been used to alleviate the pain in the setting of multiple painful tumors [19–21]. Individuals suspected of having the syndrome should undergo genetic testing and functional assay of FH from cultured fibroblasts or lymphoblastoid cells. Affected individuals should undergo renal CT or MRI periodically and be referred to an oncologic surgeon early given the aggressiveness of the renal tumors. In women, serial physical examinations and imaging should be undertaken because of a risk of leiomyosarcoma. Serial skin exams should also be performed given a small risk of cutaneous leiomyosarcoma. At-risk family members should also be evaluated [22].

Multiple cutaneous leiomyomas have recently been added to the list of cancer susceptibility syndromes that may first present in the skin. These tumors may represent the presenting manifestation of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. Recognition of the cutaneous leiomyomas may have life-saving implications for the patient and relatives.

References

1. Launonen V, Vierimaa O, Kiuru M, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci U S A. 2001;98:3387–92.
2. Reed WB, Walker R, Horowitz R. Cutaneous leiomyomata with uterine leiomyomata. Acta Derm Venereol. 1973;53:409–16.
3. Tomlinson IPM, Alam NA, Rowan AJ, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cancer. Nat Genet. 2002;30:406–10.
4. Rustin P. Mitochondria, from cell death to proliferation. Nat Genet. 2002;30:352–3.
5. Desideri E, Vegliante R, Ciriolo MR. Mitochondrial dysfunctions in cancer: genetic defects and oncogenic signaling impinging on TCA cycle activity. Cancer Lett. 2015;356:217–23.
6. Alam NA, Rowan AJ, Wortham NC, et al. Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumarate hydratase deficiency. Hum Mol Genet. 2003;12:1241–52.
7. Kiuru M, Launonen V, Hietala M, et al. Familial cutaneous leiomyomatosis is a two-hit condition associated with renal cell cancer of characteristic histopathology. Am J Pathol. 2001;159:825–9.
8. Lehtonen R, Kiuru M, Vanharanta S, et al. Biallelic inactivation of *fumarate hydratase* (FH) occurs in nonsyndromic uterine leiomyomas but is rare in other tumors. Am J Pathol. 2004;164:17–22.
9. Wei M-H, Toure O, Glenn GM, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. J Med Genet. 2006;43:18–27.
10. Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. Br J Dermatol. 2005;153:11–7.
11. Toro JR, Nickerson ML, Wei M-H, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73:95–106.
12. Raj S, Calonje E, Kraus M, et al. Cutaneous pilar leiomyoma: clinicopathologic analysis of 53 lesions in 45 patients. Am J Dermatopathol. 1997;19:2–9.
13. Cook DL, Pugliano-Mauro MA, Schultz ZL. Atypical pilar leiomyomatosis: an unusual presentation of multiple atypical cutaneous leiomyomas. J Cutan Pathol. 2013;40:564–8.

14. Weiler L, Poulalhon N, Slama A, Guillaud-Bataille M, Thomas L. Isolated cutaneous leiomyosarcoma revealing a novel germ-line mutation of fumarate hydratase gene. Br J Dermatol. 2015. doi:10.1111/bjd.13867 [Epub ahead of print].

15. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum or kidney tumors in Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome. Am J Surg Pathol. 2007;31:1578–85.

16. Vergani R, Betti R, Uziel L, Tolomio E, Crosti C. Eruptive multiple sporadic cutaneous piloleiomyomas in a patient with chronic lymphocytic leukemia. Br J Dermatol. 2000; 143:907–9.

17. Kanitakis J, Carbonnel E, Chouvet B, Labeille B, Claudy A. Cutaneous leiomyomas (piloleiomyomas) in adult patients with human immunodeficiency virus infection. Br J Dermatol. 2000;143:1338–40.

18. McClain K, Leach C, Jenson H. Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. N Engl J Med. 1995;332:12–8.

19. George S, Pulimood S, Jacob M, Chandi SM. Pain in multiple leiomyomas alleviated by nifedipine. Pain. 1997;73:101–2.

20. Onder M, Adişen E. A new indication of botulinum toxin: leiomyoma-related pain. J Am Acad Dermatol. 2008;60:325–8.

21. Batchelor RJ, Lyon CC, Highet AS. Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. Br J Dermatol. 2004;150:775.

22. Pithukpakorn M, Toro JR. Hereditary Leiomyomatosis and Renal Cell Cancer. 2006 Jul 31 [Updated 2010 Nov 2]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle: University of Washington; 1993–2015. http://www.ncbi.nlm.nih.gov/books/NBK125.

15

Lethal Hereditary Vascular Disorders: Osler-Weber-Rendu Syndrome, Ataxia-Telangiectasia, and Fabry's Disease

■ Synonyms:	OWR—hereditary hemorrhagic telangiectasia AT—Louis-Bar syndrome FD—Anderson-Fabry disease and angiokeratoma corporis diffusum
■ Etiology:	OWR—AD and chromosome 9- and 12-defect in endoglin or activin receptor-like kinase 1 AT—AR and 11q22.3 phosphatidylinositol-3-kinase p53 checkpoint regulation FD—XL, Xq22.1, and alpha-galactosidase A
■ Associations:	OWR—arteriovenous malformations of the brain and lungs; hepatic fibrovascular tumors AT—B-cell non-Hodgkin's lymphoma, T-cell CLL, breast cancer, and growth retardation FD—none
■ Clinical:	OWR—mucocutaneous telangiectasias, epistaxis, hemoptysis, clubbing, and cyanosis AT—oculocutaneous telangiectasias, skin photoaging, and cerebellar ataxia FD—cutaneous nonblanching angiectases, neuropathic pain, cardiomyopathy, and renal failure
■ Pathology:	OWR—mucosal and dermal telangiectasias AT—dermal elastosis, telangiectasias, and pulmonary bronchiectasis CNS demyelination FD—mucosal and dermal telangiectasias and angiokeratomas, and interstitial lipid deposits
■ Staging:	N/A
■ Prognosis:	OWR—good in the absence of pulmonary or CNS malformation or abscess AT—invariably fatal, usually early adulthood secondary to infection or lymphoma/leukemia FD—poor without renal transplantation and better recent outcome with enzyme replacement
■ Complications:	OWR—arteriovenous malformations and abscesses of CNS and lungs AT—bronchiectasis, cerebellar ataxia, T-cell leukemia, and B-cell lymphoma FD—cardiomyopathy, cerebrovascular accident, and renal failure
■ Treatment:	OWR—supportive measures AT—supportive measures FD—alpha-galactosidase A gene therapy shows promise

Mucocutaneous vascular ectasia, otherwise referred to as telangiectasia, can be an important harbinger of serious systemic disease. Among a variety of acquired conditions, including hepatic cirrhosis, that are responsible for their development, are a heterogeneous group of inherited conditions that entail the development of multiple cutaneous and mucous membrane vascular lesions associated with other life-threatening complications. This chapter deals with the clinical and pathologic features of three such conditions, namely, Osler-Weber-Rendu syndrome, ataxia-telangiectasia, and Fabry's disease.

Osler-Weber-Rendu (OWR) syndrome, synonymously referred to as hereditary hemorrhagic telangiectasia, was first described by Dr. William Osler in 1907 [1]. He described many of the attributes of this distinctive disorder known today, including the characteristic triad of the superficial cutaneous vessels that undergo irreversible dilatation forming *telangiectasis*, bloody nasal discharge (*epistaxis*), and its familial tendency [2]. The disorder affects all races, although it has been described with a higher incidence in the Dutch Antilles and parts of France. It is known to be an inherited or spontaneously acquired autosomal dominant trait. The overall incidence of the disorder is about 1 in 5000–8000 persons [3]. The defect involves segments of chromosomes 9 and 12, which encodes for two important endothelial transmembrane receptors, termed endoglin and activin receptor-like kinase 1, respectively. The latter protein is the receptor for transforming growth factor beta, an important modulator of tissue repair and angiogenesis that when defective is thought to lead to defects in endothelial cell junctions and weakness of the supporting perivascular connective tissue resulting in telangiectasis and *arteriovenous malformation* (AVM). The disease typically manifests in early to mid-adulthood with the development of epistaxis. Other common presenting signs include mucosal and cutaneous telangiectasis and other signs of bleeding diathesis including melena and hemoptysis. The telangiectasias consist of discrete red puncta, spiderlike branching, and/or linear vascular lesions located in particular on the face, fingers, and oral and nasal mucous membranes [4] (Fig. 15.1). Less common findings include headaches stemming from complications associated with cerebral arteriovenous malformation, cyanosis and/or clubbing associated with pulmonary arteriovenous malformation, signs and symptoms of high-output cardiac failure produced from pulmonary vascular shunting, fatigue from blood loss and anemia, visual disturbances following intraocular hemorrhage, and fever associated with abscesses following bacterial seeding of the pulmonary or cerebral vascular anomalies [5]. Important complications to consider include gastrointestinal and pulmonary bleeding, often necessitating transfusion; cerebrovascular accident; and infectious complications stemming from the vascular anomalies. The overall mortality is approximately

Figure 15.1. Diffuse palmar telangiectasis in Osler-Weber-Rendu syndrome.

10 % with patients generally succumbing to one of the aforementioned complications. Although estrogen has been reported in the past as producing some measure of therapeutic improvement, current recommendations include supportive measures including prompt recognition and cessation of bleeding [6]. A recent phase II trial has found a vascular endothelial growth factor antagonist, bevacizumab, as being a promising therapeutic option, especially for those with large hepatic AVMs. This drug reduces liver size and cardiac output and decreases the severity of epistaxis [7].

Ataxia-telangiectasia (AT), or *Louis-Bar syndrome*, was first described by Syllaba and Henner in 1926 and later by the Belgian neuropathologist Dr. Denise Louis-Bar in 1941, who detailed the progressive nature of the cerebellar ataxia and distinctive cutaneous telangiectasis of the disorder [8]. Its final designation of ataxia-telangiectasia would come in 1957 with the discovery of its association with immunologic defects and the predisposition of afflicted patients to develop recurrent sinopulmonary infections. Today, we know this autosomal recessively inherited disease to involve the 11q22–23 gene that encodes for the ataxia-telangiectasia mutated (ATM) protein [9]. This protein is an important regulatory phosphoprotein involved with p53-regulated cell cycling and DNA maintenance. Defective ATM function results in increased unregulated DNA synthesis and defective DNA strands predisposed to instability and hypersensitivity to ionizing radiation. These defects are thus thought to predispose to neoplastic transformation, and the increased risk these patients possess for solid organ and lymphoreticular malignancy as well as impact upon T-lymphocyte receptor function lead to immunologic dysfunction and a predisposition toward certain types of infection [10, 11]. The mechanisms that underlie the cerebellar ataxia, growth retardation, and mucocutaneous telangiectasis are not known but have been hypothesized to

FIGURE 15.2. Conjunctival telangiectasis in ataxia-telangiectasia.

involve accelerated telomere loss. The disease affects all races and regions of the world and has an estimated incidence of 1 in 100,000 individuals [12]. The disease is generally heralded by the development of ataxia in the first years of life. The ataxia commences with abnormal head movements and progresses to involve the gait and abnormal arm movements including tremor and myoclonus, later. Other neurologic findings include choreoathetosis, masklike facies, and saccadic eye deviation with absent optokinetic nystagmus. The pathogenesis involves *spinocerebellar degeneration* with demyelination. The mucocutaneous telangiectasias develop by the age of 5 years and in particular involve the conjunctival angles and adjacent periocular skin (Fig. 15.2). Accelerated aging (*progeric changes*) including graying of the hair, facial skin atrophy, seborrheic dermatitis, and mottled pigmentation are also common. Other cutaneous findings include café au lait macules, vitiligo, hypertrichosis, acanthosis nigricans, keratosis pilaris, actinic keratosis, and the presence of nonmelanoma skin cancer. Other major impairments associated with AT are immunologic dysfunction with increased sinopulmonary and ear infections associated with thymic hypoplasia, defective cell-mediated immunity, and reduced serum IgA and IgE immunoglobulin levels. Less prominent features of the disease include mental retardation, atherosclerotic heart disease, diabetes mellitus, and growth impairment. Pathology of the brain shows degeneration of the cerebellar Purkinje and granule cells and spinal column anterior horn and spinal tract degeneration and demyelination. The cutaneous findings include epidermal atrophy with solar elastosis and capillary telangiectasis. Less common findings include the presence of dermal noncaseating granulomas, pigmentary incontinence, and superimposed changes of seborrheic dermatitis or keratosis pilaris. The dermal granulomas consist of epithelioid granulomas that may masquerade as sarcoidosis. Cases of ulcerating or perforating granulomatous dermatitis and palisaded granulomatous

dermatitis have been described as well [13]. Actinic keratosis and basal cell and squamous cell carcinoma may be seen in young patients and as such may suggest the possibility of this disorder. Important complications primarily involve neoplastic and infectious diseases. AT patients have an estimated 100-fold increase in the incidence of malignancy, particularly Hodgkin's and non-Hodgkin's lymphoma, leukemia, and gastric and breast adenocarcinoma [11, 12]. An important complication of recurrent pulmonary infection is bronchiectasis. AT is invariably fatal with few afflicted individuals living beyond their third decade. The major causes of mortality include pulmonary infection and malignancy. Treatment consists of the aggressive management of infectious disease with antibiotics and prevention with prophylactic administration of immunoglobulins and vaccination. Sunscreens and sun avoidance are important with respect to the cutaneous complications. *Increased awareness of oncologic disease with appropriate screening is recommended.* Physical, speech, and occupational therapies should be instituted, and genetic counseling for the patient and family is encouraged.

Fabry's disease, otherwise referred to as Anderson-Fabry disease or angiokeratoma corporis diffusum, was independently described by Drs. Anderson and Fabry in 1898 [14, 15]. The disease is inherited as an *X-linked trait* and involves a defect in glycosphingolipid metabolism caused by a deficiency of *alpha-galactosidase A*. Over 160 mostly missense-type mutations have been identified within encoding gene segments for alpha-galactosidase [16]. Although males are predominantly afflicted, females may rarely present with milder forms of the disease. The disease is worldwide in distribution, and although it afflicts all races, whites are overrepresented. The estimated incidence is 1 in 40,000 individuals. The etiology involves the accumulation of glycosphingolipid substrate following the lack of enzymatic activity in the tissues of the principal organs involved with the disease [17]. As the gene is located on Xq22, males are more severely afflicted, possessing very low to absent galactosidase levels. Carrier females and females with incomplete lyonization of the abnormal X-chromosome allele may develop milder disease stigmata. The disorder has been rarely reported in individuals with normal measured enzyme activity [18]. The most important glycosphingolipids that accumulate due to the enzymatic defect are globotriaosylceramide and galabiosylceramide. These compounds accumulate primarily within the lysosomes and cytosol of endothelial, pericyte, and smooth muscle cells of the skin, renal, and neurovascular organs. The pathologic alterations stem from endothelial accumulation and disruption with consequent ischemic and degenerative changes. Symptoms are generally ushered in by the development of limb neuropathic pain and cutaneous vascular anomalies in late adolescence or early adulthood. The limb pain is usually exacerbated by exposure to cold and is typically described as burning in quality. The

Figure 15.3. Diffusely scattered telangiectatic papules on the scrotum of a patient with angiokeratoma corporis diffusum.

cutaneous changes consist of the development of myriad punctate red-to-blue nonblanching angiectasis particularly situated in the "bathing suit" area of the lower abdomen and perineum (Fig. 15.3) [17]. The nonblanching quality of the lesions is an important contrast with telangiectasia, which typically blanches with external pressure or diascopy. Similar vascular lesions can be found on the oral mucosa. Other attendant cutaneous findings include lymphedema and hypohidrosis. Important additional systemic signs include various lens opacities that are pathognomonic for the disorder. Distinctive corneal opacities referred to as *cornea verticillata* are also commonly seen. The cutaneous and ocular findings are overshadowed by the serious systemic complications of visceral organ involvement. The kidneys are severely affected, and renal failure is common by the fourth decade. Important signs of renal disease include increasing proteinuria and the demonstration of characteristic birefringent lipid globules with a "Maltese cross" pattern in the urinary sediment. The heart is particularly prone to complications stemming from the accumulation of lipids within the vessel walls and myocardium resulting in ischemic complications and left ventricular hypertrophy. Congestive heart failure and myocardial infarction are important causes of morbidity and mortality. Additional organs involved include the brain, where cerebrovascular accident is a common complication, and the gastrointestinal tract, where intestinal ischemia may be observed. The pathologic changes involve the progressive

dilatation of capillaries and post-capillary venules within the dermis (Fig. 15.4). Over time, the abutment adjacent to the epithelium produces epidermal hyperplasia and angiokeratoma formation. Systemic pathologic changes additionally include vascular ectasia, accelerated atherosclerosis, and degenerative changes ascribed to ischemic alteration. The heart shows increased interstitial fibrous and lipid deposits. Glomerular and renal tubular deposits are seen in the kidney. Characteristic lysosomal organelle lamellar inclusions are observed ultrastructurally. The diagnosis can be confirmed by direct enzymatic assay of serum, leukocytes, or cultured fibroblasts or by DNA analysis of the gene. A presumptive diagnosis can be rendered upon the careful assessment of the ophthalmologic findings, the widespread nature of the angiokeratomas, and/or the urinary sediment findings. Important entities to consider in the differential diagnosis are other inherited enzyme deficiency syndromes with similar clinical stigmata. These disorders include alpha-L-fucosidase and neuraminidase deficiency, among other rarer entities [18, 19]. Important clues that suggest the latter entities include disseminated angiokeratomas in a female patient and psychomotor and cognitive impairment. The long-term prognosis of patients is determined by renal function status. Renal transplantation has dramatically improved the outcome of patients as transplanted kidneys generally possess normal enzyme activity. Important morbidities, including neuropathic pain and cerebrovascular and cardiovascular disease, are treated symptomatically with pain and antiseizure medications, aggressive blood pressure control, and smoking cessation. Recent advances in recombinant gene therapy have revolutionized the treatment and long-term outlook of these patients. Enzyme replacement therapy is now in the forefront, with a new drug called Fabrazyme (agalsidase beta) [16]. This drug replaces the deficient enzyme alpha-galactosidase A, reducing the amounts of accumulated globotriaosylceramide (GL-3) deposition in the capillary endothelium and thereby improving many of the symptoms of FD [20]. A recent study has shown this drug to reduce the progression of vascular disease, suggesting stabilization of white matter lesions and stroke risk present in FD patients [21]. Another enzyme, PRX-102, derived from the tobacco plant is said to have an even longer half-life than Fabrazyme and is currently being investigated [22].
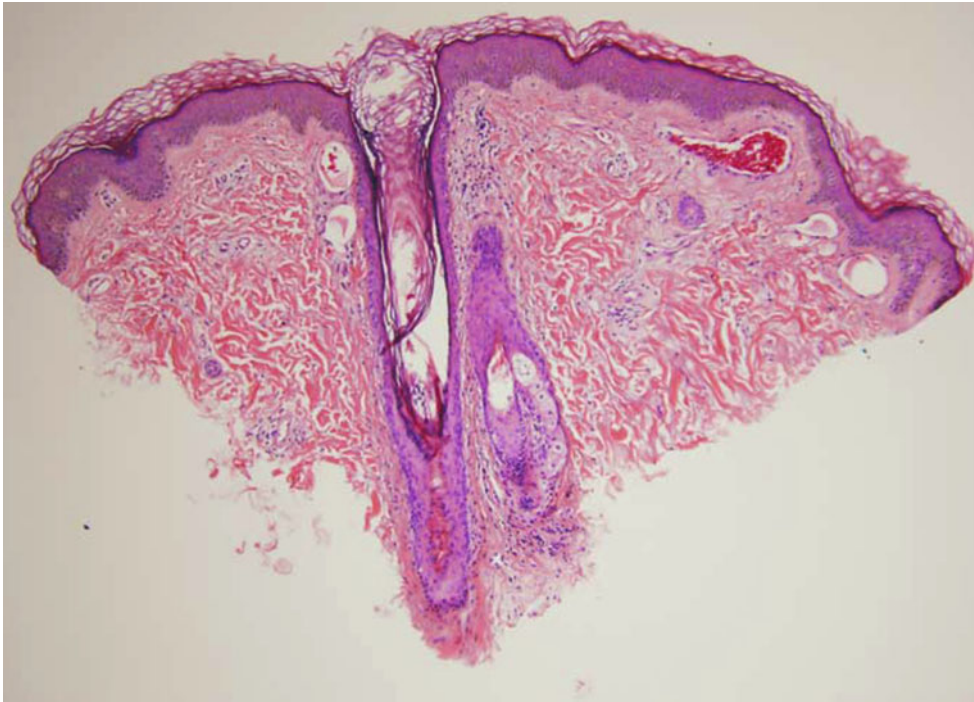
Figure 15.4. Low-power photomicrograph depicting superficial dermal capillary telangiectasis in Osler-Weber-Rendu syndrome.

References

OWR

1. Osler W. On multiple hereditary telangiectasis with recurrent ring hemorrhages. Q J Med. 1907;1:53.
2. Perry W. The clinical spectrum of hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu disease). Am J Med. 1987;5:989.
3. Garg N, Khunger M, Gupta A, Kumar N. Optimal management of hereditary hemorrhagic telangiectasia. J Blood Med. 2014;5:191.
4. Chandler D. Pulmonary and cerebral arteriovenous fistula with Osler's disease. Arch Intern Med. 1965;116:277.
5. Swanson D, Dahl M. Embolic abscesses in hereditary hemorrhagic telangiectasia. J Am Acad Dermatol. 1991;24:580.
6. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia: a double blind controlled clinical trial. Acta Med Scand. 1981;209:393.
7. Dupuis-Girod S, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA. 2012;307:948.

AT

8. Smith L, Conerly S. Ataxia-telangiectasia or Louis-Bar syndrome. J Am Acad Dermatol. 1985;12:686.
9. Li A, Swift M. Mutations at the ataxia-telangiectasia locus and clinical phenotypes of A-T patients. Am J Med Genet. 2000;92:170.
10. Khanna K. Cancer risk and the ATM gene: a continuing debate. J Natl Cancer Inst. 2000;92:795.
11. Swift M, Morrell D, Massey R, et al. Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med. 1991;325:1831.
12. Peterson R, Funkhouser J. Speculations on ataxia-telangiectasia: defective regulation of the immunoglobulin gene superfamily. Immunol Today. 1989;10:313.
13. Drolet B, Drolet B, Zvulunov A, et al. Cutaneous granulomas as a presenting sign in ataxia-telangiectasia. Dermatology. 1997;194:273.

FD

14. Anderson W. A case of angiokeratoma. Br J Dermatol. 1898;10:113.
15. Fabry J. Ein Beitrag Zur Kenntnis der Purpura haemorrhagica nodularis. Arch Dermatol Syphilis. 1898;43:187.
16. Eng C, Guffon N, Wilcox W, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med. 2001;345:9.
17. Wallace H. Anderson-Fabry disease. Br J Dermatol. 1973;88:1.
18. Holmes R, Fenson A, McKee P, et al. Angiokeratoma corporis diffusum in a patient with normal enzyme activities. J Am Acad Dermatol. 1984;10:384.
19. Epinette W, Norins A, Drew A, et al. Angiokeratoma corporis diffusum with a L-fucosidase deficiency. Arch Dermatol. 1973;107:754.
20. Thomas AS, Hughes DA. Fabry disease. Pediatr Endocronil Rev. 2014;1:88–101.
21. Fellgiebel A, et al. Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis. 2014;38:448–56.
22. Kizhner T, et al. Characterization of a chemically modified plant cell culture expressed human alpha-galactosidase-A enzyme for treatment of Fabry disease. Mol Genet Metab. 2015;114:259–67.

Part III
Cutaneous Manifestations of Systemic Disease

16

Acquired Ichthyosis, Acanthosis Nigricans, and Palmar Hyperkeratosis

■ Synonyms:	AI—Pityriasis rotunda
	AN—None
	PH—Tylosis, Howel-Evans syndrome, tripe palms, acrokeratosis of Bazex
■ Etiology:	Unknown
■ Associations:	AI—Lymphoma
	AN—Gastric carcinoma
	PH—Esophageal carcinoma
■ Clinical:	AI—Diffuse xerosis
	AN—Axillary pigmentation
	PH—Palmar/plantar hyperkeratosis
■ Histology:	AI—Hypogranulosis with hyperkeratosis
	AN—Acanthosis with hyperkeratosis
	PH—Acanthosis with hyperkeratosis and hypergranulosis
■ IHC repertoire:	N/A
■ Staging:	N/A
■ Prognosis:	Generally poor, associated with advanced internal malignancy
■ Adverse variables:	Dependent upon underlying malignancy type and stage of disease
■ Treatment:	Dependent upon tumor type and stage

Serious systemic diseases, including visceral cancer, may be indirectly signaled by the development of distinctive cutaneous eruptions. Important aspects of these eruptions include the development of the rash concurrent with the diagnosis of the neoplasm and the fact that the two entities, though individually uncommon, are commonly seen together and pursue a similar clinical course. The more important, albeit uncommon, dermatoses that develop in conjunction with visceral cancer involve disorders of the epithelium and entail alterations in keratinization. This chapter will deal with the clinical and pathologic attributes of acquired ichthyosis, acanthosis nigricans, and paraneoplastic palmar/plantar keratoderma as they relate to underlying malignancy.

Ichthyosis refers to the presence of fish-like (Latin, *ichthus*) or scaly skin. The characteristic clinical appearance is due to an inherited defect in keratinization involving the epithelium that with rare exception represents little more than a lifelong cosmetic nuisance. Acquired ichthyosis, however, referring to the sudden development of scaly dry skin in the adult, may herald the presence of a serious underlying malignancy. The eruption usually develops over the extensor aspects of the extremities and scalp resembling the appearance of the most common autosomal dominant form, *ichthyosis vulgaris* [1]. The rash typically spares the flexural folds. Erythema may be seen between the scaly fissures. The most common underlying malignancy is Hodgkin's lymphoma, occurring in conjunction with an

estimated 70 % of all cases of acquired ichthyosis with the severity of the rash reflecting the progression of disease [2, 3]. The rash may, however, presage the malignancy by many years. Important systemic illnesses that may also produce or be associated with acquired ichthyosis include malnutrition, HIV disease, hypothyroidism, leprosy, sarcoidosis, lupus erythematosus, dermatomyositis, bone marrow transplant in the setting of graft-versus-host disease, and eosinophilic fascitis and may follow exposure to certain medications such as nicotinic acid, triparanol, butyrophenone, dixyrazine, nafoxidine, clofazimine, and cetrimide [4, 5]. Among HIV-positive individuals, its development may be a marker for concomitant infection by the *human T-cell leukemia/lymphoma virus (HTLV-II)* [6]. In dark-skinned races, the rash may produce sharply demarcated round-to-oval scaly patches termed *pityriasis rotunda* [7]. The histopathology is distinctive and consists of a normally thickened epithelium with compacted hyperkeratosis. The epidermal granular layer is characteristically absent. The altered keratin layer may also extend down the adjacent follicular ostia (acrotrichia). Supportive therapy is directed toward hydration of the skin (bathing, high ambient humidity) and the application of lubricants (creams and ointments). Investigation for the possibility of underlying malignancy, particularly hematologic cancer, with appropriate imaging studies and consideration for bone marrow examination is indicated.

Acanthosis nigricans (AN) is a common cutaneous malady associated with myriad unrelated systemic diseases including underlying cancer [8, 9]. The most common association involves obesity with or without insulin resistance and hyperinsulinemia. In most instances, the eruption begins as gray-black thickening of the flexural areas and, in particular, the axillae (Fig. 16.1). Palpation of the involved areas yields a textural change likened to velvet. The eruption may rarely spread to involve the non-flexural areas and even the oral and anogenital mucosa. Certain demographic groups are overrepresented, including Hispanics and African-Americans. Rare familial tendencies have also been identified, suggestive of an underlying genetic predisposition. The pathogenesis is thought to involve a patterned response of the skin to increased serum levels of trophic epithelial hormones and cytokines, presumably released in conjunction with the underlying endocrinologic or neoplastic dyscrasia. In the setting of hyperinsulinemia and diabetes mellitus, it has been shown that excess binding of insulin to IGF receptors located on keratinocytes and fibroblasts results in increased proliferation. Similarly, increased transforming growth factor (TGF) released by neoplastic cells has been shown to increase keratinocyte proliferation via surface epidermal growth factor receptors. Other important disease associations include *h*yper*a*ndrogen states with *i*nsulin *r*esistance and *a*canthosis *n*igricans (*HAIR-AN syndrome*). Certain medi-


FIGURE 16.1. Velvety hyperpigmented intertriginous plaque in acanthosis nigricans.

cations including nicotinic acid, glucocorticoids, and triazinate and the sex hormones including estrogen have also been implicated in its development. AN associated with underlying malignancy, alternatively referred to as *malignant* AN, is morphologically similar yet characterized by rapid onset and progression [10–13]. It more commonly is associated with keratoderma or rugose-like thickening of the palms in which there is accentuation of the fingerprints, otherwise known as pachydermatoglyphy (or *tripe palm*) [14, 15]. Other important associations include oral involvement and the presence of multiple eruptive seborrheic keratosis (the sign of *Leser-Trelat*) (Fig. 16.2). The most common internal malignancy is visceral adenocarcinoma of the stomach, intestines, or lung. Bladder, renal, and esophageal carcinoma and lymphoma have also been reported. In most instances, the lesions are discovered in conjunction with internal malignancy diagnosis. The eruption, however, may precede or follow diagnosis of internal malignancy. The histopathology yields slight epidermal acanthosis with papillomatosis and hyperkeratosis (Fig. 16.3). Although the basilar layer keratinocytes may show increased amounts of cytoplasmic melanin, the clinical appearance of hyperpigmentation is largely due to the epidermal hyperkeratosis.

The acquired *palmar/plantar keratodermas* comprise a heterogeneous group of keratinizing disorders characterized by thickening of the palms and soles that in many instances are associated with the development of visceral cancer (Fig. 16.4) [16]. These conditions are distinct from the more common forms of inherited palmoplantar keratoderma that typically manifest in children and are associated with inherited defects in keratinization. The acquired keratodermas can be broadly separated into three categories that involve diffuse thickening, punctate areas of thickening, or additional areas of the non-acral skin. The most well-documented form of diffuse acquired keratoderma was described by Dr. Howel-Evans in 1958 among two kin-

Figure 16.2. Sign of Leser-Trelat. Multiple seborrheic keratosis on the trunk of patient with metastatic colorectal carcinoma.
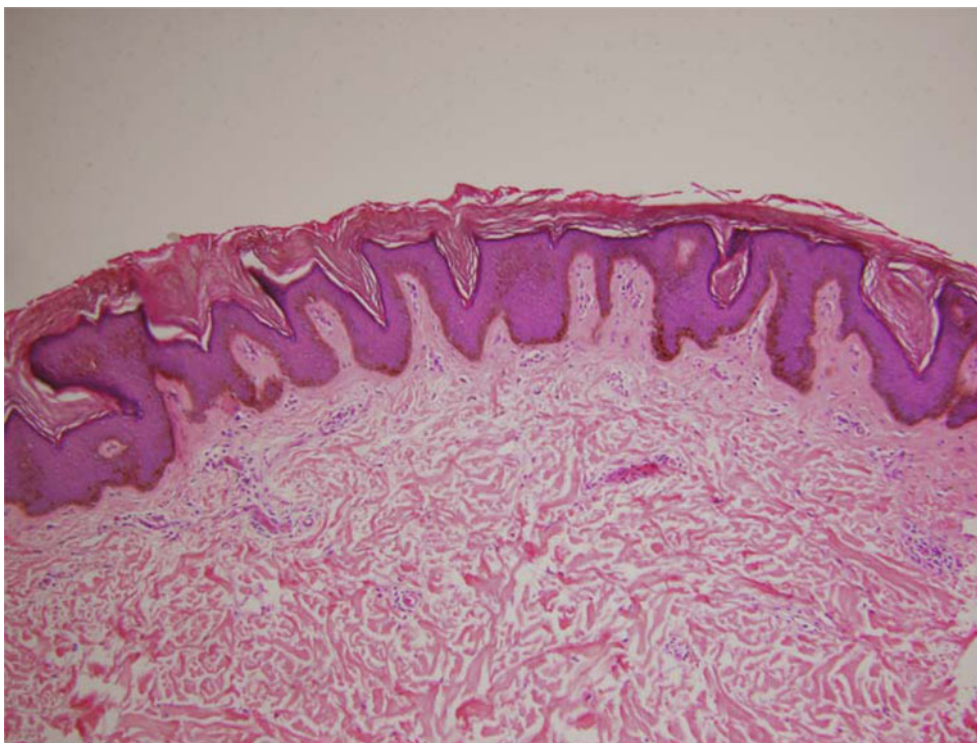
Figure 16.3. Medium-power photomicrograph depicting dome-like epidermal acanthosis with hyperpigmented basilar layer keratinocytes seen in acanthosis nigricans.

FIGURE 16.4. Hyperkeratosis of the palmar skin seen in the keratodermas. Note the accentuated palmar creases.
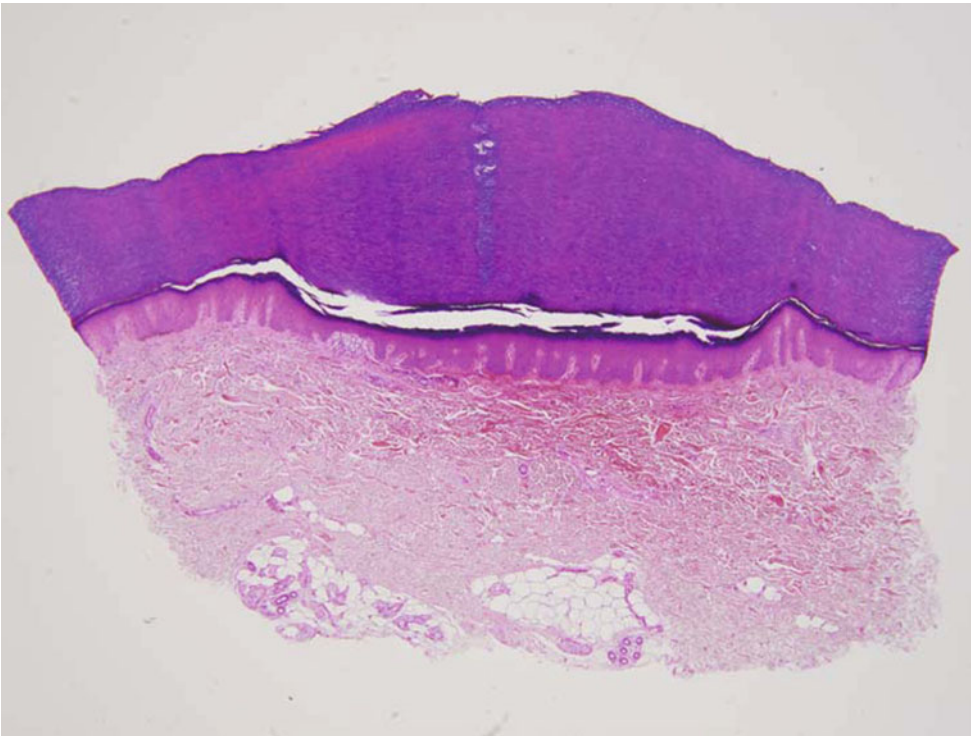
FIGURE 16.5. Low-power photomicrograph depicting the exaggerated hyperkeratosis with central swelling observed in punctate keratoderma.

dreds afflicted with esophageal carcinoma [17, 18]. This condition, alternatively referred to as *tylosis* or *Howel-Evans* syndrome, involves the development of poorly demarcated and irregular areas of palmar or plantar thickening in children who later develop esophageal carcinoma as adults [19]. The gene responsible for this condition has been linked adjacent to the keratin type I gene cluster (17q24) [20]. The punctate form of acquired keratoderma is associ- ated with the development of breast and gynecologic malignancies. Finally, acquired keratoderma may be associated with an erythematous and psoriasiform dermatitis involving the non-acral skin. Referred to as *acrokeratosis of Bazex,* patients with this entity are typically male and are predisposed to develop carcinoma of the upper and lower aerodigestive tracts [21]. The thickened areas of the palms and soles often appear erythematous or violaceous.

Keratoderma has also been described among patients with hematologic malignancies including multiple myeloma, lymphoma, and mycosis fungoides. Nonneoplastic conditions including myxedema, arsenic exposure, menopause (*keratoderma climactericum*), water exposure (*aquagenic keratoderma*), and following ingestion of certain medications including glucan, tegafur, and fluorouracil have been shown to also produce acquired keratoderma [16]. The diffuse form of keratoderma histologically shows epidermal acanthosis and orthokeratotic hyperkeratosis with occasional epidermolytic hyperkeratosis. The punctate form shows a dense keratin plug of the stratum corneum with underlying depression of the stratum malpighi and adjacent pitting of the stratum corneum (Fig. 16.5). Biopsy changes observed in conjunction with acrokeratosis of Bazex include acanthosis, hyperkeratosis, and exocytosis of lymphocytes with accompanying spongiosis and epidermal dyskeratosis.

References

Acquired ichthyosis

1. Aram H. Acquired ichthyosis and related conditions. Int J Dermatol. 1984;23:458.
2. Patel N, Spencer LA, English III JC, Zirwas MJ. Acquired ichthyosis. J Am Acad Dermatol. 2006;55:647–56.
3. Word AP, Cayce R, Pandya AG. Beware of underlying malignancy: acquired ichthyosis. Am J Med. 2014;127(3):202–4.
4. Dykes P, Marks R. Acquired ichthyosis: multiple causes for an acquired generalized disturbance in desquamation. Br J Dermatol. 1977;97:327.
5. Spleman L, Strutton G, Robertson I, et al. Acquired ichthyosis in bone marrow transplant recipients. J Am Acad Dermatol. 1996;35:17.
6. Kaplan M, Sadick N, McNutt N, et al. Acquired ichthyosis in concomitant HIV-1 and HTLV-11 infection: a new association with intravenous drug abuse. J Am Acad Dermatol. 1993;29:701.
7. Aste N, Pau M, Aste N, et al. Pityriasis rotunda: a survey of 42 cases observed in Sardinia, Italy. Dermatology. 1997;194:32.

Acanthosis nigricans

8. Lee SS, Jung NJ, Im M, Lee Y, Seo YJ, Lee JH. Acral-type malignant acanthosis nigricans associated with gastric adenocarcinoma. Ann Dermatol. 2001;23 Suppl 2:S208–10.
9. Schwartz R. Acanthosis nigricans. J Am Acad Dermatol. 1994;31:1.
10. Phiske MM. An approach to acanthosis nigricans. Indian Dermatol Online J. 2014;5(3):239–49.
11. Andreev V. Malignant acanthosis nigricans. Semin Dermatol. 1984;3:265.
12. Rigel D, Jacobs M. Malignant acanthosis nigricans: a review. J Dermatol Surg Oncol. 1980;6:923.
13. Brown J, Winkelman R. Acanthosis nigricans: a study of 90 cases. Medicine. 1968;47:33.
14. Stawczyk-macieja M, Szczerkowska-dobosz A, Nowicki R, Majewska H, Dubowik M, Sokołowska-wojdyło M. Malignant acanthosis nigricans, florid cutaneous papillomatosis and tripe palms syndrome associated with gastric adenocarcinoma. Postepy Dermatol Alergol. 2014;31(1):56–8.
15. Breathnach S, Wells G. Acanthosis Palmaris: tripe palms. Clin Exp Dermatol. 1980;5:181.

Palmoplantar keratoderma

16. Zemtsov A, Veitschegger M. Keratodermas. Int J Dermatol. 1993;32:493.
17. Howel-Evans W, McConnell R, Clarke C, et al. Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis). Q J Med. 1958;27:413.
18. Marger R, Marger D. Carcinoma of the esophagus and tylosis. A lethal genetic combination. Cancer. 1993;72:17.
19. Ilhan M, Erbaydar T, Akdeniz N, Arslan S. Palmoplantar keratoderma is associated with esophagus squamous cell cancer in Van region of Turkey: a case control study. BMC Cancer. 2005;5:90.
20. Stevens H, Kelsell D, Bryant S, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Arch Dermatol. 1996;132:640.
21. Bazex A, Griffiths A. Acrokeratosis paraneoplastica: a new cutaneous marker of malignancy? Br J Dermatol. 1980;102:301.

17
Amyloidosis: Systemic, Nodular, and Epidermal Derived

- Synonyms:
  S—
  N—none
  ED—macular and lichenoid
- Etiology:
  S—plasma-cell-derived light chains
  N—plasma-cell-derived light chains
  ED—epidermal keratins
- Associations:
  S—multiple myeloma in 1/3 pts
  N—10 % with systemic amyloidosis
  ED—none
- Clinical:
  S—hemorrhagic papules/plaques
  N—waxy nodules
  ED—hyperpigmented macules and lichenoid papules
- Histology:
  S—fissured hyaline deposits and perivascular deposits
  N—hyaline deposits with plasma cells
  ED—hyaline dermal globules
- IHC:
  S—monoclonal kappa or lambda light chain
  N—monoclonal kappa or lambda light chain
  ED—keratins
- Staging:
  N/A
- Prognosis:
  S—poor in myeloma patients
  N—dependent upon systemic status
  ED—excellent
- Adverse outcome:
  S—myeloma and cardiac disease
  N—systemic amyloidosis
  ED—none
- Treatment:
  S—chemotherapy
  N—excision, laser and cryotherapy
  ED—topical retinoids

Amyloidoses encompass a broad category of cutaneous and systemic disorders with important pathogenic consequences. These derive from the direct deposition of abnormal proteins or indirectly relate to potentially deadly systemic disorders that produce such deposits. Each of amyloidoses can be defined by certain histomorphologic and chemical properties that permit their identification and inclusion into disease categories [1]. These designations can be loosely grouped into systemic and cutaneous delimited forms.

The term *amyloidosis* historically derives from the gross starch-like deposits seen in conjunction with systemic amyloidosis. Despite the appellation, the chemical constituency of amyloid is either protein or glycoprotein. Each of the 16 chemical types possesses similar histomorphologic and chemical properties including a predominantly extracellular location, an amorphous eosinophilic appearance on hematoxylin and eosin staining, and a meshwork of hollow 7.5–10-nm linear nonbranched fibrils on ultrastructural examination [2]. The fibrils often align into a

three-dimensional beta-pleated sheet configuration that is held responsible for their birefringence properties on diagnostic polaroscopic examination. Amyloid fibrils often associate with certain disease defining nonamyloid glycoproteins including *protein P* (systemic disease) and *apolipoprotein E* (Alzheimer's disease). Among the various types of amyloid, only a few are commonly observed in the skin and thus merit discussion. The two most important responsible for the bulk of dermatologic disease derive from plasma-cell-produced immunoglobulin kappa or lambda light chains or from epidermal keratinocyte keratins. The former are seen in conjunction with primary or systemic amyloidosis and *nodular amyloidosis*, whereas the latter are seen in *macular* and *lichenoid amyloidosis*. The light chains may be monoclonal and systemically produced from abnormal collections of bone marrow or reticuloendothelial associated plasma cells in multiple myeloma or lymphoma or monoclonal and produced locally within the skin from associated plasma cells. The keratins deposited in macular/lichenoid amyloidosis derive from degenerated epidermal keratinocytes and as such are typically seen as aggregates in the superficial dermis juxtaposed to the overlying epithelium.

Primary and *myeloma-associated amyloidosis* involves the skin in approximately one-third of patients [3]. Typical patients are in their 60s with a slight male predominance. There is no known ethnic predilection. Although the dermatologic manifestations may be overshadowed by the systemic stigmata of macroglossia, bilateral or unilateral carpal tunnel syndrome, or hepatosplenomegaly, distinctive cutaneous changes are often present. Waxy papules and nodules are typically seen on the flexural folds of the face, trunk, and extremities. The papules may undergo secondary hemorrhage and are rarely ulcerated. Mucocutaneous nodules may assume a warty appearance reminiscent of condyloma or a flattened plaque-like configuration suggestive of xanthoma. Non-vasculitic purpuric macules, petechiae, and ecchymoses are common, particularly in flexural fold areas such as the eyelids. Purpuric lesions may be elicited with trauma (*pinch purpura*) (Fig. 17.1) or following a precipitous increase in intrathoracic pressure (Valsalva maneuver). Less common manifestations include diffuse involvement of the scalp (cutis verticis gyrata) and alopecia, scleroderma-like induration of the extremities, bullous lesions, nail dystrophy, cutis laxa, and cord-like thickening of the blood vessels. Important systemic signs and complications stemming from visceral organ involvement include the heart, reticuloendothelial system, blood vessels, and peripheral and autonomic nervous system. Cardiac disease is the most important cause of mortality with most cases resulting in cardiomyopathy, arrhythmias, congestive heart failure, or ischemic heart disease [4]. Hepatosplenomegaly is seen in approximately one-half of patients and is an important cause of morbidity. Amyloid infiltration of the blood vessels may produce ischemic clau-

Figure 17.1. Periorbital purpura seen in systemic amyloidosis.

dication of the gastrointestinal tract, extremities, or heart. Peripheral and autonomic neuropathy is common, with the latter often producing orthostatic hypotension. Massive amyloid deposits within the soft tissues of the wrist or when located around the shoulders (providing the *shoulder pad sign*) may result in carpal tunnel syndrome.

Other less common forms of systemic amyloidosis that rarely manifest in the skin include *secondary* or inflammatory-associated amyloidosis and the extremely rare heredofamilial syndromes of *familial Mediterranean fever* (urticaria, vasculitic purpura, fever, serositis, and renal amyloid) and *Muckle-Wells* syndrome (urticaria, fever, deafness, and renal amyloidosis) [1].

The lesions of *nodular* or *localized amyloidosis* tend to be less numerous and individually larger than systemic amyloidosis. Demographically, most patients are in their 60s and there tends to be a male predominance. Lesions may occur on the extremities as well as the face or trunk. Although most lesions are asymptomatic, they tend to gradually enlarge in time. In recent studies, as low as 7 % of

patients are found to have or subsequently develop systemic amyloidosis, which is indicative of an overall good prognosis. Management of these nodules, however, is difficult since there is no consistently effective treatment, likely due to their high rate of recurrence [5].

The epithelial-derived forms of cutaneous *lichenoid* and *macular amyloidosis* have distinctive demographic and clinical attributes [6]. Both forms may coexist and likely represent a spectrum of disease with similar etiologic origins. Often pruritic, many believe that the lesions follow excoriation and represent the turnover of epithelial-derived keratinocytes. The lesions are more commonly encountered among races of darker skin color including individuals of Asian or Latin-American ancestry and consist of hyperpigmented macules or lichenoid papules. The former tend to occur over the trunk, in particular the interscapular area, with the lichenoid lesions typically seen over the extensor aspects of the lower extremities and penis. Less common forms of cutaneous limited amyloidosis include *anosacral amyloidosis*, consisting of lichenified plaques located on the buttocks of Chinese persons; *familial primary cutaneous amyloidosis*, a rare autosomal dominant genodermatoses consisting of amyloid-containing keratotic papules and swirled areas of cutaneous hypo-/hyperpigmentation, encompassing subtypes such as *cutis dyschromica*; and *poikilodermatous amyloidosis*, in which typical patients possess a short stature and show photosensitivity and palmoplantar keratoderma [7, 8]. In the latter, amyloid deposition is due to failed DNA repair secondary to sunlight-induced damage [9]. Keratinocyte-derived amyloid may also be seen as part of a degenerative phenomenon permeating and surrounding the stroma of epithelial-derived tumors such as basal cell carcinoma, squamous cell carcinoma, and various adnexal tumors.

Biopsy of skin lesions and blind abdominal fat pad and rectal aspirations are the most reliable means to establish a diagnosis [10]. The latter techniques have a high diagnostic yield in systemic and myeloma-associated forms of the disease only. The histomorphologic features of amyloid are identical regardless of the type examined or clinical context and consist of amorphous aggregates of slightly eosinophilic extracellular material. Larger aggregates may contain internal artifactual clefts or fissures and may be associated with chronic inflammatory cells including plasma cells. The systemic and myeloma-associated forms of disease are more often characterized by larger aggregates of amyloid deposition located throughout the dermis and subcutaneous fat (Figs. 17.2 and 17.3). Furthermore, the deposits are found within and surrounding vascular structures associated with purpura and may similarly outline the cell membranes of adipocytes within the panniculus, producing *amyloid rings*. Localized forms of the disease are characterized by smaller aggregates of amyloid usually located in the superficial dermis adjacent to the epithelium. The excep-

tion to this is the nodular localized form of disease in which large amyloid deposits are observed with abundant associated plasma cells [11]. The deposits are accentuated surrounding the blood vessels and adnexal structures. This infiltration of the reticular dermis and subcutaneous tissue is indistinguishable from systemic amyloidosis but differentiates the nodular amyloidosis from other cutaneous localized types of amyloidosis [12]. In the lichenoid form, the overlying epithelium usually shows slight acanthosis. In both the macular and lichenoid forms, the overlying epithelial keratinocytes are hyperpigmented, and scattered dyskeratotic or apoptotic basilar keratinocytes are observed (Fig. 17.4). Dermal incontinence of melanin and a sparse interface or superficial dermal perivascular lymphocytic infiltrate may be seen.

Several diagnostic adjuncts may be employed to confirm the diagnosis and establish the subtype of amyloidosis. Special stains may be employed that metachromatically stain the deposits (crystal or methyl violet) or that when exposed to polarized light produce birefringence (green with Congo red and yellow with thioflavine T). It is important to realize that all forms of amyloid stain, as do nonamyloid deposits including elastin, colloid milium, and the deposits of lipoid proteinosis. Specificity of the staining can be improved with the addition of immunohistochemical antibodies including amyloid P protein, immunoglobulin light chains, and keratins [12, 13]. Immunolabeling for P protein is found in all forms of amyloidosis. Monoclonal light chain restriction is typically observed within the plasma-cell-associated forms of nodular and systemic/myeloma amyloidosis. Keratin antibodies are positive in the cutaneous derived forms of amyloidosis, most notably CK5, and are negative in the remainder [13–15]. The specific types of amyloid may be determined through mass spectroscopy or amino acid sequencing. Electron microscopy can also be employed to identify the characteristic filaments.

The treatment is type dependent [6]. Patients with systemic and myeloma-associated forms of the disorder are usually administered systemic chemotherapy with or without autologous bone marrow transplantation. Organ transplantation of severely affected organs, most often the liver, heart, or kidney, can be performed, but amyloid may reaccumulate in the transplanted organ. Localized nodular amyloidosis may be removed surgically or ablated with laser or cryotherapy. Lichenoid/macular amyloidosis is difficult to treat, although some have reported variable success with topical retinoids, calcipotriol, and dermabrasion.

The prognosis is similarly impacted by the type and stage of disease [1]. The mean survival of patients with myeloma-associated disease is 5 months with most patients succumbing to complications stemming from cardiac or renal failure. The prognosis is slightly better for patients with systemic non-myeloma-associated disease with a mean survival of 2 years. Response to chemotherapy and
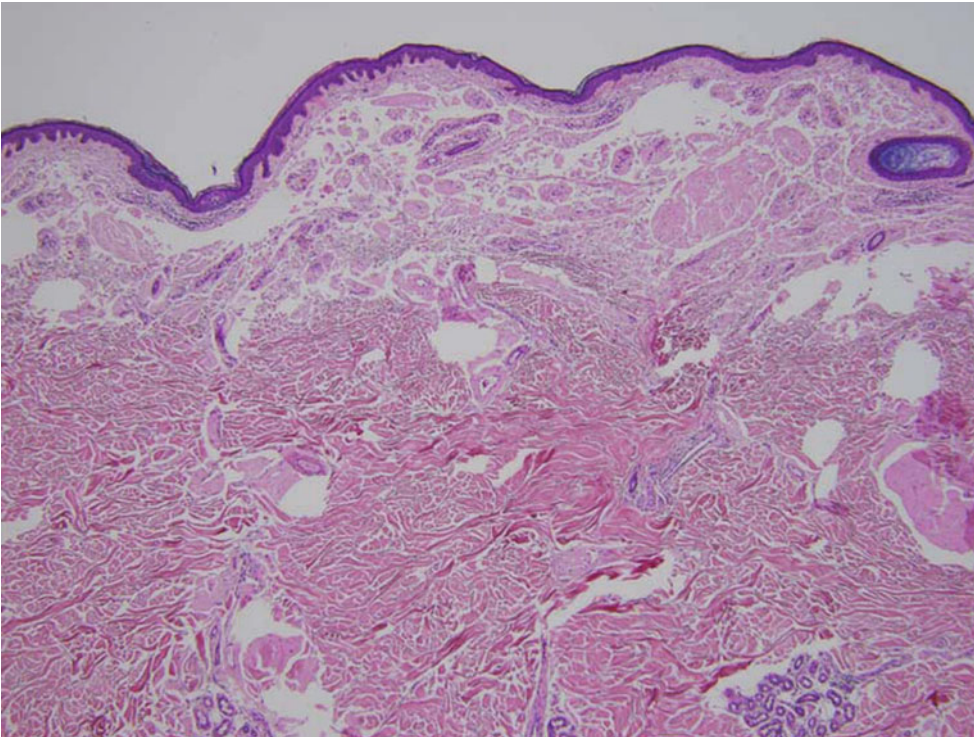
FIGURE 17.2. Low-power photomicrograph depicting superficial dermal eosinophilic (amyloid) deposits.
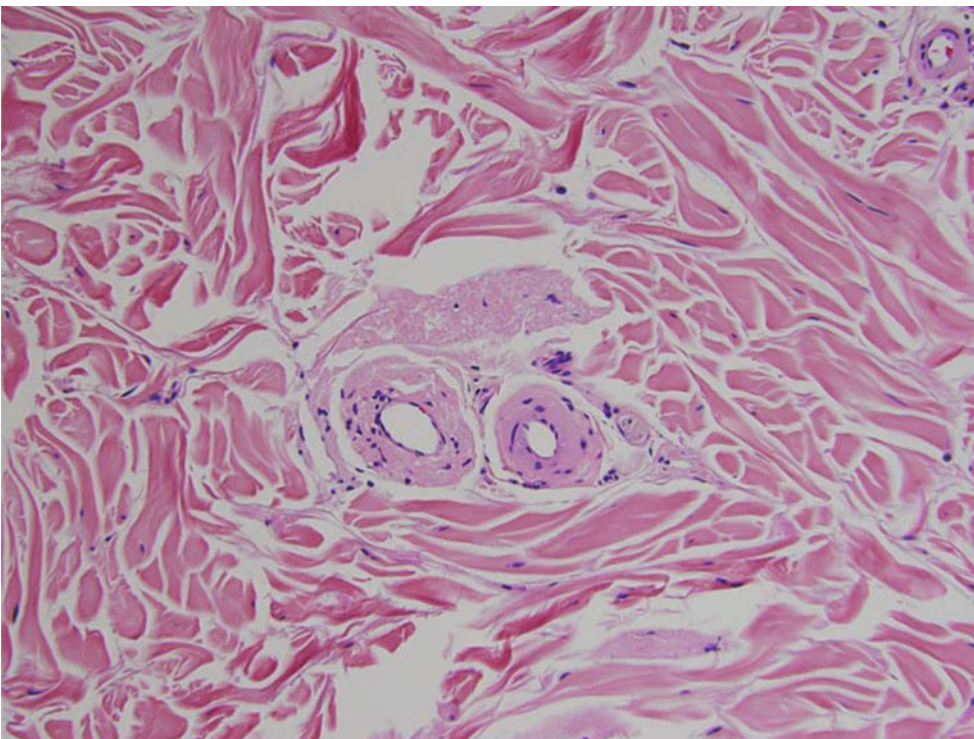
FIGURE 17.3. High-power photomicrograph depicting amyloid deposits within the wall of the dermal blood vessels and perivascular stroma.

Figure 17.4. High-power photomicrograph depicting fissured amyloid deposits at the dermoepidermal junction. Note additional changes of interface dermatitis.
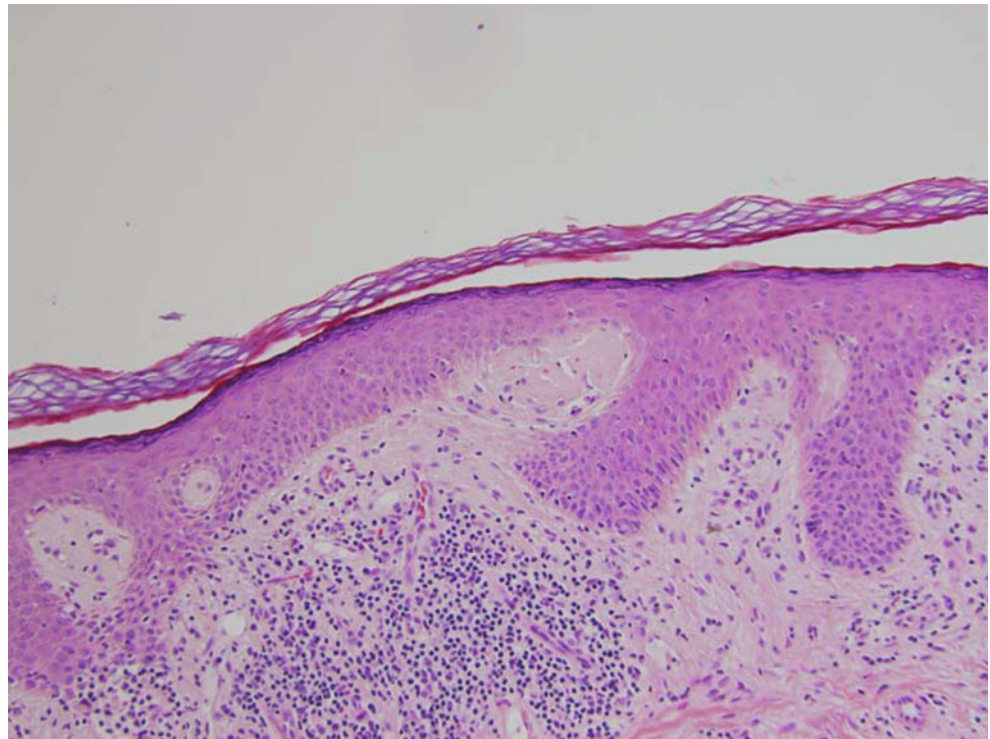
single-organ limited forms of the disease (i.e., neuropathy) fare better than most patients. Cardiac disease usually indicates a very poor overall prognosis.

References

1. Breathnach S. Amyloid and amyloidosis. J Am Acad Dermatol. 1988;18:1.
2. Tan S, Pepys M. The amyloidosis. Histopathology. 1994;25:403.
3. Wright J. Clinico-pathologic differentiation of common amyloid syndromes. Medicine. 1981;69:429.
4. Palecek T, Fikrle M, Nemecek E, Baueroca L, Kuchynka P, Louch WE, Sicka I, Rysava R. Contemporary treatment of amyloid heart disease. Curr Pharm Des. 2014;21:4.
5. Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. Br J Dermatol. 2001;145(1):105–9.
6. Brownstein M, Helwig E. The cutaneous amyloidoses: localized forms. Arch Dermatol. 1970;102:8.
7. Qiao J, Fang H, Yao H. Amyloidosis cutis dyschromica. Orphanet J Rare Dis. 2012;7:95.
8. Ratz J, Bailin P. Cutaneous amyloidosis. J Am Acad Dermatol. 1981;4:21.
9. Unni M, Ankad B, Naidu V, Sudakar RK. A familial poikiloderma-like cutaneous amyloidosis. Indian J Dermatol. 2014;59(6):633.
10. Hashimoto K. Diseases of amyloid, colloid, and hyaline. J Cutan Pathol. 1985;12:322.
11. Lee D, Huang C, Wong C. Dermatopathologic findings in 20 cases of systemic amyloidosis. Am J Dermatopathol. 1998;20:438.
12. Noren P, Westermark P, Cornwell G, et al. Immunofluorescence and histochemical studies of localized cutaneous amyloidosis. Br J Dermatol. 1983;108:277.
13. Breathnach S, Bhogal B, Dyck R, et al. Immunohistochemical demonstration of amyloid P component in skin of normal subjects and patients with cutaneous amyloidosis. Br J Dermatol. 1981;105:115.
14. Chang YT, Liu HN, Wang WJ, Lee DD, Tsai SF. A study of cytokeratin profiles in localized cutaneous amyloids. Arch Dermatol Res. 2004;296(2):83–8.
15. Kobayashi H, Hashimoto K. Amyloidogenesis in organ-limited cutaneous amyloidosis: an antigenic identity between epidermal keratin and skin amyloid. J Invest Dermatol. 1983;80:66.

18

Gyrate Erythemas: Erythema Gyratum Repens and Erythema Chronicum Migrans

■ Synonyms:	EGR—none
	ECM—
■ Etiology:	EGR-unknown, possibly hypersensitivity
	ECM—infection with *Borrelia burgdorferi*
■ Associations:	EGR—internal malignancy, tuberculosis, autoimmune disease, and pityriasis rubra pilaris
	ECM—outdoor activities in endemic areas for *Ixodes* ticks
■ Clinical:	EGR—truncal arcuate erythematous bands with trailing scale
	ECM—expanding erythematous solid or annular patch
■ Histology:	EGR—mild spongiosis with superficial perivascular lymphocytic infiltrate
	ECM—nonspecific superficial and deep lymphocytic perivascular infiltrate
■ IHC repertoire:	none
■ Staging:	EGR—none
	ECM—early, early disseminated, and chronic/late
■ Prognosis:	EGR—poor with internal malignancy
	ECM—good with appropriate antibiotic therapy, <5 % with serious complications including encephalopathy, heart block, and fetal death
■ Adverse variables:	EGR—most cases associated with advanced visceral adenocarcinoma
	ECM—neuroborreliosis, heart block, and gestational disease
■ Treatment:	EGR—supportive measures for disseminated carcinoma
	ECM—uncomplicated: doxycycline 100 mg bid, amoxicillin 500 mg tid 14 days, or cefuroxime axetil 500 mg bid
■ Complicated:	as above, 30-day regimen or IV ceftriaxone

The gyrate erythemas are a heterogeneous group of dermatoses clinically defined by the presence of circinate, annular, and/or polycyclic lesions that are often associated with serious underlying systemic diseases [1]. The gyrate erythemas consist of the entities erythema annulare centrifugum (EAC), erythema marginatum rheumaticum (EMR), erythema gyratum repens (EGR), and erythema chronicum migrans (ECM). The latter two entities, namely, EGR and ECM, are associated with potentially deadly underlying disorders and thus will be discussed in greater detail.

18.1 Erythema Gyratum Repens

This distinctive dermatosis is the rarest of the gyrate erythemas with only 83 cases reported to date [2]. Initially reported by Gammel in 1953 as a distinctive rash with a "wood grain" appearance that appeared to move or "creep" (hence the Latin designation of *repens*), he correctly surmised its development in conjunction with underlying breast carcinoma and subsequent resolution with removal of the tumor [3].

Of the patients reported to date, there is a 2:1 male-to-female gender ratio with an average age at presentation of 60 years. Although previously considered an obligate paraneoplastic syndrome, recent reviews have concluded that approximately 70 % of patients possess an underlying malignancy and EGR should therefore no longer be considered an obligate paraneoplastic syndrome. The most commonly associated malignancies involve the lung and represent carcinoma [2]. Lymphoreticular malignancy or sarcoma is seldom seen. Carcinoma of the breast, cervix, bladder, prostate, and kidney, among others, may also be seen [4]. The rash usually precedes the discovery of the malignancy but may present concomitant with, or rarely, following the diagnosis of internal malignancy. Approximately 30 % of the cases are non-paraneoplastic. A majority of the non-paraneoplastic cases are idiopathic, with others being associated with a variety of conditions including pulmonary tuberculosis, CREST syndrome, lupus erythematosus, secondary Sjögren's syndrome, pityriasis rubra pilaris, hypereosinophilic syndrome, and drug intake [2, 5].

The pathogenesis of this disorder is unknown. Among the possible mechanisms postulated are immune-mediated models in which cross-reactivity between tumor and endogenous skin antigens occurs, the tumor antigens bind in situ to endogenous skin antigens, or tumor antigen immune complexes circulate and deposit within the skin. Alternatively, the cytokine-rich milieu of malignancy may incite an abnormal localized inflammatory cell response resulting in increased matrix elaboration responsible for the observed clinical patterns and migration of the rash.

The clinical features consist of a pruritic rash with broad erythematous bands of polycyclic and arcuate arranged patches with a trailing scale that commonly assumes the appearance of wood grain or marble (Fig. 18.1). The lesions typically migrate at a rate of approximately 1 cm per day. The rash is usually located on the trunk and rarely involves the face or extremities. The most important diagnoses to exclude are ECM and EAC. In contrast to EGR, EAC generally produces more slowly evolving, palpable plaques that characteristically clear within the center. Although EAC may be associated with underlying malignancy, most cases are either idiopathic or follow drug hypersensitivity.

Histology shows epidermal spongiosis with surmounted scale crust and exocytosis of lymphocytes [6]. The dermis discloses a predominantly superficial perivascular lymphocytic infiltrate with interspersed eosinophils (Fig. 18.2). Involvement of the deeper vascular plexus and abnormal collections of Langerhans cells have also been reported. Direct immunofluorescence may show granular deposits of IgG and C3 and C4 along the basement membrane [2, 7]. Laboratory abnormalities frequently include hypereosinophilia. Some patients have been shown to have abnormal numbers of circulating T- and B-lymphocytes.

Although the rash is itself innocuous, it is associated with underlying malignancy in the majority of cases. Many of the patients have advanced-stage visceral cancers at diagnosis and thus succumb to their underlying disease. However, a minority of patients, particularly those individuals discovered to have early-stage disease or less-aggressive forms of cancer such as cervical carcinoma, may expect a favorable outcome and resolution of the rash following removal of the tumor.

FIGURE 18.1. Multiple annular and serpiginous patches likened to the appearance of wood grain seen in erythema gyratum repens.

Figure 18.2. Low-power photomicrograph depicting superficial and deep lymphocytic dermatitis and dermal edema seen in the gyrate erythemas including erythema gyratum repens.
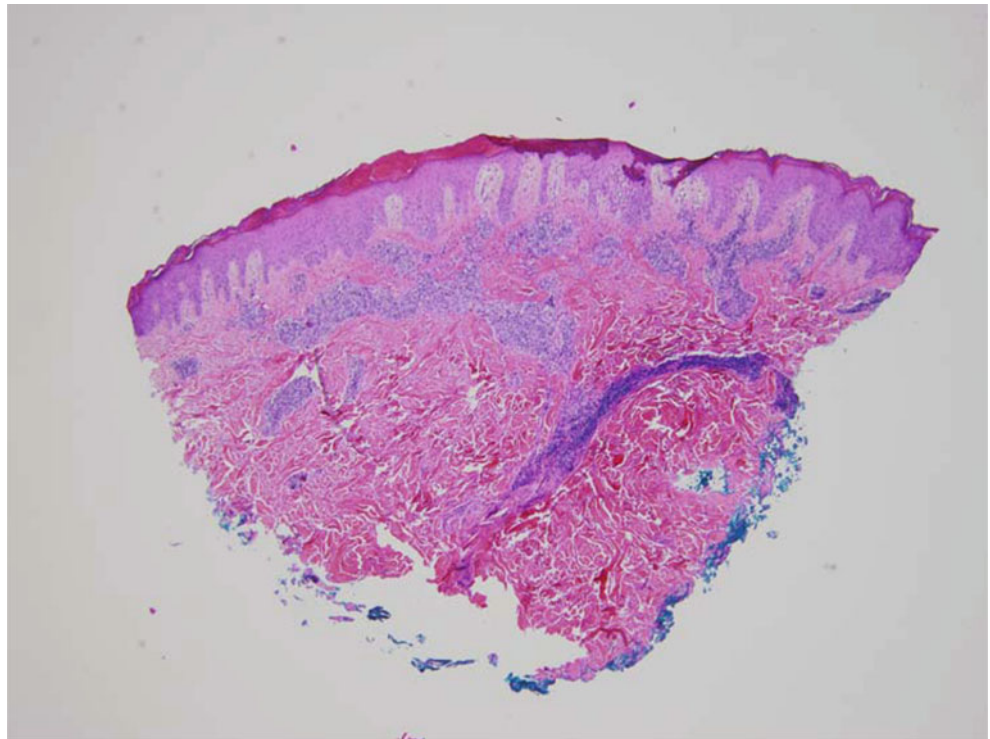
Treatment should be principally aimed at timely diagnosis and removal of the underlying malignancy. Patients should undergo chest X-ray and CT scanning of the abdomen and pelvis and should also be considered for esophagogastroduodenoscopy and colonoscopy. The rash itself does not respond to topical or intralesional corticosteroid therapy. Most cases resolve with removal of the underlying malignancy.

18.2 Erythema Chronicum Migrans

This dermatosis is one of the more common examples of gyrate erythema that derives its name from the distinctive manner of its clinical presentation. Coined by Afzelius as *erythema migrans* in 1909, it was later designated by Lipschutz as *erythema chronicum migrans* [8]. Both investigators rightly surmised the relationship between the expanding erythematous rash and an antecedent tick bite. The association between tick bite and the constellation of neurologic and rheumatologic symptoms, however, would not come until 1977, with a landmark epidemiologic study conducted at the time around the communities neighboring Lyme, Connecticut. Shortly thereafter, the disease vector (*Ixodes* tick) and the etiologic agent (*Borrelia burgdorferi*) of Lyme disease were determined.

Lyme disease afflicts persons of all ages and ethnic backgrounds and with a nearly equal gender distribution. The disease has been reported across North America, Europe, and Asia and is the most common of the bacterial-borne arthropod diseases in North America. The common denominator for acquiring the disease is outdoor exposure or contact with the disease-carrying tick species *Ixodes*. Although most infections follow feeding with the hard tick *Ixodes*, infection following the bite of other tick genera and non-tick vectors has been reported. Human infection constitutes an exceptional event as the principal hosts of the infection are rodents, particularly the white-footed mouse, deer, and avian populations. The tick acquires infection with the spirochetal bacterial organism *Borrelia burgdorferi* following blood meal on an infected host and usually retains infectivity for life. Other cutaneous manifestations of Lyme borreliosis are *Borrelial lymphocytoma* and *acrodermatitis chronica atrophicans* [9].

The principal cutaneous manifestation of Lyme borreliosis is erythema chronicum migrans. The rash can initially be seen around the site of tick bite or may develop without the patient being aware of a previous tick bite [10]. The rash typically follows an incubation period of 1–3 weeks but may occur as soon as 3 days following the bite or up to 3 months following exposure. The rash begins as a solid and slowly expanding erythematous patch. Central clearing of the patch is reported to occur in approximately 50 % of adults and 90 % of children and results in a distinctive annular appearance (Fig. 18.3) [11]. Occasionally, the central site of the tick bite may persist as a small erythematous patch forming a bull's-eye-like or targetoid configuration. The erythematous band expands peripherally at a variable rate with the largest

Figure 18.3. Annular erythematous patch with central clearing seen in erythema chronicum migrans.

lesions generally occurring in individuals with the longest duration of symptoms. The band itself is generally between 1- and 2-cm wide and usually assumes a symmetrical annular pattern, although exceptional cases of eccentric or elliptical-shaped rings have been reported [12]. The rash has been rarely reported to form a scale or to vesiculate. The natural history of untreated cases is for gradual fading and complete resolution of the lesion within 1 year. The rash can develop anywhere on the skin surface, most commonly occurring on the lower extremities, back, groin, and axilla [11]. Other signs commonly found in conjunction with the cutaneous manifestations include lymphadenopathy, and fever, additional complaints of headache, and malaise are common [13]. Other less common cutaneous manifestations include the development of multiple erythema migrans lesions with secondary spirochetal dissemination, localized lymphocytoma usually involving the earlobe, and the sclerotic bands and nodules of the lower extremities seen in acrodermatitis chronica atrophicans. The latter entities are more commonly observed in Europe [14].

The histologic findings observed in Lyme disease are nonspecific and consist of a superficial or superficial and deep lymphocytic perivascular infiltrate with variable numbers of interstitial eosinophils and plasma cells [15, 16]. Spirochetes may be observed within the papillary dermis with the aid of the Warthin-Starry or Steiner silver stains [17]. Recent ancillary diagnostic methods incorporating the use of the PCR reaction and indirect immunofluorescence have also been reported. The diagnosis may be verified serologically by the demonstration of elevated IgM or IgG titers to *B. burgdorferi*. As outdoor enthusiasts often harbor antibody titers to the organism from previous exposure, borderline elevations in IgG antibody titers should be regarded with suspicion. Further compounding the limita-

tions of serologic diagnosis are a lack of serologic standardization, low yield of the test in early infection, and false-positive results in patients with relapsing fever and syphilis [18]. Finally, *Borrelia* species may be cultivated using specialized media such as the modified Kelly media, although the procedure is laborious, requires a delay in diagnosis, and has a relatively low sensitivity [19].

Lyme disease can be staged or classified based upon the scope of disease activity. *Early* Lyme disease consists of the erythema migrans rash with or without lymphadenopathy and has an excellent prognosis with appropriate antibiotic therapy. *Early disseminated* disease consists of disseminated erythema migrans lesions with early manifestations of neurologic, cardiac, or rheumatologic involvement. The prognosis is excellent with longer-term administration of antibiotics. *Chronic or late* Lyme disease is associated with persistent or remitting neurologic, rheumatologic, or cardiac manifestations. The neurologic manifestations can include chronic depression, dementia, fatigue, and encephalopathy producing hemiparesis and ataxia. These symptoms develop in approximately 5 % of untreated patients and may prove refractory to antibiotic therapy. Rheumatologic symptoms include intermittent episodes of asymmetric mono- or polyarthralgia and migrating musculoskeletal pain. Joint swelling may also be seen. The cardiac manifestations include atrioventricular conduction disturbances, myocarditis, pericarditis, and heart failure. Each of these complications may eventuate in death.

Treatment of Lyme disease varies with the stage of the disease, and most cases resolve following the appropriate therapy. First-line treatment options for uncomplicated Lyme disease involve the oral administration of either amoxicillin 500 mg tid or doxycycline 100 mg bid for 14–21 days. In the absence of contraindications such as pregnancy or age less than 8 years, doxycycline is preferred because it is also active against additional tick-borne diseases, including human granulocytic ehrlichiosis and southern tick-associated rash illness (STARI). For children less than 8 years of age who do not tolerate amoxicillin, oral cefuroxime axetil may be prescribed at 30 mg/kg/day divided into two doses but not exceeding 500 mg per dose. Complicated, disseminated, or chronic cases may be treated with the same regimen for 30–60 days or with 2 g/day of intravenous ceftriaxone for 14–30 days. Alternatives include intravenous regimens of cefotaxime or penicillin G [17].

References

1. Hurley H, Hurley J. The gyrate erythemas. Semin Dermatol. 1984;3:327.
2. Rongioletti F, Fausti V, Parodi A. Erythema gyratum repens is not an obligate paraneoplastic disease: a systematic review of the literature and personal experience. J Eur Acad Dermatol Venereol. 2014;28(1):112–5.

3. Gammel JA. Erythema gyratum repens; skin manifestations in patient with carcinoma of breast. AMA Arch Derm Syphilol. 1952;66(4):494–505.

4. Appell ML, Ward WQ, Tyring SK. Erythema gyratum repens. A cutaneous marker of malignancy. Cancer. 1988;62(3):548–50.

5. Verma P, Samson S, Monk B. A curious eruption: erythema gyratum repens in resolving pustular psoriasis. J Eur Acad Dermatol Venereol. 2008;22:637–8. Netherlands.

6. Wakeel RA, Ormerod AD, Sewell HF, White MI. Subcorneal accumulation of Langerhans cells in erythema gyratum repens. Br J Dermatol. 1992;126(2):189–92.

7. Albers SE, Fenske NA, Glass LF. Erythema gyratum repens: direct immunofluorescence microscopic findings. J Am Acad Dermatol. 1993;29(3):493–4.

8. Trevisan G, Cinco M. Lyme disease. A general survey. Int J Dermatol. 1990;29(1):1–8.

9. Asbrink E, Hovmark A. Cutaneous manifestations in Ixodes-borne Borrelia spirochetosis. Int J Dermatol. 1987;26(4):215–23.

10. Berger BW. Erythema chronicum migrans of Lyme disease. Arch Dermatol. 1984;120(8):1017–21.

11. Bhate C, Schwartz RA. Lyme disease: part I. Advances and perspectives. J Am Acad Dermatol. 2011;64(4):619–36. quiz 637–618.

12. Krafchik B. Lyme disease. Int J Dermatol. 1989;28(2):71–4.

13. Abele DC, Anders KH. The many faces and phases of borreliosis. I. Lyme disease. J Am Acad Dermatol. 1990;23(2 Pt 1):167–86.

14. Wu YS, Zhang WF, Feng FP, Wang BZ, Zhang YJ. Atypical cutaneous lesions of Lyme disease. Clin Exp Dermatol. 1993;18(5):434–6.

15. Berg D, Abson KG, Prose NS. The laboratory diagnosis of Lyme disease. Arch Dermatol. 1991;127(6):866–70.

16. Berger BW, Clemmensen OJ, Ackerman AB. Lyme disease is a spirochetosis. A review of the disease and evidence for its cause. Am J Dermatopathol. 1983;5(2):111–24.

17. Bhate C, Schwartz RA. Lyme disease: part II. Management and prevention. J Am Acad Dermatol. 2011;64(4):639–53; quiz 654, 653.

18. Wienecke R, Neubert U, Volkenandt M. Molecular detection of Borrelia burgdorferi in formalin-fixed, paraffin-embedded lesions of Lyme disease. J Cutan Pathol. 1993;20(5):385–8.

19. Barbour AG. Isolation and cultivation of Lyme disease spirochetes. Yale J Biol Med. 1984;57(4):521–5.

19
Multicentric Reticulohistiocytosis

■ Synonyms:	Multicentric giant-cell reticulohistiocytosis, lipoid dermatoarthritis, giant-cell histiocytoma, and reticulohistiocytic granuloma
■ Etiology:	Unknown
■ Associations:	Mutilating inflammatory arthritis and visceral malignancies
■ Clinical:	Discrete red-brown papules on the distal extremities, periarticular areas, and face
■ Histology:	Aggregations of histiocytes with "ground-glass" cytoplasm
■ IHC:	CD68, CD3, CD45, CD11b, and HAM-568
■ Prognosis:	Poor, although arthritis stabilizes after 6–8 years
■ Treatment:	Methotrexate combined with TNF-alpha inhibitors

Multicentric reticulohistiocytosis (MR) was first named by Goltz and Laymon in 1954 [1], although the literature is muddled with prior reports of conditions with similar features. Rheumatoid arthritis and multicentric reticulohistiocytosis were likely thought of as one entity for many years, prior to delineation of cutaneous histopathology and subtle differences in joint disease. Multiple cutaneous papules and nodules arise most distinctly on the dorsum of the hands and the face but also less commonly involving the extensor extremities, scalp, and mucosa. Papules arise over a period of weeks to months and present before, with, or after a characteristic mutilating arthritis which is symmetric and involves the distal and the axial skeleton. Adding to the morbidity of a disabling condition is an unsettling association with internal malignancy. Demographic features include a predominance of Caucasian patients (>75 %). Disease often begins in the fourth decade of life, and most studies reveal a female predominance of 3:1. There is no documented tendency to occur with familial predisposition.

Proper recognition and characterization of associated arthritis are important, as it is often the presenting symptom (50–65 % of patients), with skin manifestations often occurring months to years later. Symmetric interphalangeal joint arthritis, especially involving the distal joints of the fingers which is present in 75 % of patients, is somewhat unique, although hardly characteristic. Larger, more proximal joints of the arms and legs such as the knees, shoulders, hips, and elbows are also symmetrically involved.

Disease of the atlantoaxial joint of the spine can cause substantial morbidity. Another unique feature is rapid progression to arthritis mutilans in the absence of aggressive treatment in 50 % of patients. Patients who are younger at presentation strangely seem to have more aggressive and destructive joint disease. The arthritis is usually highly active for 6–8 years followed by a period of relative stability.

Radiologic findings provide useful diagnostic clues, and nuclear isotope scans can identify involved joints. Features include bilateral symmetry and sharply defined bony erosions which begin on the joint margins and spread to the joint surfaces. As mentioned, distal interphalangeal joints and atlantoaxial joint disease can be quite severe. There is minimal periosteal reaction and minimal associated osteoporosis. Soft tissue nodules which are noted on radiographs are bilateral, symmetric, and noncalcified. Fibroblastic rheumatism is a close radiologic and clinical mimic, with juxta-articular osteoporosis being one of the few differentiating features (aside from cutaneous histopathology) [2]. Psoriatic arthritis is usually a more slowly progressive process, which is usually asymmetric and poorly defined on radiographs, with associated periosteal new bone formation. Rheumatoid arthritis is often symmetric yet involves the metacarpophalangeal and metatarsophalangeal joints with more severity and is associated with severe adjacent osteoporosis. Arthritis associated with severe gout is asymmetric and slowly progressive, with the presence of calcified nodules (gouty tophi). Erosive osteoarthritis displays

erosions which begin at the central aspect of the joint (rather than the margins) [3].

Skin disease is the presenting symptom in roughly 10–20 % of patients, and individual lesions can appear and regress for years before stabilizing. Pruritus is present in a third of patients. Distribution includes the face and hands most commonly but also includes the forearms, elbows, neck, trunk, and less often the lower extremities. Lesions cluster in periarticular locations, occasionally forming multinodular, cobblestoned plaques. Facial disease is especially prominent on and around the ears and in the perinasal areas, as well as clustering in the oral mucosa and on the tongue. The hands also have a relatively characteristic periarticular distribution of papules (Fig. 19.1), also including the classic "coral beading" arrangement on the proximal and lateral nail folds. Individual lesions are usually reddish brown to skin colored and range in size from pinpoint to several centimeters. Facial xanthelasma is also present in 20–30 % of patients. Photoinduction has been described in some patients and has been demonstrated with exposure to ultraviolet B to uninvolved skin [4].

Constitutional symptoms such as fever, fatigue, and weight loss are common throughout the course of multicentric reticulohistiocytosis. Systemic findings which are more common include cardiac and pulmonary manifestations. Pulmonary issues include pleural effusions and usual interstitial pneumonia. Constrictive pericarditis and myocardial infiltration have been reported [5]. Hyperlipidemia, positive tuberculin skin test, and a variety of autoimmune diseases have been reported in association with MR. Reported association with underlying malignancy requires careful scrutiny. Latency between onset of MR and discovery of malignancy can be many years, and reports as to the exact incidence of malignancy vary (15–31 %). In the vast majority of cases, malignancy and MR do not run a parallel course, although occasional full remission of MR occurs after treatment of associated malignancy [6]. Breast

and ovarian carcinomas are most commonly described, although many other anecdotal associations have been reported (Table 19.1). Aggressive screening for associated malignancy is advocated in most studies.

Differential diagnosis includes a group of heterogenous disorders associated with dermal papules/nodules and variable joint and muscle involvement. At the top of the list, especially when larger skin lesions are present in a periarticular location, is rheumatoid arthritis. Fibroblastic rheumatism is a recently described entity for which histopathology is essential to diagnosis and differentiation from MR in most cases. Less akin to MR are dermatomyositis (although cutaneous findings of the hands may be difficult to differentiate), lepromatous leprosy, and sarcoidosis, mostly due to the lack of significant inflammatory arthritis.

Also in the differential diagnosis includes solitary reticulohistiocytoma, which presents as single (or occasionally multiple) yellow-brown dermal papules or nodules, occasionally with overlying erythema. Distribution is often on the dorsal surfaces of the hand, overlying the joints [7]. These lesions occur in adults, with a mean age of 40 years, and there is a slight female predominance. The diagnosis is made ordinarily only following biopsy. These lesions are benign and may resolve spontaneously after an initial period of growth. Affected patients have normal serum lipid levels.

Histopathology of MR is classic, and only the isolated reticulohistiocytoma would share the distinctive features. The epidermis is usually uninvolved, but some flattening of the rete ridges can be present. The reticular dermis is usually filled with a well-circumscribed but unencapsulated collection of multinucleated giant cells and individual histiocytes (Fig. 19.2). The giant cells can be described as foreign-body type, with numerous, variably arranged vesicular nuclei and granulated, eosinophilic cytoplasm reminiscent of ground glass (Figs. 19.3 and 19.4). Mononuclear histiocytes display similar cytoplasmic features. Occasional multinucleated cells may be seen. Scattered and occasionally perivascularly arranged lymphocytes and eosinophils are invariably present in and around these nodular infiltrates, with no granuloma formation or caseation. Histiocytes stain for CD68, CD3,


FIGURE 19.1. Multiple tan-red papules on digits with periungual accentuation seen in multicentric reticulohistiocytosis.

TABLE 19.1. Tumors associated with multicentric reticulohistiocytosis [18–21]

Breast carcinoma
Pancreatic adenocarcinoma
Squamous cell carcinoma—lung
Melanoma
Non-Hodgkin lymphomas
Gastric adenocarcinoma
Ovarian mucinous adenocarcinoma
Colonic adenocarcinoma
Pleural mesothelioma
Cervical squamous cell carcinoma

FIGURE **19.2.** Multicentric reticulohistiocytosis, low power. Loose aggregates of giant cells with interspersed lymphocytes and neutrophils.
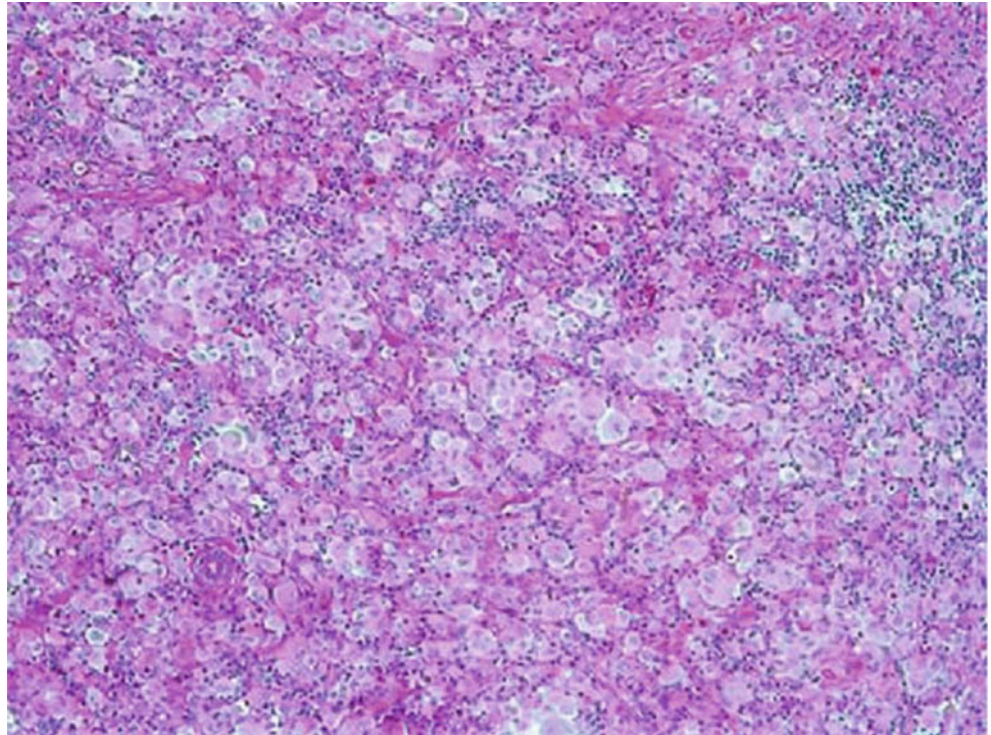
FIGURE **19.3.** Multicentric reticulohistiocytosis, high power. Histiocytes with ground-glass cytoplasm, dark periphery, and central clearing.
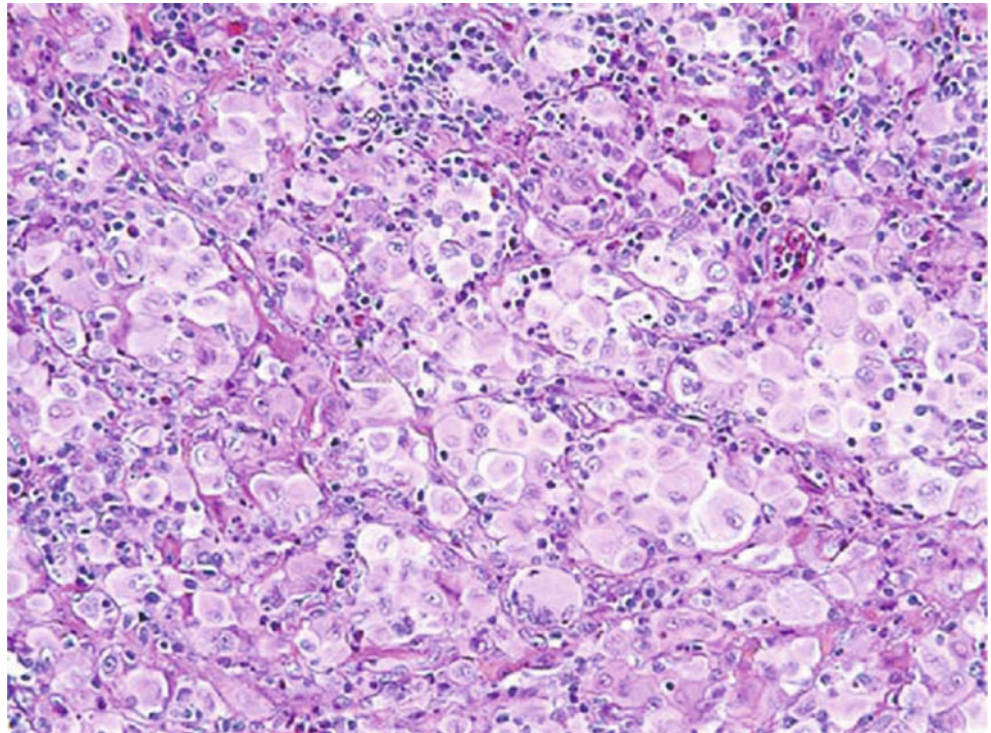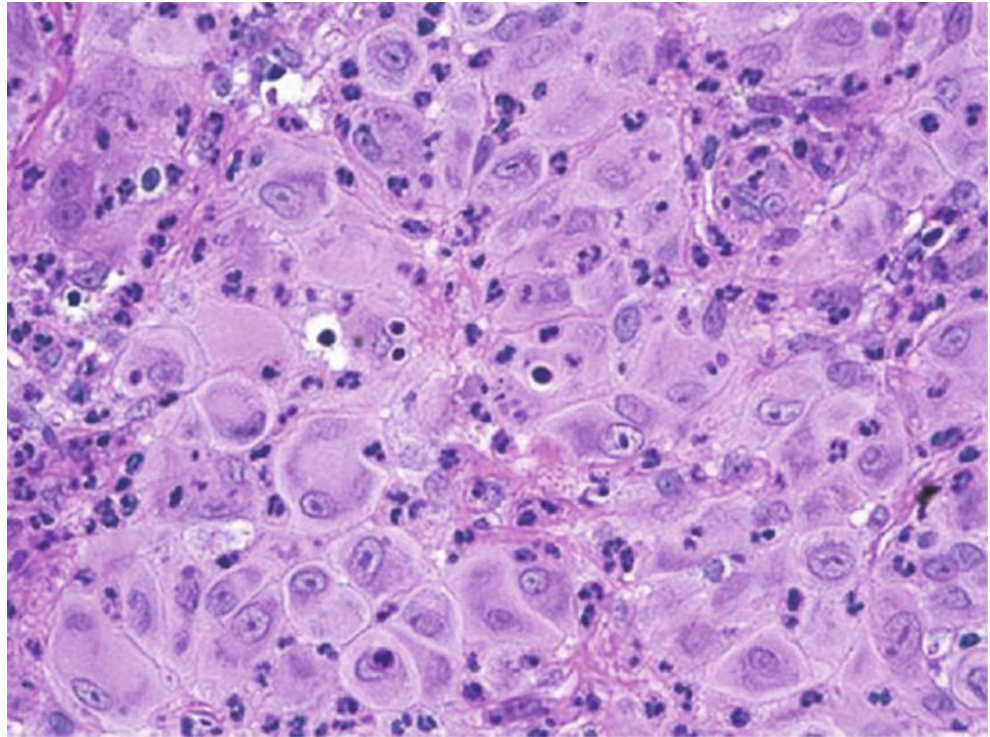
CD45, CD11b, and HAM-56 [8]. These cells do not stain for S100 protein, CD1a, or Mac387.

The rarity of the condition and variable association with internal malignancy make treatment difficult to customize to the individual patient, and most evidence is anecdotal.

Medications such as chlorambucil and cyclophosphamide have fallen out of favor due to toxicity, although have been noted to be effective and potential for long-term remission has been demonstrated [9]. Infliximab and etanercept have been shown to be effective, particularly in combination

with methotrexate [10–13]. This treatment seems logical given high levels of TNF-alpha found in synovial fluid of MR and other inflammatory arthritides [14]. Methotrexate has been a mainstay of the treatment of joint disease for years, and methotrexate in combination with corticosteroids is effective in some patients [15–17]. Agents such as leflunomide, hydroxychloroquine, and azathioprine are occasionally effective in combination therapy and should be reserved for recalcitrant cases.

References

1. Goltz RW, Laymon CW. Multicentric reticulohistiocytosis of the skin and synovia; reticulohistiocytoma or ganglioneuroma. AMA Arch Derm Syphilol. 1954;69(6):717–31.
2. Trotta F, Colina M. Multicentric reticulohistiocytosis and fibroblastic rheumatism. Best Pract Res Clin Rheumatol. 2012;26(4):543–57.
3. Gold RH, Metzger AL, Mirra JM, Weinberger HJ, Killebrew K. Multicentric reticulohistiocytosis (lipoid dermatoarthritis): an erosive polyarthritis with distinctive clinical, roentgenographic and pathologic features. Am J Roentgenol Radium Ther Nucl Med. 1975;124:610–24.
4. Taniguchi T, Asano Y, Okada A, Sugaya M, Sato S. Ultraviolet light-induced Köbner phenomenon contributes to the development of skin eruption in multicentric reticulohistiocytosis. Acta Derm Venereol. 2011;91:160–3.
5. Yee KC, Bowker CM, Tan CY, Palmer RG. Cardiac and systemic complications in multicentric reticulohistiocytosis. Clin Exp Dermatol. 1993;18:555–8.
6. Janssen BA, Kencian J, Brooks PM. Close temporal and anatomic relationship between multicentric reticulohistiocytosis and carcinoma of the breast. J Rheumatol. 1992;19:322–4.
7. Caro MR, Senear FE. Reticulohistiocytoma of the skin. Arch Derm Syphilol. 1950;65:701–13.
8. Snow JL, Muller SA. Malignancy-associated multicentric reticulohistiocytosis: a clinical, histological and immunophenotypic study. Br J Dermatol. 1995;133:71–6.
9. Ginsburg WW, O'Duffy JD, Morris JL, Huston KA. Multicentric reticulohistiocytosis: response to alkylating agents in six patients. Ann Intern Med. 1989;111:384–8.
10. Kalajian AH, Callen JP. Multicentric reticulohistiocytosis successfully treated with infliximab: an illustrative case and evaluation of cytokine expression supporting anti-tumor necrosis factor therapy. Arch Dermatol. 2008;144(10):1360–6.
11. Macia-Villa CC, Zea-Mendoza A. Multicentric reticulohistiocytosis: case report with response to infliximab and review of treatment options. Clin Rheumatol. 2014;35:527–34.
12. Kovach BT, et al. Treatment of multicentric reticulohistiocytosis with etanercept. Arch Dermatol. 2004;140(8):919–21.
13. Matejicka C, Morgan GJ, Schlegelmilch JG. Multicentric reticulohistiocytosis treated successfully with an anti-tumor necrosis factor agent: comment on the article by Gorman et al. Arthritis Rheum. 2003;48(3):864–6.
14. Gorman JD, Danning C, Schumacher HR, Klippel JH, Davis Jr JC. Multicentric reticulohistiocytosis: case report with immunohistochemical analysis and literature review. Arthritis Rheum. 2000;43:930–8.
15. Gourmelen O, Le Loet X, Fortier-Beaulieu M, Thomine E, Ledan G, Lauret P, et al. Methotrexate treatment of multicentric reticulohistiocytosis. J Rheumatol. 1991;18(4):627–8.

16. Sakamoto A, Nagamine R, Maeda T, Shuto T, Hirata G, Nakashima Y, Matsuda S, Iwamoto Y. Multicentric reticulo-histiocytosis with hydrarthrosis in both knee joints: disease stabilization with synovectomy, and medication with a steroid and low-dose methotrexate. Mod Rheumatol. 2002;12(2):155–9.

17. Franck N, Amor B, Ayral X, Lessana-Leibowitch M, Monsarrat C, Kahan A, Escande JP. Multicentric reticulohistiocytosis and methotrexate. J Am Acad Dermatol. 1995;33(3):524–5.

18. Ridgway HA, Rhodes EL. Multicentric reticulohistiocytosis with carcinoma-in-situ of the cervix. Br J Dermatol. 1979;101(Suppl):61–2.

19. Nunnick JC, Krusinski PA, Yates JW. Multicentric reticulohis-tiocytosis and cancer: a case report and review of the literature. Med Pediatr Oncol. 1985;13:273–9.

20. Kuramoto Y, Iizawa O, Matsunaga J, Nakamura N, Tagami H. Development of Ki-1 lymphoma in a child suffering from multicentric reticulohistiocytosis. Acta Derm Venereol. 1991;71:448–9.

21. Gibson G, Cassidy M, O'Connell P, Murphy GM. Multicentric reticulohistiocytosis associated with recurrence of malignant melanoma. J Am Acad Dermatol. 1995;32:134–6.

20

Lethal Non-Langerhans Cell Histiocytoses: Necrobiotic Xanthogranuloma and Xanthoma Disseminatum

- **Synonyms:** NXG—necrobiotic xanthogranuloma with paraproteinemia
  XD—Montgomery's syndrome
- **Etiology:** NXG—unknown
  XD—unknown
- **Associations:** NXG—myeloma, Grave's disease, primary biliary cirrhosis, and paraproteins
  XD—myeloma, Waldenström's macroglobulinemia, and paraproteins
- **Clinical:** NXG—ulcerating red-orange plaques, particularly of the periorbital area
  XD—disseminated red-brown papules into plaques
- **Histology:** NXG—palisading granulomatous dermatitis with bizarre giant cells
  XD—diffuse epithelioid histiocytes, foam cells, and siderosis
- **IHC repertoire:** NXG—CD-68(+), S-100(−), and CD-1(−)
  XD—CD-68(+), S-100(−), and CD-1(−)
- **Staging:** NXG—none
  XD—none
- **Prognosis:** NXG—overall 5 % 5-year mortality
  XD—overall 2 % 5-year mortality
- **Adverse variables:** NXG—cases associated with myeloma
  XD—cases associated with myeloma and Waldenström's macroglobulinemia
- **Treatment:** NXG—corticosteroids and alkylating agents
  XD—corticosteroids

The histiocytic disorders encompass a broad range of malignant and nonmalignant entities capable of presenting in a variety of clinical and pathologic guises. The histiocytic disorders are generally classified by the cell of the origin and specifically as bone marrow tissue-derived monocytes that migrate secondarily to the skin serving as either phagocytic macrophages or antigen-presenting dendritic or Langerhans cells. Langerhans cells typically reside closely to the epithelium and traffic to the lymph nodes. They are important in immunologic surveillance and are defined by the presence of Birbeck granules on ultrastructural exami-

nation, as well as S-100 and CD-1a immunopositivity. This discussion will focus upon the entities composed of the phagocytic non-Langerhans cell macrophages and specifically the disorders within this category capable of producing or being associated with significant morbidity or mortality.

The two most important entities associated with serious systemic disorder including hematopoietic malignancy are necrobiotic xanthogranuloma (NXG) and xanthoma disseminatum (XD). Despite a marked difference in their clinical and histologic appearance, both

share a common histogenesis, an association with abnormal amounts or types of circulating immunoglobulins (paraproteins) and hematopoietic malignancies including multiple myeloma.

20.1 Necrobiotic Xanthogranuloma

This rare non-Langerhans cell histiocytosis was first described in 1980 by Winkelman and Kossard, who correctly surmised its association with paraproteinemia and risk for development of multiple myeloma [1]. Since its initial description, over 60 cases have been described with nearly all patients presenting as adults. There is no gender or ethnic predisposition [2]. The etiology of the disorder is unknown, but various theories regarding its development have been proposed, including abnormal immunoglobulin or lipid storage leading to the formation of xanthomatous histiocytic cells and faulty phagocytic mechanisms leading to the characteristic clinical and pathologic findings. Each of the theories, however, fails to wholly account for its rarity, associated laboratory findings, or peculiar anatomic predisposition.

NXG is associated with a variety of unrelated disorders including, most importantly, multiple myeloma (10 % of patients), Hodgkin's disease, arthropathy, hypertension, neuropathy, primary biliary cirrhosis, and Grave's disease [3].

The clinical findings consist of firm red-orange to violaceous papules that typically enlarge into plaques, finally undergoing central atrophy and ulceration. The plaques may attain dimensions of greater than 25 cm and can be solitary or multiple. The lesions typically develop on the head and neck area, particularly the periorbital region (Fig. 20.1). Lesions have been described on the trunk and extremities. Involvement in the oral mucosa has also been reported. The lesions themselves are typically asymptomatic although an antecedent pruritic and/or burning sensation has been documented. Other physical findings include hepatosplenomegaly, which has been documented in approximately 20 % of patients. Although the skin is the principal organ involved, the eye, lungs, heart, and CNS may be afflicted.

The histopathologic features are distinctive and consist of a deep dermal and subcutaneous fat granulomatous inflammation with intervening zones of collagen degeneration, lymphoid follicles, and foam cells (Fig. 20.2) [4]. The granulomas take the form of palisading mono- and multinucleate giant cells with the latter often assuming irregular silhouettes and containing increased numbers of atypical nuclei as well as epithelioid granulomas, Touton-type wreath-like giant cells, and foreign body-type giant cells (Figs. 20.3 and 20.4). The degenerated collagen foci often contain zones of cholesterol clefting (Fig. 20.5). The histiocytes of NXG immunostain with CD-68 and CD-15 and are negative with S-100 and CD-1a.

The most important diagnoses to consider in the histologic differential diagnosis are necrobiosis lipoidica, granuloma annulare, and rheumatoid nodule. Although each of the foregoing shows palisading granulomatous foci, the collagen degeneration seen in NXG is more extensive, often extending deep into the panniculus, and is associated with cholesterol clefting.
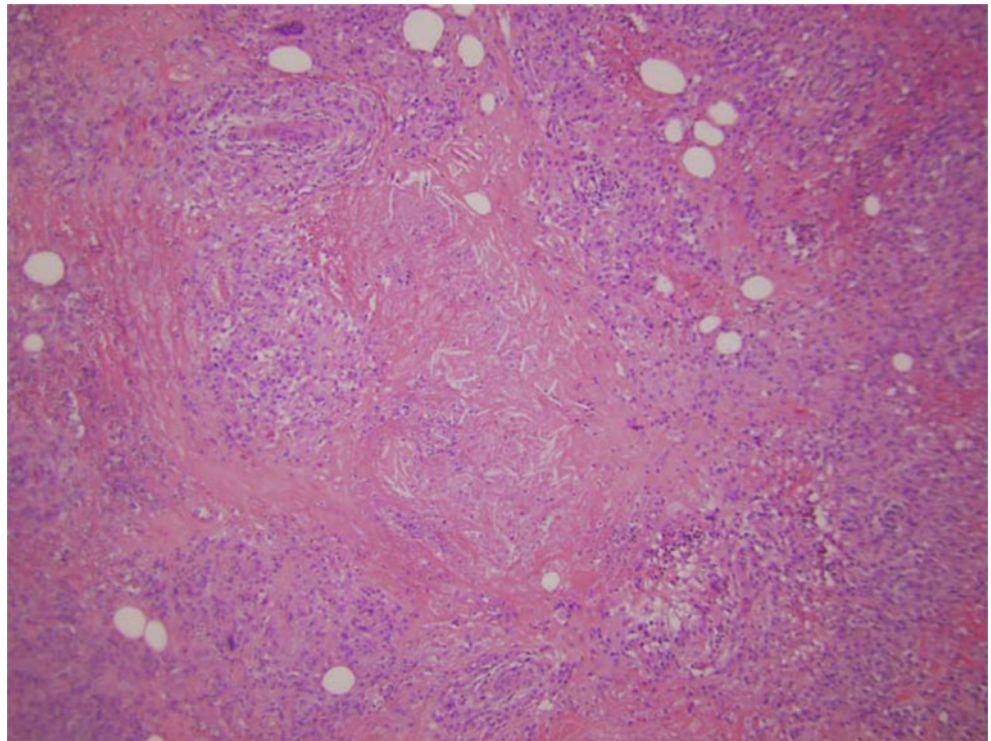

FIGURE 20.1. Infraorbital ulcer typical of necrobiotic xanthogranuloma.

Figure 20.2. Low-power photomicrograph depicting deep dermal palisading granuloma.
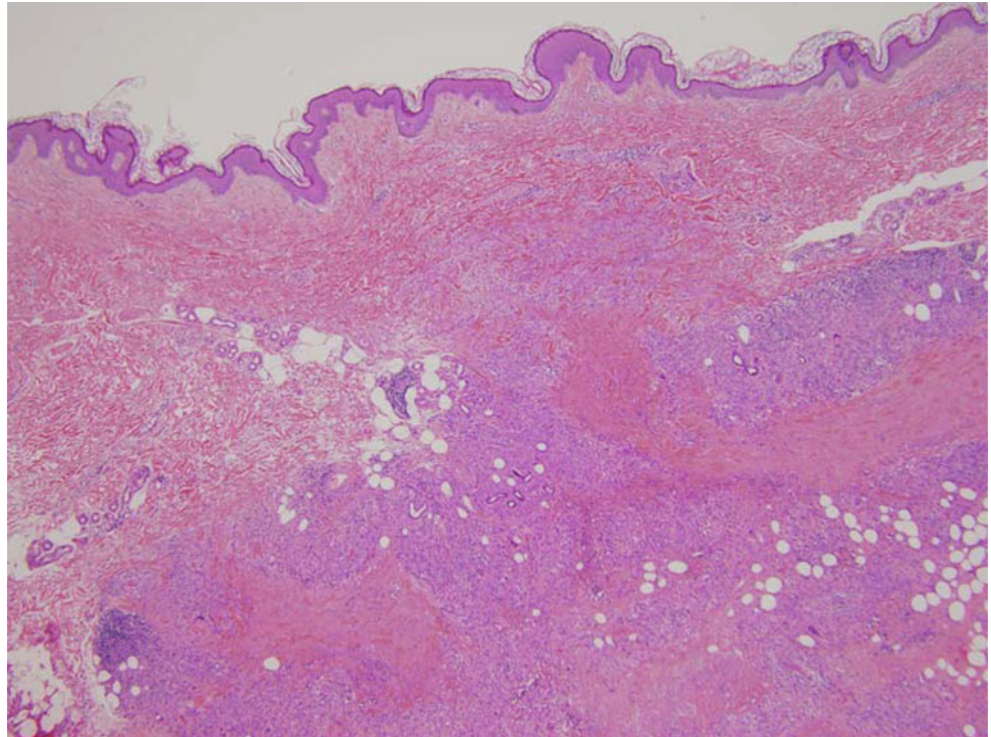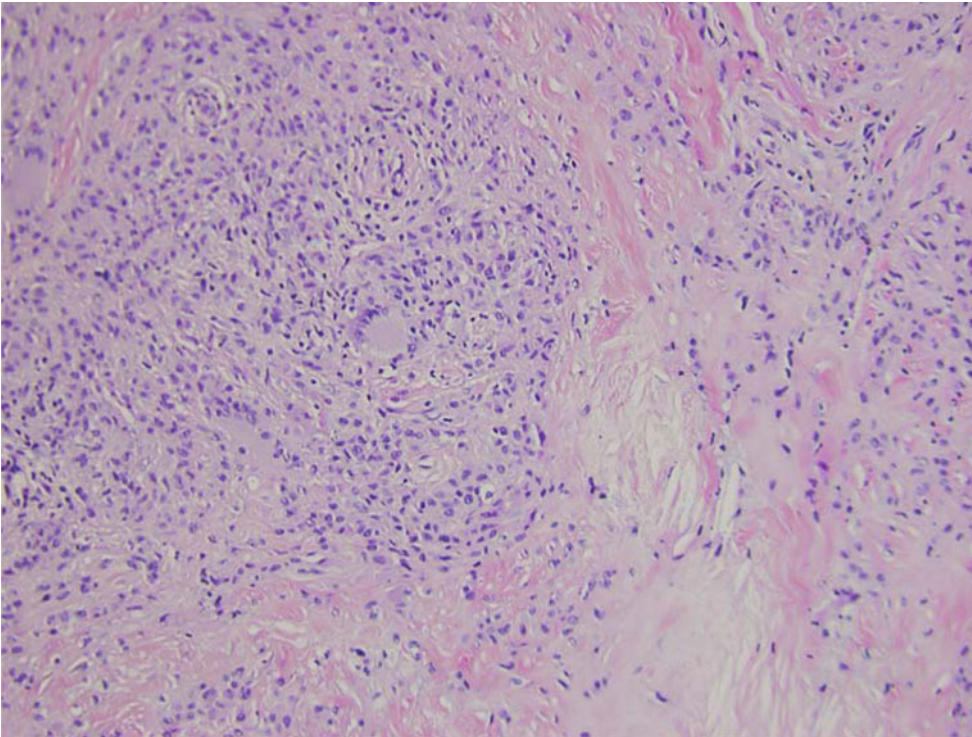

Figure 20.3. Medium-power photomicrograph depicting central necrobiotic material replete with cholesterol clefts and peripheral palisade of granulomatous inflammation.


Laboratory findings include paraproteinemia, found in approximately 90 % of patients (usually IgG with mostly kappa or occasionally lambda light chains), cryoglobulins (~40 % of cases), decreased complements, hyper-/hypolipidemia, neutropenia, and elevated erythrocyte sedimenta-

tion rate. Bone marrow biopsy often yields increased numbers of atypical plasma cells.

The course of NXG is usually chronic with episodic lesional development followed by healing and remission. Important complications involve its proximity to the eye and

Figure 20.4. Medium-power photomicrograph depicting nodular aggregates of lymphocytes with interspersed giant cells.
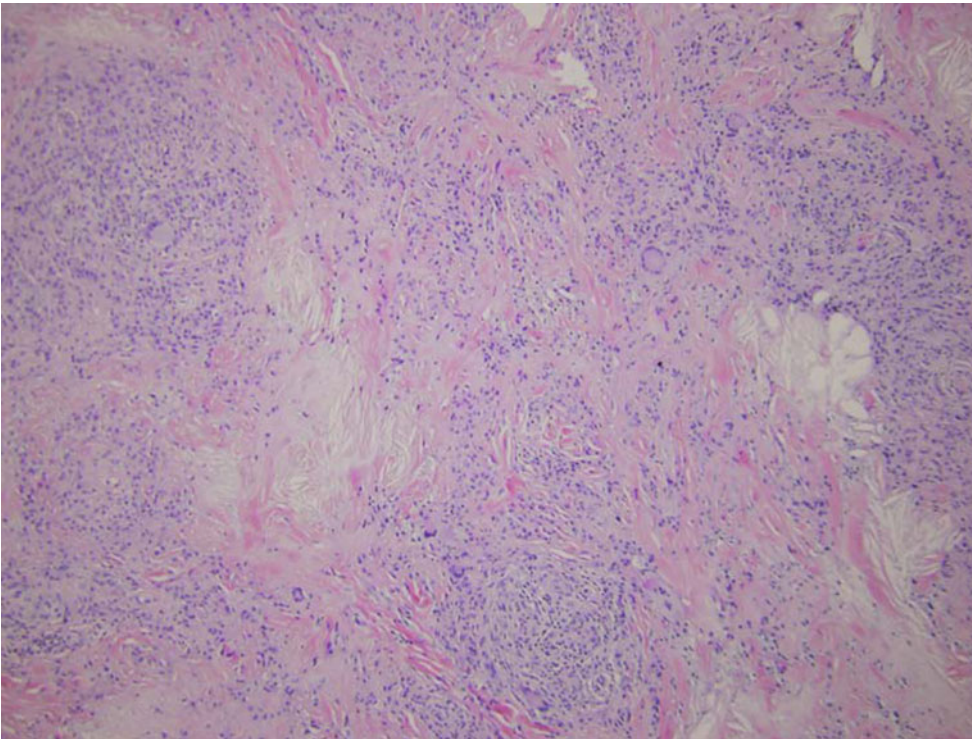
Figure 20.5. High-power detail of lymphoid aggregates. Note the central giant cell.

include conjunctivitis, keratitis, scleritis uveitis, corneal ulceration, and, exceptionally, blindness. The development of multiple myeloma is particularly ominous and may present prior to, concomitant with, or following the diagnosis of NXG. The overall 5-year mortality of multiple myeloma is 40%.

The treatment consists of corticosteroids and low-dose alkylating agents such as chlorambucil and melphalan.

Temporary remission has also been reported with radiation therapy and plasmapheresis.

20.2 Xanthoma Disseminatum

This uncommon systemic non-Langerhans cell histiocytosis was first described by Montgomery and Osterberg in 1938. Since its initial description, over 100 cases have been described. The disorder is slightly more common among males, and most patients described with this condition have been children [5]. There is no ethnic predisposition. The etiology and pathogenesis of this disorder are unknown. Like NXG, it is associated with multiple myeloma, Waldenström's macroglobulinemia, and paraproteinemia [6, 7]. Notably, each of these disorders is typically exceptional among children.

The clinical findings consist of disseminated red-brown papules that have a tendency to become yellow and coalesce, forming plaques. Similar lesions are often found in approximately 50 % of patients involving the mucous membranes of the mouth, pharynx, conjunctiva, and cornea. Lesions of the pharynx and larynx may produce symptoms of dysphagia and an altered voice. Diabetes insipidus secondary to involvement of the hypothalamus and vasopressin deficiency is observed in approximately 50 % of patients.

The histologic features of well-developed lesions are suggestive of the disorder and consist of diffuse dermal aggregates of foam cells with interspersed Touton-type wreath-like giant cells [8]. Early lesions usually show an admixture of characteristically scalloped histiocytes with acute and chronic inflammatory cells. Extension into the subcutaneous fat or epidermal ulceration is exceptional. The lesional cells are CD-68 (+), S-100(−), and CD-1a (−).

Laboratory findings usually show normal lipid levels. Serum vasopressin levels are typically depressed. The overall prognosis is favorable with the exception of those patients who develop hematopoietic malignancy. The dermatologic manifestations may pursue three clinical courses: spontaneous resolution; remain persistent; or, rarely, progress. Important complications include diabetes insipidus and obstructive upper aerodigestive tract disease. Treatment consists of symptomatic removal of mucosal lesions and vasopressin administration in cases complicated by diabetes insipidus. The cutaneous lesions do not usually respond to topical or systemic medication.

References

1. Kossard S, Winkelman R. Necrobiotic xanthogranuloma with paraproteinemia. J Am Acad Dermatol. 1980;3:257.
2. Finan M, Winkelman R. Necrobiotic xanthogranuloma with paraproteinemia: a review of 22 cases. Medicine. 1986;65:376.
3. Macfarlane A, Verbov J. Necrobiotic xanthogranuloma with paraproteinemia. Br J Dermatol. 1985;113:339.
4. Finan M, Winkelman R. Histopathology of necrobiotic xanthogranuloma with paraproteinemia. J Cutan Pathol. 1987;14:92.
5. Caputo R, Veraldi S, Grimalt R, et al. The various clinical patterns of xanthoma disseminatum. Dermatology. 1995;190:19.
6. Maize J, Ahmed A, Provost T. Xanthoma disseminatum and multiple myeloma. Arch Dermatol. 1974;110:758.
7. Goodenberger M, Piette W, Macfarlane D, et al. Xanthoma disseminatum and Waldenström's macroglobulinemia. J Am Acad Dermatol. 1990;23:1015.
8. Mishkel M, Cockshott W, Nazir D, et al. Xanthoma disseminatum: clinical, metabolic, pathologic, and radiologic aspects. Arch Dermatol. 1977;113:1094.

21
Pancreatic Panniculitis

- Synonyms: Pancreatic fat necrosis, Nodular fat necrosis of pancreatic disease
- Etiology: In part, due to cutaneous enzymatic fat necrosis from circulating pancreatic enzymes
- Associations: Acute and chronic pancreatitis, acinar cell carcinoma
- Clinical: Erythematous subcutaneous nodules favoring lower extremities, may drain spontaneously; arthritis, serositis, abdominal pain, nausea, vomiting, lytic bone lesions
- Histology: Subcutaneous fat necrosis with loss of adipocyte nuclei, "ghost" cells, stippled basophilia of calcification, neutrophils early, mixed infiltrate late
- Evaluation: Serum amylase, lipase, CBC with differential (eosinophilia correlates with acinar cell carcinoma), pancreatic imaging studies
- Treatment: Correct underlying pancreatic disease
- Prognosis: Usually poor in carcinoma-associated disease because of advanced disease, and variable in pancreatitis-associated, depending upon severity of underlying disease

Pancreatic panniculitis is a form of subcutaneous fat necrosis that occurs as a rare manifestation of various pancreatic diseases, most commonly pancreatitis, or pancreatic carcinoma. Fat necrosis at remote sites occurs in only a small percentage of those with pancreatic disease. Its pathogenesis is uncertain. A review of 893 hospital admissions for various pancreatic diseases revealed only three cases of pancreatic panniculitis [1]. Circulating pancreatic enzymes, lipase and amylase, are elevated in most but not all cases of pancreatic panniculitis [2]. Human pancreatic lipase has been identified in lesions of pancreatic panniculitis, supporting its role in the pathogenesis of the disease [3]. In vitro and clinical observations suggest that factors other than circulating amylase and lipase are necessary for the development of pancreatic panniculitis. In vitro incubation of human adipose tissue with pancreatic enzymes and serum from a patient with pancreatic panniculitis and elevated enzymes failed to induce fat necrosis, suggesting that there are other local factors or a labile circulating factor needed to induce the necrosis [4]. Clinical observations indicate that pancreatic panniculitis occurs in only a small number of patients with pancreatic disease. It does not develop in many with striking elevation of pancreatic enzymes and may arise in patients with normal circulating enzymes. Lesions of pancreatic panniculitis have been induced at sites of injury from a vascular procedure, suggesting that local trauma in a susceptible individual is capable of inducing disease [5]. Localized lesions have also been induced by paracentesis in a patient with acute pancreatitis, most likely the direct effect of peritoneal pancreatic enzymes on subcutaneous fat reached via the needle tract from the procedure [6].

Most cases of pancreatic panniculitis occur in association with acute and chronic pancreatitis and pancreatic adenocarcinoma. Most of the pancreatitis-associated cases are due to chronic alcoholism, but some are due to cholecystitis with biliary tract obstruction and trauma.

Malignancy-induced pancreatic panniculitis is almost always due to acinar cell carcinoma. Although this tumor accounts for fewer than 5 % of pancreatic malignant neoplasms, it produces large quantities of lipase and other digestive enzymes, likely accounting for the association [7]. Other triggers of pancreatic panniculitis include pancreatic pseudocyst, post-traumatic pancreatitis [8], and structural anomalies such as pancreas divisum [9]. A case of gastric adenocarcinoma metastatic to the pancreas inducing pancreatic panniculitis has been described [10].

Patients who develop pancreatic panniculitis present with erythematous to brown, usually painful, subcutaneous nodules (Fig. 21.1). The most common site of involvement is pretibial, but lesions may involve the upper extremities and trunk and may spare the legs. Nodules are indurated, and many have some softening or fluctuation in the central portion, indicating liquefactive necrosis. In some patients, spontaneous ulceration occurs, with drainage of creamy or brown viscous fluid, representing degenerated adipose tis-
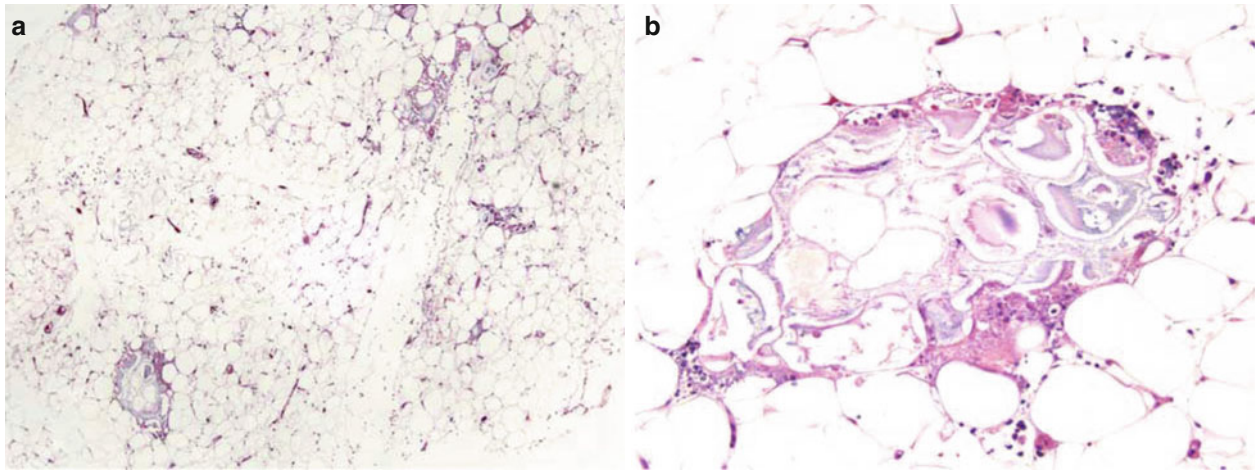

FIGURE 21.1. Pancreatic panniculitis: dusky acral subcutaneous nodules with some depressions from sites of prior spontaneous drainage (Photo courtesy of Cleveland Clinic Foundation, Department of Dermatology).

sue. Spontaneous involution with lipoatrophy and dyspigmentation occurs in several weeks and may or may not correlate with improvement of the underlying disease. Paradoxically, pancreatic panniculitis associated with alcoholic pancreatitis and markedly elevated pancreatic enzymes tends to have more localized cutaneous disease with less likelihood of spontaneous rupture, drainage, and ulceration than that associated with pancreatic carcinoma [8].

Many presentations of pancreatic panniculitis appear to represent localized disease, but others have numerous systemic manifestations, including those directly associated with pancreatitis such as abdominal pain, nausea, vomiting, chest pain, jaundice, and fever. Approximately 40 % of pancreatitis-associated cases and 90 % of malignancy-associated cases present without abdominal pain, nausea, or vomiting. Peripheral eosinophilia may occur and is far more likely to be associated with underlying carcinoma than pancreatitis [11]. Arthritis, described in approximately 60 % of cases, usually represents periarticular fat necrosis. In some instances, the fat necrosis extends into the joint space resulting in a true arthritis. The most commonly affected joints are ankles, fingers, knees, and elbows [1]. Ascites, pleural, and pericardial effusions may also occur [12]. In one case with polyserositis, the presence of pleural deposition of IgG and C3 and reduced levels of hemolytic complement in blood, pleural, and pericardial fluid were detected, suggesting immune-mediated injury [12]. Lytic bone lesions due to medullary fat necrosis have also been described. These may be mistaken for metastatic disease in malignancy-associated cases [13].

Pancreatic panniculitis may be the presenting sign of previously undiagnosed pancreatic disease. The clinical presentation of subcutaneous nodules with arthritis and serositis is not specific, but may suggest connective tissue disease accompanied by erythema nodosum. Pancreatic panniculitis is one of several disparate entities that may resemble erythema nodosum, but is readily distinguished from it based upon histologic features (Fig. 21.2a, b). The epidermis and dermis are usually normal. The subcutaneous tissue has extensive fat necrosis with loss of adipocyte nuclei. Retained cell borders form "ghost-like" fat cells. There is stippled basophilia caused by calcification and a mixed inflammatory cell infiltrate varying with the age of the lesion. Neutrophils predominate early [14]. A septal pattern of inflammation has been described in an early lesion [15].

Most cases of pancreatic panniculitis wax and wane. The only effective treatments are to correct the underlying disease, tumor resection for localized malignancy, bowel rest and supportive measures for pancreatitis, or surgical correction of developmental anomalies or mechanical obstruction. Injected octreotide, a somatostatin analog which inhibits pancreatic enzyme secretion, was reported to be beneficial in a report of a patient with pancreatic acinar cell

FIGURE 21.2. (**a**, **b**) Multifocal fat necrosis with "ghost cell" formation, neutrophils, and stippled calcification.

adenocarcinoma and pancreatic panniculitis [16]. Pancreatic panniculitis is important to recognize because it may closely mimic erythema nodosum, a common cause of panniculitis. A distinctive histologic pattern in pancreatic panniculitis is a valuable clue to the recognition of serious previously undiagnosed pancreatic disease.

References

1. Mullin GT, Ceperton EM, Crespin SR, et al. Arthritis and skin lesions resembling erythema nodosum in pancreatic disease. Ann Intern Med. 1968;68:75–87.
2. Schrier RW, Melmon KL, Fenster LF. Subcutaneous nodular fat necrosis in pancreatitis. Arch Intern Med. 1965;116:832–6.
3. Dhawan SS, Jiminez-Acosta F, Poppiti RJ, Barkin JS. Subcutaneous fat necrosis associated with pancreatitis: histochemical and electron microscopic findings. Am J Gastroenterol. 1990;85:1025–8.
4. Berman B, Conteas C, Smith B, Leong S, Hornbeck L. Fatal pancreatitis presenting with subcutaneous fat necrosis: evidence that lipase and amylase alone do not induce lipocyte necrosis. J Am Acad Dermatol. 1987;17:359–64.
5. Cutlan RT, Wesche WA, Jenkins JJ, Chesney TM. A fatal case of pancreatic panniculitis presenting in a young patient with systemic lupus. J Cutan Pathol. 2000;27:466–71.
6. Levine N, Lazarus G. Subcutaneous fat necrosis after paracentesis. Arch Dermatol. 1976;112:993–4.
7. Thompson LDR, Heffess CS. Pancreas. In: Mills SE, Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH, editors. Sternberg's diagnostic surgical pathology. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 1623–5.
8. Sibrack LA, Gouterman IH. Cutaneous manifestations of pancreatic diseases. Cutis. 1978;21:763–8.
9. Haber RM, Assaad DM. Panniculitis associated with a pancreas divisum. J Am Acad Dermatol. 1986;14:331–4.
10. Beyazit H, Aydin O, Demirkesen C, et al. Pancreatic panniculitis as the first manifestation of the pancreatic involvement during the course of a gastric adenocarcinoma. Med Oncol. 2011;28:137–9.
11. Hughes PSH, Apisarnthanarax P, Mullins JF. Subcutaneous fat necrosis associated with pancreatic disease. Arch Dermatol. 1975;111:506–10.
12. Potts DE, Mass MF, Iseman MD. Syndrome of pancreatic disease, subcutaneous fat necrosis and polyserositis. Am J Med. 1975;58:417–23.
13. Good AE, Schnitzer B, Kawanishi H, Demetropoulos C, Rapp R. Acinar pancreatic tumor with metastatic fat necrosis: report of a case and review of rheumatic manifestations. Am J Dig Dis. 1976;21:978–87.
14. Szymanski FJ, Bluefarb SM. Nodular fat necrosis and pancreatic diseases. Arch Dermatol. 1961;83:224–9.
15. Ball NJ, Adams SPA, Marx LH, Enta T. Possible origin of pancreatic fat necrosis as a septal panniculitis. J Am Acad Dermatol. 1996;34:362–4.
16. Hudson-Peacock MJ, Regnard CFB, Farr PM. Liquefying panniculitis associated with acinous carcinoma of the pancreas responding to octreotide. J R Soc Med. 1994;87:361–2.

22
Scleromyxedema

■	Synonyms:	Generalized lichen myxedematosus, Arndt-Gottron syndrome
■	Etiology:	Unknown
■	Associations:	Paraproteinemia, multiple myeloma, hepatitis C, HIV infection
■	Clinical:	Generalized coalescing indurated waxy papules
■	Histology:	Increased dermal mucin with increased fibroblasts
■	Prognosis:	Slowly progressive—increased mortality rate
■	Adverse variables:	Monoclonal gammopathy
■	Treatment:	Intravenous immunoglobulin, melphalan, cyclophosphamide

While the entity which is currently known as scleromyxedema had been described as early as 1906 [1], the term did not enter the dermatologic lexicon until the work of Gottron in 1954 [2]. At this time it became clear that scleromyxedema was a unique entity, sharing features of the benign cutaneous mucinoses and scleroderma, with specific, recognizable morphologic features. In most classification systems, scleromyxedema falls under the umbrella of lichen myxedematosus, along with several other localized conditions, all of which share similar histopathologic features.

Scleromyxedema is a rare condition, which occurs without gender predilection, usually in the 6th decade of life. Eighty percent of patients will have an associated paraproteinemia, the most common being composed of IgG heavy chain and gamma light chain [3]. A small percentage develop multiple myeloma or have this diagnosis at the time of development of skin manifestations.

The relationship between the paraproteinemia and disease pathogenesis remains unclear, as the severity of skin changes is not reflected in paraprotein burden. Deposition of excess immunoglobulins may lead to dermal synthesis of collagen and glycosaminoglycans. The serum of patients with scleromyxedema can induce in vivo fibroblast proliferation and activity, although purified immunoglobulin does not produce the same findings [4]. The deposition of IgG and occasionally IgM immunoglobulins is demonstrated with direct immunofluorescence in the dermis of approximately 35 % of patients, the significance of which is

unclear [5]. Clearly, the pathogenesis of scleromyxedema remains elusive.

Fully developed cases of scleromyxedema have a unique constellation of cutaneous features, which can be mistaken for little else by the experienced dermatologist. Insidious, subacute development of thousands of monomorphic, waxy, skin-colored papules, usually 2–3 mm in size, begin to appear on the acral upper extremities and become generalized (Fig. 22.1). Symptoms of pruritus are present in approximately 30 % of patients [6]. Adjacent clustering of papules leads to coalescing plaques, with underlying induration. Facial involvement results in exaggeration of facial convexities and leonine or occasionally sclerodermoid disfigurement, in addition to characteristic linear arrangement of papules on the eyelids (Fig. 22.2). Involvement of the proximal interphalangeal joint can result in "doughnut sign," which refers to depressed central skin and an annular, peripheral ring of firm, mucinous infiltration. Acral calcification is absent. Clinical differential diagnosis includes diffuse scleroderma, scleredema, and nephrogenic systemic fibrosis. Clustered papules, such as found in scleromyxedema, are usually not encountered in these entities.

Systemic features of scleromyxedema, other than associated monoclonal gammopathy, include neurologic, rheumatologic, and cardiac sequelae (Table 22.1). Peripheral neuropathy and proximal muscle weakness occur in 15 % and 27 % of patients, respectively, and a seronegative polyarthritis can cause further disability [7]. Less commonly, Raynaud's phenomenon and carpal tunnel syndrome

Figure 22.1. Multiple monomorphic waxy smooth papules on the arms.

Table 22.1. Systemic conditions associated with scleromyxedema

Condition	Percent of cases of scleromyxedema with this association
Paraproteinemia	83.2
Multiple myeloma	10
Proximal muscle weakness	27
Central or peripheral neuropathies	15
Joint involvement	10.5
Carpal tunnel syndrome	9.6
Raynaud's phenomenon	8.8
Dyspnea	16.7
Dysphagia	31.6
Renal disease/coronary artery disease	Reported
Ophthalmologic disorders (corneal opacities, ectropion, lagophthalmos)	18%
Hepatitis C	
AIDS	

Figure 22.2. Scleromyxedema with extensive indurated plaques of the face resulting in leonine features.

occur. Dysphagia related to esophageal dysmotility occurs in a significant portion of patients (32%) and also occurs in the context of the so-called dermato-neuro syndrome. This includes fevers, convulsions, and occasional progression to coma in patients with scleromyxedema, and can also include acute psychosis, dysphagia, dysarthria, ataxia, and tremor. Thankfully, dermato-neuro syndrome is rare.

Histopathology at low power usually reveals a normal epidermis, although occasional atrophy, acanthosis, or hyperkeratosis may be present. Early disease shows reticular dermal involvement consisting of a modest increase in fibroblasts with disorganized collagen bundles and intermittent deposits of mucin. In established scleromyxedema, numerous fibroblasts are intermingled with fibrotic collagen within a thickened dermis, along with increased dermal mucin and a superficial perivascular lymphohistiocytic infiltrate [8] (Figs. 22.3 and 22.4). Mucinous infiltration of blood vessels and occasionally renal papillae found at autopsy is rare [9]. A histologic mimic is nephrogenic systemic fibrosis, which requires clinical, rather than histopathologic, differentiation [10].

Once a definitive diagnosis is rendered, comorbidities should be sought out and treated. A comprehensive cutaneous, neurologic, musculoskeletal, and ophthalmologic examination should take place, as well as a targeted review of systems. Reported symptoms of dysphagia, dyspnea, or Raynaud's phenomenon should be further evaluated. Complete blood count, metabolic profile, serum and urine protein electrophoresis should be checked, as well as serum tests for hepatitis C antibody and HIV.

Scleromyxedema is quite refractory to treatment, with incomplete response to therapy, inability to induce durable remission, and toxicity of treatments being the main limitations to disease control. For many years, melphalan and cyclophosphamide were considered to be mainstays of

FIGURE 22.3. Scleromyxedema, medium power. Increased number of spindled fibroblasts with interspersed lymphocytes.
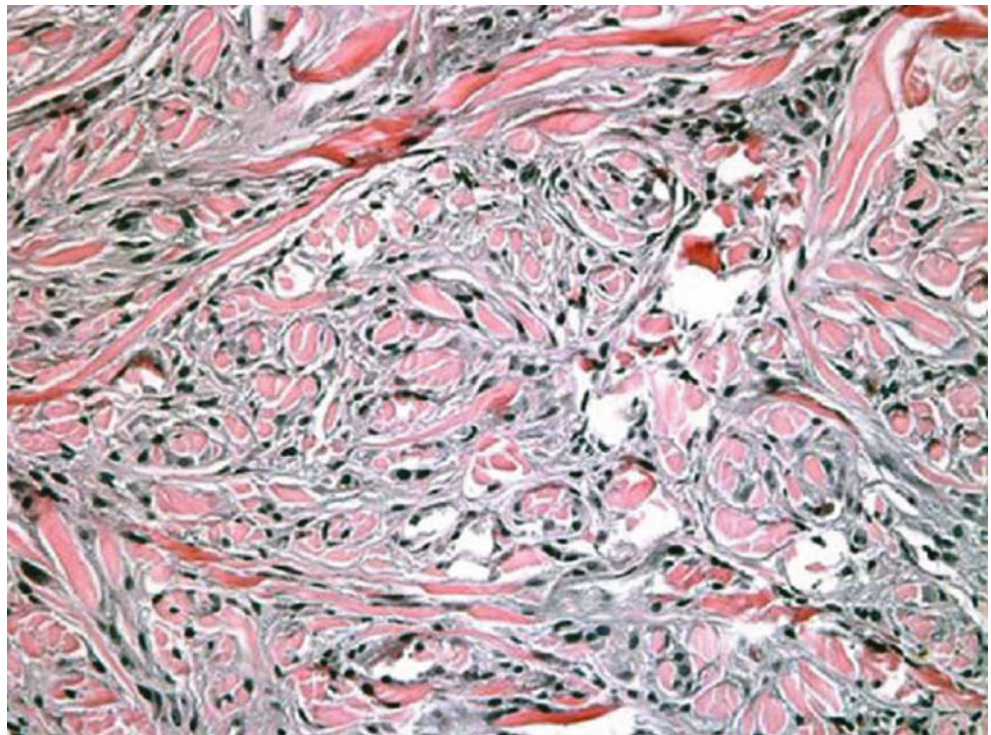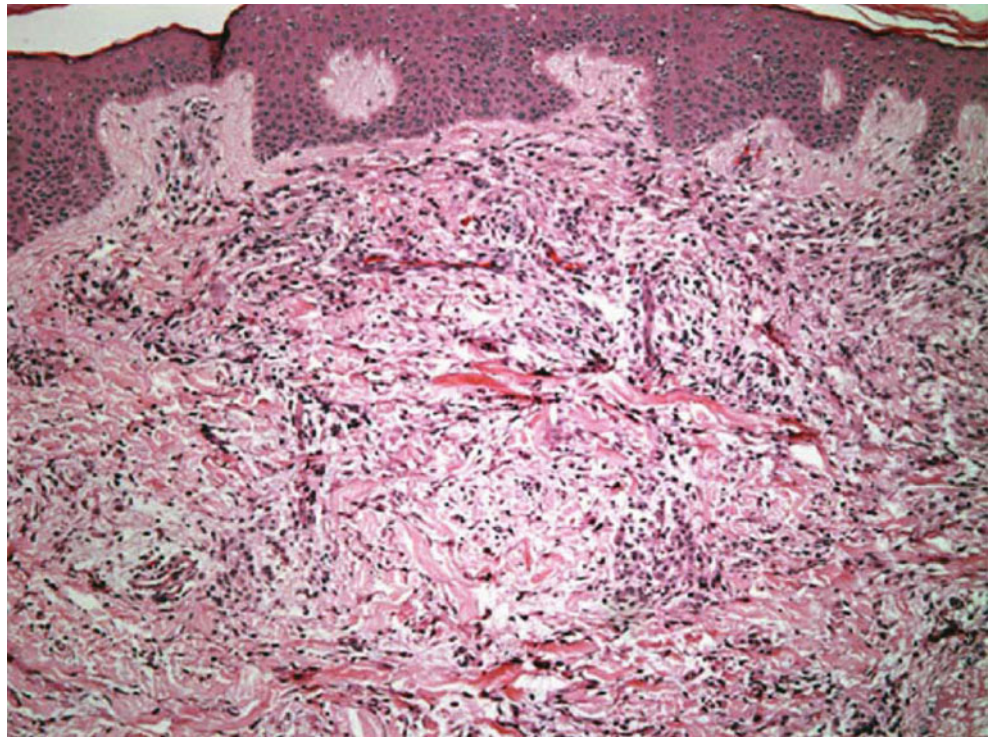
FIGURE 22.4. Scleromyxedema, high power. Spindled fibroblasts with interspersed mucin.

treatment, resulting in improvement, but secondary induction of hematologic malignancies was a constant concern. Thalidomide and lenalidomide result in improvement in high dosage but are rendered as adjunctive treatments given their inability to induce remission as monotherapy [11, 12]. If a "treatment of choice" exists for scleromyxedema, intravenous immunoglobulin is the only realistic suitor, usually employed at a dose of 2 mg per kilogram body weight and

administered monthly. Rates of improvement and maintained remission are impressive, although treatments are expensive and must be maintained for months. Addition of thalidomide or lenalidomide is optional for recalcitrant cases [11–13], and the limited immunosuppression induced with these combinations is a far cry from that induced by melphalan or cyclophosphamide. In truly recalcitrant cases in which multiple myeloma or dermato-neuro syndrome has become life-threatening, autologous bone marrow transplant and the anti-myeloma agent bortezomib have shown success in carefully selected patients [14–16].

References

1. Dubreuilh W. Fibromes miliaires folliculaires: sclerodermie consecutive. Ann Dermatol Syphiligr. 1906;37:569–72.
2. Gottron HA. Scleromyxedema; a strange manifestation of myxothesaurodermy. Arch Klin Exp Dermatol. 1954;199:71–91.
3. Dineen AM, Dicken CH. Scleromyxedema. J Am Acad Dermatol. 1995;33:37–43.
4. Cokonis Georgakis CD, Falasca G, Georgakis A, Heymann WR. Scleromyxedema. Clin Dermatol. 2006;24:493–7.
5. Farmer ER, Hambrick Jr GW, Shulman LE. Papular mucinosis: a clinicopathologic study of four patients. Arch Dermatol. 1982;118:9–13.
6. Rongioletti F, Merlo G, Cinotti E, et al. Scleromyxedema: a multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. J Am Acad Dermatol. 2013;69(1):66–72.
7. Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. JAAD. 2001;44:274–81.
8. Ronglioletti F, Rebora A. Cutaneous mucinosis. Microscopic criteria for diagnosis. Am J Dermatopathol. 2001;23:257–67.
9. Kantor GR, Bergfeld WF, Katzin WE, et al. Scleromyxedema associated with scleroderma renal disease and acute psychosis. J Am Acad Dermatol. 1986;14:879–88.
10. Kucher C, Xu X, Pasha T, Elenitsas R. Histopathologic comparison of nephrogenic fibrosing dermopathy and scleromyxedema. J Cutan Pathol. 2005;32(7):484–90.
11. Dolenc-Voljc M, Jurcic V, Hocevar A, Tomsic M. Scleromyxedema with subcutaneous nodules: successful treatment with thalidomide and intravenous immunoglobulin. Case Rep Dermatol. 2013;5(3):309–15.
12. Brunet-Possenti F, Hermine O, Marinho E, Crickx B, Descamps V. Combination of intravenous immunoglobulins and lenalidomide in the treatment of scleromyxedema. J Am Acad Dermatol. 2013;69(2):319–20.
13. Blum M, Wigley FM, Hummers LK. Scleromyxedema: a case series highlighting long-term outcomes of treatment with intravenous immunoglobulin. Medicine. 2008;87(1):10–20.
14. Fett NM, Toporcer MB, Dalmau J, Shinohara MM, Vogl DT. Scleromyxedema and dermato-neuro syndrome in a patient with multiple myeloma effectively treated with dexamethasone and bortezomib. Am J Hematol. 2011;86(10):893–6.
15. Cañueto J, Labrador J, Román C, Santos-Briz A, Contreras T, Gutiérrez NC, García-Sanz R. The combination of bortezomib and dexamethasone is an effective therapy for relapsed/refractory scleromyxedema: a rare disease with new clinical insights. Eur J Haematol. 2012;88(5):450–4.
16. Lacy MQ, Hogan WJ, Gertz MA, Dispenzieri A, Rajkumar SV, Hayman S, Kumar S, Litzow MR, Schroeter AL. Successful treatment of scleromyxedema with autologous peripheral blood stem cell transplantation. Arch Dermatol. 2005;141(10):1277–82.

23
Necrolytic Migratory Erythema

■ Synonyms:	Glucagonoma syndrome
■ Etiology:	Glucagon-secreting tumors, usually malignant and located principally in the pancreas
■ Associations:	MEN I syndrome, Zollinger-Ellison syndrome, zinc deficiency, amino acid deficiency
■ Clinical:	Rash—erythematous, scaly patches, intertriginous and acral area, angular cheilitis, diabetes mellitus, diarrhea, weight loss, depression, deep vein thrombosis
■ Histology:	Mild epidermal acanthosis with confluent parakeratosis and vacuolar degeneration of the superficial epithelial layers
■ IHC repertoire:	N/A
■ Staging:	None
■ Prognosis:	Overall 5-year survival—50 %
■ Adverse variables:	Malignant pancreatic tumor, weight loss, metastases

Necrolytic migratory erythema (NME) is a major component of glucagonoma syndrome, a rare paraneoplastic syndrome consisting of the classic triad of diarrhea, diabetes mellitus, and rash associated with serum hyperglucagonemia [1–3]. Originally described by Becker et al. in 1942, NME has an incidence of approximately 1 in 20 million [4, 5]. There is no ethnic or gender predilection, and peak age of onset is during the fourth and fifth decades [6, 7]. NME occurs in 70 % of those with glucagonoma syndrome [5]. Glucagonomas are associated with type 1 multiple endocrine neoplasia (MEN I) syndrome sequence and/or Zollinger-Ellison hypergastrinemia syndrome in a minority of the cases (about 5 % of cases) [8–11]. The most common etiology involves the elaboration of glucagon from an islet cell tumor of the pancreas but may rarely follow the metabolic consequences of cirrhosis, pancreatic insufficiency, or celiac disease.

The rash consists of an expanding erythematous and scaly patch typically observed within the intertriginous areas including the inguinal creases, nasolabial sulcus, and popliteal fossae (Fig. 23.1) [12]. Other frequently involved areas include acral sites, perineum, and areas subject to greater pressure [13]. In time, the patches develop into blistering plaques with perilesional pustules. Lesional pain and intense pruritus are commonly observed. The rash typically waxes and wanes cyclically with concurrent lesions showing different levels of healing. Approximately 30 % of patients develop angular cheilitis and glossitis. Onychoschizia has also been reported [4].

Systemic manifestations that commonly accompany this syndrome include the 6 Ds: diabetes mellitus, diarrhea, depression (or neuropsychiatric disorders), deep vein thrombosis, dilated cardiomyopathy, and, of course, dermatitis [14]. Other features include weight loss and a host of laboratory abnormalities. Diabetes mellitus develops in approximately 85 % of patients with NME. The hyperglycemia results from the antagonistic effect of glucagon upon insulin, by increasing gluconeogenesis in the liver and kidney and glycogenolysis in the liver and skeletal muscle and inhibiting glycogen synthesis in the liver [15]. Hormone-sensitive lipase is activated in the adipose tissue to increase fatty acid delivery to the liver and lipoprotein production is reduced [4]. Glycemic management of patients with this syndrome can be difficult. Weight loss and tumor-associated cachexia is frequently observed and are particularly evident in the

FIGURE 23.1. Erythematous and focally scaly eruption involving genitalia and inguinal regions seen in necrolytic migratory erythema (Photo courtesy of Cleveland Clinic Foundation, Department of Dermatology).

terminal stages of the disease. Diarrhea is observed in approximately one-third of patients and can be debilitating. Neuropsychiatric disturbances consist of depression, psychoses, as well as ataxia and visual disturbances and will be present in 20 % of patients [16]. Thromboembolic complications are common and presumably due to tumor-associated hypercoagulability. Migratory thrombophlebitis (*Trousseau's syndrome*), deep venous thrombosis of the leg with attendant risk of pulmonary embolism, and cerebral artery thrombosis are observed. Laboratory abnormalities include spectacular elevation of the serum glucagon level, elevated erythrocyte sedimentation rate, normochromic normocytic anemia, hypoalbuminemia, and hypoaminoacidemia.

There are multiple theories explaining how elevated glucagon levels result in NME. One theory suggests that it is glucagon itself that induces the skin lesions; another postulates that the subsequent amino acid deficiency causes epidermal protein depletion and necrolysis. Zinc deficiency has also been associated with NME and is required for the synthesis of essential fatty acids. If this pathway is blocked, inflammatory mediators involving the arachidonic acid pathway could also result in the epidermal changes. Zinc, amino acid, and essential fatty acid deficiencies may all possess a common pathway contributing to the pathogenesis of NME. Evidence of this comes from improvement of NME with supplementation of these nutrients [6]. Hypovitaminosis B is thought to play a role, and there are various overlaps in presentation (stomatitis, cheilitis, anemia). The catabolic effects of glucagon are far-reaching, and enhanced protein breakdown is even theorized to interfere with synthesis of dopamine, thyroxine, serotonin, and more [4]. Liver disease can exacerbate the disease state because albumin is the predominant carrier for zinc and essential fatty acids [17]. A pseudoglucagonoma syndrome, in which NME arises in the absence of a pancreatic tumor, may further shed light on these pathways in the context of liver disease, malabsorption disorders, short bowel syndrome, inflammatory bowel disease, and other malignancies [13, 18]. Cases of NME with small-cell lung cancer have been reported [19].

The diagnosis can be established by histologic criteria in the appropriate clinical setting or with laboratory testing [20]. The histologic features are distinctive though not pathognomonic of the disorder. The histologic features are entirely limited to the epithelium and consist of alterations in all of its layers. Overall, the epithelium shows acanthosis and confluent parakeratosis with loss of the granular layer (Fig. 23.2). At high-power examination, the keratinocytes, particularly in the middle portion of the stratum spinosum, show ballooning and vacuolar degeneration. Intraepidermal bullae and neutrophilic exocytosis may also be observed (Fig. 23.3).

Although the differential includes disorders capable of showing exocytosis of neutrophils, such as psoriasis, as well as disorders that may induce keratinocyte degeneration, such as sunburn or viral infection, seldom do they constitute a diagnostic dilemma after clinical correlation. The most important disorders that are capable of producing histologic alterations that may mimic NME include the nutritional deficiency states of pellagra and acrodermatitis enteropathica. Pellagra or niacin deficiency has distinctive clinical attributes that usually permit its distinction from NME. *Pellagra* is primarily observed in two clinical settings including children with an inherited disorder involving tryptophan metabolism (*Hartnup disease*) and among nutritionally impoverished adults [21, 22]. The cutaneous manifestations include photodistributed erythematous and burning patches that in time develop into scaly and fissured hyperpigmented plaques. The cutaneous manifestations are often accompanied by diarrhea and dementia that, if not corrected in time, eventuate in death.
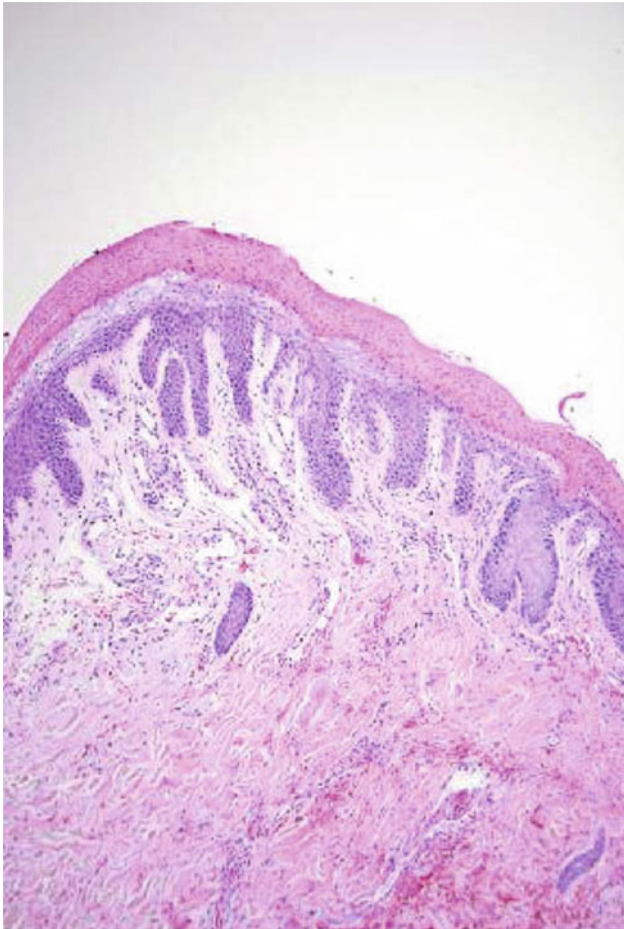
FIGURE 23.2. Low-power photomicrograph depicting epidermal acanthosis with hyperkeratosis.
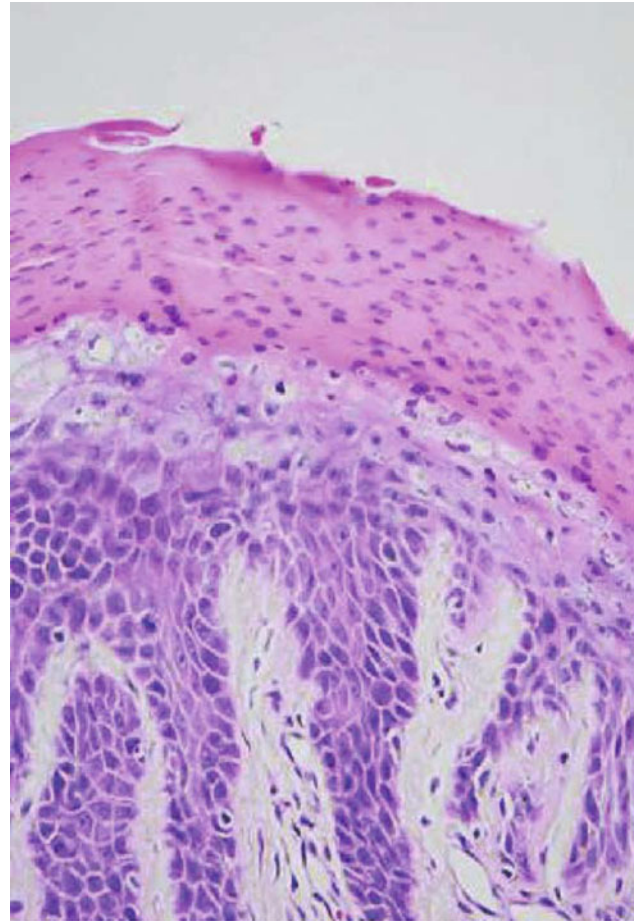
FIGURE 23.3. High-power detail of stratum spinosum showing vacuolar alteration with loss of the granular layer and coarse parakeratosis typical of necrolytic erythema.

Additional settings in which niacin deficiency may be observed include the carcinoid syndrome in which the metabolic precursor of niacin, tryptophan, is usurped by the tumor. Niacin deficiency may follow impaired absorption or interaction with certain medications such as isoniazid, mercaptopurine, 5-fluorouracil, sulfonamides, anticonvulsants, and antidepressants. *Acrodermatitis enteropathica* consists of a distinctive acral and periorificial rash observed in infants and less commonly in adults, who are deficient in zinc or other micronutrients (Fig. 23.4) [23–25]. The metabolic defect in infants often involves a defect in the zinc transporter genes. Among adults, this condition may be observed in patients receiving total parenteral nutrition.

Laboratory confirmation can be achieved by measuring the serum level of glucagon. Levels are usually above 1000 pg/ml (normal 100 pg/ml). Although elevated serum glucagon levels are observed in 100 % of cases, other causes of elevated serum glucagon to consider include cirrhosis, renal failure, prolonged fasting, diabetic ketoacidosis,

and other islet cell tumors of the pancreas. Iatrogenic hyperglucagonemia has been shown to produce NME, as in the case of IV glucagon administration in the treatment of patients with persistent hypoglycemia [4].

Computerized tomography can be utilized to visualize the tumor that in the majority of cases resides within the pancreas. PET-CT scans have also proven useful in identifying pancreatic glucagonomas and metastasis by using radionuclides that target somatostatin receptors expressed on the cell surface [14]. Tumors tend to arise in the tail of the pancreas where alpha islet cell density is highest. Neuroendocrine tumors can be differentiated from other tumors on imaging due to their rich vascular supply and the presence of calcification, both of which are considerably less likely in pancreatic adenocarcinomas [7]. Pancreatic neuroendocrine neoplasms (pNENs) comprise less than 5 % of all pancreatic malignancies, and glucagonomas are an even rarer subset of functional pNENs [11, 16]. A minority of glucagonomas result from ectopic islet cell tumors located in the small intestine, stomach, or

Figure 23.4. Acral distributed erythematous papules in child with acrodermatitis enteropathica because of zinc deficiency.

appendix. Selective celiac arteriography with serum sampling for glucagon also remains an important means of establishing the diagnosis.

Approximately 50 % of patients succumb to their disease within 5 years of diagnosis [26]. The majority of patients possess metastatic malignant islet cell tumors at the time of diagnosis. In fact, approximately 50–100 % of patients have metastasis [4, 6]. The liver is the most common site of metastasis. Other sites include peripancreatic lymph nodes, bone, adrenal glands, kidneys, and lungs [7]. Early recognition of the disease is difficult as these tumors are rare and aggressive, and the clinical manifestations including the rash often develop following metastases. One study showed that a diagnosis of glucagonoma was made a median of 4 years after the manifestation of NME or diabetes mellitus [26]. Adverse prognostic signs include the development of metastatic disease and weight loss.

Treatment is aimed toward curative surgical extirpation of the tumor. Subsequent drops in serum glucagon levels correlate with resolution of the dermatitis [17]. Metastatic and unresectable disease may be palliated with various chemotherapeutic agents including streptozotocin and 5-fluorouracil. Phase III trials of everolimus (mTOR inhibitor) and sunitinib (tyrosine kinase inhibitor) in low-grade metastatic pancreatic neuroendocrine tumors have shown some improvement in progression-free survival. Investigations into the use of temsirolimus (mTOR inhibitor) and bevacizumab (VEGF-A monoclonal antibody) are currently under way [27]. Clinical improvement of symptoms can in most instances be achieved with the administration of potent glucagon inhibitors such as octreotide. Parenteral administration of zinc, fatty acids, and amino acids has also proven useful in improvement of dermatoses [17].

References

1. Leichter SB. Clinical and metabolic aspects of glucagonoma. Medicine (Baltimore). 1980;59(2):100–13.
2. Hashizume T, et al. Glucagonoma syndrome. J Am Acad Dermatol. 1988;19(2 Pt 2):377–83.
3. Frankton S, Bloom SR. Gastrointestinal endocrine tumours. Glucagonomas Baillieres Clin Gastroenterol. 1996;10(4): 697–705.
4. van Beek AP, et al. The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. Eur J Endocrinol. 2004;151(5):531–7.
5. Lobo I, et al. Glucagonoma syndrome and necrolytic migratory erythema. Int J Dermatol. 2010;49(1):24–9.
6. Tierney EP, Badger J. Etiology and pathogenesis of necrolytic migratory erythema: review of the literature. MedGenMed. 2004;6(3):4.
7. Prout TM, Taylor AJ. Case of the season: glucagonoma syndrome. Semin Roentgenol. 2005;40(1):4–7.
8. Chastain MA. The glucagonoma syndrome: a review of its features and discussion of new perspectives. Am J Med Sci. 2001;321(5):306–20.
9. Boden G. Insulinoma and glucagonoma. Semin Oncol. 1987;14(3):253–62.
10. Doll DC. Necrolytic migratory erythema. Arch Dermatol. 1980;116(8):861–2.
11. Balachandran A, et al. Pancreatic neuroendocrine neoplasms: diagnosis and management. Abdom Imaging. 2013;38(2): 342–57.
12. Thorisdottir K, et al. Necrolytic migratory erythema: a report of three cases. J Am Acad Dermatol. 1994;30(2 Pt 2):324–9.
13. Lakdawala N, et al. The role of nutrition in dermatologic diseases: facts and controversies. Clin Dermatol. 2013;31(6): 677–700.
14. Sahoo MK, et al. Necrolytic migratory erythema associated with glucagonoma syndrome diagnosed by (6)(8) Ga-DOTANOC PET-CT. Asia Pac J Clin Oncol. 2014;10(2):190–3.
15. Goodenberger DM, et al. Necrolytic migratory erythema without glucagonoma. Arch Dermatol. 1979;115(12): 1429–32.
16. Halvorson SA, et al. Putting the pieces together: necrolytic migratory erythema and the glucagonoma syndrome. J Gen Intern Med. 2013;28(11):1525–9.
17. Fedeles F, et al. Nutrition and bullous skin diseases. Clin Dermatol. 2010;28(6):627–43.
18. Nakashima H, et al. Necrolytic migratory erythema without glucagonoma in a patient with short bowel syndrome. J Dermatol. 2006;33(8):557–62.
19. Mignogna MD, Fortuna G, Satriano AR. Small-cell lung cancer and necrolytic migratory erythema. N Engl J Med. 2008;359(25):2731–2.
20. Kheir SM, et al. Histologic variation in the skin lesions of the glucagonoma syndrome. Am J Surg Pathol. 1986;10(7):445–53.
21. Hendricks WM. Pellagra and pellagralike dermatoses: etiology, differential diagnosis, dermatopathology, and treatment. Semin Dermatol. 1991;10(4):282–92.
22. Stratigos JD, Katsambas A. Pellagra: a still existing disease. Br J Dermatol. 1977;96(1):99–106.

23. Wong PW, Pillai PM. Clinical and biochemical observations in two cases of hartnup disease. Arch Dis Child. 1966; 41(218):383–8.

24. Neldner KH, Hambidge KM, Walravens PA. Acrodermatitis enteropathica. Int J Dermatol. 1978;17(5):380–7.

25. Graves K, Kestenbaum T, Kalivas J. Hereditary acrodermatitis enteropathica in an adult. Arch Dermatol. 1980;116(5):562–4.

26. Wermers RA, et al. The glucagonoma syndrome. Clinical and pathologic features in 21 patients. Medicine (Baltimore). 1996;75(2):53–63.

27. Hobday TJ, et al. Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumors. J Clin Oncol. 2014;33(14):1551–6.

24
Pyoderma Gangrenosum

■	Synonym:	Geometric phagedenism
■	Associations:	Inflammatory bowel disease, arthritis, monoclonal gammopathy, hematologic malignancy
■	Clinical:	Painful expanding ulcer with violaceous undermined borders
■	Histopathology:	Ulceration with heavy surrounding neutrophilic infiltration and abscess formation and variable findings of vasculitis in established lesions
■	Prognosis:	Depends on severity, underlying disease
■	Treatment:	Prednisone, cyclosporine, infliximab (severe), topical class I steroids (mild, localized)

Current use of the term "geometric phagedenism" will result in confusion, unless the term is defined in relation to its word origin and historical meaning to dermatologists. In 1908, Louis Brocq used this term to refer to a series of patients with rapidly extending, destructive ulcers, often with circular, elliptical, or geometric edges. Using the term phagedenism (phageton [Greek] means consumption) emphasizes the destructive nature, the "consuming" of surrounding tissue. Brocq also included elegant descriptions and trends in morphology of ulcers, including the gradually sloping infiltrated and erythematous area external to the "ridge" (border of the active ulcer), the sharp, often undermined internal edge "dimpled by purulent cavities." Histopathology was noted to include a heavy neutrophilic infiltrate with extensive necrosis, and Brocq correctly noted the lack of transmissibility [1, 2].

This name was later changed by Brunsting to pyoderma gangrenosum (PG), a similarly descriptive yet somewhat misleading substitution. His 1930 case series noted a link to ulcerative colitis in 80 % of patients [3]. Despite implying an infectious nature to the condition, this title has maintained its hold in dermatologic literature throughout the years despite early evidence to the contrary. It has become obvious with time that the majority (50–70 %) of patients will have an underlying disease such as inflammatory bowel disease, arthritis, or hematologic disease. While there is speculation that bacterial antigens can play a role in pathogenesis [4], it is well-known that despite clinical and histopathological findings similar to that of infectious processes, pyoderma gangrenosum is not contagious and is not caused by a known human pathogen.

As mentioned, greater than half of patients will have an underlying disease (Table 24.1) [5, 6]. Inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis represent the most likely underlying cause overall, with 9–34 % of patients affected. Two percent of IBD patients will have PG. Rheumatoid and seronegative arthritis are also commonly associated. Hematologic disorders, including specifically IgA monoclonal gammopathy and acute myelogenous leukemia, also underlie pyoderma gangrenosum in a subset of patients [7]. PG is occasionally associated with infectious and autoimmune liver disease, connective tissue disease and systemic vasculitis, and diseases related to follicular occlusion. Drug causation occasionally results from the use of colony-stimulating factors, epidermal growth factor inhibitors, and interferon. Given difficulty establishing a definitive diagnosis of PG, skepticism with interpretation of anecdotal association is advised.

Most theories involving pathogenesis of pyoderma gangrenosum revolve around induction of lesions via uncontrolled immunologic activity in the lesional skin. Support for involvement of humoral immunity includes the presence of autoantibodies against the skin and bowel. Complement and immunoglobulin (often IgM) can be found in the vessels upon direct immunofluorescence (DIF) of the lesional skin, but results are inconsistent with a

TABLE 24.1. Conditions associated with pyoderma gangrenosum

Comorbidity	% associated
Inflammatory bowel disease	9–34 %
Hematologic malignancy	3–11 %
Monoclonal gammopathy	2–10 %
Arthritis (general)	18–30 %
Viral hepatitis	4–7 %
Diabetes	25–34 %
Solid organ tumors	2–8 %
Thyroid disease	11 %
Diverticulosis	0–4 %
Depression	20 %
Psoriasis	0–10 %
Peripheral vascular disease	30 %
Anemia	65 %
Positive antinuclear antibody	17 %
Leukocytosis	65 %
Autoimmune hepatitis	Uncommon
Systemic vasculitis	Uncommon
Gastric/duodenal ulcers	Uncommon
Hidradenitis suppurativa	Uncommon

significant minority of patients with negative DIF findings [8]. Leukocytoclastic vasculitis is found in some patients, usually adjacent to the edge or floor of the ulcer, leading most to the conclusion that it is a consequence of ulceration. However, findings of lymphocytic vasculitis early in the disease process lead some to believe that vasculitis is the preceding event that causes ulcer formation [9]. Some believe that immunologic cross-reactivity between antigens of gut flora and those of the skin, especially in cases associated with IBD, could play a role. Cell-mediated immunity certainly also plays a role, although again the explanation is an incomplete patchwork of research. Neutrophil and monocyte function can be impaired in some patients although the contribution to pathogenesis is debated [10, 11]. Delayed hypersensitivity to common antigens is absent in some patients. Interleukin-8 is overexpressed in the lesional skin,

which may attract high numbers of neutrophils. Induction of high levels of local IL-8 in mice resulted in an impressive match of pyoderma gangrenosum clinically and histopathologically [12].

Due to the relatively nonspecific histopathologic picture and variable clinical morphology, classification of pyoderma gangrenosum has been difficult and usually involves some attempt to categorize by either body distribution of involvement or morphologic features. Morphology and body location can occasionally give clues to the type and severity of underlying disease, thus reaching a consensus regarding classification would be beneficial (Table 24.2).

Classic ulcerative pyoderma gangrenosum, which is the most common type, usually presents as a papule or pustule which rapidly expands into an exquisitely painful ulcer with violaceous, undermined borders (Figs. 24.1 and 24.2). Proposed diagnostic criteria are based on these important features: compatible neutrophil-rich histology, exclusion of other causes, and response to corticosteroid therapy. This form is often localized to the lower extremities (>50 %) and associated with inflammatory bowel disease. A review of 30 case reports revealed variable presence of pathergy (50 %), pustules (17 %), purulent discharge (20 %), undermined borders (30 %), and cribriform scarring (7 %), indicating that no clinical finding is pathognomonic [13].

References to "atypical PG" allow all other types of PG which do not fit the mold of classic ulcerative PG to be separated into a group which includes disease of atypical distribution and morphology and includes the following entities. Pustular PG is marked by the acute eruption of painful pustules on the extensor extremities with flares of IBD. Bullous PG presents with hemorrhagic bullae on the arms, often in the setting of underlying hematologic disease. Atypical PG also refers to a variant occurring on the arms and face, often forming violaceous plaques, often without ulceration or bullae, with marked overlap with Sweet's syndrome and neutrophilic dermatosis of the

TABLE 24.2. Subtypes of pyoderma gangrenosum

PG subtype	Morphologic features	Distribution	Associations	Comments
Classic/ulcerative	Expanding ulcer	70 % lower extremities	IBD, arthritis, monoclonal gammopathy, internal malignancy	25 % pathergy
Pustular PG	Painful pustules, halo of erythema	Extensor aspect of the limbs	During acute IBD flares	
Bullous PG	Superficial hemorrhagic bullae	Arms (commonly)	Myeloproliferative disease or acute IBD flare	
Atypical PG	Variable; bullous	Dorsal hands, trunk, face	Myelogenous leukemia, IgA gammopathy	Difficult to differentiate from Sweet's syndrome
Superficial PG (vegetative)	Solitary, nonpainful superficial expanding ulcer	Trunk, face > other sites	Not commonly associated with underlying disease	
Peristomal PG	Expanding ulcer	Circumferentially around stoma sites	IBD ≫ other associations	15 % of cases
Pyostomatitis vegetans	Multiple pustules, "snail track" ulcers on oral mucosa	Oral mucosa, often sparing the tongue	IBD, acute flares	Early pathology shows eosinophils ≫ neutrophils

FIGURE 24.1. Pyoderma gangrenosum: ulcer with purulent base and undermined, violaceous border.
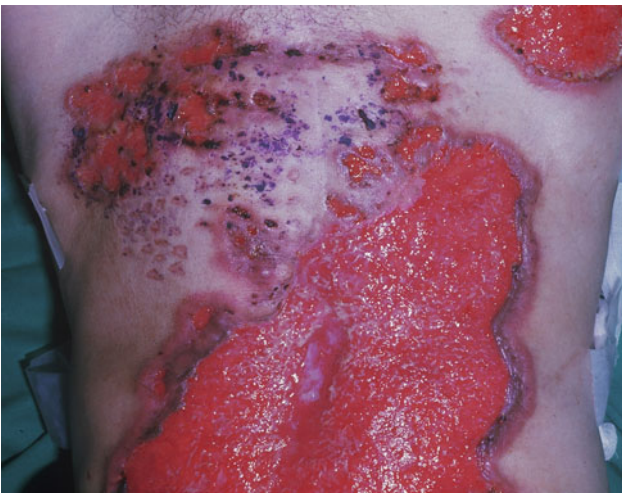
FIGURE 24.2. Pyoderma gangrenosum: multiple discrete pustules coalescing into broad ulcerations.

dorsal hands, and marked association with underlying hematologic disease [14, 15]. Site-specific subtypes including peristomal, genital, breast, and facial PG have been described. It is debatable whether the so-called vegetative PG (otherwise known as superficial granulomatous pyoderma) and pyostomatitis vegetans represent PG subtypes or distinct entities, although their classification varies depending on author's opinion. Given significant clinical and histopathological difference between pyostomatitis vegetans and all other PG subtypes, most consider this a separate entity.

Morbidity from ulcerations extends beyond concerns regarding ulcer pain and infection risk. Complications including osteomyelitis, Achilles tendon rupture, cicatricial entropion, splenic abscesses, saddle nose deformity, and pulmonary involvement lead to a mortality rate that is three times that of the general population [16]. However, the tendency toward potentially lethal underlying disease and immunosuppressive treatments likely boosts mortality

rate far more than that caused by complications of PG alone.

Histopathology reveals ulceration of variable depth and extensive surrounding neutrophil infiltration, at times forming abscesses (Figs. 24.3 and 24.4). Subcorneal pustules may be present at the periphery of ulcers or in early lesions. Leukocytoclastic vasculitis adjacent to margins of the ulcer is not uncommon, but it is rarely seen in early lesions. Giant cell accumulation, when present, can be indicative of association with inflammatory bowel disease [17]. Acute and chronic inflammatory infiltrate in the surrounding reticular dermis is usually present, which is where the entire process is usually centered. Pertinent negatives include lack of bacterial or fungal organisms and lack of a significant degree of leukocytoclasis.

Pyoderma gangrenosum is a diagnosis of exclusion. The most important group to definitively exclude is infectious diseases which can present in a similar fashion. Adding to the confusion, secondary infection can occur in established pyoderma gangrenosum lesions. A study of 23 patients admitted for pyoderma gangrenosum found *Staphylococcus aureus* and *Pseudomonas aeruginosa* surface and tissue culture positivity to be high (>50% of specimens for each organism), although colony-forming units were not quantified and some degree of surface colonization is to be expected [18]. Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes* can also cause ecthyma, which can appear similar to early ulcerative pyoderma gangrenosum. Sending a sizable specimen for ground tissue culture is often necessary to rule out clinically significant infection with some degree of certainty. Necrotizing fasciitis of any cause can have some features in common histologically, although inflammation is usually at the subcutaneous layer or deeper with a greater degree of necrosis. Numerous bacterial organisms are also a conspicuous feature. The so-called "neutrophilic dermatoses" (of which pyoderma gangrenosum is a member) have clinical and histologic overlap with PG. Sweet's syndrome has overlapping histology, clinical features, subtypes, systemic disease associations, and (fortunately) treatments. The lack of epidermal involvement, edema of the papillary dermis, and marked leukocytoclasia are all supportive of a diagnosis of Sweet's syndrome [19].

Treatment is complicated and fraught with complications, although immunosuppression or treatment of underlying condition (or both) is the cornerstone of success. Oral glucocorticoids such as prednisone are rapid acting and successful in the vast majority of cases, starting at a dose of approximately 1 mg/kg/day and slowly tapering with improvement. Severe progressive disease may require pulse IV methylprednisolone, usually with a starting dose of 1 g daily for 3–5 days [20]. Severe disease may also be controlled with rapidly acting steroid-sparing agents such as cyclosporine or infliximab. Cyclosporine dosage is higher
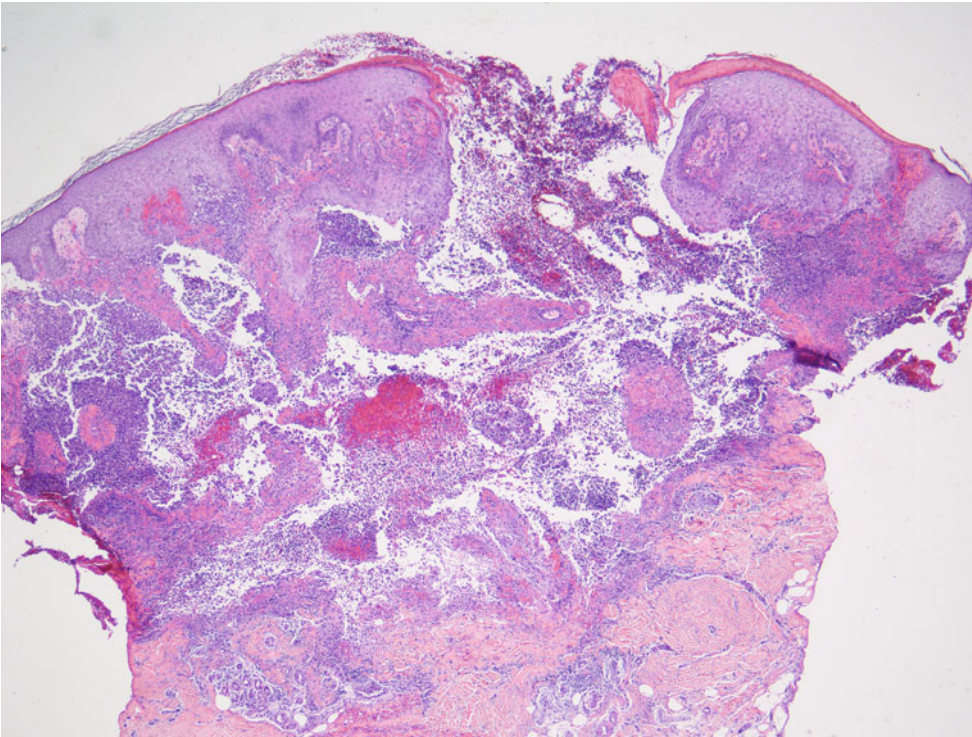
FIGURE 24.3. Pyoderma gangrenosum, 4× magnification: ulcer with dense dermal inflammation.
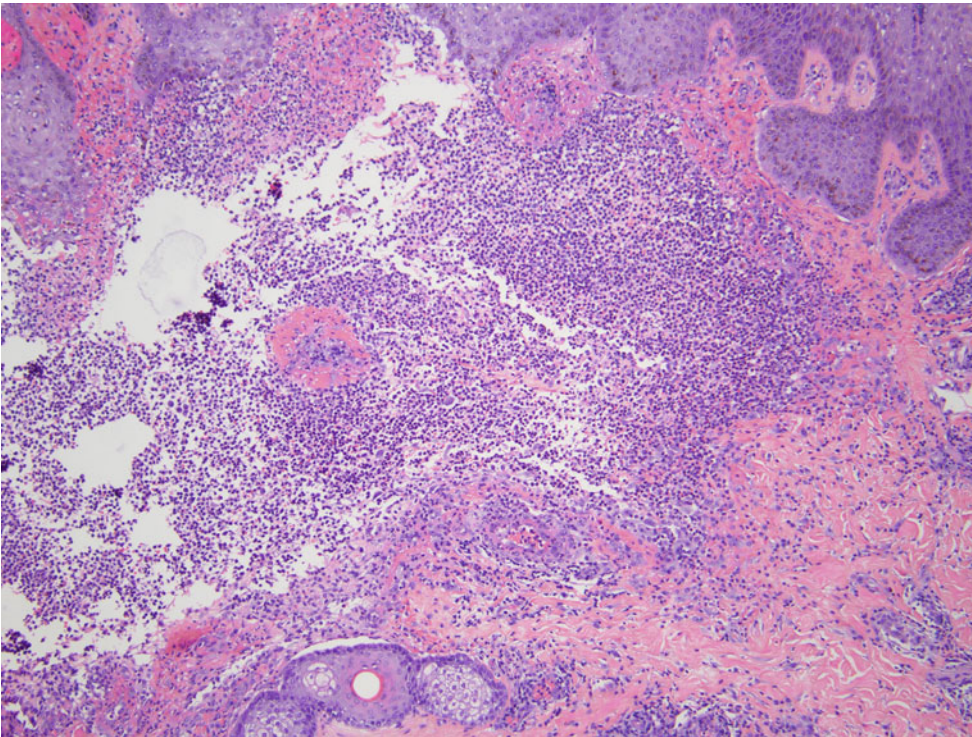
FIGURE 24.4. Pyoderma gangrenosum, 20× magnification: dermal abscess formation with foci of neutrophilic vasculitis.

than that used in psoriasis, with maximum dosage used at 10 mg/kg/day [21]. Infliximab at a dose of 5 mg/kg has been demonstrated to be effective in one of the few placebo-controlled trials performed in the context of pyoderma

gangrenosum. Response of treatment of PG with the other anti-TNF-alpha agents is generally encouraging, with one study reflecting a 92 % response rate in 34 inflammatory bowel disease patients treated with either infliximab or

adalimumab [22]. Other steroid-sparing agents are used with some degree of frequency for pyoderma gangrenosum including mycophenolate mofetil, cyclophosphamide, azathioprine, and methotrexate [23], although mycophenolate mofetil has a relatively benign side-effect profile and the most literature support [24, 25].

In patients in which treatments with lower degrees of toxicity are desired, there are a few reasonable options. Topical treatment with high-potency topical corticosteroids or topical tacrolimus has been shown to be effective in localized PG, with tacrolimus being comparable to clobetasol [26]. Intralesional triamcinolone shows efficacy, although pain with injection can be severe. Dapsone and sulfasalazine have shown benefit, likely due to effects on neutrophil chemotaxis [27]. Effective dosage of dapsone varies and depends to some degree on disease severity. Minocycline has also been shown to be surprisingly effective in seven patients, with relatively rapid onset [28]. Hyperbaric oxygen therapy can be effective in reduction in ulcer size and pain reduction, but most anecdotal evidence supports its use as an adjunctive treatment rather than monotherapy [29].

References

1. Brocq L. A new contribution to the study of geometric phagedenism. Ann Dermatol Syphiligy (Paris). 1916:1–39.
2. Farhi D. The clinical and histopathological description of geometric phagedenism (pyoderma gangrenosum) by Louis Brocq one century ago. Arch Dermatol. 2008;144(6): 755.
3. Brunsting LA, Goeckerman WH, O'Leary PA. Pyoderma (ecthyma) gangrenosum. Clinical and experimental observations in five cases occurring in adults. Arch Derm Syphilol. 1930;22:655–80.
4. Marks DJB, Rahman FZ, Yu RC, McCartney S, Bloom S, Segal AW. An exuberant inflammatory response to E coli: implications for the pathogenesis of ulcerative colitis and pyoderma gangrenosum. Gut. 2006;55(11):1662–3.
5. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. Br J Dermatol. 2011;165(6):1244–50.
6. Al Ghazal P, Herberger K, Schaller K, et al. Associated factors and comorbidities in patients with pyoderma gangrenosum in Germany: a retrospective multicentric analysis in 259 patients. Orphanet J Rare Dis. 2013;8:136.
7. Von den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. Br J Dermatol. 1997;137(6):1000–5.
8. Powell FC, Schroeter AL, Perry HO, Su WP. Direct immunofluorescence in pyoderma gangrenosum. Br J Dermatol. 1983;108(3):287–93.
9. Su WP, Schroeter AL, Perry HA, Powell FC. Histopathologic and immunopathologic study of pyoderma gangrenosum. J Cutan Pathol. 1986;13(5):323–30.

10. Nerella P, Daniela A, Guido M, Fabbri P. Leukocyte chemotaxis and pyoderma gangrenosum. Int J Dermatol. 1985;24(1):45–7.
11. Norris DA, Weston WL, Thome G, Humbert JR. Pyoderma gangrenosum. Abnormal monocyte function corrected in vitro with hydrocortisone. Arch Dermatol. 1978;114(6):906–11.
12. Oka M, Berking C, Nesbit M, et al. Interleukin-8 overexpression is present in pyoderma gangrenosum ulcers and leads to ulcer formation in human skin xenografts. Lab Invest. 2000;80:595–604.
13. Hadi A, Lebwohl M. Clinical features of pyoderma gangrenosum and current diagnostic trends. JAAD. 2011;64:950–4.
14. Callen JP, Jackson JM. Pyoderma gangrenosum: an update. Rheum Dis Clin North Am. 2007;33:787–802.
15. Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. Expert Rev Dermatol. 2006;1:391–401.
16. Langan SM, Groves RW, Card TR, Gulliform MC. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. J Invest Dermatol. 2012;132(9):2166–70.
17. Sanders S, Tahan SR, Kwan T, et al. Giant cells in pyoderma gangrenosum. J Cutan Pathol. 2001;28:97–100.
18. Saracino A, Kelly R, Liew D, Chong A. Pyoderma gangrenosum requiring inpatient management: a report of 26 cases with follow up. Australas J Dermatol. 2011;52(3):218–21.
19. Sitjas D, Puig L, Cuatrecasas M, de Moragas JM. Acute febrile neutrophilic dermatosis (Sweet's syndrome). Int J Dermatol. 1993;32:261–8.
20. Johnson RB, Lazarus GS. Therapeutic efficacy in the treatment of pyoderma gangrenosum. Arch Dermatol. 1982;118:76–84.
21. Elgart G, et al. Treatment of pyoderma gangrenosum with cyclosporine: results in seven patients. J Am Acad Dermatol. 1991;24:83–6.
22. Agarwal A, Andrews JM. Systemic review: IBD-associated pyoderma gangrenosum in the biologic era, the response to therapy. Aliment Pharmacol Ther. 2013;38(6):563–72.
23. Al Ghazal P, Dissemond J. Therapy of pyoderma gangrenosum in Germany: results of a survey among wound experts. J Dtsch Dermatol Ges. 2015;13(4):317–24.
24. Li J, Kelly R. Treatment of pyoderma gangrenosum with mycophenolate mofetil as a steroid-sparing agent. J Am Acad Dermatol. 2013;69(4):565–9.
25. Eaton PA, Callen JP. Mycophenolate mofetil as therapy for pyoderma gangrenosum. Arch Dermatol. 2009;145(7):781–5.
26. Lyon CC, et al. Topical tacrolimus in the management of peristomal pyoderma gangrenosum. J Dermatolog Treat. 2001;12:13–7.
27. Lorincz AL, Pearson RW. Sulfapyridine and sulphone-type drugs in dermatology. Arch Dermatol. 1962;85:42–56.
28. Berth-Jones J, Tan SV, Graham-Brown RA, Pembroke AC. The successful use of minocycline in pyoderma ganagrenosum-a report of seven cases and review of the literature. J Dermatol Treat. 1989;1:23–5.
29. Mazokopakis EE, et al. Improvement of ulcerative pyoderma gangrenosum with hyperbaric oxygen therapy. Dermatol Ther. 2011;24(1):134–6.

Part IV
Drug Eruptions

25
Eruptive Xanthoma

■ Synonym:	Diabetic xanthoma, xanthoma diabeticorum
■ Etiology:	Serum hypertriglyceridemia and/or elevated VLDL
■ Associations:	Diabetes mellitus, oral estrogens, acute ethanol ingestion, lipoprotein lipase deficiency, Apo-CII deficiency, type IV/V hyperlipoproteinemia, chylomicronemia syndrome, pregnancy, nephrotic syndrome, hypothyroidism, HIV infection, Cushing's syndrome, acute spinal cord injury, systemic lupus erythematosus (SLE), intravenous miconazole, oral 13-*cis*-retinoic acid, olanzapine, protease inhibitors, steroids, tamoxifen, thiazides, non-cardioselective beta-blockers
■ Clinical:	Crops of red-yellow papules on the buttocks and thighs
■ Histology:	Normal epithelium, early-perivascular lipid and neutrophils, later perivascular histiocytes, and foam cells seen
■ IHC repertoire:	N/A
■ Staging:	None
■ Prognosis:	5 % mortality
■ Adverse variables:	Acute pancreatitis, serum triglycerides >2000 mg/dL
■ Treatment:	Dietary modification, weight loss, exercise, fibrates, statins

Eruptive xanthoma (EX) is a distinct cutaneous entity that most commonly manifests in the skin following a severe systemic dyslipidemia. Although the dermatologic manifestations are not in themselves serious, their presence may be the harbinger of serious visceral disease. EX is an uncommon disease with a near equal gender incidence, principally seen in two age groups with different predisposing factors. Elevated serum triglyceride levels and/or very low-density lipoproteins (VLDL) appear to be a common underlying feature in both age groups. Primary causes occur more often among children and young adults. They include genetic disturbances in lipid metabolism like *lipoprotein lipase deficiency* and types I and V hyperlipoproteinemias [1]. Secondary causes are observed more in older adults, such as acute ethanol ingestion and endocrinologic disturbances including hypothyroidism and diabetes mellitus.

Products of fat acquired during digestion, including triglycerides, are packaged into a composite with apolipoprotein B-48 (Apo-B48) to produce nascent chylomicrons.

This packaging process is mediated by microsomal triglyceride transfer protein (MTP). The apolipoproteins are critical in the metabolism of the chylomicrons. Chylomicrons are synthesized in the intestine and circulated in the serum. In the serum, they acquire apolipoproteins C and E and cholesteryl esters from serum high-density lipoproteins (HDL). While circulating, the chylomicrons pass off triglycerides to the peripheral tissue endothelial capillaries via the enzymatic action of lipoprotein lipase (LPL) and the binding of cofactor apolipoprotein CII. Cholesterol-rich chylomicron remnants return to the liver via apolipoprotein E receptors or low density lipoprotein (LDL)-receptor-like protein (LRP) receptors for metabolic breakdown. VLDL particles are synthesized in the liver and complexed with Apo-B100 to perform a similar function as chylomicrons in delivering triglycerides to peripheral tissues and returning to the liver for breakdown [2].

In primary hyperlipidemia syndromes, these lipids are markedly elevated in the serum due to a directly inherited

consequence of faulty lipid metabolism. Lipoprotein lipase deficiency and Apo-CII deficiency are two etiologies that can produce chylomicronemia syndrome (Fredrickson type I). Both are autosomal recessive disorders that arise during childhood and result in eruptive xanthomatous skin manifestations [2]. Chylomicronemia syndrome is defined as triglyceride levels that exceed 1000 mg/dL and includes at least one of the following: eruptive xanthomas, lipemia retinalis, or abdominal findings (abdominal pain, acute pancreatitis, and/or hepatosplenomegaly) [3].

Types IV and V hyperlipoproteinemias are also associated with EX. These have a later age of onset, usually during adulthood [2]. Type V hyperlipoproteinemia is the most common hereditary-mediated cause of EX and is inherited as an autosomal dominant trait. It presents as a combined elevation of chylomicrons and VLDL [3, 4]. This disorder is aggravated by secondary acquired factors such as obesity, which is known to be associated with elevated VLDL levels and insulin resistance. Insulin resistance and diabetes mellitus are also associated with defective lipolysis of chylomicrons and VLDL [3, 5, 6].

Secondary causes of hyperlipidemia and hypercholesterolemia include hypothyroidism, excessive ethanol consumption, metabolic syndrome, HIV infection, nephrotic syndrome, Cushing's syndrome, acute spinal cord injury, and even systemic lupus erythematosus [3]. Multiple myeloma can produce chylomicronemia syndrome via immunoglobulin-lipoprotein complexes disrupting lipoprotein metabolism [7]. Certain medications have also been associated, including miconazole, isotretinoin, olanzapine, protease inhibitors (ritonavir and lopinavir), corticosteroids, oral estrogens, tamoxifen, cyclophosphamide, non-cardioselective beta-blockers, thiazides, and bile-acid binding resins [8–11]. Pregnancy can affect the dynamics of liver lipoprotein synthesis, resulting in a plasma triglyceride level increase of up to three times the normal [11, 12].

EX presents as 1-mm to 4-mm reddish-yellow papules on the buttocks or extensor surfaces of the thighs and arms (Fig. 25.1) [13]. The lesions may be surrounded by an erythematous halo and usually occur in crops that may coalesce, forming plaques. Their presence is indicative of a triglyceride level that typically exceeds 2000 mg/dL. Among 95 patients studied with triglyceride levels greater than 20 mM (1772 mg/dL), 8.5% exhibited eruptive xanthomas. Curiously, the average triglyceride level for those expressing eruptive xanthomas (6007 mg/dL) was considerably higher than the average level of those with a history of pancreatitis (3376 mg/dL) [14]. Eruptive xanthomas can take on a linear appearance in response to trauma or scratching due to Koebner's isomorphic reaction [15]. A Wolf's isotopic response has also been described in which eruptive xanthomas developed at sites of previous herpes zoster eruption [16].

FIGURE 25.1. Orange-yellow grouped papules on the buttocks of a patient with eruptive xanthoma.

The pathogenesis of the skin lesions and associated visceral findings relate to the presence of intravascular lipid as well as the escape of lipids from the circulation, evoked inflammation, and resulting foam cell formation. Marked elevation in intravascular lipids may induce platelet clumping and vascular plugging as observed in the retinal artery and the complications of *lipemia retinalis*, capable of inducing blindness. Extravascular lipids may incite acute inflammation that, in conjunction with the lipid itself, produces free radical and oxidant-mediated cell membrane destruction. In time, the extravascular lipid is scavenged by histiocytes forming foam cells. A relevant receptor-independent mechanism of macrophage lipid uptake is fluid-phase pinocytosis [17]. Free cholesterol undergoes reesterification to cholesteryl fatty acid esters by enzyme acyl-CoA creating foam cells [18].

These mechanisms underlie the formation of the typical cutaneous lesions and the development of the most important systemic complication of *acute pancreatitis*. The risk for acute pancreatitis rises precipitously when triglyceride levels exceed 2000 mg/dL. One study showed that approximately 15.8% of patients with triglyceride

levels above 20 mM (1772 mg/dL) had a history of pancreatitis [14].

Other clinical stigmata of EX include ocular, abdominal, and pulmonary findings. The most important ophthalmic complication is lipemia retinalis. On fundoscopic examination, the retinal arteries and veins appear white and engorged with a salmon-pink retina. The appearance of the retinal vessels is due to the triglycerides in the plasma scattering light. Early signs of lipemia retinalis occur in the peripheral retina. At triglyceride levels between 2500 and 3499 mg/dL, these peripheral vessels are creamy and thin. As levels increase to between 3500 and 5000, posterior retinal vessels take on a creamy color. Above 5000 mg/dL, the characteristic features occur: the salmon-colored fundus with creamy arteries and veins. Other ocular manifestations include lipemic aqueous, corneal arcus, xanthelasma, and palpebral xanthomas. Retinal blood vessel sludging and vein occlusion have also been described [19]. Abdominal pain is a common accompaniment toEX. The source of the pain may be due to acute pancreatitis or hepatosplenomegaly. Chest pain or dyspnea may also occur due to decreased pulmonary oxygen diffusing capacity that may be aggravated by abnormal hemoglobin oxygen affinity. The natural history of the cutaneous lesions is gradual resolution with successful treatment within 6–8 weeks of instituting therapy.

The histologic changes of EX are often subtle, particularly in early lesions [20]. The changes principally involve the dermal capillaries and perivascular tissue and consist of initial accumulations of neutrophils that in time are replaced by lymphocytes and histiocytes, including foam cells (Figs. 25.2, 25.3, and 25.4). Extravascular lipid or fibrin may be identified as a granular precipitate seen within the vicinity of the blood vessels.

The prognosis of EX is generally favorable with prompt recognition and institution of therapy [13, 21]. Delayed diagnosis, marked elevation of serum triglycerides, or acute pancreatitis is associated with a worse prognosis. In its initial setting, acute pancreatitis constitutes the most important cause of mortality with an overall rate of 5 %. Approximately 20 % of patients with acute pancreatitis have severe cases. Of those with severe acute pancreatitis, the morality rate is between 10 and 30 % [22]. Therapy should be aimed at measures that reduce serum levels of triglyceride and/or VLDL and that palliate complications of EX or its disease associations such as diabetes mellitus, obesity, or ethanolism [13, 14]. Nonpharmacologic approaches include weight reduction, dietary modification, and exercise. The National Cholesterol Education Program recommends a diet composed of 55–60 % carbohydrates, 15–20 % proteins, and no more than 30 % total fat or 7 % saturated fat. A consumption of 4 g of omega-3 fatty acids daily
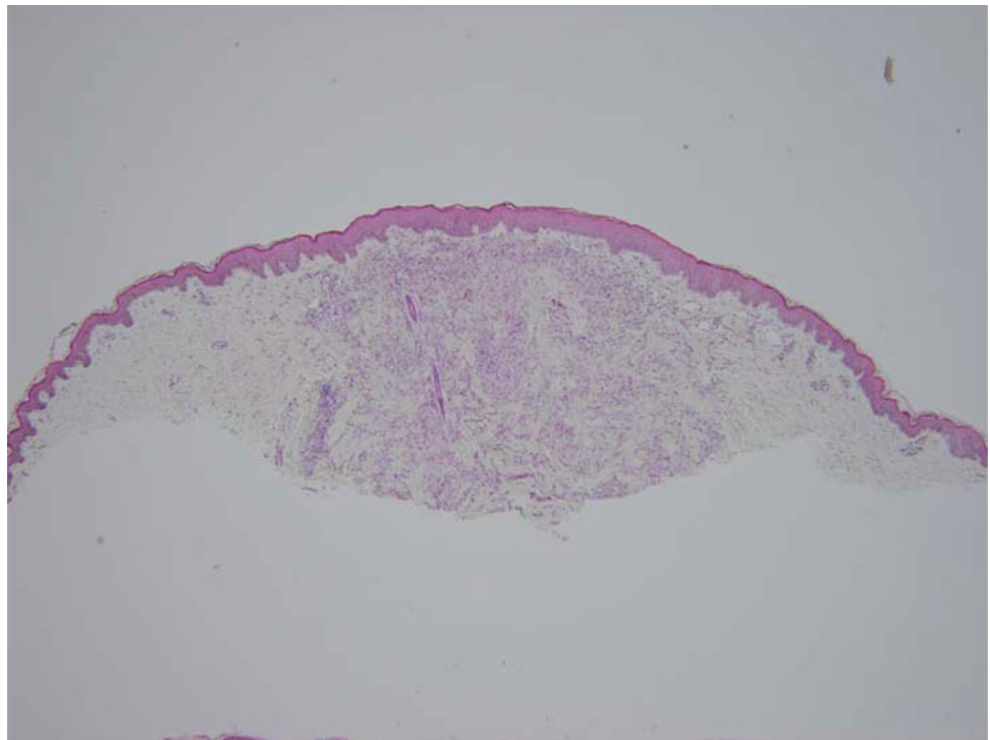
FIGURE 25.2. Dome-shaped papule with dermal inflammatory infiltrate.
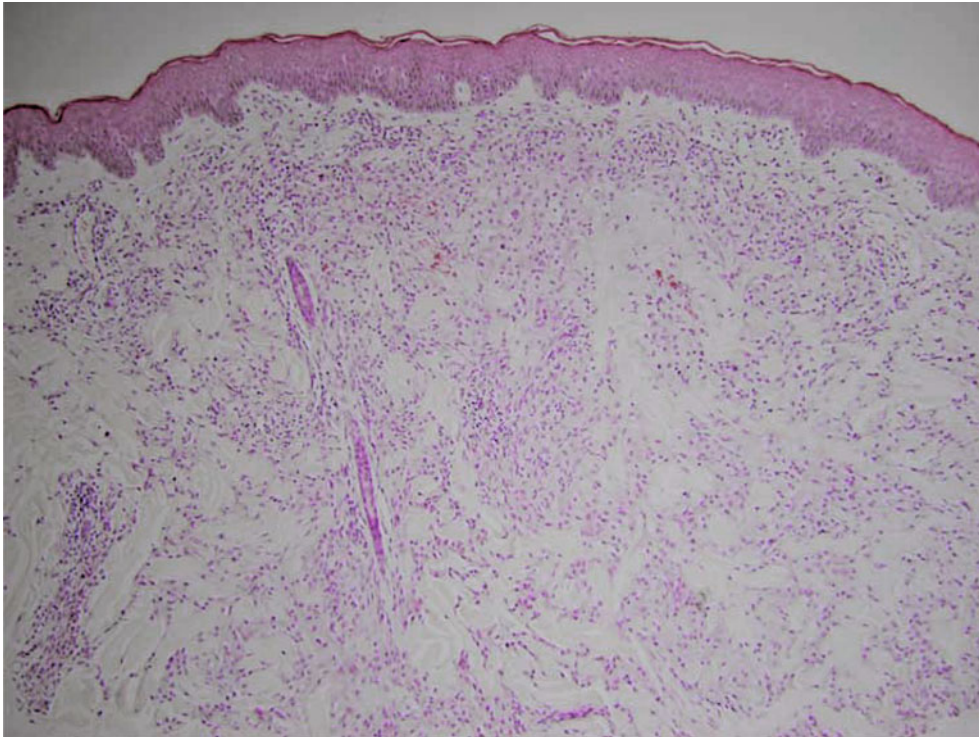
FIGURE 25.3. Medium-power photomicrograph depicting perivascular and interstitial inflammatory infiltrates.
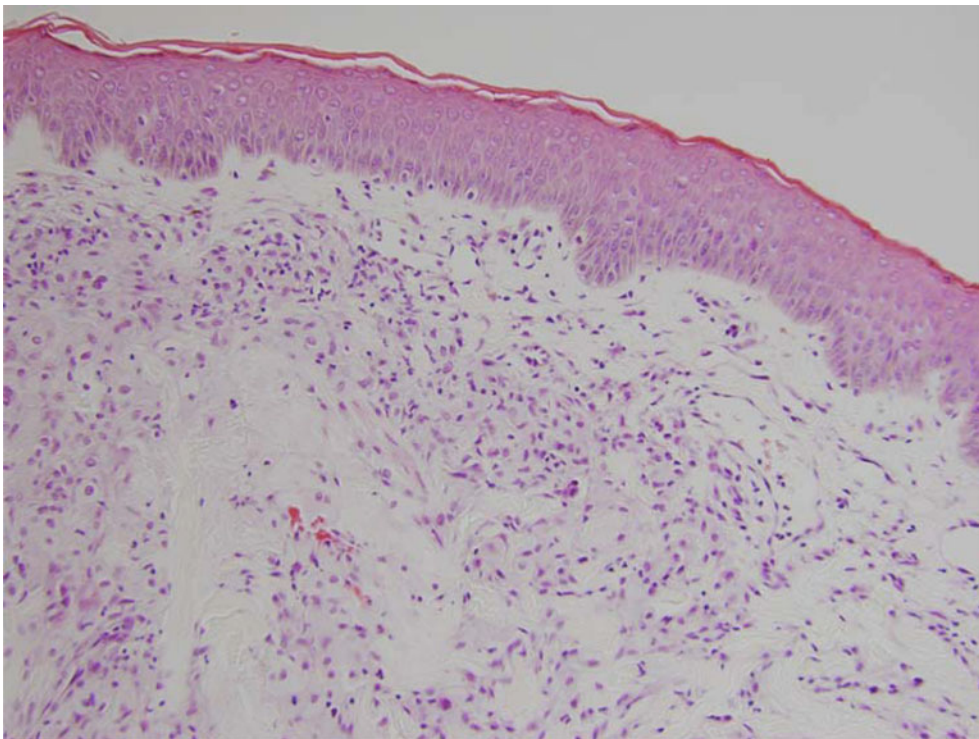
FIGURE 25.4. High-power detail with perivascular foamy histiocytes and neutrophils.

has been shown to lower plasma triglycerides as much as 20 %. Pharmacologic treatments include fibrates and statins [11]. Plasmapheresis has been used to reduce serum chylomicrons, although its effects on morbidity and mortality are unknown thus far [21].

References

1. Parker F. Xanthomas and hyperlipidemias. J Am Acad Dermatol. 1985;13(1):1–30.
2. Ranjan N. Management of hyperlipidemias: an update. Indian J Dermatol Venereol Leprol. 2009;75(5):452–62.
3. Leaf DA. Chylomicronemia and the chylomicronemia syndrome: a practical approach to management. Am J Med. 2008;121(1):10–2.
4. Archer CB, MacDonald DM. Eruptive xanthomata in type V hyperlipoproteinaemia associated with diabetes mellitus. Clin Exp Dermatol. 1984;9(3):312–6.
5. Brunzell JD, Bierman EL. Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia. Med Clin North Am. 1982;66(2):455–68.
6. Vermeer BJ, et al. Xanthomatosis and other clinical findings in patients with elevated levels of very low density lipoproteins. Br J Dermatol. 1979;100(6):657–66.
7. Burnside NJ, et al. Type III hyperlipoproteinemia with xanthomas and multiple myeloma. J Am Acad Dermatol. 2005;53(5 Suppl 1):S281–4.
8. Barr RJ, Fujita WH, Graham JH. Eruptive xanthomas associated with intravenous miconazole therapy. Arch Dermatol. 1978;114(10):1544–5.
9. Dicken CH, Connolly SM. Eruptive xanthomas associated with isotretinoin (13-cis-retinoic acid). Arch Dermatol. 1980;116(8):951–2.
10. Chang HY, et al. Eruptive xanthomas associated with olanzapine use. Arch Dermatol. 2003;139(8):1045–8.
11. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ. 2007;176(8): 1113–20.
12. Jaber PW, et al. Eruptive xanthomas during pregnancy. J Am Acad Dermatol. 1992;27(2 Pt 2):300–2.
13. Maher-Wiese VL, Marmer EL, Grant-Kels JM. Xanthomas and the inherited hyperlipoproteinemias in children and adolescents. Pediatr Dermatol. 1990;7(3):166–73.
14. Sandhu S, et al. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: a retrospective cohort study. Lipids Health Dis. 2011;10:157.
15. Loeckermann S, Braun-Falco M. Eruptive xanthomas in association with metabolic syndrome. Clin Exp Dermatol. 2010;35(5):565–6.
16. Li CN, Lee WR, Tseng JT. Dystrophic xanthomatization as a type of Wolf's isotopic response: eruptive xanthomata at a herpes zoster site. J Am Acad Dermatol. 2013;68(2):e53–5.
17. Kruth HS. Receptor-independent fluid-phase pinocytosis mechanisms for induction of foam cell formation with native low-density lipoprotein particles. Curr Opin Lipidol. 2011;22(5):386–93.
18. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell. 2011;145(3):341–55.
19. Zahavi A, Snir M, Kella YR. Lipemia retinalis: case report and review of the literature. J AAPOS. 2013;17(1):110–1.
20. Cooper PH. Eruptive xanthoma: a microscopic simulant of granuloma annulare. J Cutan Pathol. 1986;13(3):207–15.
21. Valdivielso P, Ramirez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med. 2014;25(8):689–94.
22. Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med. 2006;354(20):2142–50.

26
Toxic Epidermal Necrolysis

- Synonyms: Lyell syndrome
- Etiology: Response to medication, infection
- Associations: AIDS, certain Human leukocyte Antigen [HLA] types
- Clinical: Flat atypical targets, widespread dusky patches, and denudation of the skin
- Histology: Full-thickness epidermal necrosis with minimal inflammation
- IHC: None
- Prognosis: Dependent on several clinical variables
- Treatment: Meticulous wound care, cessation of causative medication

When multiple entities in a "spectrum" of disease are described in vastly different periods of time, with vastly different available technology, confusion and debate regarding classification is the rule. This is never more apparent than in the setting of drug or infection-induced "acute skin failure." Epidermal necrosis, usually full-thickness, involves a variable proportion of the skin surface and is usually associated with an underlying stimulus. Necrosis can be restricted to the center of a classic target lesion or a rapid assault of the entire skin and mucosal surface can occur, resulting in death. The main source of confusion is that although there are differences between entities caused predominantly by infections (erythema multiforme [EM] spectrum) and those caused predominantly by drugs (Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]), there can be considerable overlap. Added to this clinical overlap is histologic overlap, although the degree of inflammation and epidermal necrosis are cited as potential differentiating factors.

Ferdinand von Hebra described erythema multiforme (EM) in 1866 in his treatise "On Disease of the Skin." A half-century later, classification became more complicated. In 1922, Stevens and Johnson described two children with a severe condition associated with severe mucous membrane disease, which eventually became known as Stevens-Johnson syndrome (SJS) [1]. A 1950 attempt at classification allowed the term erythema multiforme major to develop, which at the time was synonymous with SJS [2]. Lyell described four cases of a severe generalized "scalding" condition which he named toxic epidermal necrolysis (TEN) in 1956 [3]. This condition will be the focus of this chapter, although relationship between these entities deserves further discussion.

Current classification is based mainly on clinical criteria, and the EM group (erythema multiforme minor and erythema multiforme major) is separated from the SJS/TEN group on the basis of perceived differences in etiology [4]. Some believe that the presence of raised versus flat targetoid lesions can also differentiate these two groups [5]. The SJS/TEN group, classically drug-induced, is further divided into SJS, SJS/TEN overlap, and TEN based on the percent of body surface involvement. The classifications can be summarized (Table 26.1), but differentiation clinically can be difficult, particularly when initial presentation occurs in the mucous membranes without early skin involvement.

Pathogenesis is likely through overlapping mechanisms. Fas-Fas ligand interactions between cytotoxic T lymphocytes and keratinocytes are thought to allow caspase-mediated apoptosis. Fas ligand can be upregulated by medications and can mediate cell death in keratinocytes which express the Fas "death receptor" at baseline. Cytotoxic T lymphocytes may also produce local mediators such as perforin and granzymes, which allow for the penetration and induction of the apoptosis of keratinocytes, respectively. In addition, the possibility of widespread release of granulysin from T and NK cells can cause widespread apoptosis without the need for proximity to keratinocytes. The role of tumor necrosis factor in the induction of keratinocyte necrosis via caspase activation is a tantalizing treatment target, although requires further review [6].

TABLE 26.1. Classification and features of erythema multiforme, SJS, and TEN

Criteria	EM minor	EM major	SJS	SJS/TEN overlap	TEN
% skin involvement	<10%	<10%	<10%	10–30%	>30%
Distribution	Extremities	Extremities	Trunk, face, neck	Trunk, face, neck	Widespread
Typical target lesions	Present	Present	Absent	Absent	Absent
Atypical target lesions	Raised	Raised	Flat	Flat	Flat
Macules	Absent	Absent	Present	Present	Present when scattered
Mucous membranes	1–2 involved	Multiple sites	Multiple sites	Multiple sites	Multiple sites
Cause (majority)	Infections: herpes simplex virus [HSV], parvovirus	Infections: mycoplasma, HSV	Drugs	Drugs	Drugs

The most common pharmacologic causes of SJS/TEN include allopurinol, the aromatic anticonvulsants such as phenytoin, carbamazepine, and barbiturates, antibiotic sulfonamides, lamotrigine, nevirapine, and oxicam nonsteroidal anti-inflammatory drugs (NSAIDs). To a lesser extent, most beta-lactam antibiotics have been implicated in the causation of SJS/TEN, as have macrolide and fluoroquinolone antibiotics [7]. Drug exposure usually precedes the onset of disease by 1–4 weeks with first exposure, with shorter latency on rechallenge, and occurrence of SJS/TEN after more than 2 months of therapy with a particular drug is quite rare. Risk of administration also varies based on the features of the individual patient. Certain HLA types predispose to higher risk, including an elevated risk with HLA-B*5801 and allopurinol-induced SJS/TEN and HLA-B*1502 and aromatic anticonvulsant-induced SJS/TEN. The latter allele is more prevalent in those of Asian ancestry (10%) [8]. Patients with AIDS are at higher risk for SJS/TEN and other severe drug reactions, with some studies indicating the risk increases 1000-fold [9]. Tendency for prophylactic use of trimethoprim/sulfamethoxazole as well as direct implication of antiretroviral therapy as causative agents may inflate these figures beyond any increased risk related to HIV itself. However, it is thought that loss of regulatory T cells as a consequence of HIV infection may predispose these patients to SJS/TEN [10].

Symptoms of early SJS/TEN are quite nonspecific and consist of high fevers, myalgia, and malaise. A few days later, mucosal symptoms develop. Ocular findings such as pruritus, photophobia, conjunctival injection, and oral mucosa pain with chewing and swallowing can be a red flag for impending skin disease. Ocular disease is absent in 20% of patients. This progression is not without variability, and skin disease develops prior to mucosal disease in 20% of patients. Morphology and color of skin lesions reflect the degree of epidermal necrosis and stage of disease to the adept clinician. Early lesions are usually flat, pink, and variably extensive, with tendency to involve the face and trunk. When distribution is scattered, lesions can be round and can have a vaguely targetoid appearance (Fig. 26.1). As necrosis of individual keratinocytes progresses to full-thickness cell death, skin pain increases and lesions take on a dusky red to violaceous hue (Fig. 26.2). This change takes

FIGURE 26.1. Early, individual lesion of SJS with flat targetoid morphology with the central vesicle.


FIGURE 26.2. Early TEN with confluent dusky patch in the axilla.

place initially in the center of targetoid lesions and involves large confluent areas of the skin in patients with more extensive disease. Dusky epidermis can be easily dislodged from the underlying dermis at this stage, as all semblance of a viable dermoepidermal junction have been abandoned. By this time oral mucositis is usually severe and hemorrhagic with impaired alimentation, with concomitant worsening of ocular disease (Fig. 26.3). There is variable involvement of other mucous membranes. The pharynx is

FIGURE 26.3. Early TEN with focal epidermal detachment, severe mucositis, and multiple coalescing dusky macules and patches.
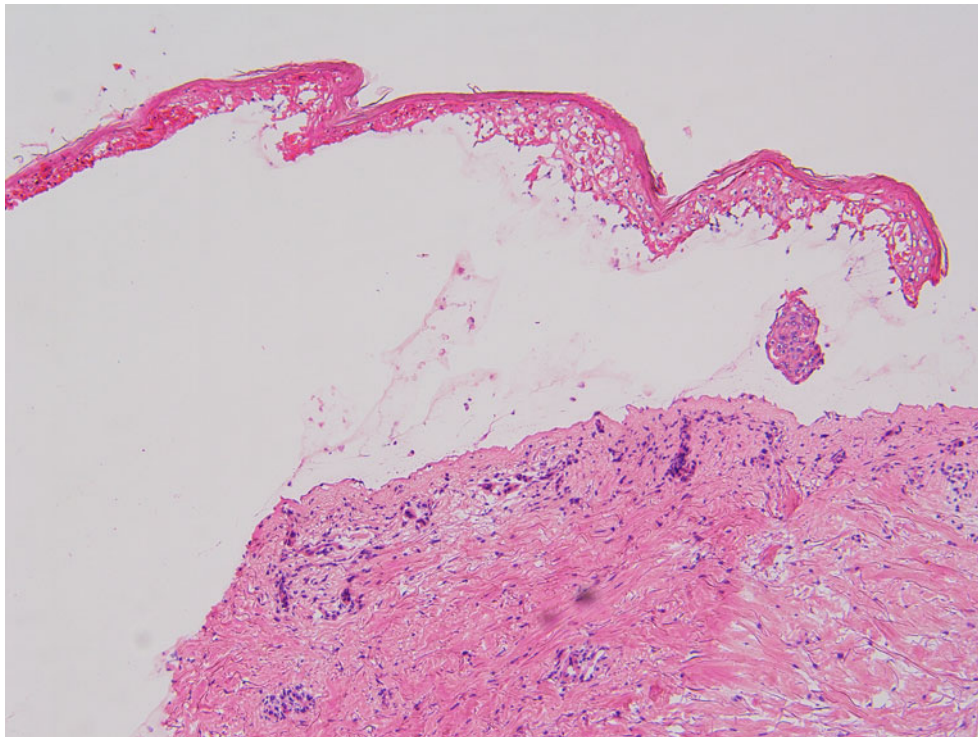
FIGURE 26.4. TEN—complete epidermal necrosis with subepidermal separation and scant dermal inflammation.

usually involved. Urethral involvement is present in two-thirds of patients and can cause pain and urinary retention. Vaginal mucosal disease can be present and can result in permanent cicatricial sequelae. Otolaryngologic endoscopic evaluation should take place if dysphonia or dyspnea is present, as laryngeal lesions with the risk of airway obstruction can be predictive of impending pulmonary infection and substantial morbidity [11].

Histology of TEN in early stages can be quite nonspecific and cannot be differentiated from erythema multiforme, as scattered necrotic keratinocytes and variable lymphohistiocytic inflammation can be present in both entities [12]. Late TEN shows confluent epidermal necrosis with associ-

ated subepidermal split and scant inflammation [13] (Fig. 26.4). Frozen section analysis is useful only in that an absence of epidermal necrosis in involved skin makes TEN extremely unlikely, although differentiation from erythema multiforme is often not possible [14]. Frozen section examination can also allow differentiation from staphylococcal scalded skin syndrome. Direct immunofluorescence should be performed in the setting of atypical histological or clinical findings, as autoimmune bullous disease can mimic SJS/TEN [15].

Treatment of SJS/TEN at the present time is grounded in meticulous wound care and aseptic technique, fluid and electrolyte supplementation, and prevention of long-term

Table 26.2. Severity-of-illness score for toxic epidermal necrolysis (SCORTEN)

Criteria: 1 point per condition	
Age	>40 years
Heart rate	>120 beats/min
Comorbid malignancy	Yes
Epidermal detachment	>10% BSA on day 1
Blood urea nitrogen	>28 mg/dL or >10 mmol/L
Glucose	>252 mg/dL or >14 mmol/L
Bicarbonate	<20 mEq/L
Total score	*Mortality rate*
0–1	3.2%
2	12.2%
3	35.5%
4	58.3%
>5	90%

ocular and oral mucosal sequelae. The optimal environment, particularly when >10% body surface area (BSA) is involved, is a burn unit, as there is some overlap with the management of patients with extensive cutaneous thermal injury. Ophthalmologic and otolaryngologic consultations are usually necessary. Beyond specialized supportive care, active treatment is extremely controversial and somewhat dependent on the severity of disease. Severity of disease and mortality risk can be approximated with the TEN-specific severity-of-illness score (SCORTEN, Table 26.2) [16]. For many years, particularly among dermatologists, oral corticosteroids were used frequently for disease classified as Stevens-Johnson syndrome. Corticosteroid use had fallen out of favor for use in TEN, as it was found in some studies to lengthen hospital stay and increase the rate of infections [17]. Studies in which corticosteroids are given early in treatment, especially with concomitant use of intravenous immunoglobulin (IVIG), show some benefit [18, 19].

The idea of treatment with IVIG alone or in combination with other agents is supported by the Fas-FasL theory of pathogenesis, in that pooled human immunoglobulins may block this pathway of cell death and arrest the progression of epidermal necrosis. IVIG treatment for SJS/TEN was initially met with great enthusiasm, which has faded to skepticism as more patient data accumulates. Substantial cost of treatment has also tempered the regular use of this treatment, especially given the high doses which are recommended. It is relatively clear that lower total doses (<3 g/kg body weight) are not beneficial to any greater extent than supportive care. Doses from 3 to 5 g/kg (a commonly administered dose is 1 g/kg daily for 3 days) have previously been thought to reduce mortality. A recent meta-analysis by Huang and colleagues did not show significant benefit from IVIG treatment [20]. Recent comparison study of 64 patients treated with either IVIG or cyclosporine showed survival benefit from cyclosporine and potentially increased mortality and a trend toward the progression of disease with IVIG [21].

The enthusiasm for the use of cyclosporine in SJS/TEN has waxed and waned over time. Dosage is usually 3–5 mg/kg daily for 3–7 days. While relatively low cost is an advantage, immunosuppression and renal toxicity can loom large in the critically ill patient. Two studies support the use of cyclosporine in TEN, with data included from 40 total patients. Both reported a mortality rate of 0% and rapid cessation of disease progression [22, 23].

References

1. Stevens A, Johnson F. A new eruptive fever associated with stomatitis and ophthalmia. Am J Dis Child. 1922;24:526.
2. Thomas B. The so-called Stevens-Johnson syndrome. Br Med J. 1950;1:1393–7.
3. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol. 1956;68:355–61.
4. Bastuji-Garin S, Rzany B, Stern RS. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129:92–6.
5. Wolf R, Wolf D, Davidovici B. In the pursuit of classifying severe cutaneous adverse reactions. Clin Dermatol. 2007;25:348–9.
6. Nagy N, McGrath JA. Blistering skin diseases: a bridge between dermatopathology and molecular biology. Histopathology. 2010;56:91–9.
7. Mockenhaupt M, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The Euro-SCAR-study. J Invest Dermatol. 2008;128(1):35.
8. Hung SI, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006;16(4):297.
9. Rzany B, Mockenhaupt M, Stocker U, Hamouda O, Schopf E. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with the acquired immunodeficiency syndrome in Germany. JAMA Dermatol. 1993;129(8):1059.
10. Yang C, Mosam A, Mankahla A, Dlova N, Saaavedra A. HIV infection predisposes skin to toxic epidermal necrolysis via depletion of skin-directed CD4+ T cells. J Am Acad Dermatol. 2014;70(6):1096.
11. Bequignon E, Duong TA, Sbidian E, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: ear, nose and throat description at acute stage and after remission. JAMA Derm. 2015;151(3):302–7.
12. Rzany B, Hering O, Mochenhaupt M, Schroder W, Goerttler E, Ring J, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 1996;135(1):6–11.
13. Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. J Am Acad Dermatol. 2008;59:995–9.
14. Hosaka H, Ohtoshi S, Nakada T, Iijima M. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: frozen section diagnosis. J Dermatol. 2010;37:407–12.

15. Kakar R, Paugh H, Jaworsky C. Linear IgA bullous disease presenting as toxic epidermal necrolysis: a case report and review of the literature. Dermatology. 2013;227(3):209–13.

16. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149–53.

17. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg. 1986;204:503–12.

18. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2007;87:144–8.

19. Avakian R, Flowers FP, Araujo OE, Ramos-Caro FA. Toxic epidermal necrolysis: a review. J Am Acad Dermatol. 1991;25: 69–79.

20. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systemic review and meta-analysis. Br J Dermatol. 2012;167:424–32.

21. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol. 2014;71(5):941–7.

22. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010;163:847–53.

23. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporine A. J Trauma. 2000;48:473–8.

27

Drug Reaction with Eosinophilia and Systemic Symptoms

■	Synonyms:	Drug-induced hypersensitivity syndrome (DIHS), drug hypersensitivity, drug-induced delayed multi-organ hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome (AHS)
■	Etiology:	A wide range of drugs including antiepileptics, antibacterials, antidepressants, antihypertensives, antituberculosis agents, nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, etc.
■	Incidence:	1/1000–1/10,000 drug exposures
■	Clinical:	Severe cutaneous reaction (e.g., maculopapular rash and generalized erythematous rash), fever, eosinophilia or atypical lymphocytes, and internal organ involvement.
■	Distribution:	Generalized
■	Histology:	Superficial perivascular lymphocytic infiltrate, erythrocyte extravasation, focal interface changes
■	Adverse variables:	End-organ failure
■	Treatment:	Withdrawal of the offending drug, administration of corticosteroids, intravenous immunoglobulin (IVIG)
■	Prognosis:	Relapses may occur, long-term complications may develop
■	Mortality rate:	10 %

Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) was originally described in 1996 by Bocquet et al. in their description of patients who developed fever, a severe cutaneous reaction with infiltrated papules, facial edema or an exfoliative dermatitis, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement within 2 months after initiation of the offending drug [1]. The current literature defines DRESS as a syndrome with varying combination of the following factors: drug-induced immunological background, late onset drug reaction, longer duration than other drug rashes, multi-organ involvement, lymphocyte activation, eosinophilia, and frequent virus reactivation [2].

DRESS is a severe drug-induced adverse reaction that has commonly been associated with anticonvulsants including phenytoin, carbamazepine, phenobarbital, and lamotrigine and with sulfonamides. Additional drugs include allopurinol, nevirapine, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and antituberculosis drugs [3]. The risk factors for DRESS include cranial irradiation, young age, HIV infection, and viral reactivation of Human Herpes Virus HHV4, HHV5, HHV6, and HHV7. Cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [4]. The significance of the human leukocyte antigen (HLA) as a risk factor for developing DRESS has been demonstrated in the scientific literature. In a Taiwanese study of 30 patients with allopurinol-induced DRESS, they reported 100 % prevalence of

HLA-B*5801 [5]. The association was also reported in a European study of 19 patients with allopurinol-induced DRESS, which demonstrated 12 patients as carriers for HLA-B*5801 [6]. Additionally, HLA-B*5701 has been identified as a risk factor for DRESS in Caucasians receiving abacavir [7, 8]. In addition to HLA genotypes, the role of genetic polymorphisms as a risk factor for DRESS has been hypothesized. Polymorphisms in epoxide hydroxylase, an enzyme responsible for detoxification of aromatic anticonvulsants, result in the buildup of toxic metabolites and subsequent immunologic activity [9]. Furthermore, individuals with genetic variability of N-acetylation, an enzyme reaction involved in the metabolism of sulfonamides, demonstrate an increased susceptibility to the development of DRESS [10].

The pathogenesis of DRESS is not completely understood; however, the current viewpoint associates several factors as implicated in the development of the syndrome including detoxification abnormalities resulting in toxic metabolite accumulation, slow acetylation, and the reactivation of human herpes viruses [9–11].

The incidence of DRESS ranges from 1/1000 to 1/10,000 exposures in patients taking the culprit drug [12]. DRESS was previously reported to have no predilection for gender or age [13]; however, a more recent prospective observational study of 117 patients with DRESS demonstrated a male to female ratio of 0.8 and a borderline significance of younger females than males [14].

DRESS syndrome is characterized by a long latency period; symptoms usually develop 2–8 weeks following the introduction of the offending drug. Early features of DRESS include a fever greater than 38 °C, lymphadenopathy, dysphagia, flu-like symptoms, pruritus, and burning pain [14]. A polymorphous rash, often a morbilliform eruption and frequent facial edema, will subsequently develop; in later stages of DRESS, the rash will progress into an exfoliative dermatitis or erythroderma. Mild involvement of mucous membranes may be present [14]. Organ involvement in DRESS may include the liver, kidney, lung, muscle/heart, pancreas, or additional organs. Laboratory findings in patients with DRESS commonly demonstrate leukocytosis with either eosinophilia or atypical lymphocytes. Because of the diversity in clinical presentation, onset of symptoms, and clinical course, DRESS is challenging to diagnose. The clinical course of DRESS is commonly around 15 days or greater. A prolonged or more severe course of DRESS has been implicated with the reactivation of HHV6 [15].

Skin biopsy demonstrates a dense perivascular lymphocytic infiltrate in the papillary dermis; eosinophils, atypical lymphocytes, spongiosis, and erythrocyte extravasation may be present. Biopsy of affected lymph nodes may show either benign lymphoid hyperplasia or a pseudolymphoma pattern. Biopsy of internal organ involvement may demonstrate an eosinophilic infiltrate.

Three different sets of diagnostic criteria currently exist for DRESS including Bocquet's criteria [1], the RegiSCAR criteria [2], and Japanese DIHS criteria [13]. Bocquet's criteria includes a cutaneous drug eruption, hematologic abnormalities such as eosinophilia or the presence of atypical lymphocytes and systemic involvement including lymphadenopathy (greater than 2 cm in diameter), hepatitis, interstitial nephritis, interstitial pneumonia, or carditis [1]. The RegiSCAR criteria includes at least three of the following seven characteristics: skin eruption, fever greater than 38 °C, lymphadenopathy at two sites or more, involvement of one or more internal organs, lymphocytosis or lymphocytopenia, eosinophilia, and thrombocytopenia [2]. The RegiSCAR scoring system categorizes DRESS cases as definite, probable, possible, or no case based on the following characteristics: fever equal to or greater than 38.5 °C, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, resolution equal to or greater than 15 days, and evaluation of other potential causes (including antinuclear antibody, blood culture, hepatitis A virus (HAV)/ hepatitis B virus (HBV)/hepatitis C virus (HCV) serologies, and *Chlamydia/Mycoplasma*) [2]. The Japanese DIHS criteria is defined by a maculopapular rash developing more than 3 weeks after drug onset, prolonged clinical symptoms lasting 2 weeks following discontinuation of the offending drug, fever greater than 38 °C, liver abnormalities, leukocyte abnormalities (including leukocytosis, atypical lymphocytosis, and/or eosinophilia), lymphadenopathy, and HHV6 reactivation [13].

The treatment of DRESS involves the removal of the offending drug and administration of systemic corticosteroids. Corticosteroids combined with intravenous immunoglobulin have also been used successfully for DRESS treatment [16]. In mild cases, topical corticosteroids and antihistamines may be utilized.

Although a rare condition, DRESS syndrome is potentially life-threatening and has an estimated 10 % mortality rate, most frequently due to end-organ failure. In a retrospective review of 172 cases of DRESS, the authors reported no predictive factors for serious cases, as no differences in demographic or clinical variables were found between resolved cases and case fatalities [12]. Of note, however, specific drugs, such as allopurinol and minocycline, have been implicated to result in more serious DRESS cases [17]. Relapses may occur weeks to months after drug withdrawal. It has been hypothesized that when corticosteroids are either tapered or stopped, relapse may occur as these drugs may promote reactivation of herpes virus [11]. Long-term complications of DRESS include autoimmune conditions such as type 1 diabetes mellitus, thyroiditis, or systemic lupus erythematosus [18].

References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250–7.
2. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609–11.
3. Nam YH, Park MR, Nam HJ, Lee SK, Kim KH, Roh MS, et al. Drug reaction with eosinophilia and systemic symptoms syndrome is not uncommon and shows better clinical outcome than generally recognised. Allergol Immunopathol (Madr). 2015;43:19–24.
4. Dodiuk-Gad RP, Laws PM, Shear NH. Epidemiology of severe drug hypersensitivity. Semin Cutan Med Surg. 2014;33(1):2–9.
5. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005;102(11):4134–9.
6. Goncalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, et al. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. Br J Dermatol. 2013;169(3):660–5.
7. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics. 2004;14(6):335–42.
8. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. Curr Opin Allergy Clin Immunol. 2007;7(4):317–23.
9. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. J Clin Invest. 1988;82(6):1826–32.
10. Shear NH, Spielberg SP, Grant DM, Tang BK, Kalow W. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med. 1986;105(2):179–84.
11. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med. 2010;2(46):46ra62.
12. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588–97.
13. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156(5):1083–4.
14. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071–80.
15. Tohyama M, Hashimoto K, Yasukawa M, Kimura H, Horikawa T, Nakajima K, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol. 2007;157(5):934–40.
16. Galvao VR, Aun MV, Kalil J, Castells M, Giavina-Bianchi P. Clinical and laboratory improvement after intravenous immunoglobulin in drug reaction with eosinophilia and systemic symptoms. J Allergy Clin Immunol Pract. 2014;2(1):107–10.
17. Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol. 2009;145(1):67–72.
18. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin North Am. 2010;94(4):743–59.

28
Acute Generalized Exanthematous Pustulosis: AGEP

■ Synonyms:	Toxic pustuloderma, pustular drug rash, pustular psoriasiform eruption with leukocytosis
■ Etiology:	Drugs, infectious triggers, spider bites, exposure to mercury
■ Incidence:	1–5 cases/1 million/year
■ Clinical:	Acute onset of numerous sterile pinhead-sized pustules accompanied by fever and leukocytosis
■ Distribution:	Main flexural folds, face
■ Histology:	Subcorneal, intracorneal, and intraepidermal pustules, spongiosis, necrotic keratinocytes, eosinophils in pustules and within the dermis, erythrocyte extravasation, leukocytoclasia, interstitial and dermal infiltrate of neutrophils, papillary edema, perivascular lymphocytic inflammation
■ Adverse variables:	Significant comorbidities, secondary infection
■ Treatment:	Self-resolving; topical/oral/systemic corticosteroids for symptomatic relief or for severe cases with or without organ involvement
■ Prognosis:	Favorable prognosis; resolution within 15 days following withdrawal of the offending drug
■ Mortality rate:	5 %

Acute generalized exanthematous pustulosis (AGEP) is a rare clinical entity characterized by an acute onset of numerous sterile, nonfollicular, pinhead-sized pustules arising on an erythematous, edematous base accompanied by fever (>38 C), neutrophilia, and occasionally eosinophilia. In 1968, Baker and Ryan reported 104 cases of pustular psoriasis and specifically detailed five patients whom they diagnosed as having "exanthematic pustular psoriasis" most likely due to a drug or infectious etiology [1]. These five patients did not have a history of psoriasis and were characterized as having pustular skin reactions of acute onset that quickly resolved and did not recur. Subsequently, in 1980, Beylot et al. reviewed the existing literature regarding pustuloses and reported four additional cases; they are responsible for coining the name of this distinct entity as "acute generalized exanthematic pustulosis" [2]. Additional literature reports by Macmillan in

1973 and Staughton and Harper in 1984 denote pustular skin eruptions most likely representing AGEP which they termed as "generalized pustular drug rash" and "toxic pustuloderma," respectively [3, 4].

The vast majority (>90 %) of AGEP cases are attributable to drugs. A large-scale multinational case-control study, the EuroSCAR study, reported 97 cases of AGEP highly associated with pristinamycin, ampicillin/amoxicillin, quinolones, hydroxychloroquine, anti-infective sulfonamides, terbinafine, and diltiazem. Additional suspected drugs with less strong associations include corticosteroids, macrolides, oxicam nonsteroidal anti-inflammatory drugs (NSAIDs), and antiepileptic drugs [5]. Atypical medications in association with AGEP include atenolol, nifedipine, itraconazole, minocycline, clindamycin, paracetamol, allopurinol, dexamethasone, icodextrin (a peritoneal dialysate), and IV radiocontrast media [6].

Additional suspected causes of AGEP include infectious etiologies such as enteroviruses, adenovirus, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, *Mycoplasma pneumoniae*, parvovirus B19, *Chlamydia pneumoniae*, *Escherichia coli* of the urinary tract, cystic echinococcosis of the liver, exposure to mercury, and spider bites [7–13]. The influence of infectious agents as a cause of AGEP has been described with contrasting theories in the literature. The role of infection in causing AGEP has been demonstrated to lack stringent evidence; rather, the use of anti-infective drugs to treat the infectious agent has been reported as the primary cause of AGEP [5]. Contrastingly, another theory suggests that infectious agents may trigger the AGEP response to the offending drug via priming of the Th1 immune response, leading to release of CXCL8 (IL-8) and GM-CSF and subsequent neutrophilia [6].

The pathogenesis of AGEP is largely a T-cell-mediated phenomenon involving CD4 and CD8 T cells. The pathogenesis of the disease is hypothesized to occur from drug-specific CD4 and CD8 T cells that are activated in lymph nodes following APC presentation of the drug. Once activated, the CD4 and CD8 T cells expand and infiltrate the dermis and epidermis. Keratinocytes within the epidermis are killed by CD8 T cells via granzyme and perforin release in addition to the Fas/FasL mechanism. These initial steps result in the formation of a subcorneal vesicle filled mainly with CD4 T cells which subsequently release CXCL8 (IL-8) and GM-CSF. These chemokines attract neutrophils and occasionally eosinophils to the epidermis, converting the subcorneal vesicle into a sterile pustule [14].

AGEP is a rare clinical entity with an incidence rate of approximately 1–5 cases out of every 1 million individuals per year [15]. While previous literature demonstrates an equal distribution of AGEP between men and women [15], the more recent EuroSCAR study reported a female predominance, with a male to female ratio of 0.8 [5]. The EuroSCAR study also reported a mean age of AGEP at 56 years with a SD of 21 years. AGEP has also been reported in children [16]. While reports of AGEP have been reported in North America, the majority of cases are represented in European literature.

AGEP is characterized by the rapid development (within a few hours) of dozens to hundreds of sterile, nonfollicular pinhead-sized (less than 5 mm in diameter) pustules on an erythematous, edematous background commonly on the main flexural folds. Additional dermatologic manifestations include edema of the face, purpura, atypical targets, blisters, and vesicles. A small percentage of cases (20 %) involve mucous membranes, however; the involvement is mild and commonly occurs in one site, most frequently oral mucous membranes. Systemic features of the disorder include a high fever usually above 38 C and marked leukocytosis, from a predominance of neutrophils (greater than 7,000 neutrophils/μL) and occasionally eosinophils (in approximately 1/3 of patients). While internal organ involvement is not usually observed, atypical presentations of AGEP have reported systemic involvement including renal insufficiency, hepatocellular involvement, acute respiratory failure, hemodynamic instability, and bone marrow involvement [17]. Following discontinuation of the drug, spontaneous resolution of the disorder occurs within 15 days and is characterized by resolution of the pustules followed by postpustular desquamation.

It is important to note that atypical presentations of AGEP with clinical similarity to toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS) have been reported. While the clinical presentation of these cases resemble TEN and DIHS, histopathologically, the cases are typical of AGEP. Cases simulating TEN were described as having mucosal involvement, diffuse exfoliation with bullae formation, and occasionally atypical target formation [6]. In most AGEP-TEN overlap cases, the prognosis of patients clinically modeled AGEP with complete recovery; however, some cases resulted in end-organ dysfunction requiring aggressive treatment, and another case was recently reported to result in mortality [18]. AGEP-DIHS cases have been reported to have systemic involvement including organ dysfunction, most frequently hepatic and renal involvement. These cases resulted in complete recovery (resolution of dermatological manifestation, transaminitis, and renal dysfunction) following drug discontinuation, supportive measures, and topical corticosteroids [6]. Atypical localized presentations of AGEP have also been reported including AGEP resembling contact dermatitis in association with methylchloroisothiazolinone and hydrocortisone butyrate, and photodistributed AGEP following sertraline administration [6].

AGEP is characterized histologically by subcorneal, intracorneal, and intraepidermal pustules often large in size with greater than 15 keratinocytes; pustules may also contain eosinophils. Spongiform features are common in the intraepidermal pustules as compared to subcorneal or intracorneal pustules. Follicular pustules may also be observed. Perivascular lymphocytic inflammation is also typical with neutrophils and some eosinophils. Epidermal features recognized in AGEP include necrotic keratinocytes with segmental necrosis and spongiosis with exocytosis of neutrophils. Dermal characteristics include papillary edema, mixed superficial, interstitial, and middle to deep dermal infiltrates of neutrophils and eosinophils. While vasculitis has rarely been observed, erythrocyte extravasation and leukocytoclasia are more frequently noted. Additional histologic features of AGEP include parakeratosis, rete ridge elongation, fusion of rete ridges, mild clubbing, and the presence of a granular cell layer [19].

AGEP has similar clinical and histological features to generalized pustular psoriasis, specifically the most severe form of generalized pustular psoriasis – the von Zumbusch type, which is marked clinically by an abrupt generalized onset of

pustules on an erythematous background lasting for up to several weeks and frequently accompanied by fever and leukocytosis. Distinguishing the histopathological features of these two diseases may pose a challenge; thus, reliance on clinical information such as association with drugs and quick resolution following drug withdrawal, nonrecurrence, a lack of family history of psoriasis, and a lack of arthritis favor a diagnosis of AGEP. Differentiating features between AGEP and generalized pustular psoriasis may include eosinophils in the pustules or dermis, necrotic keratinocytes, an interstitial and dermal infiltrate of neutrophils, and the absence of tortuous, dilated blood vessels which are frequently noted in AGEP as compared to generalized pustular psoriasis [20].

The EuroSCAR study group developed the AGEP validation score, a standardized scoring system based upon clinical features including morphology (pustules, erythema, distribution, postpustular desquamation), course of the disease (mucosal involvement, acute onset of less than 10 days, resolution in less than 15 days, fever >38 C, neutrophils >7000/mm), and histopathologic data. The scoring system ranges from 0 to 12 and categorizes cases into one of four categories: no AGEP (<0), possible AGEP (1–4), probable AGEP (5–7), and definite AGEP (8–12).

The course of AGEP typically features spontaneous resolution following withdrawal of the offending agent; thus treatment for AGEP includes supportive measures during the acute pustular reaction phase. Treatments include disinfectant solutions to prevent infection and moist dressings with drying. During the postpustular desquamation phase, emollients have been used to promote the integrity of the skin barrier. Topical corticosteroids may provide symptomatic relief; systemic corticosteroids may be appropriate in severe cases of AGEP such as those with organ involvement.

AGEP has a favorable prognosis, with most patients experiencing resolution of dermatologic and/or systemic involvement within 15 days of onset if the offending drug is removed. The mortality rate of AGEP is approximately 5 %; mortality most frequently occurs in elderly individuals with secondary infections or in those with significant comorbidities.

References

1. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771–93.
2. Beylot C, Bioulac P, Doutre MS. Acute generalized exanthematic pustuloses (four cases) (author's transl). Ann Dermatol Venereol. 1980;107(1–2):37–48.
3. Macmillan AL. Generalised pustular drug rash. Dermatologica. 1973;146(5):285–91.
4. Staughton RC, Payne CM, Harper JI, McMichen H. Toxic pustuloderma–a new entity? J R Soc Med. 1984;77 Suppl 4:6–8.
5. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157(5):989–96.
6. Kostopoulos TC, Krishna SM, Brinster NK, Ortega-Loayza AG. Acute generalized exanthematous pustulosis: atypical presentations and outcomes. J Eur Acad Dermatol Venereol. 2014;8:209–14.
7. Feio AB, Apetato M, Costa MM, Sa J, Alcantara J. Acute generalized exanthematous pustulosis due to Coxsackie B4 virus. Acta Med Port. 1997;10(6–7):487–91.
8. Naides SJ, Piette W, Veach LA, Argenyi Z. Human parvovirus B19-induced vesiculopustular skin eruption. Am J Med. 1988;84(5):968–72.
9. Roujeau JC, Bioulac-Sage P, Bourseau C, Guillaume JC, Bernard P, Lok C, et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol. 1991;127(9):1333–8.
10. Klein N, Hartmann M, Helmbold P, Enk A. Acute generalized exanthematous pustulosis associated with recurrent urinary tract infections. Hautarzt. 2009;60(3):226–8.
11. Manzano S, Guggisberg D, Hammann C, Laubscher B. Acute generalized exanthematous pustulosis: first case associated with a Chlamydia pneumoniae infection. Arch Pediatr. 2006;13(9):1230–2.
12. Davidovici BB, Pavel D, Cagnano E, Rozenman D, Halevy S. EuroSCAR, et al. Acute generalized exanthematous pustulosis following a spider bite: report of 3 cases. J Am Acad Dermatol. 2006;55(3):525–9.
13. Cannistraci C, Parola ILL, RiganÒ R, Bassetti F, Ortona E, Santucci B, et al. Acute generalized exanthematous pustulosis in cystic echinococcosis: immunological characterization. Br J Dermatol. 2003;148(6):1245–9.
14. Schmid S, Kuechler PC, Britschgi M, Steiner UC, Yawalkar N, Limat A, et al. Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. Am J Pathol. 2002;161(6):2079–86.
15. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)–a clinical reaction pattern. J Cutan Pathol. 2001;28(3):113–9.
16. Meadows KP, Egan CA, Vanderhooft S. Acute generalized exanthematous pustulosis (AGEP), an uncommon condition in children: case report and review of the literature. Pediatr Dermatol. 2000;17(5):399–402.
17. Hotz C, Valeyrie-Allanore L, Haddad C, Bouvresse S, Ortonne N, Duong TA, et al. Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. Br J Dermatol. 2013;169(6):1223–32.
18. Krishna S, Ortega-Loayza A, Malakouti N, Brinster N. A rapidly progressive and fatal case of atypical acute generalized exanthematous pustulosis. J Am Acad Dermatol. 2014;71(3):e89–90.
19. Halevy S, Kardaun SH, Davidovici B, Wechsler J, EuroSCAR and RegiSCAR Study Group. The spectrum of histopathological features in acute generalized exanthematous pustulosis: a study of 102 cases. Br J Dermatol. 2010;163(6):1245–52.
20. Kardaun SH, Kuiper H, Fidler V, Jonkman MF. The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis. J Cutan Pathol. 2010;37(12):1220–9.

Part V
Infectious Diseases

29
Anthrax

> - Synonym: Woolsorter's disease (inhalational anthrax)
> - Etiology: Inoculation or inhalation of spores of *Bacillus anthracis,* a gram-positive bacillus
> - Associations: None
> - Clinical: Cutaneous: papule, followed by vesicle then ulcer with eschar at the site of inoculation; septicemia in approximately 20 %
> - Histology: Partial epidermal necrosis, dermal edema with fibrin, neutrophils, and abscess formation; positive Gram stain expected
> - Evaluation: Notifying local health department and laboratory of clinical suspicion, Gram stain and culture of vesicle fluid or eschar base, skin biopsy with tissue culture
> - Treatment: Ciprofloxacin or doxycycline
> - Prognosis: 99 % survival for cutaneous disease if treated early, 20 % survival for inhalational disease, and intermediate survival for gastrointestinal disease

Anthrax is an infection caused by the spore-forming bacterium, *Bacillus anthracis.* Infection occurs in mammals, particularly herbivores that ingest bacterial spores from soil. Human infection occurs from inhalation of spores, ingestion of animal meat contaminated with spores, or percutaneous inoculation of spores from exposure to infected animals or contaminated animal products. Anthrax has been an occupational disease of textile workers, farmers, butchers, veterinarians, and shepherds.

Anthrax is a historically important infection, thought to be the fifth and sixth plagues of ancient Egypt, brought by Moses. It was the cause of several disastrous animal plagues in Europe in the eighteenth and nineteenth centuries. In 1877, Robert Koch cultured *Bacillus anthracis*, the first proof of a microbial agent causing human disease [1]. This discovery supported "germ theory" and gave birth to the science of modern microbiology. Subsequently, Pasteur and Greenfield successfully developed the first vaccine, composed of attenuated *B. anthracis* [2]. Anthrax has been explored as an agent of biological warfare because of its exceptional virulence and capability to create an aerosol of odorless, invisible spores. Its spores could potentially be dispersed over densely populated areas and generate disease in a multitude of people with high morbidity. This organism has gained notoriety more recently because of the anthrax attacks of 2001, in which anthrax spores were distributed by mail using the US Postal Service, resulting in inhalational or cutaneous anthrax infection in 22 people.

Bacillus anthracis is a gram-positive, nonmotile, aerobic, spore-forming rod. The organism grows readily on standard culture media, especially sheep's blood agar, forming nonhemolytic irregular white-gray colonies, with tapered extensions [3]. Gram stain of cultures reveals long chains of bacilli. Notifying the laboratory of clinical suspicion of *B. anthracis* is important because of the prevalence of the similar-appearing organism, *Bacillus cereus*, which is a frequent laboratory contaminant [4].

The infective unit of the organism is the endospore, which may reside in soil for decades. It is resistant to heat, ultraviolet and gamma irradiation, drying, and antimicrobial agents [5]. Spores enter the body through broken skin, the lungs, or the gastrointestinal tract, and are engulfed by macrophages, and then transported to lymph nodes. Within the macrophage, they transform to the vegetative form and then multiply within the lymphatic system. They are eventually released in high concentrations into the bloodstream, resulting in sepsis. The organism achieves its virulence by the production of three polypeptides and an

antiphagocytic capsule, encoded on two plasmids, pXO1 and pXO2. Both plasmids are needed for the organism to achieve complete virulence. pXO1 encodes the three polypeptides, protective antigen (PA), lethal factor (LF), and edema factor (EF), which combine as binary toxins. PA combines with LF to form lethal toxin and combines with EF to form edema toxin. The PA component of the toxin facilitates access to the host cell by its binding to cellular receptors. The complex is cleaved by the serine protease furin, causing oligomerization and subsequent transport of toxins into the cell. The lethal toxin is a zinc metalloproteinase that activates oxidative burst pathways, forming reactive oxygen intermediates. It also induces the production of tumor necrosis factor-α and interleukin-1β, which are involved in inducing septic shock. Plasmid pXO2 encodes three genes involved in production of the polyglutamic acid capsule that inhibits phagocytosis of the vegetative state of *B. anthracis* [4, 6, 7].

The three forms of anthrax infection in humans are cutaneous, inhalational, and gastrointestinal. The disease is spread to humans via contact with infected animals or contaminated animal products. Naturally occurring anthrax has been almost eradicated in the United States and in Western Europe due to the presence of long-standing vaccination programs for at-risk livestock, but is still relatively common in Asia Minor.

Cutaneous anthrax is by far the most common form of the disease. Infection usually occurs from contact with infected animals or animal products such as hides, wool, hair, or bones. The primary lesion is a papule, sometimes pruritic, occurring 3–5 days after inoculation. The face, neck, and extremities are most commonly affected [4]. Within 2 days, vesiculation occurs, with central necrosis, and formation of a 1–3 cm painless ulcer and subsequent eschar (Fig. 29.1) [3]. The eschar accounts for the derivation of the organism's name from the Greek word *anthrakos*, meaning coal [1]. Lymphadenopathy and lymphangitis may develop, with satellite hemorrhagic vesicles and edema. Inoculation sites on the extremities usually result in "malignant pustule" formation. More central sites tend to have prominent edema, resulting in the "malignant edema" presentation [3]. The latter form is more likely to be complicated by airway obstruction, requiring concomitant use of systemic steroids and antibiotics. Secondary bacterial infection of the site is common, so that treatment with extended spectrum antibiotics may be needed. While many cases of cutaneous anthrax are self-limited, antibiotic treatment is recommended because of the approximately 20 % of cases in which disseminated infection associated with high mortality occurs. Case fatality rate is less than 1 % in treated cases [8]. Cutaneous lesions are reported to heal without scarring in the large majority of cases [4]. However, in one series, considerable scarring requiring reconstructive surgery in 23 % of cases was noted [3].

Inhalational anthrax is exceptionally uncommon, but was more prevalent in occupational settings as "Woolsorter's disease" before adequate hygienic standards were employed. In contrast to inoculation anthrax, disease caused by inhalation of anthrax spores is usually fatal because the disease causes nonspecific influenza-like symptoms followed by rapid onset of septic shock and death. Important information regarding inhalational anthrax was yielded by an accidental release of anthrax spores from a biological weapon facility in Sverdlovsk in 1979, in which 66 deaths occurred. The incubation time ranged from 2 to 43 days, with an average of about 10 days. The mortality rate was approximately 80 % [9]. Despite its rarity, inhalational anthrax was the mode of infection in 50 % of the anthrax cases in the 2001 attacks and would be expected to be the prevalent form of the disease in a biological weapon attack [10]. In the setting of an anthrax outbreak, clinical features favoring inhalational anthrax over an influenza-like illness include presence of dyspnea, hypoxemia, chest pain, lack of sore throat or rhinorrhea, and presence of mediastinal widening, pulmonary infiltrate, or pleural effusion on chest radiography. Laboratory evaluation may reveal neutrophilia with bandemia and elevated liver enzyme tests [11].

Gastrointestinal tract and oropharyngeal anthrax are also uncommon. These infections result from ingestion of contaminated meat from infected animals. The incubation period is 2–5 days. Infection probably occurs in a manner similar to that in the skin, with ulcer formation and bacterial proliferation in lymphatic tissues. Inoculation may occur at any point along the gastrointestinal tract, including the oropharynx. Symptoms and signs vary depending on the site of inoculation and may include fever, abdominal pain, nausea, vomiting, dysphagia, constipation, diarrhea, melena, and ascites. Mortality is considerable and may be the result of sepsis or intestinal perforation [4].

Cutaneous, inhalational, and gastrointestinal anthrax may all be complicated by anthrax meningitis, a complication occurring during bacteremia. Central nervous system involvement portends a grave prognosis despite therapy [4].

Diagnosis of anthrax may be made by blood culture in the setting of disseminated infection. Growth usually occurs in 6–24 h [10]. For cutaneous anthrax, vesicle fluid culture may grow the organism, and 64 % of cases in one series had organisms identified by gram-stained smears of cutaneous lesion contents [3]. The organism is unlikely to grow from the skin or blood if the patient has received antibiotics prior to obtaining culture material [10]. A rapid diagnostic test for anthrax that detects antibodies to anthrax-protective antigen in 45 min is US Food and Drug Administration approved [12, 13]. PCR may be used in diagnosis, but does not offer real-time detection. Future diagnostic technologies are likely to involve peptide-based
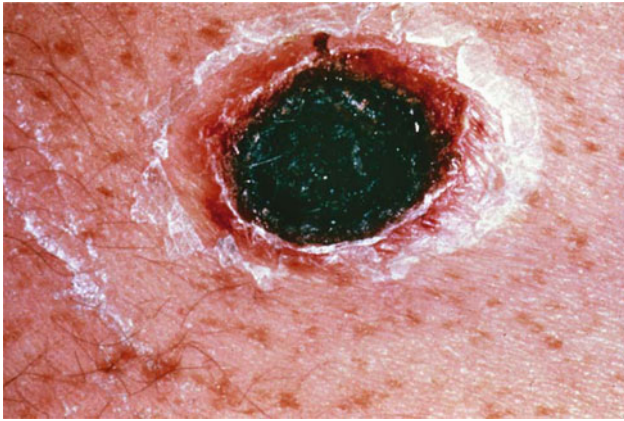
Figure 29.1. Cutaneous anthrax: ulcer, with central eschar, and surrounding erythema and edema.

biosensors which are small peptides adapted to specific binding to *B. anthracis* proteins and adsorbed to nanorods, subsequent to which *B. anthracis*-specific fluorescent probes can be used in detecting the presence of specific viral protein [14].

The differential diagnosis of cutaneous anthrax is considerable and includes ecthyma, insect or arachnid bite reaction, tularemia, glanders, rickettsialpox, diphtheria, syphilitic chancre, ecthyma gangrenosum, and orf. In endemic or occupational settings, history of contact with animals or animal products is expected in cases of anthrax. Clinical features that may point to anthrax include relative lack of symptoms given impressive clinical findings and prominent edema. Gram stain and culture of cutaneous vesicles or ulcers will yield the organism in the majority of cases. Skin biopsy specimens of *Bacillus anthracis* infection have prominent superficial dermal edema with variable epidermal necrosis and an infiltrate of neutrophils throughout the dermis, with abscess formation. There is prominent dermal fibrin, with foci of vasculitis. Gram stain reveals gram-positive rods within the dermis (Fig. 29.2a–c) [15, 16]. Should there be clinical suspicion of cutaneous anthrax, the following list of procedures should be employed:

29.1 Diagnostic Evaluation of Suspected Cutaneous Anthrax

1. Patient should be under contact precautions only, since the infective unit, the spore, is not shed.
2. Gram stain and culture of vesicle fluid or unroofed eschar.
3. Two punch biopsy specimens, one for tissue culture and one in formalin for routine processing.
4. Blood cultures if clinical suspicion of bacteremia is present.
5. Contact laboratory and local health department with clinical suspicion, blood work as recommended for serologic and diagnostic studies.

Diagnostic and management information on anthrax is available on the Internet from the US Centers for Disease Control (CDC) [17].

Cutaneous anthrax in endemic areas is treated successfully with penicillin, given intravenously in cases of "malignant edema" [3, 18]. Current CDC recommendation calls for ciprofloxacin 500 mg p.o. twice daily or doxycycline 100 mg p.o. twice daily for 7–10 days. Levofloxacin, moxifloxacin, and clindamycin are alternatives [19]. However, treatment of cutaneous anthrax in the setting of a bioterrorism attack as recommended by the CDC includes ciprofloxacin 500 mg p.o. twice daily for 60 days or doxycycline 100 mg p.o. twice daily for 60 days, The rationale for extended treatment is to cover the likelihood of concomitant inhalation of anthrax spores, which may incubate for close to 60 days before resulting in clinical infection. Penicillin has not been recommended because isolates from the 2001 anthrax attacks showed an inducible β-lactamase that degrades the antibiotic. The clinical significance is uncertain, but suggests the potential for rapid onset of penicillin resistance [10]. No resistance to fluoroquinolones has been identified, but in vitro high-level resistance can be induced by serial passage of *Bacillus anthracis* in media containing fluoroquinolones, suggesting that drug-resistant strains can be cultivated [20].

In addition to antibiotic therapy, a three-dose series of anthrax vaccine adsorbed (AVA) BioThrax is recommended to provide longer-term protection [19]. The vaccine consists of a sterile filtrate of cultures of an attenuated unencapsulated, non-proteolytic strain of *B. anthracis*, containing predominantly protective antigen [2]. Doses are given subcutaneously at 0, 2, and 4 weeks, with boosters given at 6, 12, and 18 months. Further boosters are recommended if continued exposure is a possibility. The vaccine has been widely used in military personnel and in some industries that have exposures to at-risk animals from endemic areas. Given the slow immunogenicity of this vaccine, an effort has been made to develop a more rapidly acting and immunogenic vaccine. An adenovirus-vectored vaccine containing protective antigen has been used in animal trials and found to offer a more rapid and persistent antibody response than AVA, even in a single intranasal dose [21].

In a patient suspected of having systemic involvement, the addition of antitoxin therapy is recommended. Options include anthrax immune globulin intravenous (AIGIV), polyclonal antisera from persons immunized with AVA,
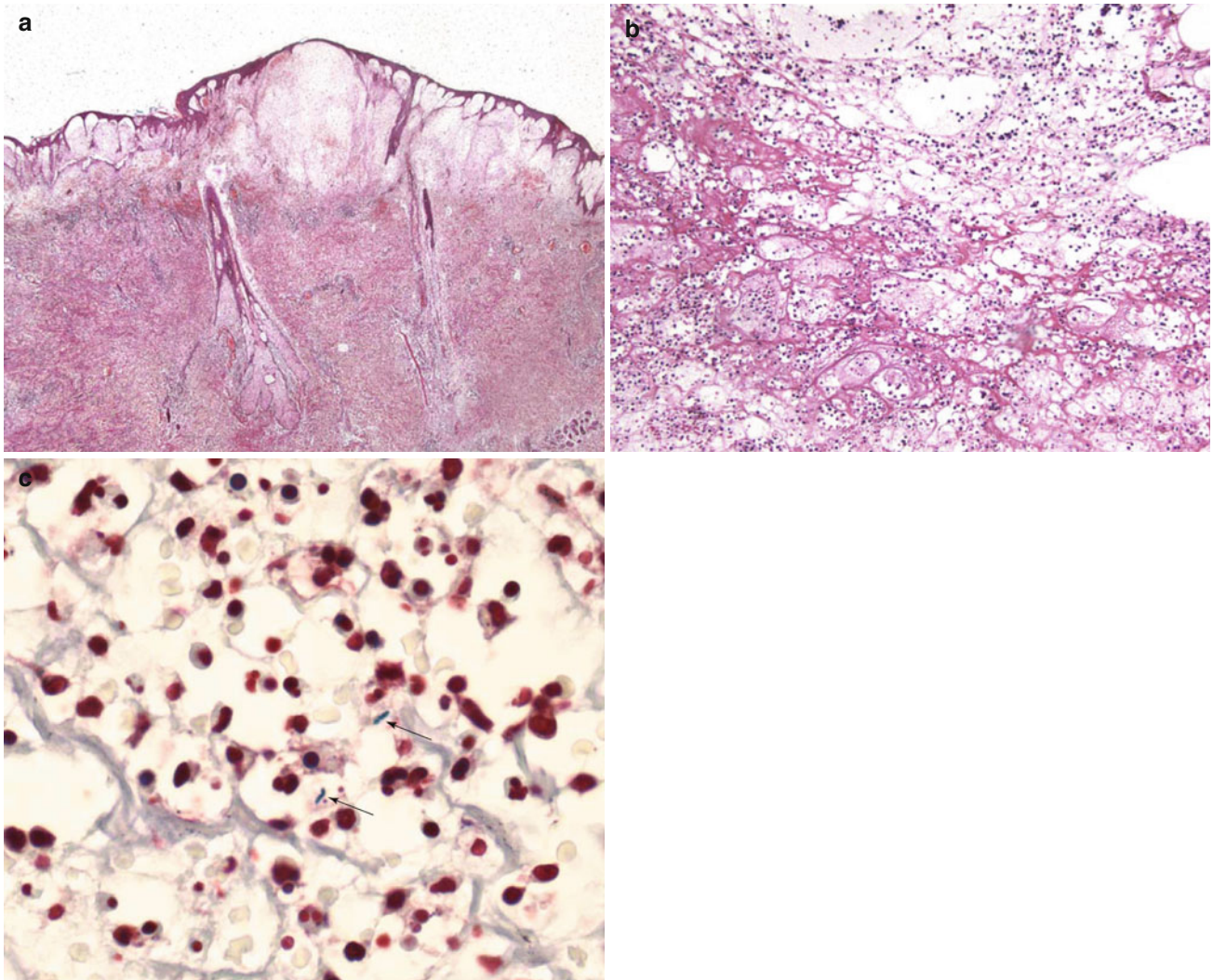
FIGURE 29.2. (**a**) Anthrax: mild epidermal hyperplasia and striking superficial dermal edema. (**b**) Deep dermal and subcutaneous mixed inflammatory infiltrate of lymphocytes, neutrophils, and plasma cells, with edema and fibrin deposition. (**c**) Mixed inflammatory infiltrate with gram-positive bacilli (*arrows*) (Courtesy of Eduardo Calonje, MD).

and raxibacumab, a monoclonal antibody to protective antigen [19].

Naturally occurring cutaneous anthrax is a disease that has become almost nonexistent in the United States and Western Europe due to vaccination programs in at-risk animal reservoirs. However, the significance of this organism has been heightened recently because of its use in bioterrorism. The anthrax attacks of 2001 focus the potential for cutaneous presentations of this disease to be the first detectable manifestation of a terrorist biological weapons attack.

References

1. Turnbull PCB. Introduction: anthrax history, disease and ecology. Curr Top Microbiol Immunol. 2002;271:1–19.
2. Grabenstein JD. Anthrax vaccine: a review. Immunol Allergy Clin North Am. 2003;23:713–30.
3. Irmak H, Buzgan T, Karahocagil MK, et al. Cutaneous manifestations of anthrax in Eastern Anatolia: a review of 39 cases. Acta Med Okayama. 2003;57:235–40.
4. Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. N Engl J Med. 1999;341:815–26.
5. Watson A, Keir D. Information on which to base assessments of risk from environments contaminated with anthrax spores. Epidemiol Infect. 1994;113:479–90.
6. Chensue SW. Exposing a killer: pathologists angle for anthrax. Am J Pathol. 2003;163:1699–702.
7. Moayeri M, Leppla SH. The roles of anthrax toxin in pathogenesis. Curr Opin Microbiol. 2004;7:19–24.
8. Brook I. The prophylaxis and treatment of anthrax. Int J Antimicrob Agents. 2002;20:320–5.
9. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. Science. 1994;266:1202–8.
10. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA. 2002;287:2236–52.

11. Cinti SK, Saravolatz L, Nafziger D, Sunstrum J, Blackburn G. Differentiating inhalational anthrax from other influenza-like illnesses in the setting of a national or regional anthrax outbreak. Arch Intern Med. 2004;164:674–6.

12. Stephenson J. Rapid anthrax test approved. JAMA. 2004;292:30.

13. http://www.immunetics.com/anthrax.html. Accessed 5/28/15.

14. Kim J, Gedi V, Cho JH, Moon JY, Yoon MY. Advances in anthrax detection: overview of bioprobes and biosensors. Appl Biochem Biotechnol. 2015;176:957–77. doi:10.1007/s12010-015-1625-z.

15. Lebowich RJ, McKillip BG, Conboy JR. Cutaneous anthrax: a pathologic study with clinical correlation. Am J Clin Pathol. 1943;13:505–15.

16. Mallon E, McKee PH. Extraordinary case report: cutaneous anthrax. Am J Dermatopathol. 1997;19:79–82.

17. http://www.cdc.gov/anthrax/. Accessed 5/28/15.

18. Kaya A, Tasyaran MA, Erol S, Ozkurt Z, Ozkan B. Anthrax in adults and children: a review of 132 cases in Turkey. Eur J Clin Microbiol Infect Dis. 2002;21:258–61.

19. Hendricks KA, Wright ME, Shadomy SV, et al. Center for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis. 2014;20(2):e130687. doi:10.3201/eid2002.130687.

20. Bast DJ, Athamna A, Duncan CL, et al. Type II topoisomerase mutations in Bacillus anthracis associated with high-level fluoroquinolone resistance. J Antimicrob Chemother. 2004;54:90–4.

21. Krishnan V, Anderson BH, Shoemaker C, et al. Efficacy and immunogenicity of a single-dose AdVAV intranasal anthrax vaccine compared to anthrax vaccine Absorbed in an aerosolized spore rabbit challenge model. Clin Vaccine Immunol. 2015;22(4):430–9. doi:10.1128/CVI.00690-14. Epub 2015 Feb 11.

30
Ecthyma Gangrenosum

■ Synonyms:	None
■ Etiology:	*Pseudomonas aeruginosa* and other Gram-negative bacteria, similar lesions caused by opportunistic fungi
■ Associations:	Immunosuppression, premature infants
■ Clinical:	Indurated plaques with black eschar and rim of erythema, favors axillae, inguinal folds, and perineum
■ Histology:	Mixed infiltrate of lymphocytes, neutrophils, plasma cells; special stains of affected skin usually demonstrate the organism
■ Evaluation:	Blood cultures, skin biopsy with fresh tissue culture, special stains on touch preps of skin biopsy, consider frozen section
■ Treatment:	Aimed at the specific infectious agent
■ Prognosis:	High mortality rate; worse with extensive skin disease, prolonged immunosuppression, and delayed treatment

Ecthyma gangrenosum describes a cutaneous infection with *Pseudomonas aeruginosa* that is manifested by necrotic plaques with an eschar. The infection usually occurs in immunosuppressed patients. Three to six percent of *Pseudomonas* septicemia is complicated by ecthyma gangrenosum [1]. The term *ecthyma gangrenosum* was given by Hitschmann and Kreibich in 1897 in Germany to describe necrotic cutaneous plaques due to cutaneous involvement in disseminated *Pseudomonas* infection. However, ecthyma gangrenosum is now known to be a morphologic pattern of cutaneous infection caused by a wide variety of organisms.

Ecthyma gangrenosum usually starts as an erythematous macule, which subsequently forms a vesicle. Multiple lesions may occur. Lesions rapidly become indurated and may develop pustules or bullae, which slough and leave an ulcer. An eschar forms, with a rim of erythema (Fig. 30.1). The disease has a strong predilection for axillae, inguinal folds, and perineum, so-called "apocrine" areas. Extremities, trunk, and face are affected less frequently. Though once regarded as cutaneous seeding during *Pseudomonas* bacteremia, most cases represent aggressive primary infection, which may disseminate in immunosuppressed patients. Synchronous multiple lesions of the perineum, genitalia, and axillae are common. This pattern of infection supports the notion that ecthyma gangrenosum arises in the skin and then disseminates. In one series, folliculitis due to

Pseudomonas aeruginosa O-11 from a hospital water supply rapidly developed into ecthyma gangrenosum in six hospitalized immunosuppressed patients [2]. This represents a common scenario in which early lesions resemble a bacterial folliculitis and then rapidly progress to typical ecthyma gangrenosum lesions. In the largest series of patients with ecthyma gangrenosum, over 75 % were felt to originate in the skin, and two thirds primarily involved apocrine areas. Some patients developed septicemia [1].

The majority of patients who develop ecthyma gangrenosum are neutropenic, either secondary to chemotherapy or due to primary immunodeficiency. The disease may be a presenting sign of underlying neutropenia in previously healthy children [3]. The disease has also been described in HIV-infected patients in the absence of neutropenia and in patients with other forms of immunosuppression [4, 5]. A neonatal form of the disease termed *noma neonatorum* occurs in premature infants. In addition to anogenital involvement, this presentation has a distinct orofacial predilection [6]. A necrotizing stomatitis, the mucosal equivalent of ecthyma gangrenosum, has also been described in immunocompromised patients [7].

Classical ecthyma gangrenosum is usually caused by *Pseudomonas aeruginosa*, but may be caused by several other Gram-negative bacteria (Table 30.1). Similar lesions in immunosuppressed patients may be caused by a multi-

Figure 30.1. Indurated erythematous plaque with central ulceration and eschar.

Table 30.1. Causes of ecthyma gangrenosum and similar lesions in immunosuppressed patients

Bacteria
   Pseudomonas aeruginosa
   Escherichia coli [8]
   Morganella morganii [9]
   Klebsiella pneumoniae [10]
   Citrobacter freundii [11]
   Xanthomonas (Stenotrophomonas) maltophilia [12]
   Aeromonas hydrophila [13]
   Chromobacterium violaceum [14]
Fungi
   Curvularia sp. [15]
   Candida sp. [16]
   Fusarium sp. [17]
   Scytalidium dimidiatum [18]
   Metarhizium anisopliae [19]
   Mucor sp. [20]
   Exserohilum sp. [21]
   Aspergillus niger [22]

tude of opportunistic fungi. These patients usually do not present with the typical apocrine folliculocentric lesions. However, the morphologic features of individual lesions may closely resemble ecthyma gangrenosum. As in bacterial ecthyma gangrenosum, cutaneous lesions due to opportunistic fungi may be a manifestation of hematogenous dissemination with secondary seeding of the skin. Alternatively, they may represent primary invasive infection, which may then disseminate. Gastrointestinal and respiratory tracts and skin are common portals of entry for disseminated infections. Invasive infections of the skin may occur in previously normal skin, but are more likely to occur in areas that have had a disrupted barrier, such as sites of vascular access, venipuncture, burns, or surgical procedures.

The clinical presentation of ecthyma gangrenosum in an immunosuppressed patient constitutes a medical emergency. Investigation into the etiologic agent must be pursued urgently, so that appropriate antibiotic therapy can be instituted. A list of organisms known to cause ecthyma gangrenosum or similar lesions in the immunosuppressed patient is given in Table 30.1.

The organisms listed in Table 30.1 cause ecthyma gangrenosum or lesions closely resembling it. However, numerous yeasts, and fungi causing hyalohyphomycosis and phaeohyphomycosis, can cause invasive cutaneous infections in immunocompromised hosts. These cutaneous lesions may include subcutaneous and dermal nodules or cellulitis. Since morphologic overlap with ecthyma gangrenosum could occur with a multitude of organisms, the list included in the table should not be viewed as comprehensive.

A clinical presentation of necrotizing papules and plaques in apocrine areas of an immunosuppressed patient strongly suggests ecthyma gangrenosum, but the differential diagnosis for a plaque or plaques with eschar is much wider, including true ecthyma caused by *Staphylococcus* or *Streptococcus* species, arachnid or arthropod bite reactions, anthrax, tularemia, diphtheria, syphilitic chancre, herpes simplex virus infection, and orf. Similar lesions may develop in patients with septicemic plague (*Yersinia pestis*) [23]. Also in the differential diagnosis is Fournier's gangrene, a polymicrobial acute necrotizing infection of the genitalia. Causes include *Streptococcus* and *Staphylococcus* species, usually in combination with various Gram-negative and anaerobic bacteria. This infection differs from ecthyma gangrenosum in its frequent occurrence in diabetics, severe pain, and tissue crepitus.

Cultures of the blood will reveal the organism in most cases of septicemic ecthyma gangrenosum. Since bacterial and fungal causes are morphologically indistinguishable, both bacterial and fungal cultures should be performed. The laboratory should be notified of the suspicion of opportunistic infection to minimize the possibility that a true positive culture will be dismissed as a contaminant. Tissue evaluation may include skin biopsy with touch preps, microbial stains, and culture. Touch preps may be stained with gram stain for bacteria and calcofluor white for fungi. Frozen sections from affected tissue with and without special stains may aid in more rapid diagnosis.

Biopsy findings in ecthyma gangrenosum include dermal edema and an infiltrate composed of neutrophils, lymphocytes, histiocytes, and plasma cells within the dermis and subcutaneous tissue (Fig. 30.2a, b). There is vascular proliferation and variable epidermal necrosis. Organisms may be found with special stains in most cases. The organisms are usually located within the interstitium and adventitia of venules. The findings in ecthyma gangrenosum differ from those of bacterial septic vasculitis in which there is vascular damage associated with fibrin thrombi and intraluminal bacteria [24].
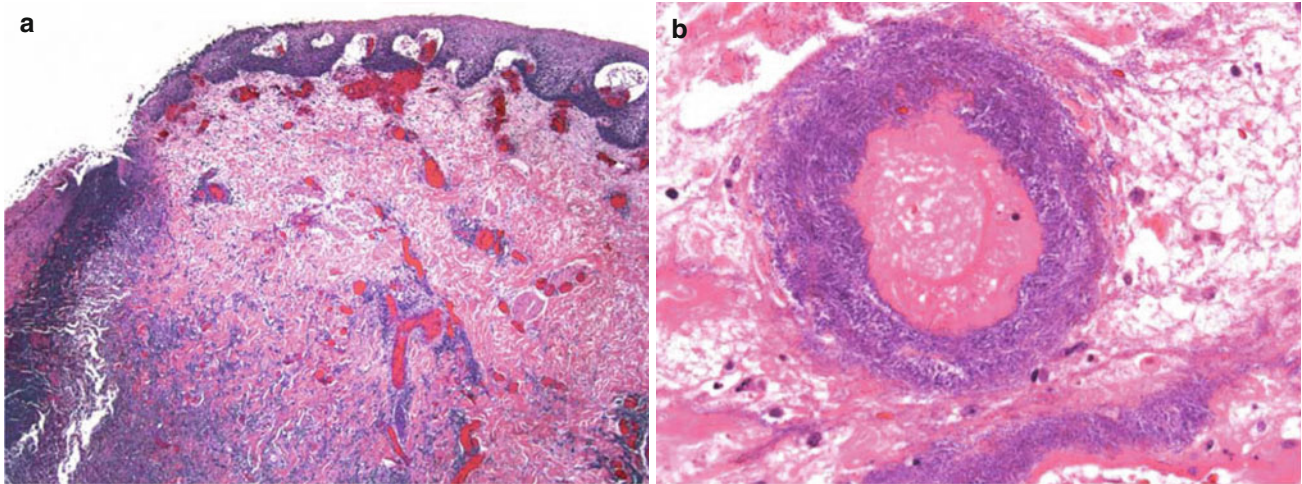
Figure 30.2. (**a**) Deep ulcer with vascular congestion and neutrophil-rich infiltrate. (**b**) Numerous intravascular, perivascular, and interstitial *Pseudomonas* bacilli.

Treatment of ecthyma gangrenosum is directed by the etiologic agent. However, initially, broad-spectrum antibiotic therapy must be undertaken urgently because of the high mortality associated with delayed treatment. Prognosis in ecthyma gangrenosum is dependent upon the infectious agent, but also the degree and duration of immunosuppression and the extent of cutaneous involvement [24].

References

1. El Baze P, Thyss A, Vinti H, Deville A, Dellamonica P, Ortonne JP. A study of nineteen immunocompromised patients with extensive skin lesions caused by *Pseudomonas aeruginosa* with and without bacteremia. Acta Derm Venereol (Stockh). 1991;71:411–5.

2. El Baze P, Thyss A, Caldani C, Juhlin L, Schneider M, Ortonne JP. *Pseudomonas aeruginosa* O-11 folliculitis: development into ecthyma gangrenosum in immunocompromised patients. Arch Dermatol. 1985;121:873–6.

3. Cohen N, Capua T, Bilavsky E, Dias-Polak H, Levin D, Grisaru-Soen G. Ecthyma gangrenosum skin lesions in previously healthy children. Acta Paediatr. 2015;104:e134–8.

4. Khan MO, Montecalvo MA, Davis I, Wormser GP. Ecthyma gangrenosum in patients with acquired immunodeficiency syndrome. Cutis. 2000;66:121–3.

5. Bettens S, Delaere B, Glupczynski Y, Schoevaerdts D, Swine C. Ecthyma gangrenosum in a non-neutropaenic, elderly patient: case report and review of the literature. Acta Clin Belg. 2008;63:394–7.

6. Freeman AF, Mancini AJ, Yogev R. Is noma neonatorum a presentation of ecthyma gangrenosum in the newborn? Pediatr Infect Dis J. 2002;21:83–4.

7. Barasch A, Gordon S, Geist RY, Geist JR. Necrotizing stomatitis: report of 3 *Pseudomonas aeruginosa*-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96:136–40.

8. Edelstein H, Cutting HO. *Escherichia coli* as cause of ecthyma gangrenosum. Postgrad Med. 1986;79:44–5.

9. Del Pozo J, Garcia-Silva J, Almagro M, Martinez W, Nicolas R, Fonseca E. Ecthyma gangrenosum-like eruption associated with *Morganella morganii* infection. Br J Dermatol. 1998;139:520–1.

10. Rodot S, Lacour JP, van Elslande L, Castanet J, Desruelles F, Ortonne JP. Ecthyma gangrenosum caused by *Klebsiella pneumoniae*. Int J Dermatol. 1995;34:216–7.

11. Reich HL, Fadeyi DW, Naik NS, Honig PJ, Yan AC. Nonpseudomonal ecthyma gangrenosum. J Am Acad Dermatol. 2004;50:S114–7.

12. Vartivarian SE, Papadakis KA, Palacios JA, Manning JT, Anaissie EJ. Mucocutaneous and soft tissue infections caused by *Xanthomonas maltophilia*. Ann Intern Med. 1994;121:969–73.

13. Shackleford P, Ratzan SA, Shearer T. Ecthyma gangrenosum produced by *Aeromonas hydrophila*. J Pediatr. 1973;83:100–1.

14. Brown KL, Stein A, Morrell DS. Ecthyma gangrenosum and septic shock syndrome secondary to *Chromobacterium violaceum*. J Am Acad Dermatol. 2006;54:S224–8.

15. Bouduel M, Santos P, Turienzo CF, Chantada G, Paganini H. Atypical skin lesions caused by *Curvularia* sp. and *Pseudallescheria boydii* in two patients after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2001;27:1311–3.

16. File Jr TM, Marina OA, Flowers FP. Necrotic skin lesions associated with disseminated candidiasis. Arch Dermatol. 1979;115:214–5.

17. Martino P, Gastaldi R, Raccah R, Girmenia C. Clinical patterns of *Fusarium* infections in immunocompromised patients. J Infect. 1994;28(S1):7–15.

18. Benne CA, Neeleman C, Bruin M, de Hoog GS, Fleer A. Disseminating infection with *Scytalidium dimidiatum* in a granulocytopenic child. Eur J Clin Microbiol Infect Dis. 1993;12:118–21.

19. Burgner D, Eagles G, Burgess M, et al. Disseminated invasive infection due to *Metarhizium anisopliae* in an immunocompromised child. J Clin Microbiol. 1998;36:1146–50.

20. Kramer BS, Hernandez AD, Reddick RL, Levine AS. Cutaneous infarction. Manifestation of disseminated mucormycosis. Arch Dermatol. 1977;113:1075–6.

21. Levy I, Stein J, Ashkenazi S, Samra Z, Livni G, Yaniv I. Ecthyma gangrenosum caused by disseminated *Exserohilum* in a child with leukemia: a case report and review of the literature. Pediatr Dermatol. 2003;20:495–7.

22. Panke TW, McManus AT, Spebar MJ. Infection of a burn wound by *Aspergillus niger*: gross appearance simulating ecthyma gangrenosum. Am J Clin Pathol. 1979;72:230–2.

23. Welty TK, Grabman J, Kompare E, et al. Nineteen cases of plague in Arizona: a spectrum including ecthyma gangrenosum due to plague and plague in pregnancy. West J Med. 1985;142:641–6.

24. Greene SL, Su WPD, Muller SA. Ecthyma gangrenosum: report of clinical, histopathologic, and bacteriologic aspects of eight cases. J Am Acad Dermatol. 1984;11:781–7.

31
Rocky Mountain Spotted Fever and Rickettsioses

■ Synonyms:	None	
■ Etiology:	*Rickettsia rickettsii* following *Dermacentor* sp. tick bite	
■ Associations:	Outdoor recreational activity	
■ Clinical:	Fever/headache followed by macules and petechial eruption of wrists/ankles with subsequent generalization	
■ Histology:	Lymphocytic vasculitis with vascular thrombosis, epidermal necrosis organisms with special stains seen in vascular wall	
■ IHC repertoire:	Organisms identified by immunohistochemical and immunofluorescent antibodies	
■ Staging:	Not applicable	
■ Prognosis:	Fatality rate of 20–30%, worse in the elderly or with coexisting G6PD deficiency	
■ Adverse variables:	Renal failure, myocarditis, arrhythmias, DIC, and ARDS	
■ Treatment:	Intravenous tetracycline, doxycycline, or chloramphenicol	

Rickettsioses constitute a diverse group of arthropod-borne human diseases capable of producing significant morbidity and mortality. They share important pathologic and clinical attributes that permit their diagnosis in most instances [1]. Rickettsioses are responsible for a great number of deaths seen particularly in times of war. It is estimated that over three million combatants and civilians in the First World War succumbed to epidemic typhus. Among the more deadly types of infection belonging to this group is Rocky Mountain spotted fever, the principal subject of this chapter.

Rickettsioses are endemic to most areas of the world where contact with arthropods, namely, biting ticks, mites, fleas, and lice, can be found. They can be broadly categorized into tick-borne agents that principally include Rocky Mountain spotted fever (*R. rickettsii*) and Mediterranean fevers (*R. conorii*), mite-borne diseases including *rickettsialpox* (*R. akari*) and *scrub typhus* (*Orientia tsutsugamushi*, formerly *R. tsutsugamushi*), flea-borne *endemic typhus* (*R. typhi*), and louse-borne *epidemic typhus* (*R. prowazekii*). *Q fever* is unique within the group as its etiologic agent *Coxiella burnetii* is acquired following aerosolization of infected tissues. They can also be subcategorized into the spotted fever group or the typhus group on the basis of shared immunologic or biologic properties [2]. The infectious agents are among the smallest of bacteria at 0.3–

10^{-6} μm. They are considered to be gram-negative and exist as pleomorphic-appearing bodies either exclusive to the cytoplasm of infected cells (typhus group) or the nucleus and cytoplasm (spotted fever group). They require passage via blood-consuming arthropod vectors that use infected mammals and the arthropods themselves as a reservoir. Once introduced into the skin, the organisms attach to endothelial cell membranes until phagocytosed by inflammatory cells with subsequent hematogenous or lymphatic passage throughout the body.

Rocky Mountain spotted fever (RMSF) was first described in the late nineteenth century among settlers in the still-wild frontier of the American West, hence the term "Rocky Mountain" fever. RMSF is the most common rickettsial infection reported in North America and, though found throughout the continent, is most common in the south Atlantic region of the United States [3]. The most important vector for disease is the dog tick or *Dermacentor variabilis* and the Rocky Mountain wood tick *Dermacentor andersoni*. The etiologic agent *R. rickettsii* is transmitted with blood meals of the infecting ticks, which usually requires at least a 6-h interval of feeding [4]. Most infections occur during the summer and are most commonly seen in children or adult males engaged in outdoor recreational activity. *American Indians also have an increased risk of contracting the disease* [5]. *Since 2000, the incidence of*

RMSF in the United States has increased from 1.7 to 7 cases per million, though the case fatality rate has decreased from 2.2 to 0.3 %. This trend may reflect changes in diagnostic and surveillance practices [6]. Insect repellants, protective outer garments, periodic tick surveillance, and timely and efficacious extraction of feeding ticks are all important means of disease prevention [7].

The clinical manifestations are ushered in by high fever, chills, myalgia, and headache at an average of 7 days following exposure (range 2–14 days). The fever often exceeds 102 degrees and may be accompanied by gastrointestinal complaints [8]. The cutaneous manifestation, namely, rash, follows within 2–4 days after the initial complaints and consists of a macular followed by papular petechial rash (Fig. 31.1). The rash initially begins on the wrists and/or ankles and spreads to the trunk over the ensuing day. Palm and/or sole involvement is fairly uncommon, yet can occur. The classic triad of fever, headache, and rash is present in about 60 % of patients. A distinct minority (~10 %) of patients may never develop rash, so-called spotless fever. This is most commonly seen in the elderly or among the dark-skinned races. The rash is most often accompanied by systemic manifestations including hypovolemia, tachycardia, and peripheral edema. Important complications include epidermal necrosis in conjunction with ischemic vascular thrombosis with digital or extremity loss, scarring, and visceral organ failure including hepatic or renal failure, cardiomyopathy with electrical instability, disseminated intravascular coagulation, the adult respiratory distress syndrome,

and CNS involvement with delirium or seizure. Motor deficits, cranial nerve palsy, or coma may also be seen. *The presence of neurologic sequelae is associated with increased morbidity and mortality* [9].

Important laboratory abnormalities routinely encountered in these patients include thrombocytopenia and normochromic normocytic anemia with increased prothrombin times and decreased fibrinogen, hyponatremia, hepatic transaminasemia with hyperbilirubinemia, and elevated BUN and creatinine levels.

Biopsies from the skin rash show perivascular lymphocytic infiltrates with variable degrees of vascular disruption including fibrin deposits and thrombosis (lymphocytic vasculitis), dermal purpura, and edema (Figs. 31.2, 31.3, and 31.4) [10]. The overlying epithelium may undergo necrosis in conjunction with ischemic vascular thrombosis. The organisms may be positively identified within the endothelia with the aid of immunohistochemical or immunofluorescent staining [11]. Molecular-based methods including in situ PCR have also been utilized but are not widely available [12]. Serologic methods remain the most important means of establishing a definitive diagnosis, although they suffer from a delay in diagnosis requiring comparison of acute and convalescent antibody titers. The Weil-Felix and complement-based serologic methods are antiquated due to poor sensitivity [13].

The differential diagnosis of RMSF is broad. Important viral entities to consider include measles, rubella, and infectious mononucleosis. Measles more often presents with upper (coryza) and lower respiratory (cough) com-

FIGURE 31.1. Maculopapular eruption with petechial hemorrhage in Rocky Mountain spotted fever.

Figure 31.2. Low-power photomicrograph depicting superficial and deep lymphocytic dermatitis with focal epithelial exocytosis. Note the prominent dermal hemorrhage.
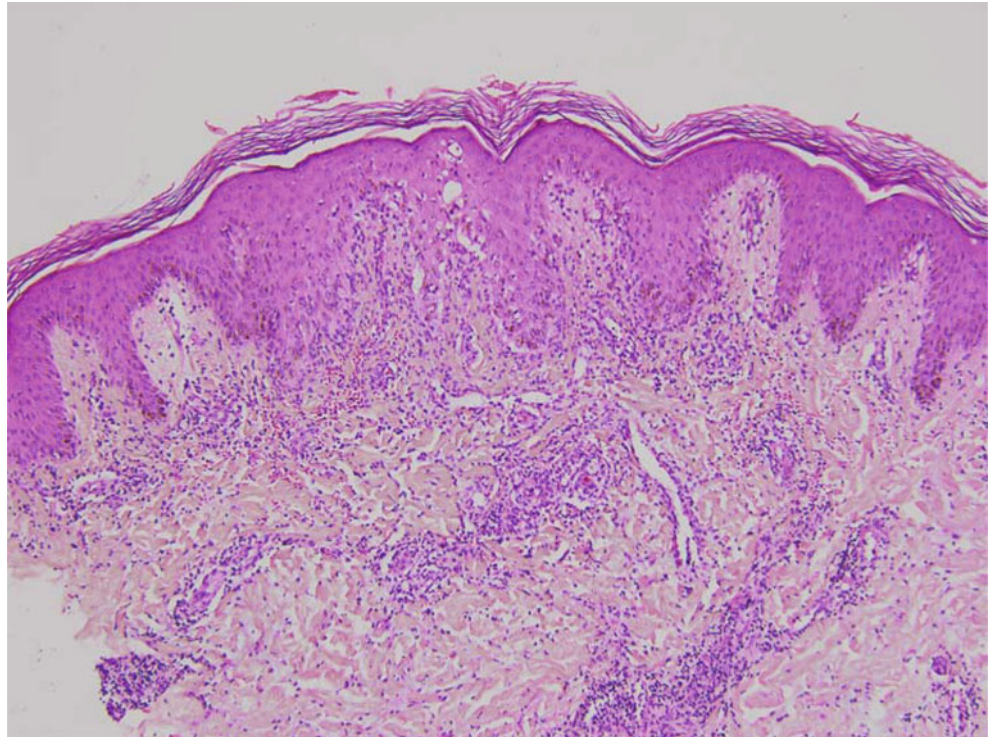

Figure 31.3. Medium-power photomicrograph detailing perivascular lymphocytic infiltrate.
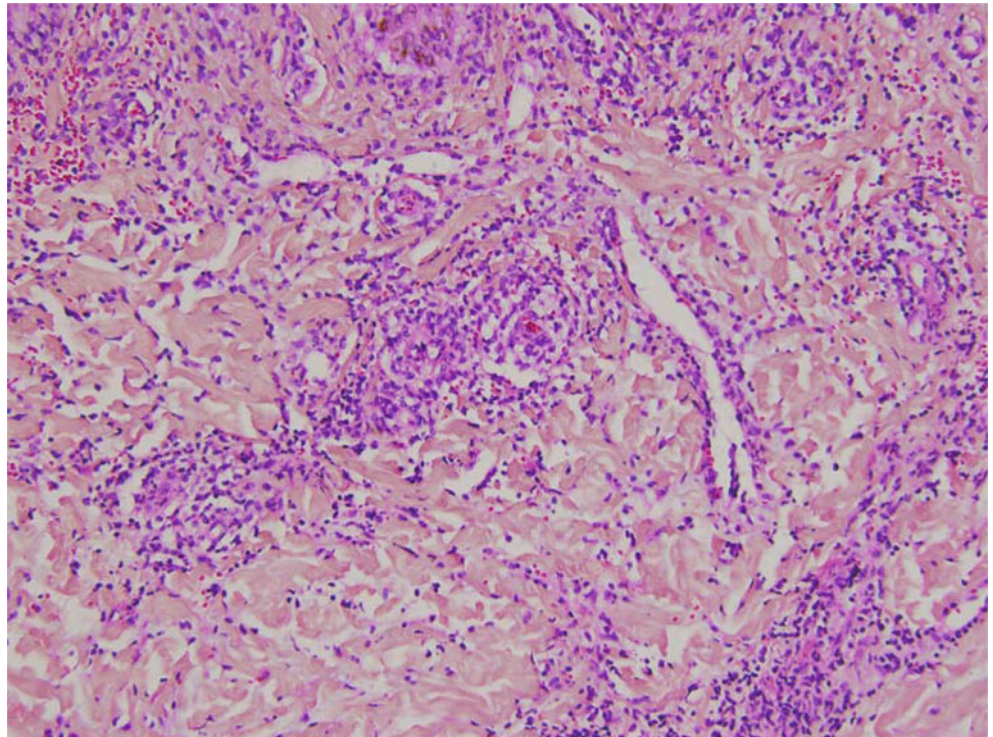
plaints and less often produces a petechial rash. Rubella tends to be less symptomatic than RMSF and produces a less dramatic rash that typically begins on the face. Infectious mononucleosis (Epstein-Barr viral infection)

less often produces a rash (~10% of patients) unless preceded by the administration of ampicillin. Important bacterial infections to exclude include in particular meningococcemia, tularemia, and leptospirosis. The rash
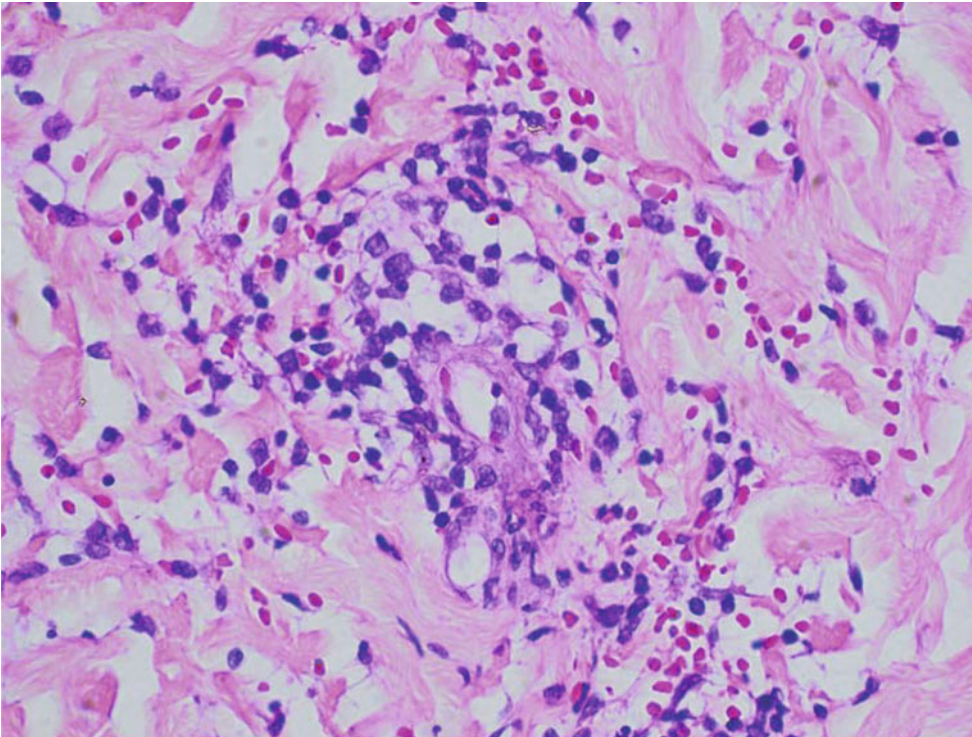
FIGURE 31.4. High-power detail with perivascular lymphocytes and erythrocytes. Note fibrin deposits in proximity to the capillaries.

of meningococcemia typically develops in conjunction with or shortly following the onset of symptoms and is often accompanied by leukocytosis. The rash of meningococcemia tends to produce larger and confluent stellate configured purpuric areas with an angulated border. Tularemia tends to produce solitary, often ulcerated, or eschar-like cutaneous lesions with draining lymphadenopathy. Leptospirosis produces a rash that typically begins on the trunk, spreading later to the extremities. A clinical variant of leptospirosis termed Fort Bragg or pretibial fever produces a petechial rash confined to the pretibial surfaces.

Empiric intravenous antibiotics should be instituted prior to biopsy or serologic confirmation as the untreated mortality approaches 30 % [8]. Treatment recommendations are tetracycline 25–50 mg/kg q 6 h or doxycycline 1 mg/lb q 12 h or chloramphenicol 50–75 mg/kg q 6 h for at least 7 days or until 2 days following resolution of symptoms. *For critically ill patients, some experts recommend initiating therapy with IV antibiotics for the first 3 days* [14]. Aggressive fluid status and electrolyte balance management is essential. The overall mortality of RMSF is between 2 and 5 % with appropriate antibiotic therapy. Most fatalities are observed between the eighth and fifteenth days of illness. *Geography appears to play a role with increased severe cases seen in Southwest Tennessee and particularly low death rates in parts of North Carolina* [15]. Elderly patients and those individuals with coexisting glucose-6-phosphate dehydrogenase deficiency have been reported to have a worse prognosis.

References

1. Zaki M. Selected tickborne infections: a review of Lyme disease. Rocky Mountain spotted fever and babesiosis. N Y State J Med. 1989;89:320.
2. Boyd A, Neldner K. Typhus disease group. Int J Dermatol. 1992;31:823.
3. Helmick C, Bernard K, d'Angelo L. Rocky Mountain spotted fever: clinical, laboratory and epidemiological features of 262 cases. J Infect Dis. 1984;150:480.
4. Woodward T. Rocky Mountain spotted fever: epidemiological and early clinical signs are keys to treatment and reduced mortality. J Infect Dis. 1984;150:465.
5. Folkema AM, Holman RC, McQuiston JH, Cheek JE. Trends in clinical diagnoses of Rocky Mountain spotted fever among American Indians, 2001–2008. Am J Trop Med Hyg. 2012;86:152.
6. Openshaw JJ, Swerdlow DL, Krebs JW, et al. Rocky Mountain spotted fever in the United States, 2000–2007: interpreting contemporary increases in incidence. Am J Trop Med Hyg. 2010;83:174.
7. Cowan G. Rickettsial diseases: the typhus group of fevers—a review. Postgrad Med J. 2000;76:269.
8. Weber D, Walker D. Rocky Mountain spotted fever. Infect Dis Clin North Am. 1991;5:19.
9. Buckingham SC, Marshall GS, Schutze GE, et al. Clinical and laboratory features, hospital course, and outcome of Rocky Mountain spotted fever in children. J Pediatr. 2007;150:180.
10. Kao G, Evancho C, Ioffe O, et al. Cutaneous histopathology of Rocky Mountain spotted fever. J Cutan Pathol. 1997;24:604.
11. Walker C, Cain B, Olmstead P. Laboratory diagnosis of Rocky Mountain spotted fever by immunofluorescent demonstration of *Rickettsia rickettsii* in cutaneous lesions. Am J Clin Pathol. 1978;69:619.

12. Woodward T, Pederson C, Oster C, et al. Prompt confirmation of Rocky Mountain spotted fever: identification of Rickettsiae in skin tissues. J Infect Dis. 1976;134:297.

13. Kaplan J, Schonberger L. The sensitivity of various serologic tests in the diagnosis of Rocky Mountain spotted fever. Am J Trop Med Hyg. 1986;35:840.

14. Cunha BA. Clinical features of Rocky Mountain spotted fever. Lancet Infect Dis. 2008;8:143.

15. Adjemian JZ, Krebs J, Mandel E, McQuiston J. Spatial clustering by disease severity among reported Rocky Mountain spotted fever cases in the United States, 2001–2005. Am J Trop Med Hyg. 2009;80:72.

32
Smallpox

- ■ Synonyms: Variola, alastrim, amaas
- ■ Etiology: Infection with variola poxvirus
- ■ Associations: Since eradication in 1979, confirmed presence should prompt consideration of biowarfare/terrorism
- ■ Clinical: Influenza-like prodrome ~ 3 days prior to erythematous macular rash into vesiculating papules to umbilicated pustules and finally scars
- ■ Histology: Intraepidermal and subepidermal vesiculation with neutrophils predominating, epithelium with eosinophilic (Guarnieri) inclusions
- ■ IHC repertoire: N/A
- ■ Staging: None
- ■ Prognosis: Overall ~30 % mortality
- ■ Adverse factors: Confluent eruption, thrombocytopenia/DIC
- ■ Treatment: Prevented with vaccination, cidofovir efficacious in animal studies

Smallpox, otherwise known as *variola*, was first described in ancient Chinese texts dating from the eleventh century B.C. The Chinese were the first to discover that purposeful inoculation of lesional material into the nose of the uninfected was preventative - disease in the sixth century B.C. [1]. Although the disease was officially eradicated in 1979, known stocks of the material have been maintained in biolabs located in Russia and the United States, where they pose a potential source of public health concern if subverted as biowarfare agents [2–5]. Smallpox belongs to the poxvirus group of double-stranded DNA-containing viruses that includes vaccinia, molluscum contagiosum, and cowpox. The poxviruses are among the largest of all human viruses, attaining a maximum diameter of 300 nm, and possess characteristic rectangular or cylindrical outer capsids and a central DNA core [6].

Natural infection follows contact with an infectious human most commonly via respiratory droplets but may also occur with skin inoculation or fomite spread. The virus is hearty and resistant to desiccation. Scales and desquamated epithelium harbor viable virus for long periods. Following exposure, there is an asymptomatic 10–14-day period in which viral replication occurs within infected respiratory mucosa and associated draining lymphatic tis-

sues. This phase of infection (primary viremia) coincides with generalized involvement of the reticuloendothelial organs including the liver, spleen, and lymph organs. Secondary viremia then follows in which systemic spread of the virus through the bloodstream occurs, heralding the onset of an influenza-like prodromal syndrome. Prodromal symptoms, which last 2–4 days, include high fever, severe headache, back pain, and vomiting [7]. Red lesions first appear on the tongue and inside the mouth, which further develop into sores that will eventually release copious amounts of virus [7]. During this prodromal phase, a characteristic and fleeting maculopapular rash involving the waist and proximal lower extremities may occur. The patient remains noninfectious during the prodromal phase, becoming infectious only when the exanthem appears. Laboratory testing during this period often yields abnormal coagulation parameters including thrombocytopenia and altered clotting times that may be associated with the development of the disseminated intravascular coagulation (DIC) syndrome. Abnormal bleeding is an ominous sign ascribed to the hemorrhagic form of the disease (*purpura variolosa*) with a generally fatal outcome. With secondary viremia, there is viral spread to the mucosa and skin epithelium, initiating the characteristic exanthematous rash of

the disorder approximately 3 days after prodromal symptoms begin.

Although the morphology and course of individual rash lesions are similar, their number can vary [6]. Mild forms of the disease (*alastrim*, *variola minor*) are characterized by a sparse number of lesions, whereas more severe forms may present with a confluent eruption. Lesions tend to be peripherally distributed with the greatest number located over the extremities and face (Fig. 32.1). The earliest lesion consists of an erythematous macule that proceeds to a deep-seated papule with a cloudy appearing surmounted vesicle. The vesicle is multiloculated and resilient. The lesions mature generally within 7 days into pustules with characteristic central umbilication. Within 10 days, the surface forms a crusted scab, healing as a depressed scar. Occasionally, the lesions may present as crusted plaques or pass through the various stages without vesicle or pustule formation. Mucosal involvement often noted at the time of the exanthem includes ocular, genital, or oropharyngeal disease including upper airway obstruction with laryngeal and tracheal involvement. Visceral disease may take the form of pneumonitis, encephalitis, osteomyelitis, orchitis, or hepatitis. Pneumonia and encephalitis constitute serious complications that may eventuate in death.

The histologic features seen in variola are suggestive of the disorder [8]. Early lesions show dermal edema with neutrophilic capillaritis. Developed lesions of smallpox show, in addition to the dermal edema, pronounced intraepidermal vesiculation with exocytosis of neutrophils (Figs. 32.2 and 32.3). The blister cavity may contain or be surrounded by epithelial cells that possess characteristic eosinophilic granular inclusions known as *Guarnieri bodies* (Fig. 32.4). Elementary or Paschen viral bodies may be demonstrated with Giemsa staining scrapped from or expressed from lesional material. Multinucleation, nuclear molding, and/or nucleus inclusions typical of the herpesvirus infections are not identified.

Diagnosis of suspected cases of smallpox has obvious global implications and public health ramifications. Once presumptively diagnosed on the basis of the clinical presentation, the disease should now be confirmed by ancillary diagnostic techniques and in conjunction with public health agencies. Genomic-based technologies, including PCR techniques and fluorescent antibody testing of infectious material, provide fairly rapid and presumptive results, but the gold standard for identification involves tissue culturing and anti-serum neutralization. The diagnosis can also be achieved serologically through retrospective analysis of paired acute and convalescent sera.

The most important disorder to distinguish from smallpox is *chickenpox*. The latter typically produces little if any prodromal symptoms and is associated with successive crops of lesions, thus showing lesions in various stages of development. There is a tendency of the lesions of smallpox to be peripherally distributed, larger, more often deep seated, to possess central umbilication, and to become confluent compared to chickenpox.

There is no effective treatment for established cases. Ongoing trials with the antiviral agent cidofovir have been

FIGURE 32.1. Multiple ulcerating pustules with erythematous bases seen in smallpox.

**Figure 32.2.** Low-power photomicrograph showing epidermal blister with subepidermal necrosis.
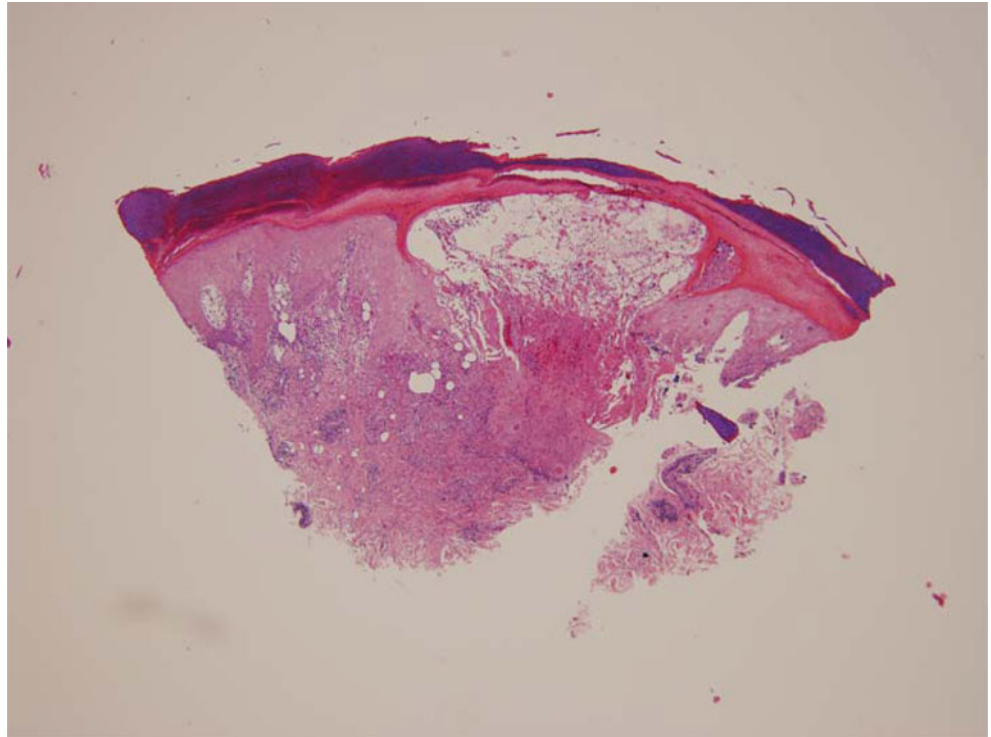
Figure 32.3. Medium-power photomicrograph showing blister with reticular degeneration.
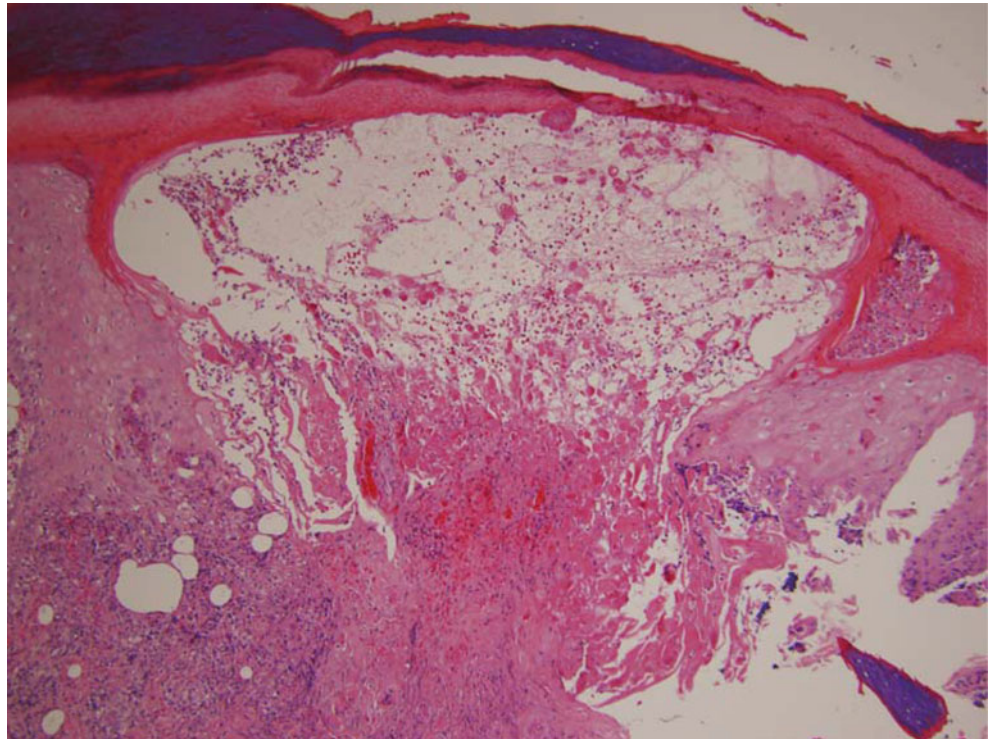
promising in animal models. Treatment with immune globulin, anti-vaccinia serum, and thiosemicarbazone has been attempted in the past with questionable efficacy. Supportive measures aimed at reducing secondary bacterial infection and monitoring fluid and electrolyte levels are important. Prevention remains the most important means of deterring smallpox. The Jennerian vaccination consists of the purposeful inoculation of vaccinia virus (a
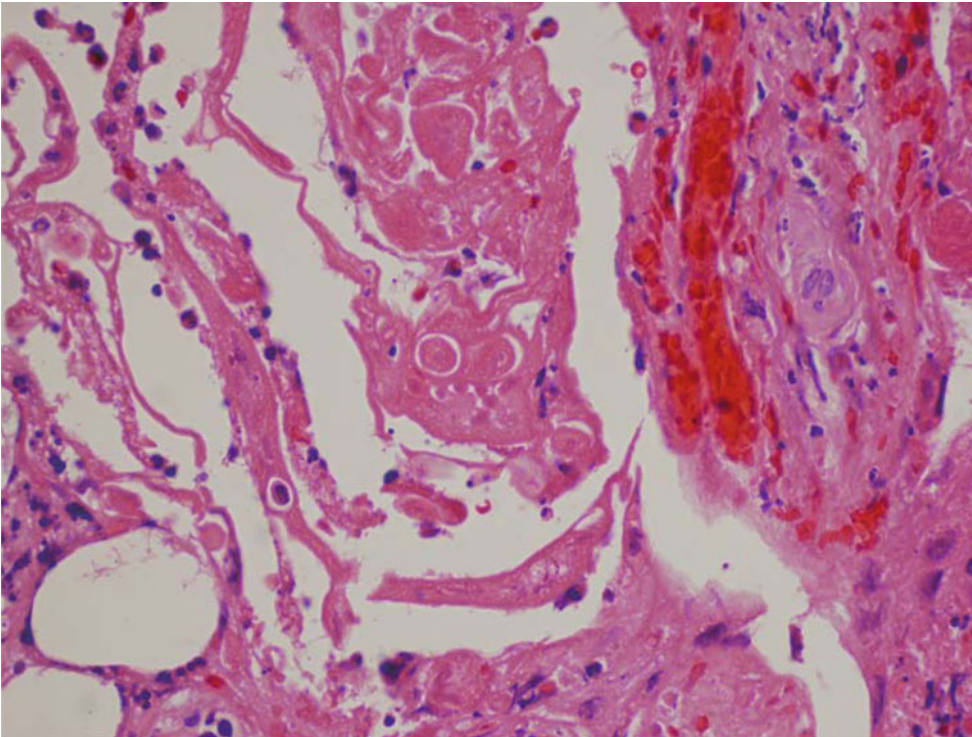
FIGURE 32.4. High-power detail of blister cavity. Note central rounded eosinophilic bodies (Guarneri) associated with smallpox cytopathic effect.

laboratory-altered form of smallpox) into the skin [9]. Following inoculation, a crusted papule should develop at the site within 10 days of administration. Failure to develop an inoculation site lesion is an indication of ineffective immunization or loss of vaccine potency, and the immunization should be repeated. Vaccination is contraindicated in the immunosuppressed, infants, or individuals with atopy or other undisclosed dermatitis that may predispose them to dissemination of the virus. Vaccination against smallpox ended in 1972, leaving approximately 65 % of the current US population who have never received vaccination and, of those vaccinated, all have a questionable ability to mount an effective immune response. While antiviral antibody responses continue to be effective 1–75 years post inoculation, antiviral T cell responses slowly decline with a half-life of 8–15 years [10]. For these reasons, interest in vaccination, particularly among health-care workers and those who might respond to its use as a bioterrorism agent, has emerged. Although intentional release/biowarfare involving this agent is an unlikely scenario, researchers believe that the risk is outweighed by the need to preserve the live virus for future developments in antiviral vaccines and biomedical research. Fortunately, recent advances in recombinant DNA technology can render the virus incapable of replicating, producing disease in the setting of accidental contamination with potential far-reaching implications as it relates to prevention and/or therapies [11]. Widespread immunization of the public engenders important practical and medical concerns. Vaccine pro-

duction has only recently been reinstituted after a long hiatus and thus limited stocks are available. Important complications of the vaccine itself include hypersensitivity reaction, systemization or progressive cutaneous spread of the virus, encephalitis, and bacterial superinfection [9, 12, 13]. An increased incidence of myocardial infarction among recipients of the vaccine has also been recently reported [14].

The overall mortality rate of smallpox is 30 %. Individuals who develop disseminated or confluent lesions, DIC, encephalitis, or pneumonitis are at greater risk.

References

1. Breman J, Arita I. The confirmation and maintenance of smallpox eradication. N Engl J Med. 1980;303:1263.
2. Breman J, Henderson D. Poxvirus dilemmas: monkeypox, smallpox, and biologic terrorism. N Engl J Med. 1998;303:556.
3. Albert M, Ostheimer K, Breman J. The last smallpox epidemic in Boston and the vaccination controversy, 1901–1903. N Engl J Med. 2001;344:375.
4. Wehrle P. A reality in our time: certification of the global eradication of smallpox. J Infect Dis. 1980;242:636.
5. Fenner F. Global eradication of smallpox. Rev Infect Dis. 1982;4:916.
6. Henderson D. Smallpox. Clinical and epidemiologic features. Emerg Infect Dis. 1999;5:537.
7. Downie AW, St. Vincent L, Meiklejohn G, Ratnakannan NR, Rao AR, Krishnan GNV, Kempe CH. Studies virus content of

mouth washings in the acute phase of smallpox. Bull World Health Organ. 1961;25:49.

8. Michelson H, Ikeda K. Microscopic changes in variola. Arch Dermatol Syph. 1927;15:138.

9. Greenberg M. Complications of vaccination against smallpox. Am J Dis Child. 1948;76:492.

10. Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, Hanifin JM, Slifka MK. Duration of antiviral immunity after smallpox vaccination. Nat Med. 2003;9:1131.

11. Institute of Medicine (US) Committee on the Assessment of Future Scientific Needs for Live Variola Virus. Assessment of future scientific needs for live variola virus. Washington, DC: National Academies Press (US); 1999. http://www.ncbi.nlm.nih.gov/books/NBK230919/.

12. Sarkany I, Caron G. Cutaneous complications of smallpox vaccination. Trans St Johns Hosp Dermatol Soc. 1962;48:163.

13. Lane J, et al. Complications of smallpox vaccination, 1968: national surveillance in the United States. N Engl J Med. 1968;281:1201.

14. CDC. Smallpox vaccine adverse events among civilians United States, March 2003. MMWR. 2003; 52:201.

33

Staphylococcal Toxin-Mediated Scalded Skin and Toxic Shock Syndromes

■ Synonyms:	SS—Ritter's disease, Ritter von Rittershain's disease
	TS—None
■ Etiology:	SS—Phage-infected strains of *S. aureus*
	TS—Non-phage toxigenic strains of *S. aureus*
■ Associations:	SS—Children with head/neck staph infections; adults with renal failure, diabetes mellitus, or HIV
	TS—90 % menstruating women, 10 % skin/soft tissue infection
■ Clinical:	SS—Red macular rash to generalized flaccid bullae
	TS—Fever, hypotension, and macular erythroderma
■ Histology:	SS—Subcorneal (intragranular layer) cell-poor blister with acantholysis
	TS—Neutrophilic pustular dermatitis with necrosis
■ IHC repertoire:	SS—Not applicable
	TS—Not applicable
■ Staging:	SS—Not applicable
	TS—Not applicable
■ Prognosis:	SS—Children 2–3 % mortality; adults ~40 %
	TS—5 %
■ Adverse signs:	SS—Bacteremia, renal failure
	TS—Shock, encephalopathy, and renal failure
■ Treatment:	SS—Oral/intravenous antibiotics
	TS—Tampon removal, intravenous antibiotics/fluids

The toxin-mediated staphylococcal syndromes of *staphylococcal scalded skin syndrome* (SSSS) and *toxic shock syndrome* (TS) constitute important dermatologic entities capable of producing significant morbidity and mortality. Distinctive clinical and pathologic attributes usually permit their early recognition, allowing for prompt institution of potentially lifesaving therapy.

Credit for the first clinical description of SS belongs to Ritter von Rittershain, who in 1878 described 297 cases of a generalized exfoliative exanthem in neonates [1]. An association with staphylococcus and subsequently the mechanism of phage-mediated toxin elaboration would be discovered in the 1940s and 1950s. Today, it is known that the epidermolytic toxins elaborated by viral phage-infected strains 71 and 55 of *Staphylococcal aureus* are responsible for the characteristic clinical and pathologic findings of this

disorder. Interestingly, the target of the exfoliative toxin is pathogenically identical to superficial pemphigus [2, 3]. Both involve the disruption of the cadherin adhesion molecule desmoglein 1 antigen, hence the pathologic similarity between these two otherwise distinctive disorders. The toxin is renally excreted, thus the epidemiologic association between the relatively decreased renal clearance mechanisms characteristic of young children and among the renally impaired adult [4–6]. Unlike children, adults with SS are more likely to have positive blood cultures. In adults, SS has also been described in patients with diabetes mellitus, HIV, and undergoing hemodialysis, possibly due to diminished capacities to excrete the toxins and form antibodies against them [7].

The historical experience with TS is much more brief. The association of a multiorgan systemic toxic syndrome

with certain strains of staphylococcus and menstruating women using superabsorbent tampons would emerge in the early 1980s [8]. Although most of the initial reports involved menstruating women, it was subsequently determined that the syndrome could occur in accordance with soft tissue and cutaneous infections by toxin-producing strains of *Staphylococcus aureus.* Important risk factors for non-menstrual TS include minor abrasions that serve as a portal for toxin entry, burns, trauma, and antecedent surgery [9, 10]. Since the removal of superabsorbent tampons from the market, non-menstrual TS is now the most common presentation of this illness. A common clinical antecedent of non-menstrual TS is streptococcal *necrotizing fasciitis.* Following entry into the bloodstream, the toxins themselves, termed TSST-1 and enterotoxin C1, are non-phage related and produce illness on the basis of *TNF*-like properties including hypotension, fever, and leukocyte activation [11]. The clinical presentations of these entities are distinctive. SS is broadly grouped into three different forms termed *generalized*, *localized*, and *abortive* disease [12]. Generalized SS is the most important manifestation of the disease and is ascribed the greatest risk for complications. This form is associated with remote staphylococcal infection of the head and neck area including conjunctivitis or otitis media. The symptoms are heralded by the development of an orange-red, often tender macular rash. The rash may show periorificial or flexural accentuation. Within 24–48 h, flaccid bullae typically develop. The blister roof is typically wrinkled and expands, forming large cavities, in particular involving flexural sites such as the groin or axillae. The blisters are typically Nikolsky's sign positive and, when removed, yield an erythematous glistening base. Despite widespread involvement of the bodily surfaces, the mucous membranes are characteristically spared. This stage is typically followed by desquamation and complete resolution within 5–7 days. Clinical improvement coincides with the presence of neutralizing serum antibodies to the toxin. The localized form of disease is synonymous with bullous impetigo and represents localized infection by toxigenic strains of *S. aureus.* As with the generalized form, this entity is typically encountered in children. The lesions are represented by superficial erosions with minimal gray exudates or by fragile vesicles or bullae filled with turbid fluid and surrounded by an erythematous rim. Lesions are typically encountered on the exposed surfaces of the skin and, in particular, periorificial sites. Unlike the generalized form of the disease, wound cultures and Gram stains are positive for staphylococcus. The abortive form of the disease is less common and essentially consists of regionally limited bullae, the dermatologic manifestations of which may be confused with TS.

The clinical presentation of TS is ushered in by the precipitous development of high fever, hypotension, and macular rash [9]. The rash is often localized to the site of infection and typically shows pronounced erythema with

FIGURE 33.1. Epidermal loss with erythematous base seen in toxic shock syndrome.

associated non-pitting edema (Fig. 33.1). The conjunctivae are often injected and the oral mucosa may show petechiae and diffuse erythema. The rash is often followed by desquamation, in particular involving the palms and soles. Important systemic accompaniments to the rash to be cognizant of include painful skeletal muscles associated with rhabdomyolysis, decreased urine flow/hematuria associated with the azotemia and encephalopathy of renal failure, jaundice with hepatitis and hemorrhage associated with thrombocytopenia, and disseminated intravascular coagulation. A related condition consisting of recurring erythematous rash and desquamation has been described in HIV patients, termed *recalcitrant erythematous desquamating disorder*, that produces a subacute illness of longer duration and high mortality [13]. Important considerations within the diagnostic differential of these entities include *Kawasaki's disease*, *drug eruption*, *scarlet fever*, and *toxic epidermal necrolysis* (TEN). Kawasaki's disease shows many of the features of TS, similarly sharing fever, conjunctivitis, and desquamative rash that can, however, usually be distinguished on the basis of the patient's age (Kawasaki's, 90% less than 5 years), lack of hypotension, and the presence of lymphadenopathy. Drug eruption and scarlet fever are seldom associated with hypotension. TEN is typically seen in adults and usually follows ingestion of an offending medication. Unlike TS, hypotension is not commonly seen in the early stages of TEN.
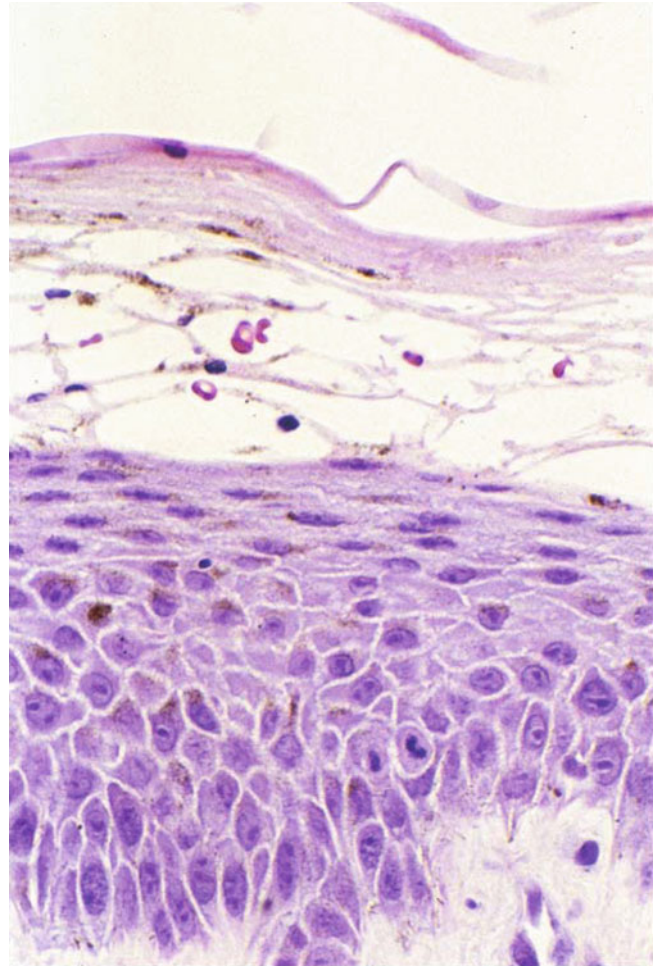
The histopathology of these entities is distinctive. SS shows blister formation situated within the epithelium just below the stratum corneum or within the granular layer (Figs. 33.2 and 33.3) [14]. The blister cavity typically contains free-floating keratinocytes (acantholysis) and is devoid of inflammatory cells. Special (Gram) stain for bacteria is negative. The dermis may show a sparse superficial perivascular lymphocytic or neutrophilic infiltrate. Localized forms of SS (bullous impetigo) show, in addition
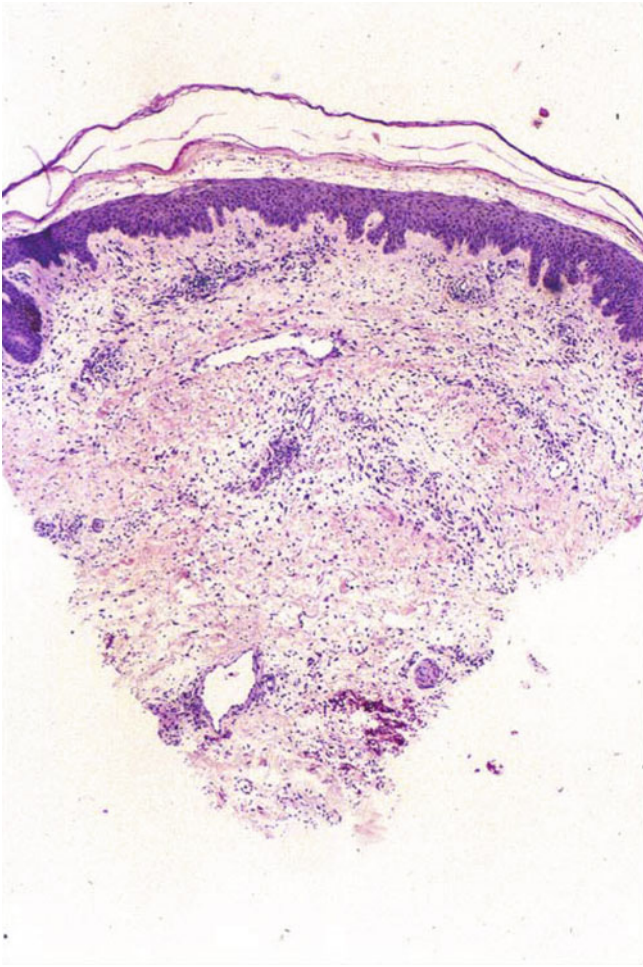
FIGURE 33.2. Low-power photomicrograph of SSSS. Note subcorneal blister formation.

FIGURE 33.3. High-power detail of subcorneal blister with scattered neutrophils. Note the absence of acantholysis.

to the blister, copious numbers of neutrophils and pyogenic organisms. The histologic findings of TS show pustular collections of intraepithelial and subcorneal neutrophils with single and grouped dyskeratotic and necrotic keratinocytes. The dermis often shows edema with a perivascular and interstitial infiltrate of neutrophils and lymphocytes.

The therapy for SS should be directed toward treatment of the underlying *S. aureus* infection. For empiric treatment or treatment of the methicillin-sensitive strains which are responsible for most cases, parenteral administration of a penicillinase-resistant penicillin, such as nafcillin or oxacillin, is recommended. Additional use of clindamycin is recommended to reduce bacterial toxin production [7, 15]. If methicillin resistance is suspected or known, intravenous vancomycin is indicated [16]. The majority of adults have antibodies against the exfoliative toxins, and therefore fresh frozen plasma (FFP) has been used successfully in pediatric cases, although its efficacy has not been established in adults. Although intravenous immunoglobulin (IVIG) is reported to be useful in some cases, one study

demonstrated longer hospitalizations in patients with SS who had received IVIG compared to those who had not received IVIG [7, 17]. Attention to fluid and electrolyte balance and local wound care precautions is important. Complications include cellulitis, osteomyelitis, pneumonia, and, in the adult, sepsis. Measures that prevent the nosocomial transmission of the organism, including patient isolation, health provider handwashing, barrier functions, and oral antibiotic therapy for infected health-care providers, should be considered.

The overall mortality rate of SS in children is about 3%, increasing to 40–50% among immunosuppressed or renally impaired adults. The management of TS involves rapid intravenous resuscitation to ameliorate hypotension, removal of infected tampon or identification of the underlying infection, and appropriate intravenous antibiotics [18]. Antimicrobial therapy generally consists of cell wall active agents (i.e., penicillin) with adjunctive clindamycin. IVIG or immunoglobulin-containing FFP has also shown promise in therapy. The overall mortality of TS is approximately 5%.

References

1. von Rittershain RG. Dermatitis jungerer sauglinge. Zentralzeitung fur Kinderheilkunde. 1878;2:3.

2. Melish M. Staphylococci, streptococci and the skin: review of impetigo and the staphylococcal scalded skin syndrome. Semin Dermatol. 1992;1:101.

3. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. Nat Med. 2000;6(11):1275–7.

4. Richard M, Mathieu-Serra A. Staphylococcal scalded skin syndrome in a homosexual adult. J Am Acad Dermatol. 1986;15(2 Pt 2):385–9.

5. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults. A clinical review illustrated with a new case. J Am Acad Dermatol. 1994;30(2 Pt 2):319–24.

6. Lyell A. The staphylococcal scalded skin syndrome in historical perspective: emergence of dermopathic strains of Staphylococcus aureus and discovery of the epidermolytic toxin. A review of events up to 1970. J Am Acad Dermatol. 1983;9(2):285–94.

7. Handler MZ, Schwartz RA. Staphylococcal scalded skin syndrome: diagnosis and management in children and adults. J Eur Acad Dermatol Venereol. 2014;28(11):1418–23.

8. Institute of Medicine Report on Toxic Shock Syndrome. Ann Intern Med. 1982;97(1):133–3.

9. Tofte RW, Williams DN. Toxic shock syndrome: clinical and laboratory features in 15 patients. Ann Intern Med. 1981;94(2):149–56.

10. Huntley AC, Tanabe JL. Toxic shock syndrome as a complication of dermatologic surgery. J Am Acad Dermatol. 1987;16(1 Pt 2):227–9.

11. Manders SM. Toxin-mediated streptococcal and staphylococcal disease. J Am Acad Dermatol. 1998;39(3):383–98; quiz 399–400.

12. Elias PM, Fritsch P, Epstein EH. Staphylococcal scalded skin syndrome. Clinical features, pathogenesis, and recent microbiological and biochemical developments. Arch Dermatol. 1977;113(2):207–19.

13. Cone LA, Woodard DR, Byrd RG, Schulz Z. J Infect DIs 1992 165: 638–43.

14. Hurwitz RM, Ackerman AB. Cutaneous pathology of the toxic shock syndrome. Am J Dermatopathol. 1985;7(6):563–78.

15. Braunstein I, Wanat KA, Abuabara K, McGowan KL, Yan AC, Treat JR. Antibiotic sensitivity and resistance patterns in pediatric staphylococcal scalded skin syndrome. Pediatr Dermatol. 2014;31(3):305–8.

16. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011;52(3):285–92.

17. Li MY, Hua Y, Wei GH, Qiu L. Staphylococcal scalded skin syndrome in neonates: an 8-year retrospective study in a single institution. Pediatr Dermatol. 2014;31(1):43–7.

18. Schlievert PM. Use of intravenous immunoglobulin in the treatment of staphylococcal and streptococcal toxic shock syndromes and related illnesses. J Allergy Clin Immunol. 2001;108(4 Suppl):S107–10.

34
Meningococcemia and Purpura Fulminans

Meningococcemia

- Synonyms: Waterhouse-Friderichsen syndrome (with purpura fulminans and adrenal hemorrhage)
- Etiology: Invasive infection with *Neisseria meningitidis*
- Associations: Inherited or acquired deficiencies of complement or immunoglobulin in some cases
- Clinical: Upper respiratory tract symptoms, then fever, myalgias, arthralgias; cutaneous involvement—macules, papules, petechiae, palpable purpura; purpuric necrotic patches of purpura fulminans
- Histology: Skin biopsy with mixed lymphocyte and neutrophil infiltrate, ±vasculitis, organism may be found by Gram's stain
- Evaluation: Blood cultures, CBC with differential, platelets, PT/PTT, other coagulation parameters, Gram's stain of smears from purpuric lesions
- Treatment: Intravenous antibiotics—penicillin G or third-generation cephalosporin, fluid and inotropic support; ± activated protein C infusion or bactericidal permeability increasing protein for severe sepsis
- Prognosis: Good if treated early, but guarded with signs of sepsis or purpura fulminans

Purpura Fulminans

- Synonyms: Symmetrical peripheral gangrene
- Etiology: Diffuse intravascular coagulation
- Associations: Inherited protein C or S deficiency, postinfectious, bacteremic sepsis
- Clinical: Widespread purpura with necrosis, skin and other organ systems
- Evaluation: PT/PTT, proteins C and S, antithrombin III, CBC with differential, platelets, fibrinogen, fibrin degradation products
- Treatment: Reversal of underlying process
- Prognosis: High incidence of long-term deformity related to necrosis and amputations, high mortality in that associated with sepsis

Meningococcemia is an invasive bacterial infection by the Gram-negative diplococcus, *Neisseria meningitidis*, which is often rapidly fatal if not detected and treated early. *Neisseria meningitidis* infections occur both endemically and epidemically. Sporadic disease occurs more commonly during winter and early spring months and affects predominantly children. The highest rate of infection is in infants 6 months to 1 year, with a steady decline in infection rate with age. This is likely explained by passive maternal immunity providing protection in the first 6 months and gradual onset of acquired immunity with age. Approximately two-thirds of invasive meningococcal disease occurs in children [1]. The human bacterial reservoir is the upper respiratory tract. In the general population, the carrier state is quite

common, but in only rare cases do carriers develop invasive disease. There are many different serotypes of *Neisseria meningitidis*, but types A, B, C, W-135, and Y account for nearly all invasive disease. Worldwide, type A is responsible for most large epidemics, but in the United States, serotypes B and C account for approximately 90 % of invasive infections. Most people exposed to an infected individual will become colonized in the upper respiratory tract. There is an approximately 5 % chance of invasive infection developing in household contacts in the first 60 days after exposure. Most of these occur in the first week [2].

The carrier state for *Neisseria meningitidis* is common, but invasive infection occurs in few individuals. The organism is able to survive in a carrier state by a number of different mechanisms. It may adhere to epithelial cells by pili and may produce IgA proteases—factors that inhibit ciliary activity. The bacterial polysaccharide capsule assists in adherence and inhibits phagocytosis [3]. Invasive disease may be precipitated by antecedent viral infections; inhalation of dry, dusty air; or passive smoke inhalation, all factors that may disrupt the integrity of mucosal epithelium [3]. Once in the bloodstream, the type IV pili of the organism binds to endothelial cells via the CD147 receptor, and then cell signaling resulting in the bacteria traversing the wall of the vessel occurs by interactions with the endothelial cell β2-adrenoreceptor [4]. Low levels of bacteremia may favor infection in the brain vasculature leading to meningitis, whereas a large bacterial load may favor a florid septic picture with purpura fulminans [4]. Immunologic response to meningococcal disease utilizes all three components of the complement pathway, the classical pathway, the alternative pathway, and the mannose-binding lectin pathway. Patients with inherited defects of the terminal components of complement C6–C8 [5, 6], properdin [7], and genetic variants of mannose-binding lectin [8] are susceptible to neisserial infections, including fulminant or chronic meningococcemia. Acquired deficiencies of complement as may occur in chronic liver disease, systemic lupus erythematosus, and multiple myeloma also predispose to invasive meningococcal infection [5, 9]. In one series of patients presenting with a first episode of meningococcemia, 30 % had either inherited or acquired deficiencies of complement [5]. In addition to complement deficiencies, deficiencies of IgG, IgG subclass 2, and IgA have been described in patients with meningococcal infections [10, 11].

The clinical manifestations of meningococcal infection are varied. Tracheobronchitis, conjunctivitis, genital tract infection, pneumonia, and meningitis may all occur, with or without septicemia. Bacteremia may be occult. Acute meningococcemia usually begins with upper respiratory tract symptoms, progressing to fever, chills, myalgias, arthralgias, headache, and nausea and vomiting. Meningococcal meningitis usually presents without distinctive clinical features. It may closely resemble viral meningitis. Bacteremia is not necessarily present.

Cutaneous findings in meningococcemia are not consistently present. In one series of adult patients, 50 % had no cutaneous findings or clinical evidence of meningitis [1]. When present, skin findings are not specific. They may include a morbilliform eruption, urticarial papules and plaques, petechiae, or purpuric patches (Fig. 34.1). Morbilliform eruptions, papules, and urticarial plaques may occur early in the disease, and then purpura subse-

FIGURE 34.1. Meningococcemia: purpuric papules of the lower extremities.

quently develops. Small purpuric necrotic papules and vesicles may occur in any anatomic site. These usually represent septic or immune complex vasculitis. Broad areas of purpura and necrosis are more likely to be manifestations of purpura fulminans, an ominous presentation of sepsis-associated disseminated intravascular coagulation (Fig. 34.2). Such cases may be rapidly fatal and in the setting of adrenal hemorrhage are referred to as Waterhouse-Friderichsen syndrome. Early literature mistook manifestations of sepsis for adrenal insufficiency due to adrenal hemorrhage. Most patients with this syndrome have elevations in cortisol [2].

In the child presenting with fever and a purpuric eruption, one must be vigilant for the possibility of meningococcemia. However, in a series of such patients, bacterial sepsis comprises about 12% of the total, and of those, meningococcemia accounts for approximately two-thirds [2]. Most children with fever and purpura have viral infections, particularly enterovirus. Enterovirus may cause aseptic meningitis, resulting in a clinical presentation similar to that of meningococcemia. The differential diagnosis also includes infection with parvovirus B19, Epstein-Barr virus, and cytomegalovirus, as well as endocarditis, gonococcemia, typhus, drug eruption, and other forms of systemic vasculitis such as Henoch-Schönlein purpura.

A chronic form of meningococcemia also occurs and generally presents with a less fulminant course and variable skin findings. These include macules, papules, erythema nodosum-like lesions, or palpable purpura due to small vessel neutrophilic vasculitis. However, cutaneous involvement is not a constant feature of the disease, particularly in adults. Other manifestations include fever, malaise, myalgias, and arthralgias. Symptoms may persist for weeks prior to diagnosis. Chronic meningococcemia may occur in immunocompetent individuals or those with HIV infection or deficiencies of complement or immunoglobulin [12, 13].

The diagnosis of meningococcal infection is made from isolation of the organism from usually sterile sites such as blood or cerebrospinal fluid. Surface cultures, especially those from the oropharynx, are not useful because of high rates of carriage in the general population. Blood drawn from puncture wounds of purpuric lesions is reported to have a high yield for organisms by Gram's stain [14]. The organism may be found in Gram's stains of biopsy specimens of skin lesions or even on the peripheral blood smear [15]. Rapid serologic tests are available to detect *Neisseria meningitidis* capsular polysaccharide antigen. These may be particularly useful for CSF or if treatment has been instituted. In cases of suspected chronic meningococcemia, PCR assay of skin biopsy specimens may be a useful adjunct in diagnosis, particularly if blood cultures are negative [16].

Fulminant sepsis may develop rapidly in meningococcemia. Endotoxin is a critical component of host immune activation, and its levels correlate with the severity of disease. Serotype C frequently has fulminant manifestations, probably because it has the highest production of endotoxin of any of the serotypes. In the circulation, CD14 on the surface of monocytes and endothelial cells is the principal receptor for endotoxin. The interaction causes production of pro-inflammatory cytokines such as TNF-α and IL-1β, which are important inflammatory mediators in

Figure 34.2. Purpura fulminans: extensive purpuric necrotic patches.

sepsis [3]. Neutrophils are activated via endotoxin and complement to produce proteases that result in tissue damage.

Complications of meningococcal sepsis may include septic arthritis, pericarditis, and endocarditis. One particularly deadly complication of meningococcemia is purpura fulminans, which occurs in 15–25 % of patients with meningococcemia [17]. Patients develop a severe form of disseminated intravascular coagulation, clinically manifested by purpuric patches with extensive cutaneous necrosis, accompanied by high mortality rates. Purpura fulminans is not specific to meningococcemia and occurs in several clinical settings.

34.1 Purpura Fulminans

Purpura fulminans (PF) occurs in three different clinical settings: neonatal homozygous protein C or S deficiency, after infection, and with bacterial sepsis. Homozygous protein C or S deficiency causes spontaneous intravascular coagulation in the neonatal period, clinically presenting as PF. Postinfectious PF usually occurs 7–10 days after an infectious trigger. Possible triggers include varicella, HHV-6 [18], scarlet fever, viral exanthem, or even hypersensitivity reactions. This form is usually less severe than other forms, with disease more frequently limited to the skin. At least some cases seem to be mediated by autoantibodies induced against protein S [19]. The third type of PF occurs in the setting of sepsis with endotoxin-producing bacteria. The majority of these cases are due to meningococcemia, but some occur in association with infection by *Streptococcus pneumoniae*, group A or B *Streptococcus*, and *Haemophilus influenzae*, among others. PF has also been induced by septicemia with *Capnocytophaga canimorsus* (DF-2), a complication of a dog bite [20]. Hypercoagulable states such as factor V Leiden mutation may predispose to some sepsis-induced PF [21].

Purpura fulminans likely represents a phenotype with multiple causes. A consumptive coagulopathy causes disseminated intravascular coagulation. In sepsis, circulating bacterial endotoxin and complement attack sequence disrupt the endothelium, resulting in release of tissue factor. Tissue factor binds to coagulation factor VII, and the complex causes activation of factors V, X, VIII, and IX, with consequent formation of thrombin and other procoagulant proteins. Protein C is a vitamin K-dependent glycoprotein that circulates in plasma in an inactive form. In a prothrombotic state, thrombin forms a complex with endothelial membrane-bound thrombomodulin. Circulating inactive protein C binds to that complex and to membrane-bound endothelial protein C receptor, resulting in activated protein C. Once it is activated, it acts with its cofactor protein S to inactivate activated factors V and VIII, thus exerting an anticoagulant effect.

A dysfunctional protein C activation system likely contributes to PF in meningococcal sepsis. In meningococcal sepsis with PF, activated protein C in plasma is undetectable in most patients, and infusions of unactivated protein C concentrate do not increase activated protein C levels. Additionally, thrombomodulin and endothelial protein C receptor expression are reduced, theoretically leaving less available for use in protein C activation. The result of this imbalance in coagulation homeostasis is a thrombotic state [22].

The classical clinical presentation of purpura fulminans is acute onset of painful purpuric papules, plaques, and patches with a rim of erythema. Necrosis quickly ensues, sometimes with formation of vesicles and bullae and subsequent eschar. Distal extremities are most commonly affected. Proximal involvement also occurs, but is more common in the postinfectious variant [17]. Similar involvement of internal organ systems occurs. A consumptive coagulopathy develops in PF, which helps distinguish it from heparin and Coumadin necrosis, thrombotic thrombocytopenic purpura, cryoglobulinemia, and thrombotic states associated with antiphospholipid antibody. Laboratory evaluation reveals reduced fibrinogen, platelets, factor V and VIII, protein C, S, and antithrombin III levels. There is a prolongation of PT and PTT and an elevation in fibrin degradation products such as D-dimers. Histopathologic evaluation reveals thrombi of vessels, with fibrin, platelets, leukocytes, and, in the case of meningococcemia, sometimes Gram-negative diplococci (Figs. 34.3 and 34.4). In cases of PF associated with bacterial sepsis, a neutrophilic vasculitis may accompany the thrombi, distinguishing it from noninfectious causes [17].

The treatment of purpura fulminans is aimed at reversing the underlying cause, but may also include a variety of measures to counter the hypercoagulable state. Early surgical consultation is advised. Patients should be monitored for compartment syndrome, particularly if aggressive fluid resuscitation is implemented. "Compartments" are fascially delineated anatomic regions susceptible to ischemic necrosis in the setting of edema and low blood flow. Urgent fasciotomy may be necessary if compartment syndrome develops [23]. Postinfectious PF may be induced by autoantibodies to protein S. These patients may benefit from plasmapheresis or intravenous immunoglobulin in addition to other therapies [19]. Treatment for sepsis-induced purpura fulminans is discussed below.

Treatment in suspected cases of meningococcemia should be instituted immediately after cultures are obtained, because prognosis is dependent upon early intervention. Generally, intravenous treatment with a third-generation cephalosporin is given until cultures and susceptibilities allow narrowing the coverage. Fluid

Figure 34.3. Meningococcemia: septic vasculitis with neutrophils, necrosis, and hemorrhage.
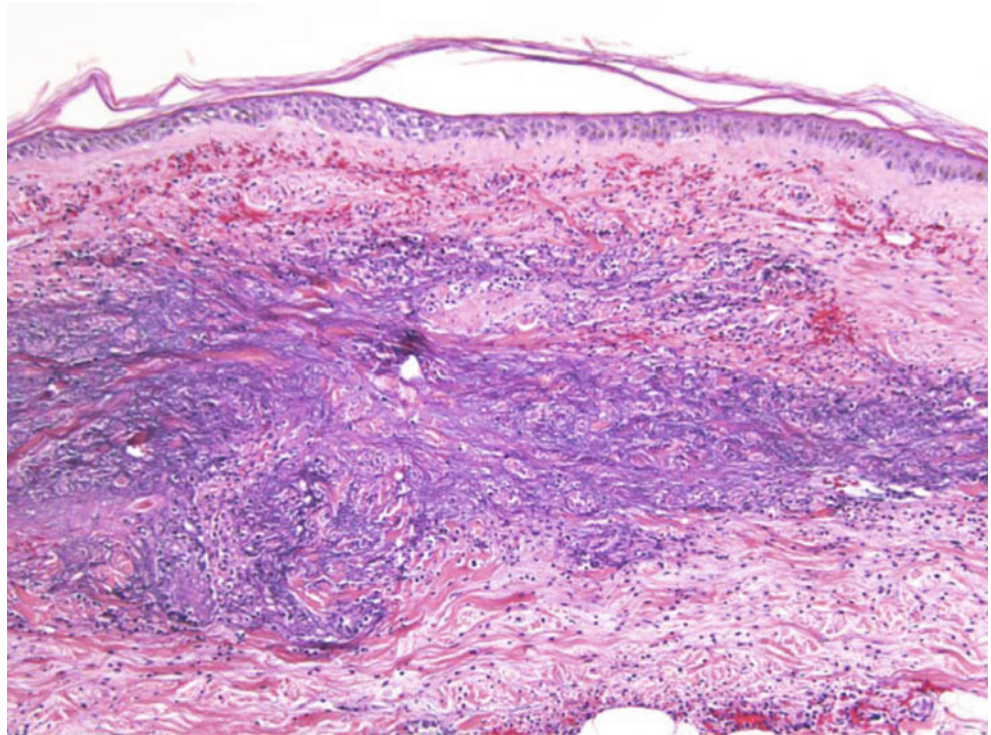
Figure 34.4. Purpura fulminans: prominent intravascular coagulation with occasional neutrophils and superficial necrosis.
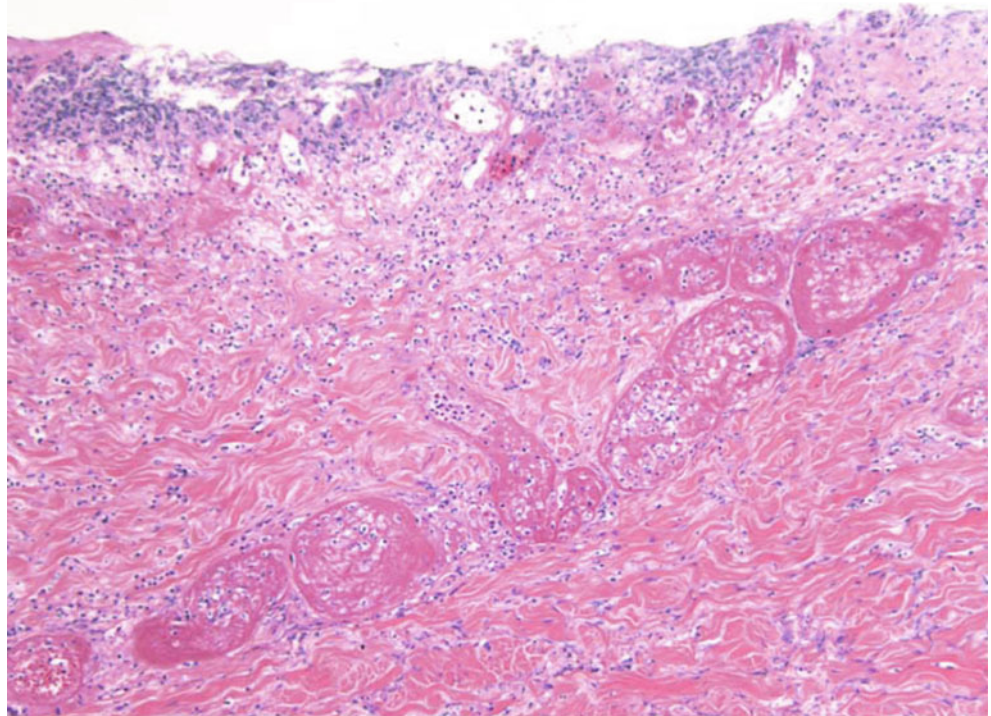
and inotropic support are given as needed. Patients should be placed on contact and droplet precautions until 24 h of antibiotic therapy has been completed [24]. In patients who develop purpura fulminans, extensive cutaneous involvement portends a poor prognosis. Beneficial effects in severe sepsis have been seen with infusions of bactericidal permeability increasing protein (which binds endotoxin, preventing

the pro-inflammatory cascades), in a randomized placebo-controlled trial [25]. No benefit was found with activated protein C infusions in a randomized controlled trial [26]. However, a retrospective case series of patients with purpura fulminans using protein C concentrate infusions in children suggested lower mortality and long-term complications compared to historical controls [27]. Unfractionated heparin was found to be of no benefit in patients with sepsis in a randomized, placebo-controlled trial [28]. In case reports, additional therapeutic measures reported to be of benefit include anti-endotoxin antibody, systemic steroids, anti-TNF-α antibody, anti-IL-1-β antibody, fresh frozen plasma, antithrombin III, tissue plasminogen activator, plasmapheresis, and extracorporeal membrane oxygenation [3]. Anticoagulation agents may be associated with bleeding complications, so if used, it should be with great caution.

Poor prognostic features in meningococcemia include petechiae present for less than 12 h prior to admission, hypotension (systolic blood pressure <70 mmHg), absence of meningitis, peripheral WBC count <10,000, erythrocyte sedimentation rate <10 mm/h, difference between rectal and skin temperature >3 °C, and parental opinion that child's condition has deteriorated in the previous hour [29, 30]. The mortality rate is 8–10 % [2]. More recently, it has been appreciated that genetic variations in host immune factors can affect the severity and outcomes in infectious diseases. Genetic polymorphisms in protein C promoter and *toll-like receptor 9* have been found to correlate with clinical outcomes in patients with meningococcemia [31, 32]. Long-term complications usually result from ischemia during acute infection and consist of amputations and abnormal bone growth. In those patients surviving the acute infection, evaluation for complement and immunoglobulin deficiency should be performed to determine if ongoing replacement therapy is needed.

Household and other close contacts should be treated prophylactically because of the potential for epidemic spread of invasive meningococcal disease. Recommended treatment protocols include oral rifampin for 2 days or single-dose ciprofloxacin or intramuscular ceftriaxone. Treatment should commence within 24 h of exposure [24]. Meningococcal vaccine consists of purified capsular polysaccharide with groups A, C, Y, and W-135. This quadrivalent vaccine is recommended for all children 11–12 years old, with a booster at age 16 years, and also for adults and younger children at risk [33]. Serogroup B was not included in early forms of the vaccine because of its lack of immunogenicity. Complement control factor H is a soluble regulator of the alternative pathway of complement activation. *Neisseria meningitidis* produces a factor H binding protein which has a permissive effect on intravascular bacterial growth. The addition of this protein to the vaccine has led to protection against serogroup B organisms [4]. This additional vaccine is recommended for at-risk groups, including those with complement deficiency or splenic dysfunction [33].

References

1. Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Ann Intern Med. 1995;123:937–40.
2. Salzman MB, Rubin LG. Meningococcemia. Infect Dis Clin North Am. 1996;10:709–25.
3. Pathan N, Faust SN, Levin M. Pathophysiology of meningococcal meningitis and septicaemia. Arch Dis Child. 2003;88:601–7.
4. Coureuil M, Bourdoulous S, Marullo S, Nassif X. Invasive meningococcal disease: a disease of the endothelial cells. Trends Mol Med. 2014;20:571–8.
5. Ellison RT, Kohler PF, Curd JG, Judson FN, Reller LB. Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. N Engl J Med. 1983;308:913–6.
6. Adams EM, Hustead S, Rubin P, Wagner R, Gewurz A, Graziano FM. Absence of the seventh component of complement in a patient with chronic meningococcemia presenting as vasculitis. Ann Intern Med. 1983;99:35–8.
7. Denson P, Weiler JM, Griffiss JM, Hoffmann LG. Familial properdin deficiency and fatal meningococcemia. N Engl J Med. 1987;316:922–6.
8. Hibberd ML, Sumiya M, Summerfield JA, et al. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Meningococcal Research Group. Lancet. 1999;353:1049–53.
9. Ellison RT, Mason SR, Kohler PF, Curd JG, Reller B. Meningococcemia and acquired complement deficiency: association in patients with hepatic failure. Arch Intern Med. 1986;146:1539–40.
10. Bass J, Nuss R, Mehta KA, Morganelli P, Bennett L. Recurrent meningococcemia associated with IgG2-subclass deficiency. N Engl J Med. 1983;309:430.
11. Castagliuolo PP, Nisini R, Quinti I, Fattorossi A, D'Amelio R. Immunoglobulin deficiencies and meningococcal disease. Ann Allergy. 1986;57:68–70.
12. Ploysangam T, Sheth AP. Chronic meningococcemia in childhood: case report and review of the literature. Pediatr Dermatol. 1996;13:483–7.
13. Assier H, Chosidow O, Rekacewicz I, et al. Chronic meningococcemia in acquired immunodeficiency infection. J Am Acad Dermatol. 1993;29:793–4.
14. McClean S, Caffey J. Endemic purpuric meningococcus bacteremia in early life: the diagnostic value of smears from the purpuric lesions. Am J Dis Child. 1931;42:1053–74.
15. Young EJ, Cardella TA. Meningococcemia diagnosed by peripheral blood smear. JAMA. 1988;260:992.
16. Parmentier L, Garzoni C, Antille C, Kaiser L, Ninet B, Borradori L. Value of a novel *Neisseria Meningitidis*-specific polymerase chain reaction assay in skin biopsy specimens as a diagnostic tool in chronic meningococcemia. Arch Dermatol. 2008;144:770–3.

17. Darmstadt GL. Acute infectious purpura fulminans: pathogenesis and medical management. Pediatr Dermatol. 1998;15:169–83.

18. Boccara O, Lesage F, Regnault V, et al. Nonbacterial purpura fulminans and severe autoimmune acquired protein S deficiency associated with human herpesvirus-6 active replication. Br J Dermatol. 2009;161:181–3.

19. Levin M, Eley BS, Louis J, Cohen H, Young L, Heyderman RS. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. J Pediatr. 1995;127:355–63.

20. Kullberg BJ, Westendorf RGJ, van't Wout JW, Meinders AE. Purpura fulminans and symmetrical gangrene caused by *Capnocytophaga canimorsus* (formerly DF-2) septicemia—a complication of dog bite. Medicine. 1991;70:287–92.

21. Jackson RT, Luplow RE. Adult purpura fulminans and digital necrosis associated with sepsis and the Factor V mutation. JAMA. 1998;280:1829.

22. Faust SN, Levin M, Harrison OB, et al. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med. 2001;345:408–16.

23. Warner PM, Kagan RJ, Yakuboff KP, et al. Current management of purpura fulminans: a multicenter study. J Burn Care Rehabil. 2003;24:119–26.

24. Campsall PA, Laupland KB, Niven DJ. Severe meningococcal infection: a review of epidemiology, diagnosis, and management. Crit Care Clin. 2013;29:393–409.

25. Levin M, Quint PA, Goldstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPi21) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. rBPi21 Meningococcal Sepsis Study Group. Lancet. 2000;356:961–7.

26. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366:2055–64.

27. Veldman A, Fischer D, Wong FY, et al. Human protein C concentrate in the treatment of purpura fulminans: a retrospective analysis of safety and outcome in 94 pediatric patients. Crit Care. 2010;14(4):R156. doi:10.1186/cc9226. Epub 2010 Aug 19.

28. Jaimes F, De La Rosa G, Morales C, et al. Unfractionated heparin for treatment of sepsis: a randomized clinical trial (the HETRASE study). Crit Care Med. 2009;37:1185–96.

29. Stiehm ER, Damrosch DS. Factors in the prognosis of meningococcal infection. J Pediatr. 1966;68:457–67.

30. Sinclair JF, Skeoch CH, Hallworth D. Prognosis of meningococcal septicemia. Lancet. 1987;350:38.

31. Binder A, Endler F, Rieger S, et al, for the Central European Meningococcal Genetic Study Group. Protein C promoter polymorphisms associate with sepsis in children with systemic meningococcemia. Hum Genet. 2007;122:183–90.

32. Sanders MS, van Well GTJ, Ouburg S, Morré SA, van Furth AM. *Toll-like receptor 9* polymorphisms are associated with severity variables in a cohort of meningococcal meningitis survivors. BMC Infect Dis. 2012;12:112. doi:10.1186/1471-2334-12-112.

33. Vaccines and Immunizations—Meningococcal: who needs to be vaccinated? Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/vpd-vac/mening/who-vaccinate.htm. Accessed 27 June 2015.

Part VI
Autoimmune Disease

35
Cutaneous and Systemic Lupus Erythematosus

■	Etiology:	Failure of surveillance for autoreactive B cells allows for production of a variety of autoantibodies which target the skin and visceral organs
■	Associations:	Ultraviolet radiation, family history, hormonal influence, complement deficiency
■	Clinical:	Variable depending on subtype
■	Histology:	Variable findings often including interface dermatitis, mucin deposition, and lymphohistiocytic inflammation
■	Prognosis:	Depends on subtype, severity
■	Treatment:	Dependent on type, extent, and severity of disease

The evolution of systemic lupus erythematosus as a disease entity began with simple dermatologic observations. Early attempts in the classification of skin disease used the term "lupus," which is Latin for wolf, in reference to ulcers which advanced and "consumed" surrounding tissue. It is likely that these ulcers included cutaneous neoplastic disease (enlarging, destructive basal cell carcinoma), infectious diseases such as cutaneous tuberculosis, and early cases of discoid lupus. Robert Willan made the first meaningful attempt at classification of the ulcers of "lupus" in *Practical Synopsis of Cutaneous Disease according to the arrangement of Dr. Willan* in 1813. It is likely that cutaneous tuberculosis (particularly lupus vulgaris) and discoid lupus erythematosus were again intertwined and described as one entity in his text.

Moritz Kaposi published groundbreaking work in 1873 which not only clearly delineated lupus erythematosus as a distinct entity but recognized the systemic manifestations of disease [1]. He also established that discoid lupus and lupus vulgaris were distinct entities. Sir William Osler coined the term systemic lupus erythematosus and described the systemic manifestations in more detail in the late twentieth and early twenty-first century [2], with Jadassohn providing detailed clinical and pathological descriptions in 1904 [3]. Discoveries of the so-called LE cell reaction in 1948 established the groundwork for the autoimmune basis of disease [4]. Criteria for the diagnosis of SLE set in 1982 were updated in 1997 (Table 35.1) [5].

SLE is eight times more common in women than in men and three times more common in blacks than in whites. Average age of onset is also earlier in black women (35) than in white men (44) [6]. Systemic disease is more common and more severe in those of black and Hispanic descent. SLE can be familial, associated with both common histocompatibility antigens and complement deficiency.

Proper understanding of the *pathogenesis* of systemic lupus requires a brief review of B cell tolerance. Through the immunologic maturation process, elimination of autoreactive B cells is accomplished both in the bone marrow and spleen. Maturation of B cells into plasma cells occurs in the germinal centers of lymph nodes. Each of these locations has the potential for dysregulation in the setting of SLE, allowing autoreactive B cells to bypass normal pathways of elimination and perpetuate production of damaging autoantibodies as plasma cells. Types of autoantibody produced can correlate with subtypes and characteristics of expressed cutaneous LE and severity of renal disease. The reason for this immunologic dysregulation is likely multifactorial, but certainly includes genetic predisposition and environmental triggers. Cases of SLE are documented to be familial in 4–10 % [7] although this number would likely rise if newer diagnostic criteria were applied. SLE has been reported to occur in identical twins with a concordance rate of 65 % [8]. Family members of those with SLE will often have elevated levels of autoantibodies and have a higher

TABLE 35.1. Criteria for systemic lupus erythematosus [5]

Criterion	Explanation
1. Malar rash	Fixed erythema over malar eminences tending to spare the nasolabial folds
2. Discoid rash	Erythematous plaques with adherent keratotic scale, follicular plugging, scarring
3. Photosensitivity	Skin rash as a result of sunlight exposure, patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, observed by the physician
5. Nonerosive arthritis	Tenderness, swelling, effusion of two or more peripheral joints
6. Pleuritis or pericarditis	Pleuritis: pleural effusion, pleuritic pain, or rubbing heard by physician or
	Pericarditis: on ECG, exam findings, or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria: >0.5 g daily or greater than 3+ if not quantified
	Cellular casts: RBC, granular, tubular, mixed
8. Neurologic disorder	Seizures or
	Psychosis in absence of other known causes
9. Hematologic disorder	Hemolytic anemia with reticulocytosis or
	Leukopenia <4000/mm^3 (more than 1 occasion) or
	Lymphopenia <1500/mm^3 (more than 1 occasion) or
	Thrombocytopenia <100,000/mm^3 (no other causes)
10. Immunologic disorder	Anti-DNA OR anti-Smith or findings of antiphospholipid antibodies
11. Positive antinuclear antibody (ANA)	Abnormal titer ANA at any point in time in the absence of causative medications

If four or more criteria are satisfied at any point in the disease course, a diagnosis of systemic lupus erythematosus is made

incidence of connective tissue disease in general [9]. Patients with lupus have increased frequencies of histocompatibility antigens HLA-B8, Dr3, A1, and DR2, and complement deficiency is common in familial cases of SLE. Potential environmental triggers and exacerbating factors include ultraviolet radiation, drugs, and hormonal imbalance. Ultraviolet radiation, both UVB and UVA, is a known trigger of onset and/or exacerbation of disease in 60 % of SLE patients and 5 % of DLE patients [10]. Low levels of androgens in both females and males with SLE as well as premenstrual flares and rare induction of disease from estrogen-containing contraceptives underscore a possible hormonal influence on disease expression [11]. Drug-induced LE is quite different from idiopathic SLE, with a virtual absence of the common subtypes of skin disease, a tendency toward occurrence in Caucasians and occurrence in an older age group. Renal and CNS diseases are also quite rare in drug-induced LE.

35.1 Subsets of Cutaneous Lupus

Discoid lupus erythematosus, of all the cutaneous lupus subsets, has the largest footprint on dermatologic literature and is most commonly seen in dermatologic clinics. Incidence spikes in the fourth and fifth decade, and development is uncommon in childhood and the elderly. There is a female predominance, although not as striking as that seen in SLE. Some believe that DLE can be separated into localized and generalized variants, with the latter group of patients developing coexistent SLE at a much higher rate. The rate of SLE in "localized" DLE is comparatively small (2–5 %). Regardless of the clinical variant, involvement of head and neck is nearly universal, with conchal bowl and scalp involvement being a strong diagnostic indicator.

A discrete plaque of discoid lupus is a complex and fascinating array of morphologic features which can be quite difficult to describe for a struggling student of dermatology. Lesions are usually well defined, although in lighter skin types the dyspigmentation is less obvious and can blend with the surrounding skin (Fig. 35.1). Scale is tough and adherent and ranges in thickness from nearly nonexistent to hyperkeratotic and platelike (Fig. 35.2). Epidermal atrophy and telangiectasias are invariably present, and follicular plugging is a key feature which can be difficult to recognize. As mentioned before, dyspigmentation ranges from peripheral darkening (especially in darker skin types) to complete depigmentation, which is more common in the center of "burnt-out" discoid lupus lesions. Symptoms range from pruritus to intolerable burning pain. When lesions are active, erythema ranges from pink to violaceous to bright red, with variable lesional edema and induration. Erythema, scale, and induration can be indicators of disease activity, with the absence of all three being a strong indicator of lesional quiescence. Each described feature, taken alone, has an extensive differential diagnosis, although the composite of all features could represent little other than discoid lupus. Scalp lesions have similar features, with more obvious follicular plugging, and the tendency to cause permanent, cicatricial alopecia (Fig. 35.3). Squamous cell carcinoma can develop in patients with discoid lupus, usually after many years, usually in those with extensive, severe disease. One series reported malignant degeneration in 3.3 % of 120 Caucasian patients [12].

There is an overlapping relationship between tumid lupus (TLE) and discoid lupus. Classically, tumid lupus refers to well-defined indurated persistent pink plaques without discernable surface change. Tumid lupus is often exquisitely photosensitive, more so than other cutaneous lupus subtypes. Distribution strays from that of DLE in that truncal involvement is more common and scalp and ear involvements are uncommon. Lesions resolve without scarring. Biopsy specimens show the dermal features of

FIGURE 35.1. Discoid lupus, left jawline.

FIGURE 35.2. Discoid lupus, conchal bowl.

FIGURE 35.3. Discoid lupus, scalp, with scarring alopecia.

discoid lupus (mucin deposition, superficial and deep perivascular lymphocytic inflammation) but minimal epidermal change aside from mild vacuolar interface dermatitis. A caveat to this relationship is that many patients show histologic overlap with DLE in clinical lesions reminiscent of TLE, often when presenting early in the course of disease. These "overlap" patients will often have both types of lesions present (DLE and TLE), with lesions of TLE developing into lesions of DLE, suggesting that TLE may be a precursor to DLE in some instances. A similar phenomenon has been noted over time in patients with the malar rash of SLE, as malar DLE occasionally develops.

Subacute cutaneous lupus (SCLE) is a more clearly defined entity which only rarely overlaps with other cutaneous lupus subtypes, although SLE develops more frequently than in the context of DLE. SCLE is classically separated into psoriasiform and annular/polycyclic variants, representing two-thirds and one-third of patients, respectively (Figs. 35.4 and 35.5). Lesions resolve with dyspigmentation but frank scarring does not occur. Distribution often spares the face but the neck, arms, and trunk are often involved, tending toward a photosensitive distribution. SLE is present in 50% of those diagnosal with SCLE, and 10 % of SLE patients have SCLE lesions. Age of presentation is similar to DLE, in the fifth to sixth decade, with a female predominance of 4:1. Unlike SLE, SCLE is much more common in light-skinned patients.

Lupus panniculitis refers to an inflammatory condition involving the subcutaneous fat, almost exclusively lymphocytic in nature, associated with SLE and other forms of cutaneous LE in a high percentage of patients. Lupus profundus refers to the coexistence of discoid lupus and lupus panniculitis within the same clinical lesions, which can occur clinically (3–5 %) or only on histologic evaluation (30 %) [13]. Subcutaneous nodules are usually skin-colored to pink, firm, rubbery, and well-defined and can be several centimeters in diameter. Clinical features which allow differentiation from other forms of panniculitis include distribution which favors the proximal extremities, face, breasts, buttocks, and shoulders and the unique crateriform subcutaneous atrophy left behind in quiescent lesions. Histologic differentiation from subcutaneous T cell lymphoma is vital, as the treatment options are obviously quite different.

The cutaneous manifestations in those with systemic lupus can take many forms beyond what has been

FIGURE 35.4. Subacute cutaneous lupus, psoriasiform subtype.

FIGURE 35.5. Subacute cutaneous lupus, annular/polycyclic subtype.

mentioned. The classic malar rash is the most recognizable of this group, presenting as smooth to slightly scaling edematous symmetric erythematous patches on the face (Fig. 35.6). There is some clinical overlap with rosacea and seborrheic dermatitis, so evaluation for a similar eruption in photosensitive sites is extremely important. Photo-exacerbation is common, and heavy sun exposure in susceptible individuals can result in widespread acute LE. Widespread acute LE with TEN-like desquamation can be abrupt and life-threatening. Hair loss occurs in approximately 50 % of patients. It is usually patchy and nonscarring, fully reversible with therapy for SLE, although scarring alopecia can occur in the setting of discoid lupus of the scalp [14].

Antiphospholipid syndrome (APS) can be present in isolation or as a component of systemic lupus erythematosus. Evidence of APS occurs in 40 % of SLE patients, although only 40 % of these patients have thrombotic complications. It can result in venous or arterial thrombosis, recurrent spontaneous abortion, and thrombotic complications of both cerebral and myocardial vessels. Laboratory findings of both antiphospholipid antibodies (such as anticardiolipin antibodies) and abnormalities in the clotting profile are usually found. Cutaneous findings associated with
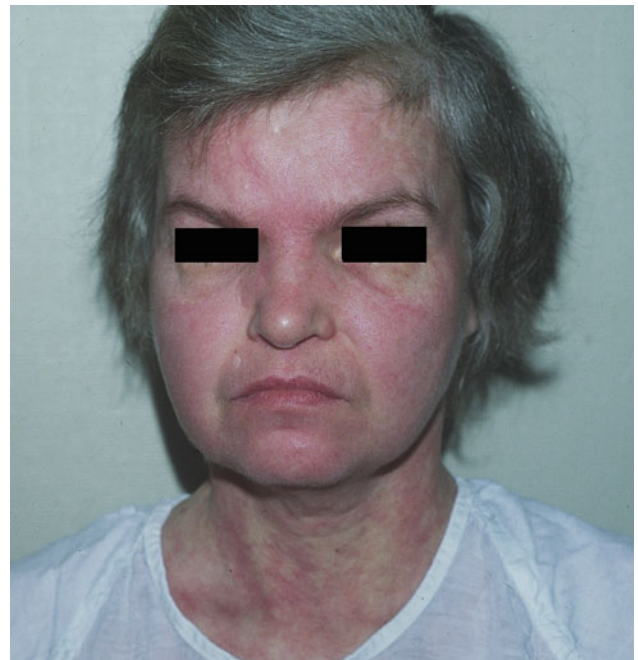
FIGURE 35.6. Acute malar rash of SLE.

antiphospholipid antibody syndrome are those reflecting unchecked thrombosis. Larger vessel occlusion can result in livedo reticularis due to vascular stasis and occurs in 25 % of patients with antiphospholipid antibody syndrome [15]. Stellate necrosis and cutaneous ulceration can occur with complete occlusion.

Bullous lupus, referring to the subcutaneous immuno-bullous disorder associated with SLE and antibodies to type VII collagen, also falls into this group. This occurs more often in young black women in the second and third decade. Multiple tense bullae develop with a variable distribution, occasionally involving mucous membranes. Scarring and mechanobullous lesions do not occur, which occur more commonly in epidermolysis bullosa acquisita, a disease which overlaps a great deal with bullous lupus [16].

Most of the aforementioned variations have some histopathologic findings in common. Most have lymphocytes as the main inflammatory cell, and most have some degree of vacuolar interface dermatitis, except those variants which do not involve the epidermis. Keeping these similarities in mind, discoid lupus will be described in more detail, with other subsets compared with this initial description.

In classic discoid lupus, clinically adherent scales are reflected in dense irregular clumps of parakeratosis. Epidermal atrophy and sparse lymphocytic inflammation of the basal layer of the epidermis causing vacuolar change are somewhat characteristic features, with interface dermatitis

spreading down along the basal layer of hair follicles plugged with keratin. An intense superficial and deep perivascular infiltrate of lymphocytes and plasma cells along with dermal mucin deposition results in clinical erythema and induration (Figs. 35.7 and 35.8).

In subacute cutaneous lupus, epidermal atrophy is more pronounced, with occasional extension into the pilosebaceous unit, and hyperkeratosis and basement membrane thickening is less apparent. Follicular plugging is minimal to nonexistent. Intensity of inflammation both at the dermoepidermal junction and at perivascular sites is markedly reduced, as is depth of inflammation and extent of mucin deposition [17] (Fig. 35.9).

Acute cutaneous lupus displays features that in early lesions consist of subtle basal layer liquefactive degeneration, mild dermal edema, and a mild superficial perivascular lymphocytic infiltrate. Mucin deposition is usually sparse. Lesions can also be reminiscent of SCLE or DLE at times. Bullous LE usually consists of a subepidermal vesicle which is typically neutrophil-rich. Adjacent skin may show subepidermal neutrophilic microabscesses, similar to those seen in dermatitis herpetiformis. Either a granular or linear pattern of IgG or IgA can be seen lining up along the dermoepidermal junction on direct immunofluorescence [18]. Indirect immunofluorescence on salt-split skin reveals exclusively dermal serum antibody aggregation, which is expected given the target antigen (type VII collagen).
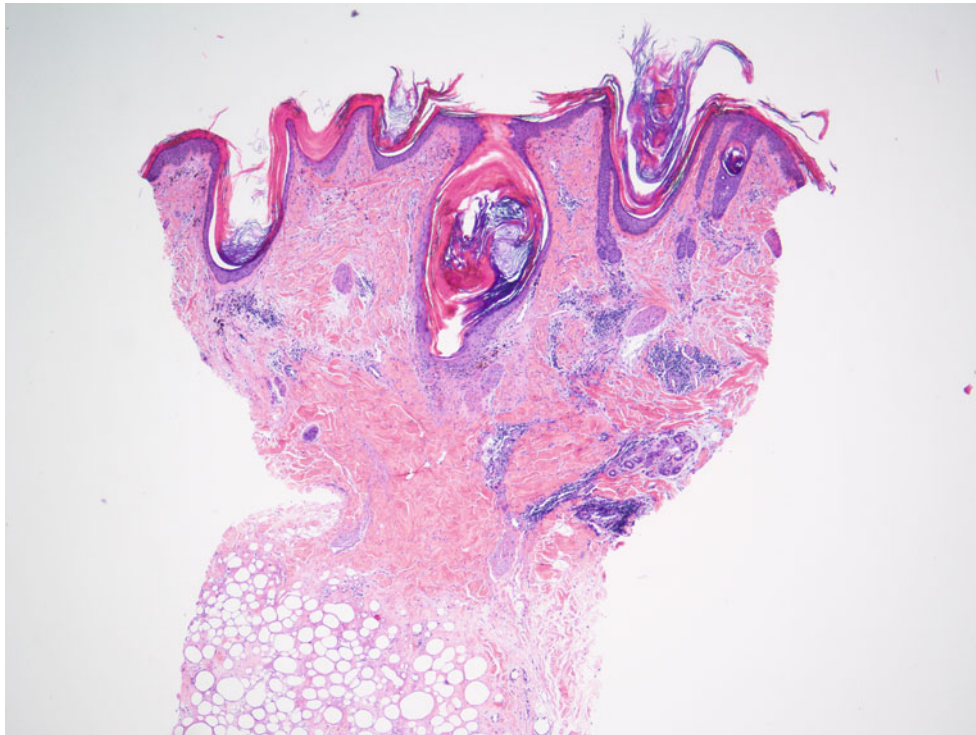
FIGURE 35.7. Discoid lupus erythematosus, low power: Follicular plugging with superficial and deep dermal inflammation with subcutaneous hyalinization.
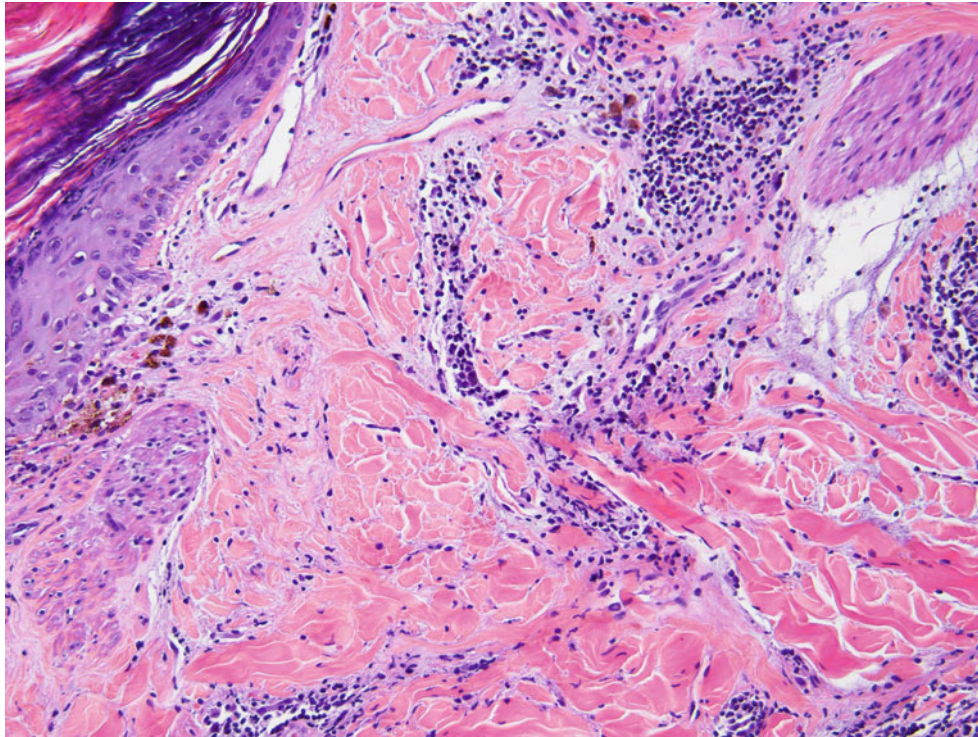
FIGURE 35.8. Discoid lupus erythematosus, high power: Chronic interface folliculitis with pigment incontinence and dermal lympho-plasmacytic inflammation with increased mucin.

In lupus panniculitis, overlying features of discoid lupus may or may not be present. Some use the term "lupus profundus" when findings of both are present in the same lesion. The deep dermis and septae of the subcutaneous fat are packed with nodular infiltrates of lymphocytes and plasma cells, occasionally spreading into fat lobules and causing fat necrosis (Fig. 35.10). There is often fibrinoid degeneration of nearby collagen [19].

Description of the use of autoantibodies in the diagnosis of SLE and subtypes of cutaneous LE deserves attention. Antinuclear antibodies are almost always positive in the setting of SLE and usually of high titer (>1:320). Antibodies to double-stranded DNA are quite specific for SLE, although with limited sensitivity. The same holds true for anti-Smith antibodies, which are insensitive, but extremely specific for SLE. Anti-Ro antibodies are often positive in SLE, but nonspecific and found in a variety of cutaneous subtypes of LE and other connective tissue diseases. Anticardiolipin antibodies are positive in 16% of SLE patients.

Diagnosis of cutaneous subsets of LE is more often a clinical diagnosis which can be supported by autoantibody presence. This is particularly true in the setting of SCLE, in which 60% are ANA positive and 80% are Ro antibody positive. DLE autoantibody profile is even less diagnostic, with ANA positivity in several studies ranging from 5 to 60%. Older age, longer duration, and more extensive cutaneous disease portend a higher rate of ANA positivity in discoid lupus. A small percentage of patients with DLE are anti-Ro positive (~10%) [20].

Treatment of SLE and cutaneous lupus is complex, and some medications used exclusively for SLE will not be discussed. Given similar histologic infiltrates and perceived similarities in pathogenesis, there is overlapping efficacy among the subtypes, particularly when it comes to response to antimalarials and corticosteroids. Response to immunomodulators varies, and benefits must always be carefully balanced with risk, especially in the context of purely cutaneous disease.

Treatment of localized cutaneous lupus, especially in TLE, SCLE, and DLE, should begin with topical treatment (high-potency steroids and/or calcineurin inhibitors), with or without intralesional injection of corticosteroids. Protection from ultraviolet radiation in photosensitive disease is paramount. First-line oral therapy for recalcitrant local disease or widespread cutaneous disease includes topical therapy in addition to hydroxychloroquine. Dosage of 200 mg twice daily is appropriate for most patients, although some advocate for an upper limit of 6 mg/kg body weight to avoid ocular complications. The use of a 4-week prednisone taper in addition to initiation of hydroxychloroquine can account for slow onset of action with use of antimalarials and halt progression of disease during this time. Failure of hydroxychloroquine (no improvement after 2–3 months) will usually result in addition of quinacrine (100 mg daily) or substitution of chloro-
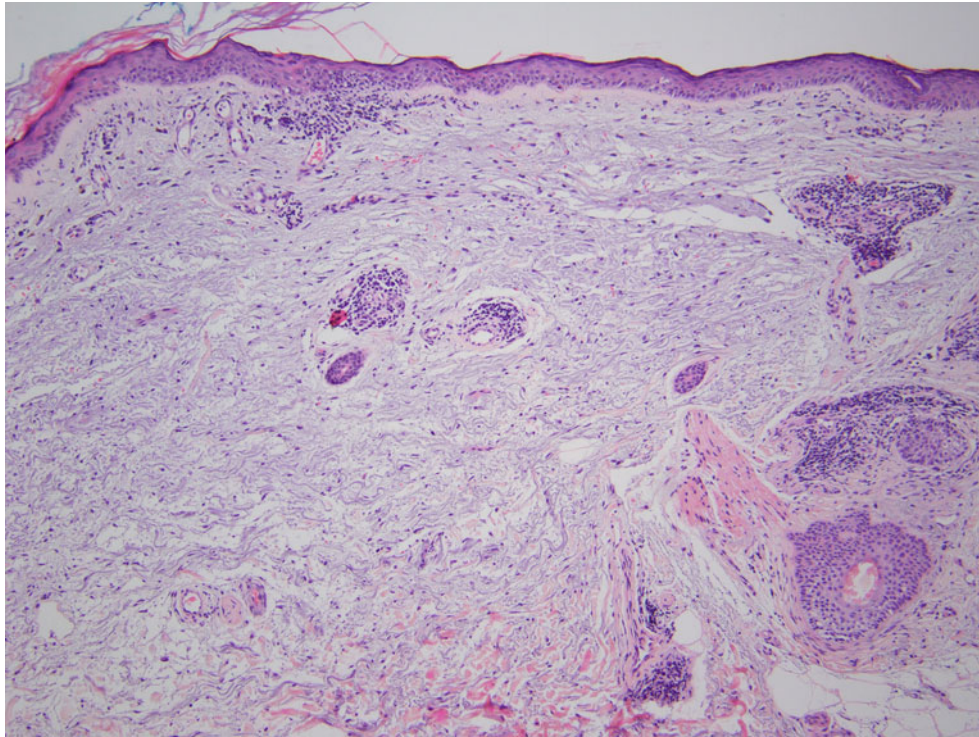
FIGURE 35.9. Subacute cutaneous lupus erythematosus, low power: Subacute interface dermatitis with increased dermal mucin and patchy lymphoplasmacytic inflammation.
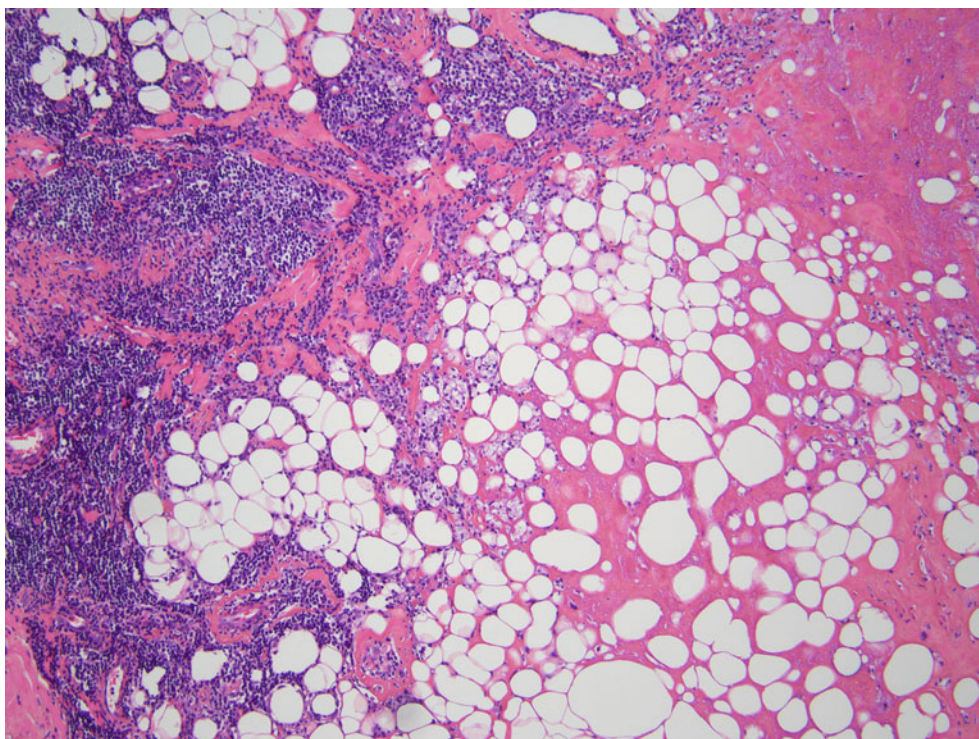
FIGURE 35.10. Lupus profundus, high power – hyalinizing panniculitis with lymphoplasmacytic inflammation.

quine (250 mg daily). Afterward, the treatment algorithm becomes somewhat controversial and varies depending on subtype of cutaneous LE and the treating physician. Methotrexate and oral retinoids (acitretin, isotretinoin) have both shown benefit in multiple studies, particularly for SCLE and DLE. The only head-to-head comparison, between acitretin and hydroxychloroquine in a group of patients with various subsets of cutaneous LE, showed similar rate of response, although dosage of acitretin used was 50 mg daily. Dapsone shows better response in SCLE and bullous LE than in DLE and can be considered a reasonable second-line agent. Mycophenolate mofetil and azathioprine can also be used for refractory skin disease, particularly in the context of concomitant SLE [21]. Thalidomide can be used as a third-line agent as well, with 98 % improvement and 85 % complete clearance in a study of 60 patients with DLE and SCLE refractory to antimalarials, although disease recurred/worsened in >70 % after discontinuation [22].

References

1. Kaposi MH. Neue Beitrage zur Keantiss des lupus erythematosus. Arch Dermatol Syphilol. 1872;4:36.
2. Osler W. On the visceral manifestations of the erythema group of skin diseases (third paper). Am J Med Sci. 1904;127:1.
3. Jadassohn J. Lupus erythematodes. In: Mracek F, editor. Handbach der Hautkrakheiten. Wien: Alfred Holder; 1904. p. 298–404.
4. Hargraves M, Richmond H, Morton R. Presentation of two bone marrow components, the tart cell and the LE cell. Mayo Clin Proc. 1948;27:25–8.
5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum. 1997;40:1725.
6. Hochbert MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970–1977. Arthritis Rheum. 1985;28:80–6.
7. Arnett FC, Shulman LE. Studies in familial systemic lupus erythematosus. Medicine. 1976;55:313–22.
8. Block SR, Winfield JB, Lockshin MD, et al. Studies of twins with systemic lupus erythematosus. Am J Med. 1975;59:533–52.
9. Leonhardt ETG. Family studies in lupus erythematosus. Clin Exp Immunol. 1967;2(suppl):743–59.
10. Werth VP. Cutaneous lupus: insights into pathogenesis and disease classification. Bull NYU Hosp Jt Dis. 2007;65:200–4.
11. Yell JA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. Br J Dermatol. 1993;129:1822.
12. Millard LG, Barker DJ. Development of squamous cell carcinoma in chronic DLE. Clin Exp Dermatol. 1978;3:161.
13. Tuffanelli DL. Lupus erythematosus panniculitis (profundus). Arch Dermatol. 1971;103:231–42.
14. Armas-Cruz R, Harneckerr J, Ducach G, et al. Clinical diagnosis of systemic lupus erythematosus. Am J Med. 1958;25:409–19.
15. Ruiz-Irastora G, Crowther M, Branch W, Khamashta MA.Antiphospholipidsyndrome.Lancet.2010;376(9751):1498–509.
16. Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. J Invest Dermatol. 1993;100:28s–34.
17. David-Bajar KM, Bennion SD, Despain JD, et al. Clinical, histological, and immunofluorescent distinctions between subacute cutaneous lupus erythematosus and discoid lupus erythematosus. J Invest Dermatol. 1992;99:251–7.
18. Rappersberger K, Tschachler MT, Wolff K. Bullous disease in systemic lupus erythematosus. J Am Acad Dermatol. 1989;21:745–52.
19. Sanchez NP, Peters MS, Winkelmann RL. The histopathology of lupus erythematosus panniculitis. J Am Acad Dermatol. 1981;5:673–80.
20. Mutasim DF, Adams BB. A practical guide for serologic evaluation of autoimmune connective tissue diseases. J Am Acad Dermatol. 2000;42(2 pt 1):159–74.
21. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options. Part II. J Am Acad Dermatol. 2011;65(6):e195–213.
22. Cortez-Hernandez J, Torres-Salido M, Castro-Marrero J, Vilardell-Tarres M, Ordi-Ros J. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. Br J Dermatol. 2012;166(3): 616–23.

36

Dermatomyositis

▪ Synonyms:	Wagner-Unverricht syndrome
▪ Etiology:	Primary autoimmune disorder predominantly affecting the skeletal muscle and skin
▪ Associations:	Interstitial lung disease, malignancy
▪ Clinical:	Pink violaceous patches and papules overlying joints of the hands, elbows, knees; symmetric violaceous upper eyelid eruption, shawl pattern eruption of the neck and upper trunk
▪ Histology:	Interface dermatitis of mild intensity with some variation depending on site of biopsy
▪ Prognosis:	Good in some juvenile types and in adults without associated malignancy
▪ Treatment:	Prolonged course of prednisone, methotrexate, hydroxychloroquine (skin disease)

Dermatomyositis was first described in the late nineteenth century by Ernst Wagner [1], and detailed descriptions of clinical course and skin disease by German physician Heinrich Unverricht led to its distinction from polymyositis [2]. This leads to the rarely used eponym "Wagner-Unverricht syndrome." Later discoveries included malignancy association (1916) [3, 4], details of cutaneous manifestations by Gottron (1930) [5], differentiation from systemic lupus erythematosus (1942) [6], and amyopathic dermatomyositis (1975) [7]. The first full postmortem examination of a child with dermatomyositis was published in 1912 [8]. Childhood cases represented 20 % of 338 cases reviewed in two large case series in the presteroid era in 1932 and 1939 [9, 10], although the differences between and childhood and adult dermatomyositis didn't become clear until 1966 [11].

Dermatomyositis is a rare multisystem disorder which can result in debilitating cutaneous and musculoskeletal disease, as well as signal the presence of occult, potentially lethal malignant neoplasms. It is closely related to polymyositis in terms of disease course, associations, and prognosis. Some believe dermatomyositis, polymyositis, and amyopathic dermatomyositis to exist on a spectrum, with many patients existing within the gray area between these established diagnoses. Indeed, diagnostic criteria proposed in 1975 by Bohan and Peter applied to both dermatomyositis and polymyositis (Table 36.1) [12]. These criteria focused mainly on muscle weakness, electromyographic findings, serum signs of skeletal muscle breakdown, and muscle biopsy pathologic findings, with the absence of other possible causes. Skin findings alone differentiate dermatomyositis from polymyositis. Dermatomyositis is an uncommon diagnosis, with a female predominance of about two to one. There is a bimodal peak of incidence both in children (average 7 years) and in adults in the fifth and sixth decade. Amyopathic dermatomyositis accounts for roughly 20 % of cases in adults [13].

Pathogenesis likely involves environmental triggers, genetic predisposition, immune system dysregulation, and vascular occlusion. Most adult patients display a positive antinuclear antibody, and some have antibodies against nuclear antigens which can reflect disease tendencies and affect prognosis. HLA-B8 and DR3 are associated with dermatomyositis and polymyositis and anti-Jo-1

TABLE 36.1 Bohan and Peter diagnostic criteria

Diagnostic criteria for dermatomyositis	
A	Proximal and symmetric muscle weakness progressive for weeks to months
B	Elevation of serum levels of skeletal muscle enzymes
C	Electromyographic findings characteristic of myopathy
D	Muscle biopsy evidence of myositis
E	Typical cutaneous findings of dermatomyositis
Criteria for dermatomyositis	
Possible	One criterion (A, B, C, or D) + E
Probable	Two criteria (A, B, C, or D) + E
Definitive	Three criteria (A, B, C, or D) + E

antibodies [14]. There is deposition of immunoglobulins and complement in blood vessels and at the dermoepidermal junction of affected skin of some patients. The components of the membrane attack complex (C5b-9) can be demonstrated in skeletal muscle arterioles and capillaries, lending more credence to pathogenetic relationship to immunologic microvascular injury [15]. This was found in a higher percentage in childhood (83%) than adult (26%) dermatomyositis. Given this information, it is likely that muscle injury in dermatomyositis is related to autoantibody and complement-mediated occlusion or destruction of blood vessels, resulting in ischemic necrosis of musculature. However, direct immunofluorescence studies of skin and muscle also show absent or nonspecific perivascular patterns of immunoglobulin and complement deposition in many cases. It is unclear whether endothelial damage is mediated directly by autoantibodies or whether endothelial cell death and vasculopathy are mediated by other means, followed by production and deposition of autoantibodies in damaged tissue.

Cutaneous findings vary, but the combination of characteristic findings in a well-developed case of dermatomyositis can be mistaken for little else. The heliotrope rash, consists of a pink to violaceous periocular eruption, classically favoring the upper eyelids occasionally associated with marked edema (Fig. 36.1). Gottron papules are closely set variably violaceous papules on the dorsum of the metacarpophalangeal and interphalangeal joints (Figs. 36.2 and 36.3). Scale is occasionally present, which can lend an appearance similar to papulosquamous diseases such as psoriasis. The definition of Gottron sign varies depending on the opinion of the clinician. Some refer to Gottron sign as patchy/macular erythema only on the elbows, knees, and ankles; others prefer this term for any raised/papular skin changes in these areas as well. As we proceed to less specific findings of dermatomyositis, we find signs which are common to other connective tissue diseases such as systemic lupus and scleroderma. A photodistributed pink to faintly violaceous eruption of the shoulders and upper trunk,

referred to as the "shawl" sign, can be intensely pruritic and develop poikilodermatous changes over time (Fig. 36.4). Minimal scale is present, and this sign may closely mimic a photosensitive flare of acute cutaneous lupus. Scalp disease can resemble seborrheic dermatitis and psoriasis. Intense pruritus, violaceous hue, and histopathological correlation can help to distinguish from these entities.

As mentioned previously, the hands can harbor many clues to diagnosis in the dermatomyositis patient. Erythema and papules typically involve the extensor aspect of the finger joints, rather than the interphalangeal joint space, although this "classic" distinguishing feature is not without exception. Periungual erythema with intermittent dilated capillary loops is accompanied by "ragged" cuticles which gradually climb the nail plate well past the lunula. Mechanic's hands, referring to rugged, often hyperpigmented hyperkeratotic plaques of the lateral aspects of the fingers, appears with more frequency in the anti-synthetase syndrome.

Muscular symptomatology can dominate the clinical picture or can present months to years after cutaneous disease develops. Usually weakness has an insidious onset, with proximal musculature such as the hip flexors and

FIGURE 36.1. Dermatomyositis: classic heliotrope eruption consisting of symmetric edema and violaceous erythema of the eyelids.
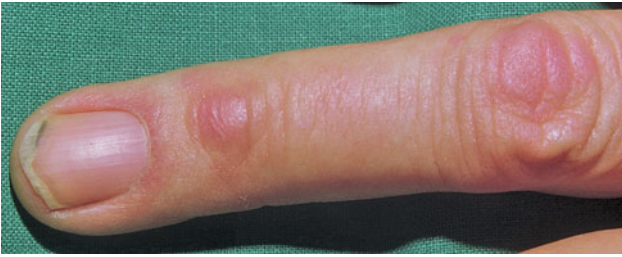
FIGURE 36.2. Dermatomyositis: Gottron papules overlying the proximal and distal interphalangeal joints of the index finger.

FIGURE 36.3. Dermatomyositis: "Shawl sign" consisting of symmetric patchy erythema of the chest with accompanying poikiloderma.

FIGURE 36.4. Dermatomyositis: Gottron papules in skin of color.

deltoids being first affected. Climbing stairs and lifting heavy objects become difficult. 50–60 % of patients with dermatomyositis have muscle weakness at presentation [16], with 25–50 % having myalgias and muscle tenderness. Facial muscles are not involved. Electromyographic features are diagnostic and included in most modern criteria for the classification of adult inflammatory myopathy [17]. Useful indicators of muscle disease include serum creatine kinase and aldolase levels, which parallel muscle inflammation as well as response to treatment. Muscle biopsy should be obtained, preferably from a weakened proximal muscle.

When EMG is used to target appropriate musculature, biopsy should be performed on undisturbed, contralateral muscle to avoid iatrogenic pathology from EMG. MRI can be used to target involved musculature in young children who are unlikely to tolerate EMG. Rates of cardiac involvement including myocardial fibrosis leading to diastolic dysfunction and ECG abnormalities are difficult to accurately quantify due to variability in sensitivity of diagnostic tests used in studies through the years [18]. Weakening of the muscles of respiration and swallowing are less common but can result in substantial morbidity.

Interstitial lung disease (ILD) is a another aotertial systemic finding 40 % of patients with polymyositis or dermatomyositis have radiologic or clinically identified lung disease (interstitial or restrictive), and the risk is higher in those with anti-Jo-1 antibodies [14, 19]. In those with ILD, patients can be asymptomatic (25 %), present with a chronic and slowly progressive course (58 %), or can result in acute respiratory failure (17 %) [20]. Amyopathic dermatomyositis carries an association with rapidly progressive ILD and poor prognosis in studies of eastern Asian populations [21, 22]. Clinically significant interstitial lung disease in JDM is rare.

The many differences between childhood and adult dermatomyositis are outlined in Table 36.2 [37]. Cutaneous vasculopathy with concomitant ulceration/necrosis and calcinosis cutis is much more common in childhood dermatomyositis reflecting a possible difference in primary pathogenesis [23]. Vasculopathy of the gastrointestinal tract and heart is also much more common in childhood disease. Myositis-specific antibodies are present in both adults (80 %) and children (>60 %), and implications are summarized in Table 36.3 [24].

Malignancy association varies based on patient population and subtype of dermatomyositis, although rates of association in adults range from 7 to 43 %, with risk increasing with age [25]. Risk is approximately threefold for adults overall, risk being highest within 1 year of diagnosis and increased risk continuing until up to 5 years after diagnosis of myositis [26]. Cases of childhood dermatomyositis and those with anti-Jo-1 antibodies are rarely associated with malignancy. Those patients with repeated attacks of severe myositis with lack of response to conventional therapy should be aggressively screened with either computed tomography or positron emission tomography scanning. Associated malignancies are often common to age group and gender of the affected individual. Otherwise healthy adults should undergo age-appropriate screening for malignancy.

Cutaneous *histopathology* is relatively nonspecific. Most sites of inflammatory skin disease will display some degree of papillary dermal edema and dermal mucin deposition associated with a mild lymphohistiocytic interface dermatitis with liquefactive degeneration of basal cells (Fig. 36.5).

The remainder of histologic findings depend somewhat on the biopsy site morphology. Not surprisingly, Gottron papules add hyperkeratosis and epidermal acanthosis to the findings mentioned above. Additional findings in the "shawl" of poikilodermatous change show epidermal atrophy, hyperkeratosis, increased mucin deposition, and dilated superficial dermal vessels [27]. Juvenile disease occasionally will add fibrosis, calcification, and occlusive vascular disease [28]. Skeletal muscle pathology and inflammatory features vary based on the site of biopsy. Necrosis of muscle tissue with associated occlusion or necrosis of nearby vasculature is more common in muscle biopsy in childhood dermatomyositis [23].

Treatment of muscle disease hinges on rapid institution of oral corticosteroids (0.5–1 mg/kg/day) until normalization of muscle enzymes followed by a very slow taper, with some advocating 1–2 years of treatment until cessation [29]. Steroid-sparing agents can be used with recalcitrant disease or with medical contraindications to oral steroid therapy. One of the most studied of these agents is methotrexate, which shows ability to induce improvement and remission as monotherapy [30] or when combined with corticosteroids in a significant number of patients. One study with a combination of patients with DM, polymyositis, and inclusion body myositis showed a 73 % response rate in those refractory to steroids [31]. Similarly, azathioprine has shown impressive results as steroid-sparing agents in doses of 2–2.5 mg/kg/day, although the side effect profile makes this a less favorable option, particularly in juvenile dermatomyositis [32]. For short-term control of exacerbations, cyclosporine has been used in doses of 3–3.5 mg/kg/day with success for refractory disease, although the need for long-term therapy makes cumulative nephrotoxicity a concern [30].

In the case of refractory skin disease or dermatomyositis sine myositis, sun protection, topical corticosteroids, and hydroxychloroquine can be useful adjunctive therapies [33]. 41–75% of patients improve with antimalarials, in particular periorbital and facial skin disease, although the response is not as impressive as in cutaneous lupus erythematosus [34]. Topical tacrolimus can be used for limited cutaneous disease. Oral mycophenolate mofetil or methotrexate can be considered in refractory severe skin disease [35, 36].

TABLE 36.2. Comparison between juvenile and adult dermatomyositis

	Juvenile poly/dermatomyositis (JDM)	Adult dermatomyositis
Incidence	2–4 per million	9.5 per million
Variants	Monocyclic, polycyclic, chronic continuous (amyopathic extremely rare)	Amyopathic (20 %), classic
Age of onset	Average age of onset: 7 years	5th–6th decade
Gender predilection	Female/male ratio 2:1	Female/male ratio 2:1
Cardiovascular	Uncommon: EKG changes, cardiomegaly, pericarditis, hypertension (25 %)	Myocardial fibrosis, ECG changes, diastolic dysfunction, congestive heart failure, increased risk of myocardial infarction
Pulmonary	Restrictive lung disease (60–70 %) due to muscle weakness with rare (3 %) interstitial lung disease	Interstitial lung disease (20–60 % with idiopathic inflammatory myopathy) or restrictive lung disease
Gastrointestinal	Oral ulceration, erythema, gingivitis (10–46 %), dysphagia/dysphonia (12–85 %), GI ulceration/perforation (common cause of death)	Less common: distal esophageal dysmotility and reflux, rare GI inflammation/ulceration
Renal	Transient mild proteinuria, hematuria, and renal dysfunction	Rare
Hepatic	Hepatomegaly (10–20 %)	Rare
Cutaneous disease	Calcinosis (30 %) occurs late in disease course; ulceration more common	Calcinosis less common (15 %)
Muscular	Weakness (95 %), muscle pain (60–85 %), contractures (62–90 %), muscular induration (50–100 %), CPK elevation (90 %)	50–60 % weak at presentation, 25–50 % muscle pain
Serology	ANA and RF positivity (<10 % initially), myositis-specific antibodies (60 %), Mi-2 (4–10 %), p155 (23 %)	80 % ANA +, myositis-specific antibody (80 %), including Jo-1 (40 %), Mi-2 (20 %), p155 (13–21 %)
Pathogenesis	Immune complex-mediated vasculopathy of capillaries and small muscular arteries leads to ischemic or infarctive muscle tissue loss	Inciting factor for production of autoantibodies may differ and be related to immunologic response to neoplasm; less occlusion and necrosis of the skin and muscle occur in general than in JDM
Malignancy association	None	7–43 % overall; threefold increased risk after diagnosis, 80 % adenocarcinoma, risk minimal if age at diagnosis <45 years
Arthritis	7–38 %, mild	Rare, mild inflammatory arthritis
Fever	50–85 %	Less common

TABLE 36.3. Features and implications of myositis

Antibody	Target	Frequency	Associations	Comments
Anti-Jo-1	Histidyl-tRNA synthetase	20 % (adults)	Anti-synthetase syndrome: myositis, ILD, mechanic's hands, Raynauds, arthritis, rapid onset	OJ, EJ, PL-7, PL-12, KS, Zo, and Ha are other anti-synthetase targets in DM and PM
Anti-Mi-2	Helicase for transcription activation	7 % adult Caucasians	Acute onset, shawl sign, respond well to treatment	Present 30 % of Central American patients
Anti-CADM-140	RNA helicase	7 % (US)	Amyopathic DM and rapidly progressive ILD (Japanese, Chinese pt), severe arthropathy, little myositis (US)	AKA anti-MDA5 (melanoma differentiation associated gene 5)
Anti-P140	NXP2	10–20 % (JDM)	Calcinosis in childhood DM	
Anti-p155-TIF1	Nuclear factor, ubiquitin ligase	13 % adult, 23 % juvenile	Severe cutaneous disease (children), 50 % malignancy assoc (adults)	Specific for dermatomyositis
Anti-SAE	Small ubiquitin-like modifier activating enzyme	3 % adult	Initial classic skin disease, followed by myositis and systemic disease	Specific for dermatomyositis

Tansley et al. [24]
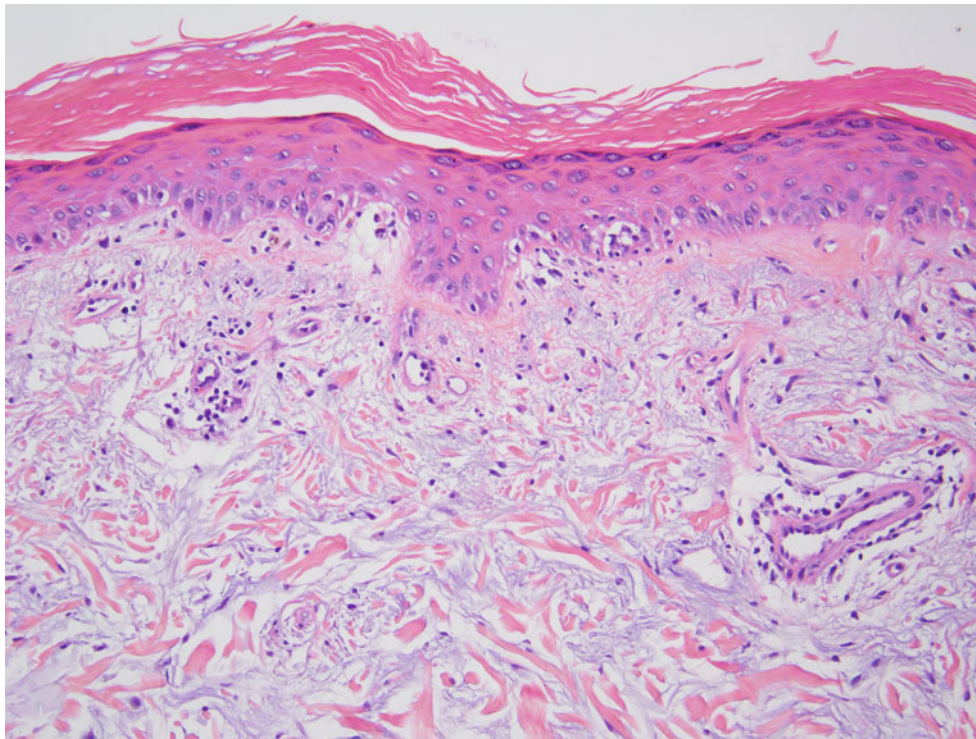
FIGURE 36.5. Dermatomyositis 20× magnification: subacute interface dermatitis with prominent dermal mucin deposition and sparse lymphoplasmacytic inflammation.

References

1. Wagner E. Fall einer seltnen Muskelkrankheit. Dtsch Arch Heilk. 1863;4:282–3.
2. Unverricht H. Dermatomyositis acuta. Dtsch Med Wochenschr. 1891;17:41–4.
3. Stertz G. Polymyositis. Berl Klin Wochenshr. 1916;53:489.
4. Kankeleit H. Über primaire nichteitrige Polymyositis. Dtsch Arch Klin Med. 1916;120:335–9.
5. Gottron H. Hautveränderungen bei Dermatomyositis. VIII Congres Intern. Dermatol. et Syphilogr., Copenhagen, 5–8 Agout, 1930, Compt rend Seancy, Ed. S.Lomholt, Copenhagen 1931; 826–830.
6. Keil H. The manifestations in the skin and mucus membranes in dermatomyositis with special reference to the differential diagnosis from systemic lupus erythematosus. Ann Intern Med. 1942;16:827.

7. Krain LS. Dermatomyositis in six patients without initial muscle involvement. Arch Dermatol. 1975;111:241–6.

8. Batten FE. Case of dermatomyositis in a child, with pathological report. Br J Child Dis. 1912;9:247.

9. Karelitz S, Welt SK. Dermatomyositis. Am J Dis Child. 1932;43:1134.

10. Scheuermann H. Zur klinik und pathogenese der dermatomyositis (polymyositis). Arch Dermal u syph. 1939;178:414.

11. Banker BQ, Victor M. Dermatomyositis (systemic angiography) of childhood. Medicine. 1966;45:261.

12. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med. 1975;292:344–7.

13. Bendewald MJ, et al. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. Arch Dermatol. 2010;146(1):26–30.

14. Plotz PH, Dalakas M, Leff RL, et al. Current concepts in the idiopathic inflammatory myopathies: polymyositis, dermatomyositis, and related disorders. Ann Intern Med. 1989;111:143–57.

15. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med. 1986;314(6):329–34.

16. Bohan A, et al. Computer-assisted analysis of 153 cases patients with polymyositis and dermatomyositis. Medicine (Baltimore). 1977;56:255.

17. Dalakas MC, Hohlbeld R. Polymyositis and dermatomyositis. Lancet. 2003;362(9388):971–80.

18. Lundberg IE. The heart and dermatomyositis and polymyositis. Rheumatology. 2006;45:iv18–21.

19. Caro I. Dermatomyositis as a systemic disease. Med Clin North Am. 1989;73:1181–92.

20. Marie I, Hachulla E, Cherin P, Dominique S, Hatron PY, Hellot MF, Devulder B, Herson S, Levesque H, Courtois H. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum. 2002;47:614–22.

21. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita T, Kuwana M. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum. 2009;60(7):2193–200.

22. Sato S, Kuwana M, Fujita T, Suzuki Y. Amyopathic dermatomyositis developing rapidly progressive interstitial lung disease with elevation of anti-CADM-140/MDA5 antibodies. Mod Rheumatol. 2012;22(4):625–9.

23. Crowe WE, Bove KE, Levinson JE, et al. Clinical and pathogenetic implications of histopathology in childhood polydermatomyositis. Arthritis Rheum. 1982;25:126–39.

24. Tansley SL, McHugh NJ, Wedderburn LR. Adult and juvenile dermatomyositis: are the distinct clinical features explained by our current understanding of serologic subgroups and pathogenic mechanisms? Arth Res Ther. 2013;15:211.

25. Cox NH, Lawrense CM, Langtry JAA, et al. Dermatomyositis. Disease associations and an evaluation of screening investigations for malignancy. Arch Dermatol. 1990;126:61–5.

26. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med. 2001;134:1087–95.

27. Kasper CS, White CL, Freeman RG. Pathology and immunopathology of polymyositis and dermatomyositis. Clin Dermatol. 1988;6:64–75.

28. Bowyer SL, Clark RA, Ragsdale CG, et al. Juvenile dermatomyositis: histologic findings and pathogenetic hypothesis for the associated skin change. J Rheumatol. 1986;13:753–9.

29. Dawkins MA, Jorizzo JL, Walker FO, Albertson D, Sinal SH, Hinds A. Dermatomyositis: a dermatology-based case series. J Am Acad Dermatool. 1998;38:397–404.

30. Vencovsky J, Jarosova K, Machacek S, Studynkova J, Kafkova J, Bartunkova J, et al. Cyclosporine a versus methotrexate in the treatment of polymyositis and dermatomyositis. Scand J Rheumatol. 2000;29:95–102.

31. Joffe MM, Love LA, Leff RL, Fraser DD, Targoff IN, Hicks JE, et al. Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. Am J Med. 1993;94:379–87.

32. Miller J, Walsh Y, Saminaden S, Lecky BRF, Winer JB. Randomized double blind trial of methotrexate and steroids compared with azathioprine and steroids in the treatment of idiopathic inflammatory myopathy. J Neurol Sci. 2002;199(Suppl):S53.

33. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, et al. Guidelines of care for dermatomyositis: American Academy of Dermatology. J Am Acad Dermatol. 1996;34:824–9.

34. Iorizzo LJ, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. J Am Acad Dermatol. 2008; 59(1):99–112.

35. Gelber AC, Nousari HC, Wigley FM. Mycophenolate Mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. J Rheumatol. 2000;27:1542–5.

36. Kasteler JS, Callen JP. Low-dose methotrexate administered weekly is an effective corticosteroid-sparing agent for the treatment of the cutaneous manifestations of dermatomyositis. J Am Acad Dermatol. 1997;36:67–71.

37. Crowe WE. Dermatomyositis and polymyositis. In: Gershwin ME, Robbins DL, editors. Musculoskeletal diseases of children. New York: Grune & Stratton; 1983. p. 113–37.

37
Diffuse Systemic Sclerosis

- ■ Synonyms: progressive systemic sclerosis, systemic scleroderma
- ■ Etiology: primary autoimmune disorder resulting in endothelial dysfunction, progressive dermal fibrosis, and visceral complications
- ■ Associations: interstitial lung disease, pulmonary hypertension, renal crisis, esophageal reflux, Raynaud phenomenon
- ■ Clinical: diffuse progressive dermal induration of the trunk > extremities, sclerodactyly, dyspigmentation, and contractures
- ■ Histology: thickened sclerotic dermis with trapping of adnexal structures, usually with minimal inflammation and flattening of rete ridges
- ■ IHC: none
- ■ Prognosis: poor, especially with concomitant interstitial lung disease or pulmonary hypertension
- ■ Treatment: multidisciplinary care with inclusion of treatment of dermatologic manifestations and monitoring and treatment of visceral manifestations

The concept of a disease which hardens the skin and creates profound disability is one that has been described for centuries. Carlo Curzio described a 17-year-old female patient in Naples, Italy, with wood-like skin, reminiscent of a dry hide, with restriction of movement of the mouth and face. She recovered completely after 11 months [1]. Although this is widely considered to be the first accurate description of scleroderma, her spontaneous remission and lack of systemic sequelae bring to mind type I scleredema. The term "scleroderma generale" was first used by Fantonetti in 1836, although his patient also had features more reminiscent of scleredema. It was not until Maurice Raynaud and Sir William Osler that a clear picture of the features (and burden) of scleroderma developed. Osler eloquently wrote, "In its most aggravated forms diffuse scleroderma is one of the most terrible of human ills. Like Tithonus, to 'wither slowly' and like him to be 'beaten down and marred and wasted' until one is literally like a mummy, encased in an ever-shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern." Although current treatments can be helpful and occasionally alter the course of diffuse systemic sclerosis, Osler's words ring true for some patients with severe progressive disease, encased in a skin of steel.

The scleroderma-like illnesses have a confusing history of classification. Morphea and its subtypes will not be discussed in this chapter, and limited systemic sclerosis (LSSC) (previously known as calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome) will be mentioned only in passing. We will focus on the subset of scleroderma which results in the most profound morbidity, diffuse systemic sclerosis. In addition to cutaneous sclerosis, joint contractures, and loss of mobility, diffuse systemic sclerosis can involve almost any organ or tissue in the human body. There is a female predominance (approximately 3–4:1 combining limited and diffuse types), with onset usually in the fourth to sixth decades of life [2].

Pathogenesis is via a two-pronged, interrelated attack of vascular endothelial dysfunction and abnormal collagen synthesis and accumulation. Endothelial cells of capillaries undergo a series of changes beginning with subtle

ultrastructural separation, proceeding to vacuolation and complete destruction of the capillary wall. Compensatory dilatation of residual vessels, best seen by nailfold capillaroscopy, is a visible manifestation of this microscopic pathology. Arteriole involvement is also marked, especially in the kidneys and is marked by concentric, fibrotic lamination of the vascular intima. As mentioned previously, deposition of collagen in the dermis is excessive and abnormal in morphology and type. It is likely that the immune response to vascular injury (and exposure of damaged collagen) results in excessive production of autoantibodies (B cells) and cytokine milieu (activated T cells) which promote collagen deposition [3]. Cytokines found in excess include transforming growth factor- beta and interleukin 4, which induce production of excess collagen via fibroblasts and likely play a key role in pathogenesis.

Skin disease in diffuse scleroderma is marked sclerotic induration which insidiously develops on the acral and (more characteristically) truncal skin (Fig. 37.1). An isolated acral (hands, feet, face) distribution is more common in limited systemic sclerosis (LSSC), formerly known as CREST syndrome. As the skin thickens and becomes immobile, salt-and-pepper dyspigmentation occurs in large patches, particularly in darker skin types (Fig. 37.2). When acral involvement is present, an initial edematous phase progresses to sclerosis and tapering of the fingers, associated with Raynaud phenomenon and occasionally ischemic ulceration of the fingertips (Fig. 37.3). Occurrence of Raynaud phenomenon from years to decades prior to cutaneous induration is more common in LSSC. The skin takes on a glossy, waxy appearance, and mobility is reduced with occasional flexion contractures of involved joints. Facial disease results in a relatively characteristic facies consisting of thinned lips, lack of ability to fully open the mouth, and perioral and periorbital wrinkling and tightening [4].

Extracutaneous manifestations are protean. The lungs are particularly severely involved, with the possibility of interstitial lung disease and pulmonary hypertension contributing markedly to morbidity and mortality. Renal involvement, particularly the scleroderma renal crisis, was previously a common cause of death before regular use of angiotensin-converting enzyme (ACE) inhibitors. Early crisis presents with new-onset arterial hypertension and/or progressive oliguric renal failure, which is often asymptomatic, with catastrophic results [5]. Cardiac involvement including pericarditis and effusion are common and often initially asymptomatic, and myocardial infiltration can occur [6, 7]. The latter can result in arrhythmia and sudden death. Gastrointestinal involvement occurs most commonly in the esophagus with reflux, pathologic dilatation, and abnormal peristalsis and can cause pain, dysphagia, and aspiration. Small and large bowel involvement cannot be ignored, as pseudo-obstruction, malabsorption, diarrhea, and constipation can occur [8].

Diagnosis is via a combination of clinical characteristics with supportive serologic and imaging studies. Classification criteria for systemic sclerosis were recently updated by the American College of Rheumatology (ACR), as the previous system (published in 1980) left many patients with early disease unclassified. The lack of adequate understanding of autoantibody profiles and the diagnostic value of telangiectasias and nailfold capillaroscopy at the time of publication reduced diagnostic sensitivity. The new classification criteria (Table 37.1) revolve around seven clinical and serologic parameters, all of which are assigned weights which allow for more "diagnostic" features to impart more impact on
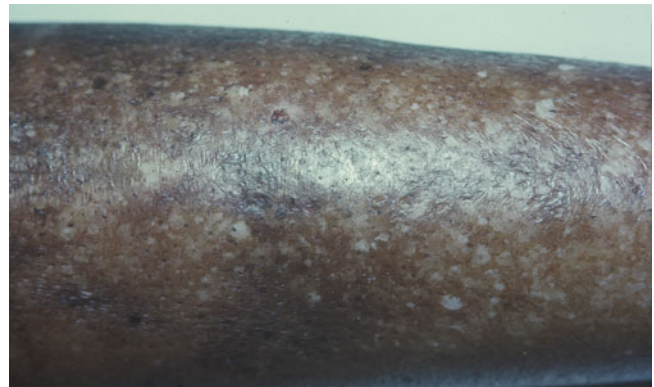
FIGURE 37.2. Diffuse systemic sclerosis: salt-and-pepper dyspigmentation of the arm occurring in skin of color.

FIGURE 37.1. Diffuse systemic sclerosis: sclerotic induration of the skin of the arm in late diffuse systemic sclerosis.

FIGURE 37.3. Diffuse systemic sclerosis: sclerodactyly and ischemic ulceration of fingertips.

Table 37.1 2013 ACR/European League Against Rheumatism (EULAR) criteria for the classification of systemic sclerosis

Item	Sub-item(s)	Weight/score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints	–	9
Skin thickening of fingers (only higher score counted)	Puffy fingers	2
	Sclerodactyly of fingers (distal to MCP joints but proximal to PIP joints)	4
Fingertip lesions (only higher score counted)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon		
SSc-related autoantibodies (any of the three)	Anticentromere 3 anti-topoisomerase I (SCL-70) anti-RNA polymerase III	3

Not applicable for those with skin thickening sparing the fingers or those with a scleroderma-like disorder that better explains their manifestations
Total score of 9 or more is classified as having definite scleroderma

the probability of proper classification. The clinical feature thought to be pathognomonic was "skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal (MCP) joints," the presence of which, in the absence of any other criteria, is sufficient for diagnosis of systemic sclerosis. Other features which carry weight include "puffy" fingers or sclerodactyly (distal to the MCP joint but proximal to the proximal interphalangeal (PIP) joint), digital ulcerations or pitted scarring, telangiectasias, abnormal nailfold capillaries, pulmonary arterial hypertension or interstitial lung disease, Raynaud phenomenon, and presence of SSc-related antibodies (anti-SCL-70, anti-centromere, anti-RNA polymerase III). The caveat to this system is that it is not to be applied to patients who are known to have a condition that better explains their constellation of symptoms [10]. As mentioned above, autoantibodies play a role in supporting diagnosis and subtype classification. Antinuclear antibodies are found in >95 % of patients, centromere antibodies are found in 50–70 % of limited systemic sclerosis, and SCL-70 antibodies are found in 35–40 % of those with diffuse systemic sclerosis.

As would be expected from the classification criteria presented above, the clinical differential diagnosis of systemic sclerosis is broad. Mixed connective tissue disease and undifferentiated connective tissue disease are similar, as one might expect, and changing symptoms or clinical signs may lead to eventual reclassification of these patients with systemic sclerosis with time. Eosinophilic fasciitis can be differentiated in that induration of the hands is usually absent in this condition, and many other criteria listed above are not present. Scleromyxedema and nephrogenic systemic fibrosis also have minimal acral involvement, and in addition, clinical lesions are more likely to be papular and coalescing in scleromyxedema. Sclerodermatous graft versus host disease can have very similar cutaneous mani-

festations, although the past medical history of the patient will usually allow for easy differentiation from idiopathic systemic sclerosis. Scleredema, while similar in terms of nomenclature, differs in that acral involvement is absent, histopathology is quite different, distribution and clinical course is usually benign, and there is a lack of systemic involvement.

Histopathology is not specific. The epidermis is usually normal, although some flattening of the rete ridges can occur in established lesions. In early lesions, there is a mild lymphohistiocytic perivascular infiltrate along with a broadening and thickening of the dermis with swelling of collagen fibers [4]. Established lesions consist of marked thickening of the dermis with a vast expanse of sclerotic collagen with a paucity of adnexal structures (Fig. 37.4). The individual collagen is elongated, swollen, and oriented parallel to surface epithelium (Fig. 37.5). Blood vessels progress through a period of endothelial cell swelling followed by medial hypertrophy and hyalinization. Morphea is a close histologic mimic, although some believe that cellular infiltrate is heavier in morphea than in scleroderma.

Treatment requires multidisciplinary cooperation and communication among healthcare personnel. Most important in reducing mortality is adequate monitoring of kidney function and blood pressure, often with the use of angiotensin-converting enzyme inhibitors. Monitoring and adequate treatment for cardiopulmonary disease is also of substantial importance, and regular evaluation for symptoms of pulmonary hypertension, interstitial lung disease, and arrhythmias is mandatory. Immunosuppressive treatments for progressive lung disease, such as cellcept and cyclophosphamide, can also be helpful for skin disease. First-line treatment for severe Raynaud phenomenon includes calcium channel blockers such as nifedipine. Sildenafil is useful for both recalcitrant Raynaud
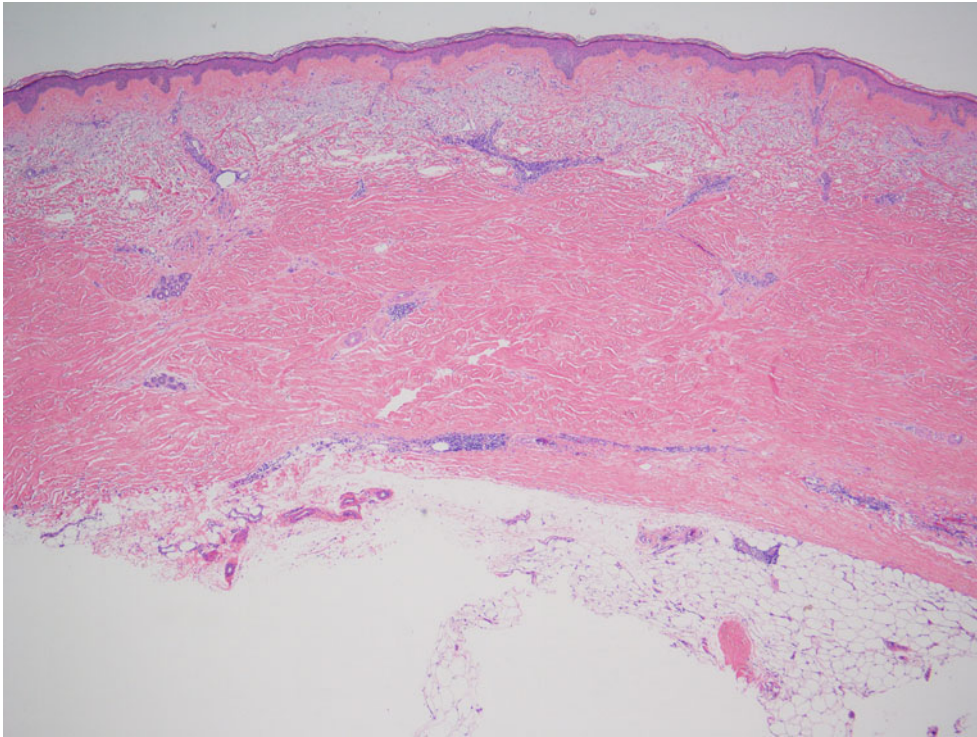
Figure 37.4. Scleroderma 4× magnification: reticular dermal sclerosis with sparse inflammation.
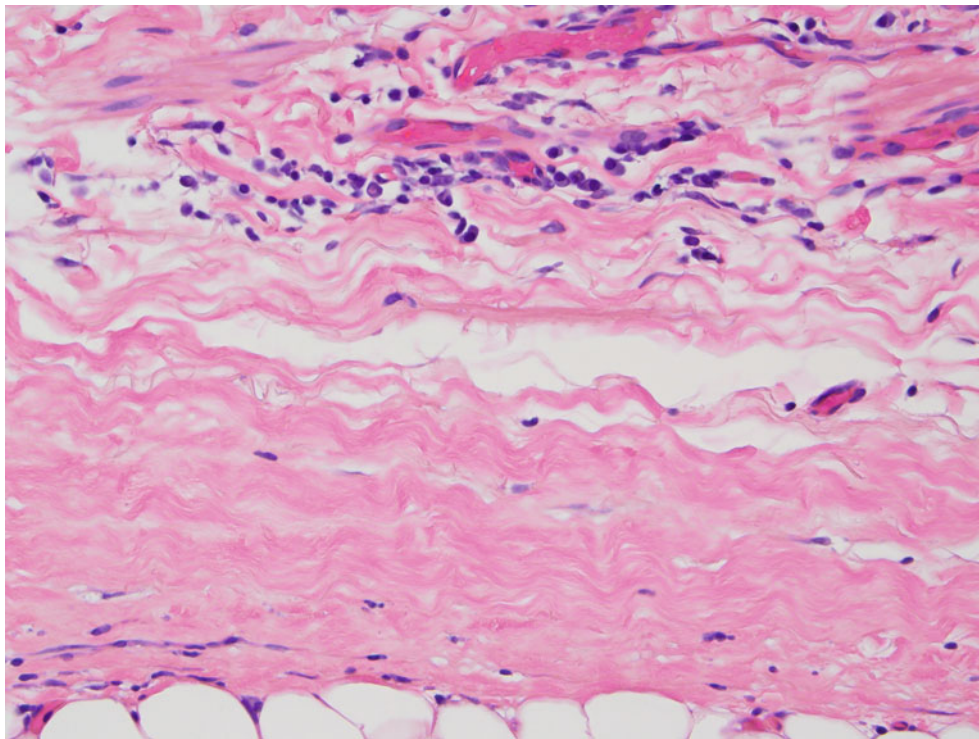
Figure 37.5. Scleroderma 40× magnification: hypocellular sclerotic collagen with lymphoplasmacytic inflammation.

phenomenon with ulcers and pulmonary hypertension. Proton pump inhibitors are almost always required for esophageal dysmotility and gastroesophageal reflux.

Phototherapy can be helpful as a "skin-directed" approach, with psoralen ultraviolet A (PUVA) and ultraviolet (UV) A-1 treatment resulting in improvement in skin thickness as evaluated by the modified Rodnan skin thickness score (MRSS) [11–13]. Penicillamine has fallen out of favor due to toxicity profile and lack of consistent, demonstrable evidence of patient improvement. Mycophenolate mofetil has recently been shown to be a promising therapeutic option for those of recent-onset skin disease, in doses averaging 2000 g/day [14, 15]. Methotrexate monotherapy has been shown to be effective in skin disease in doses of 15–25 mg weekly in two multicenter randomized placebo-controlled double blind trials [16, 17]. Treatment with methotrexate is ideal when improvement of skin thickening is a primary goal or if arthritis is a prominent symptom in addition to cutaneous manifestations. Azathioprine is used only as a second-line systemic agent for isolated skin thickening, given its lack of benefit for lung disease [18]. Intravenous immunoglobulin (IVIG) at a dosage of 2 g/kg over 5 days monthly for 6 months improved MRSS in a small sample of patients, but is also considered a second- or third-line agent [19]. Oral corticosteroids are not used with regularity in systemic sclerosis due to lack of demonstrable benefit.

References

1. Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma). Ann Intern Med. 1962;57:305–19.
2. Steen VD. Renal involvement in systemic sclerosis. Clin Dermatol. 1994;12:253–8.
3. Fleischmajer R, Perlish JS, Reeves JRT. Cellular infiltrates in scleroderma skin. Arthritis Rheum. 1972;20:975–84.
4. Leroy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets, and pathogenesis. J Rheumatol. 1988;15:202–5.
5. Steen VD, Conte C, Santoro D, et al. Twenty-year incidence survey of systemic sclerosis. Arthritis Rheum. 1988;31: A57–117.
6. Clements PJ, Furst DE. Heart involvement in systemic sclerosis. Clin Dermatol. 1994;12:267–75.
7. Janosik DL, Osborn TG, Moore TL, et al. Heart disease in systemic sclerosis. Semin Arthritis Rheum. 1989;19:191–200.
8. Kahan A, Menkes CJ. Gastrointestinal involvement in systemic sclerosis. Clin Dermatol. 1994;12:259–65.
9. Fleischmeyer R, Lebwohl M. Scleroderma. In: Theirs BH, Dobson RL, editors. Pathogenesis of skin disease. Edinburgh: Churchill Livingston; 1986. p. 233–47.
10. Van den Hoogen F, et al. Classification criteria for systemic sclerosis. Arthritis Rheum. 2013.
11. Morita A, Kobayashi K, Isomura I, Tsuji T, Krutmann J. Ultraviolet A1 (340–400 nm) phototherapy for scleroderma in systemic sclerosis. JAAD. 2000;43(4):670674.
12. Krueter A, Breuckmann F, Uhle A, Brockmeyer N, Von Kobyletzki G, Freitag M, Stuecker M, Hoffmann K, Gambichier T, Altmeyer P. Low-dose UVA1 phototherapy in systemic sclerosis: effects on acrosclerosis. JAAD. 2004;50(5):740–7.
13. Usmani N, Murphy A, Veale D, Goulden V, Goodfield M. Photochemotherapy for systemic sclerosis: effect on clinical and molecular markers. Clin Exp Dermatol. 2010;35(6):608–13.
14. Mendoza FA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. J Rheumatol. 2012;39(6):1241–7.
15. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 2011;70(6):1104–7.
16. Pope JE, Bellamy N, Seibold JR, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum. 2001;44:1351–8.
17. Van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, Van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol. 1996;35:364–72.
18. Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. Clin Rheumatol. 2006;25:205–12.
19. Levy Y, Amital H, Langevitz P, et al. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study. Arthritis Rheum. 2004;50:1005–7.

38

Pemphigus Vulgaris and Paraneoplastic Pemphigus

- **Synonyms:** None
- **Etiology:** Circulating antibodies (IgG) against keratinocyte cell surface peptides including:
  PV—desmogleins
  PP—periplakin, envoplakin, desmoplakin, desmogleins
- **Associations:** PV—Myasthenia gravis, thymoma, penicillamine, and captopril
  PP—Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease
- **Clinical:** Both variants show flaccid blisters with erosions and oral ulceration; PP is associated with variable features including targetoid- and lichenoid-appearing lesions with a tendency toward severe oral ulceration
- **Histology:** Intraepidermal acantholysis with bullae formation; PP may show a lichenoid/interface dermatitis or rarely, subepidermal bullae; both conditions show intraepidermal IgG and C3 on direct immunofluorescence (DIF)
- **IHC repertoire:** Immunohistochemical repertoire
- **Staging:** None
- **Prognosis:** PV—5-year ~90 % survival
  PP—5-year ~38 % survival
- **Adverse variables:** PV—Delay in diagnosis, advanced age, high-dose corticosteroids, and associated infection
  PP—Non-Hodgkin's lymphoma and chronic lymphocytic leukemia
- **Treatment:** PV—Corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, plasmapheresis, and IVIG
  PP—Problematic, treat underlying malignancy and corticosteroids

The disease pemphigus encompasses a group of related blistering conditions characterized by circulating antibodies against keratinocyte cell surface antigens important in mediating cell-to-cell adhesion [1, 2]. Of the various types and forms of the disease including pemphigus foliaceus, pemphigus erythematosus, IgA pemphigus, and pemphigus vegetans, it is pemphigus vulgaris (PV) and paraneoplastic pemphigus (PP) that constitute the most important causes of mortality. Overall, these disorders are quite rare,

with an estimated prevalence of between 1 in 100,000 for PV and less than 1 in 1,000,000 for PP. Both disorders are seen principally in aged adults with a near equal gender distribution. PV is more commonly observed among Jews and individuals of Mediterranean descent, whereas there is no known ethnic predilection for PP.

The etiology of both disorders involves circulating IgG antibody against specific adhesion molecules present on the cell surface of keratinocytes that mediate cell-to-cell

adhesion and are localized to the desmosome apparatus [3, 4]. The pathogenically important antigens differ among these two disorders. In mucosal PV, desmoglein 3 (130 kDa) is the predominant antigen, while both desmoglein 1 (160 kDa) and desmoglein 3 are targeted in mucocutaneous PV. In contrast, PP has multiple target antigens including plectin (500 kDa), desmoplakin I (250 kDa), bullous pemphigoid antigen 1 (230 kDa), envoplakin (210 kDa), desmoplakin II (210 kDa), periplakin (190 kDa), 170 kDa antigen, desmoglein 1, and desmoglein 3 [5, 6]. Of these antigens, antibodies against envoplakin and periplakin are the most specific for PP [7, 8]. Antibodies directed against these peptides disrupt cell-to-cell adhesion or desmosome assembly, resulting in acantholysis and blister formation. Despite a similarly evoked mechanism of blister formation, it is thought that the pathogenesis of antibody induction is different among these disorders. Patients with PV have a markedly increased frequency of certain class II major histocompatibility complex antigens including HLA-DR4 and HLA-DR14 that predispose to antibody induction against desmogleins [9, 10]. In contrast, the pathogenesis of PP is thought to involve tumor antigen cross-reactivity to normal cell surface constituents resulting in dysregulated immune modulation mediated by both humoral and cell-mediated mechanisms [11].

There are distinct disease associations with these disorders as well. PV is associated with myasthenia gravis and thymoma, as well as the administration of certain medications including penicillamine and captopril [12]. PP is invariably associated with the lymphoproliferative disorders, most commonly non-Hodgkin's lymphoma (39 %), chronic lymphocytic leukemia (18 %), Castleman's disease (18 %), carcinoma (9 %), thymoma (6 %), sarcoma (6 %), and Waldenstrom's macroglobulinemia (1 %) [13]. There are rare associations between PP and the more common solid organ malignancies such as breast, lung, colorectal, or prostate adenocarcinoma.

The clinical manifestations of PV consist of flaccid blisters with erosions that develop anywhere on the skin surface, frequently demonstrating a positive Nikolsky sign [14, 15]. The blisters may develop on normal appearing or erythematous skin (Fig. 38.1). Vegetative lesions with excessive granulation tissue may be seen in the intertriginous areas. Mucous membrane involvement, most importantly of the oral cavity, is present in nearly all cases of PV and is often a heralding symptom. It may antedate the development of skin lesions for several months and often persists following skin resolution. The most common presentation is of painful shallow ulcerations most frequently involving the buccal mucosa, palate, floor of the mouth, tongue, and less commonly the pharynx, larynx, conjunctiva, vagina, penis, or anus. The clinical findings in PP are more varied, although mucous membrane involvement is a characteristic of the disorder (Fig. 38.2). Stomatitis is usually the

FIGURE 38.1. Widespread superficial ulcers in an elderly man with pemphigus vulgaris.

FIGURE 38.2. Severe mucositis seen in paraneoplastic pemphigus. Note involvement of the nasal mucosa.

earliest sign of the condition, often persisting throughout the course of the disease, and is usually refractory to therapy. Painful erosions and ulcerations are typically encountered throughout the oropharynx, although lateral tongue
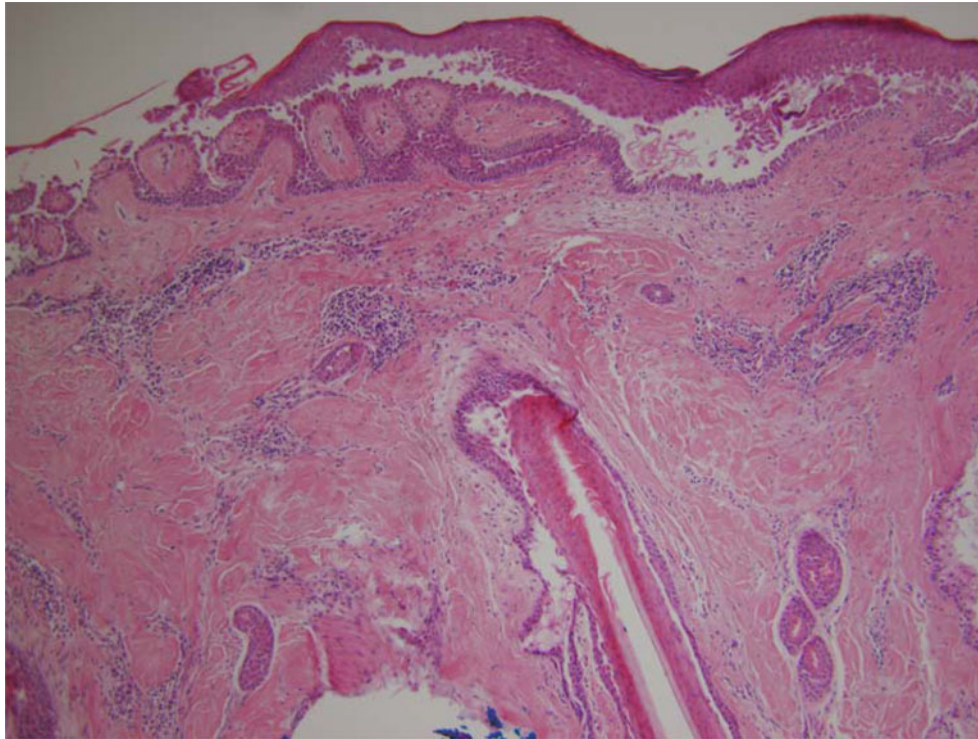
Figure 38.3. Low power photomicrograph depicting suprabasilar acantholysis with follicular involvement.

involvement with extension to and involvement of the vermilion border of the lips is characteristic. The skin lesions often occur episodically as waves of tense or flaccid blisters surmounted on an erythematous base situated on the trunk or extremities. Individually, the lesions may appear as shallow ulcerations similar to PV, as tense blisters similar to bullous pemphigoid, as confluent and erosive patches similar to erythema multiforme/toxic epidermal necrolysis, or as flat-topped papules similar to lichen planus [16–19]. Lichenoid-appearing lesions may be observed on the palms and soles as well as the paronychial skin in established cases, constituting an important means of clinically distinguishing this disorder from PV.

The histopathology of PV is distinctive. Early lesions show exocytosis of neutrophils with accompanying intercellular spongiosis and focal acantholysis. Established lesions show a mixture of dermal and epidermal neutrophils and eosinophils with conspicuous epidermal acantholysis and bullae formation (Fig. 38.3). The acantholysis characteristically spares the basilar layer of the epithelium, imparting an appearance likened to that of "tombstones." Chronic lesions, particularly derived from intertriginous areas, are apt to show acanthosis with neutrophilic and eosinophilic abscesses. Although the histopathology of PP may be identical to that of PV, more often, considerable histologic variation capable of simulating lichenoid/interface dermatitis or bullous pemphigoid is encountered. This histologic diversity may be seen in disparate lesions biopsied synchronously or in metachronous lesions from the same individual. The lichenoid interface pattern often shows striking dyskeratosis with a tendency toward confluent basilar necrolysis (Fig. 38.4). The inflammatory infiltrate of PP often shows a predominance of lymphocytes. Oral biopsies obtained from patients with both disorders show a variable degree of acantholysis with intramucosal or submucosal vesiculation. The inflammatory infiltrate characteristically shows a predominance of neutrophils.

The direct immunofluorescence (DIF) findings are similar and consist of intraepithelial staining with antibodies to IgG and C3 of the lesional skin [20, 21]. DIF is more likely to be negative among patients with PP or to additionally show basement membrane staining. Distinction of these disorders can also be attained with indirect immunofluorescence as monkey esophagus is a more sensitive substrate in PV (anti-Dsg3 autoantibodies) while rat bladder is more sensitive with PP (antiplakin autoantibodies) [22]. Additional methods for identifying the pemphigus autoantibodies include enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, and immunoblotting.

Systemic steroids are first-line treatment for PV. Various regimens and tapering schedules have been employed and cited in the literature. Other reported nonsteroidal therapies include azathioprine, mycophenolate mofetil, dapsone, cyclophosphamide, cyclosporine, methotrexate, rituximab, and intravenous immunoglobulin. These agents
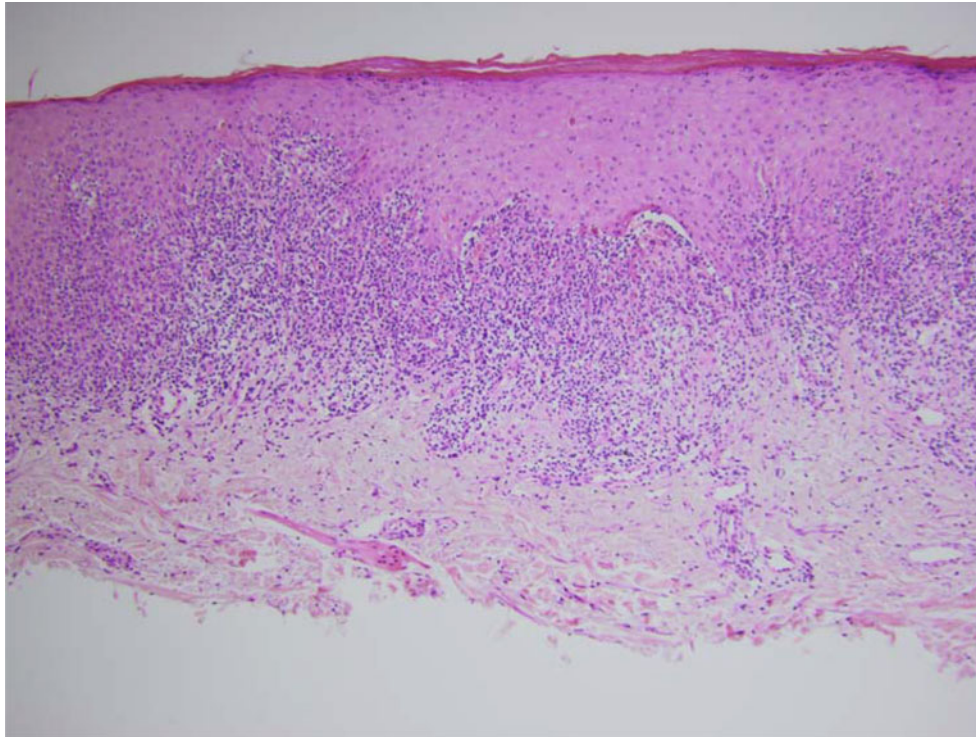
FIGURE 38.4. Dense lichenoid inflammatory infiltrate with increased necrotic keratinocytes and incipient subepidermal blister formation seen in paraneoplastic pemphigus.

are often used in combination with systemic steroids as adjuvant therapy for PV. The prognosis of PV is generally much more favorable today, particularly since the advent of multifactorial immunosuppressive therapy [23]. The mortality rate is approximately 10%. Opportunistic infection and fluid/electrolyte imbalances are the main causes of morbidity and mortality. The prognosis of younger patients with PV or those cases associated with medications, myasthenia gravis, and/or thymoma is generally more favorable. In contrast, the prognosis of PP is grave with a 1-, 3-, and 5-year survival rate of 49%, 41%, and 38% respectively [24]. Of note, in patients who present with PP prior to being diagnosed with any internal malignancy, an extensive examination for an occult neoplasm is warranted. It is recommended that a CT of the chest, abdomen, pelvis as well as CBC, LDH, and serum protein electrophoresis be performed [5]. In addition to the association with malignancy, an increased risk of bronchiolitis obliterans contributes to the high mortality rate in PP patients [25]. The mainstay of treatment is addressing the underlying neoplasm. Patients with resectable lesions such as thymoma or Castleman's disease have more favorable outcomes compared to those with indolent lymphoproliferative disorders such as chronic lymphocytic leukemia. Immunosuppressive agents are usually employed to suppress the symptoms of PP, often with very variable responses.

References

1. Becker B, Gaspari A. Pemphigus vulgaris and vegetans. Dermatol Clin. 1993;11:429.
2. Lever W. Pemphigus and pemphigoid. J Am Acad Dermatol. 1979;1:2.
3. Judd K, Lever W. Correlation of antibodies in skin and serum with disease severity in pemphigus. Arch Dermatol. 1979;115:428.
4. Fellner M, Fukuyama K, Moshell A, et al. Intercellular antibodies in blood and epidermis. Br J Dermatol. 1973;89:115.
5. Anhalt GJ. Paraneoplastic pemphigus. J Invest Dermatol Symp Proc. 2004;9:29–33.
6. Amagai M, Nishikawa T, Nousari HC, et al. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. J Clin Invest. 1998;102:775–82.
7. Huang Y, Li J, Zhu X. Detection of anti-envoplakin and anti-periplakin autoantibodies by ELISA in patients with paraneoplastic pemphigus. Arch Dermatol Res. 2009;301:703.
8. Joly P, Richard C, Gilbert D, et al. Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol. 2000;43:619.
9. Ahmed AR, Wagner R, Khatri K, et al. Major histocompatibility complex haplotypes and class II genes in non-Jewish patients with pemphigus vulgaris. Proc Natl Acad Sci U S A. 1991;88:5056.

10. Lombardi ML, Mercuro O, Ruocco V, et al. Common human leukocyte antigen alleles in pemphigus vulgaris and pemphigus foliaceus Italian patients. J Invest Dermatol. 1999; 113:107.

11. Billet SE, Grando SA, Pittelkow MR. Paraneoplastic autoimmune multiorgan syndrome: review of the literature and support for a cytotoxic role in pathogenesis. Autoimmunity. 2006;39:617.

12. Pisani M, Ruocco V. Drug-induced pemphigus. Clin Dermatol. 1986;4:118.

13. Kaplan I, Hodak E, Ackerman L, et al. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncol. 2004;40:553.

14. Ahmed A. Clinical features of pemphigus. Clin Dermatol. 1983;1:13.

15. Meurer M, Milns J, Rogers R, et al. Oral pemphigus vulgaris: a report of ten cases. Arch Dermatol. 1977;113:1520.

16. Camisa C, Helm T. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. Arch Dermatol. 1993;129:883.

17. Mutasim D, Pelc N, Anhalt G. Paraneoplastic pemphigus. Dermatol Clin. 1993;11:473.

18. Fried R, Lynfield Y, Vitale P, et al. Paraneoplastic pemphigus appearing as bullous pemphigoid-like eruption after palliative radiation therapy. J Am Acad Dermatol. 1993;29:815.

19. Tankel M, Tannenbaum S, Parekh S. Paraneoplastic pemphigus presenting as an unusual bullous eruption. J Am Acad Dermatol. 1993;29:825.

20. Rongioletti F, Truchetet F, Rebora A. Paraneoplastic pemphigoid-pemphigus? Subepidermal bullous disease with pemphigus-like direct immunofluorescence. Int J Dermatol. 1993;32:48.

21. Moy R, Jordan R. Immunopathology in pemphigus. Clin Dermatol. 1983;1:72.

22. Sabolinski ML, Beutner EH, Krasny S, et al. Substrate specificity of anti-epithelial antibodies of pemphigus vulgaris and pemphigus foliaceus sera in immunofluorescence tests on monkey and guinea pig esophagus sections. J Invest Dermatol. 1987;88:545–9.

23. Ahmed A, May R. Death in pemphigus. J Am Acad Dermatol. 1982;7:221.

24. Leger S, Picard D, Ingen-Housz-Oro S, et al. Prognostic factors of paraneoplastic pemphigus. Arch Dermatol. 2012;148:1165.

25. Maldonado F, Pittelkow MR, Ryu JH. Constrictive bronchiolitis associated with paraneoplastic autoimmune multi-organ syndrome. Respirology. 2009;14:129.

39
Relapsing Polychondritis

■ Synonyms:	None
■ Etiology:	Possible Th1-mediated disease, also antibodies against type II collagen are common; HLA-DR4 association
■ Associations:	Myelodysplastic syndromes, systemic vasculitis, connective tissue/autoimmune diseases
■ Clinical:	Erythematous, painful ear(s) and nose, arthropathy, and respiratory and ocular symptoms
■ Histology:	Frequently nonspecific, degenerative changes of the cartilage with fibrosis and lymphocytic infiltrate at the chondrofibrous junction
■ IF:	Immunoglobulin and C3 at the chondrofibrous junction
■ Evaluation:	Complete blood count (CBC), creatinine, urinalysis, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), pulmonary function tests (PFTs), ophthalmological evaluation, electrocardiogram (EKG), and possible biopsy of the involved ear
■ Treatment:	Systemic corticosteroids, nonsteroidal anti-inflammatory drugs, colchicine, methotrexate, and TNF-α blockers
■ Prognosis:	>55 % 10-year survival

In 1923, Jaksch-Wartenhorst described a 32-year-old man with polyarthritis and fever who subsequently developed bilateral auricular and nasal chondritis. He applied the term *polychondropathia* to this entity [1]. In 1960, Pearson and colleagues added four more cases and coined the term *relapsing polychondritis* (RP), which has become the accepted terminology for this disease [2].

Relapsing polychondritis (RP) is a systemic disease of unknown etiology, associated with the formation of antibodies to type II collagen, the type of collagen predominating in the cartilage. This results in inflammation of the cartilage of the ears, nose, tracheobronchial tree, and joints [3]. Involvement of the inner ear and heart may be explained by evidence suggesting that type II collagen exists in those tissues [4, 5]. Murine models suggest that tissue-specific antibody and complement activation are both necessary for expression of the disease [6]. The presence of circulating antibody to type II collagen is not specific to RP. In one investigation, these antibodies were found in 50 % of RP patients, 15 % of rheumatoid arthritis patients, and 4 % of normal controls [7]. Reactivity against different epitopes probably results in different disease manifestations. Antibodies in the sera of normal controls are specific

to bovine or chick type II collagen, suggesting that they are induced by dietary exposure to antigen. These antibodies do not cross-react with human type II collagen [7]. There is also evidence that RP is a Th1-mediated disease. T cells from mice immunized with type II collagen can be transferred to naive mice and trigger auricular chondritis in those mice [8]. It has also been noted that interferon-γ, interleukin-12, and interleukin-2 levels in serum of RP patients parallel disease activity, and Th2 cytokines that would suggest a humoral pathogenesis do not. This suggests that the autoantibodies to type II collagen could represent an epiphenomenon [9]. Genetic susceptibility to RP is associated with expression of HLA-DR4, but no predominant subtype is present in patients with the disease [10]. Further evidence of a genetic component to RP is seen in its association with multiple autoimmune diseases.

The most common presentation of RP is auricular chondritis or arthritis. Other relatively frequent presentations include nasal chondritis, laryngotracheal symptoms, ocular inflammation, auditory or vestibular dysfunction, or cutaneous eruption. The onset of disease is usually abrupt and most commonly is manifested as a tender, erythematous, indurated ear (Fig. 39.1). Local trauma has been implicated

FIGURE 39.1. Erythema and induration of the ear, with sparing of the lobe.

TABLE 39.1 Clinical features of relapsing polychondritis

Auricular and nasal chondritis
Laryngotracheal inflammation (throat pain, cough, hoarseness, dyspnea, stridor, wheezing, choking)
Arthritis
Ocular (episcleritis, scleritis, iritis, keratoconjunctivitis sicca, keratitis, optic neuritis, retinopathy, cataracts, proptosis, eyelid edema)
Neurologic (headaches, cranial nerve palsies, cerebellar ataxia, hemiplegia, encephalopathy, seizures)
Audiovestibular (hearing loss, tinnitus, vertigo, dizziness, nausea, vomiting)
Cardiovascular (aortic or mitral regurgitation, aortic aneurysm, myocarditis, pericarditis, silent myocardial infarction, conduction system abnormalities)
Renal/genitourinary (mesangial proliferation, focal and segmental necrotizing glomerulonephritis, glomerulosclerosis, IgA nephropathy, tubulointerstitial nephritis, epididymo-orchitis)
Constitutional (fever, malaise, weight loss)

as a trigger in some patients [11]. Bilateral involvement is common. Acute episodes of chondritis last from days to several weeks and resolve spontaneously. Repeated episodes result in a distorted auricular contour, with a "cauliflower ear" deformity, and a similar nasal deformity, resulting in a "saddle nose." Arthropathy is also a common presenting manifestation of RP and is usually migratory, asymmetric, non-nodular, nonerosive, and seronegative. Joint sizes involved are variable and include parasternal articulations [12]. Anemia and an elevated erythrocyte sedimentation rate may be present. Noncutaneous manifestations of RP are catalogued in Table 39.1 [13–15].

Cutaneous involvement in RP is divided into two categories: that consisting of changes overlying areas of auricular or nasal chondritis and those cutaneous manifestations not directly associated with chondritis. Typical ear and nasal involvement with cutaneous erythema and induration occurs in the majority of patients with RP at some time during the course of their disease, frequently at the outset. Other cutaneous findings attributable to RP occur in

approximately 35 % of patients. However, the actual percentage of patients with skin disease in RP is greater than that because of the cutaneous manifestations of comorbidities. Cutaneous, nonchondritic presentations of RP represent approximately 10 % of the total [16]. The more common mucocutaneous lesions seen in a series of 200 patients with RP include oral and genital aphthosis, acral subcutaneous nodules resembling erythema nodosum, and purpura, most of which is due to small vessel neutrophilic vasculitis. A summary of cutaneous findings excluding skin changes superficial to chondritis reported in this case series is given in Table 39.2 [16].

Cutaneous lesions have not been found to correlate with disease severity or specific organ system involvement, but occur with higher frequency in patients with coexistent disease, particularly those with myelodysplastic syndromes. Cutaneous disease activity correlates with systemic disease activity in approximately 50 % of cases.

RP is a multisystem disease with a wide array of clinical manifestations, the diversity of which may delay diagnosis. This is further complicated by RP's occurrence with other diseases in 25–35 % of cases [14]. The most common disease associations are myelodysplastic syndromes, in approximately 10 % of cases, other connective tissue and autoimmune diseases, and systemic vasculitis. Disease associations with RP are summarized in Table 39.3 [13, 14, 16, 17].

There is no specific diagnostic test for RP. Criteria for diagnosis as suggested by McAdam include presence of three of the following clinical features and histologic confirmation: (1) bilateral auricular chondritis, (2) nonerosive and seronegative inflammatory polyarthritis, (3) nasal chondritis, (4) ocular inflammation, (5) respiratory tract chondritis, and (6) audiovestibular damage [14]. In an attempt to diagnose RP, biopsy specimens of areas suspected to represent chondritis are frequently taken, the ear being the most common site. Sampling of the posterior

auricular skin and underlying cartilage is preferred to prevent accentuation of any contour deformities. Histopathologic changes of the affected ear are not specific and may include perichondrial fibroplasia, collagen hyalinization, angioplasia, hemosiderin deposits, vacuolated or pyknotic chondrocytes, loss of cartilaginous matrix baso-

TABLE 39.2 Mucocutaneous findings in RP (in approximate order of frequency)

Aphthosis, oral and genital
Acral subcutaneous nodules (septal panniculitis, neutrophilic vasculitis, neutrophilic panniculitis, vascular thrombosis)
Purpura (neutrophilic predominating over lymphocytic vasculitis)
Papular eruption (urticarial, or blue gray)
Sterile pustules
Superficial phlebitis
Livedo reticularis
Digital necrosis

TABLE 39.3 Relapsing polychondritis: associated diseases (in approximate order of frequency)

Hematologic (myelodysplastic syndrome, IgA myeloma, lymphoma, acute leukemia)
Connective tissue disease (rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, Sjogren's syndrome, Reiter's syndrome, psoriatic arthritis)
Autoimmune diseases (Grave's disease, hypothyroidism, Hashimoto's thyroiditis, ulcerative colitis, Crohn's disease, myasthenia gravis, primary biliary cirrhosis, pernicious anemia, diabetes mellitus)
Systemic vasculitis (Wegener's granulomatosis, polyarteritis nodosa, Behçet's disease, Churg-Strauss syndrome, temporal arteritis, Takayasu's arteritis)
Dermatologic disease (psoriasis, lichen planus, vitiligo, atopic dermatitis, Sweet's syndrome [18], erythema nodosum, erythema elevatum diutinum [19])
Infection (hepatitis C infection [20], HIV infection [21])

philia, and lymphohistiocytic and plasmacytic inflammation (Fig. 39.2a, b) [22]. Given the distinctive clinical pattern of RP in most cases and nonspecific histologic findings, it has been suggested that performing a biopsy is usually unnecessary to make the diagnosis [23]. Direct immunofluorescence of affected areas may show granular deposits of immunoglobulins and C3 at the chondrofibrous junction [24].

The differential diagnosis of relapsing polychondritis is extensive because of the wide variety of disease manifestations. In the classic presentation with auricular chondritis, the differential diagnosis includes auricular cellulitis associated with otitis externa, systemic vasculitis, trauma, frostbite, phototoxic reaction, and arthropod bite reaction. Chondritis is usually distinguished by its frequent bilateral occurrence and typical sparing of the lobe because of its lack of cartilage. With repeated episodes, distortion of the auricular contour may be noted, and there may be radiographic evidence of dystrophic calcification. Joint presentations may mimic other forms of arthritis, including rheumatoid arthritis, septic arthritis, and crystal-induced arthritis. Other organ system involvements may result in clinical presentations resembling Behcet's disease, Wegener's granulomatosis, sarcoidosis, asthma, posterior circulation stroke, or Meniere's disease.

Patients with RP should undergo diagnostic evaluation because of the possibility of multisystem disease and coexistent diseases. While evaluation should be directed by clinical symptoms and signs, general guidelines are suggested in Table 39.4. Additional diagnostic evaluation may be necessary if preliminary evaluation suggests the presence of coexistent disease.

Mortality in RP is most frequently due to complications of respiratory tract involvement, either respiratory collapse or infection. Other causes of death include cardiovascular
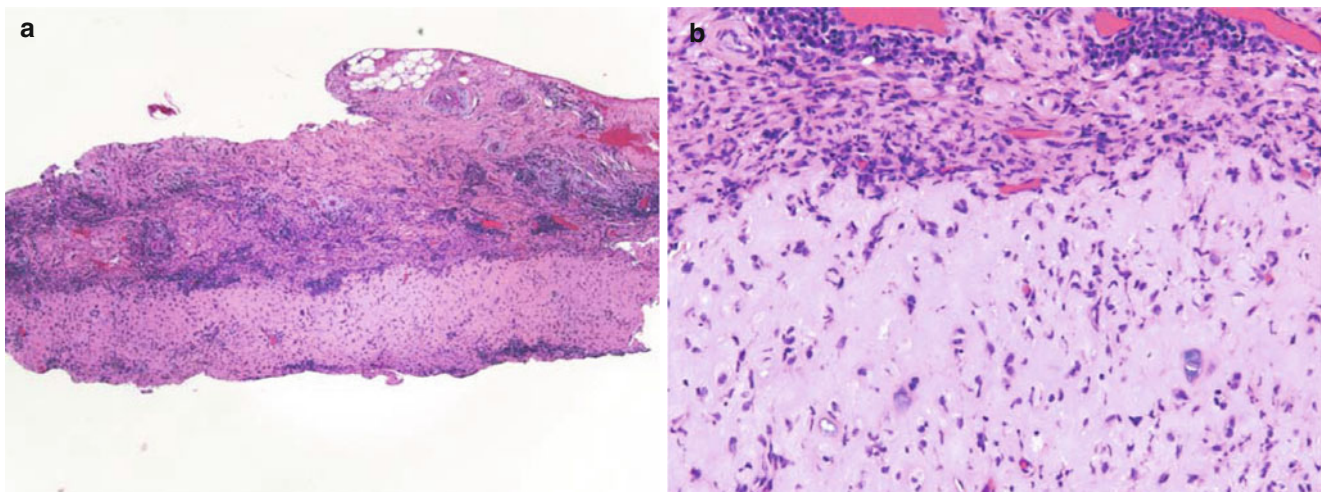
FIGURE 39.2. (**a**, **b**) Prominent degenerative changes of the ear cartilage with perichondral scarring and lymphoplasmacytic inflammation.

TABLE 39.4 Evaluation of the patient with relapsing polychondritis

1. Complete blood count
2. Erythrocyte sedimentation rate
3. Urinalysis
4. Serum creatinine
5. Rheumatoid factor
6. Pulmonary function tests, with computed tomography (CT) of the chest if abnormal
7. Ophthalmological examination
8. Electrocardiogram
9. Echocardiography if abnormal cardiac physical examination

involvement (vasculitis, aneurysm, or valve rupture) and malignancy [14]. Ten-year survival in a group of 112 patients followed at one institution was 55%, but a more recent series of 66 patients had a survival rate of 94% with a mean follow-up of 8 years [13, 15]. Anemia at the time of diagnosis predicts decreased survival. In patients less than 51 years old, saddle-nose deformity and systemic vasculitis are the worst prognostic signs, and in older patients, only anemia correlates with worse clinical outcomes [15].

The mainstay of treatment for RP is systemic corticosteroids. Doses of 10–20 mg of prednisone per day may be sufficient. Higher doses are usually required for respiratory, audiovestibular, and ocular involvement [23]. Low-dose colchicine and methotrexate may be useful as steroid-sparing agents. Nonsteroidal anti-inflammatory agents may help with mild flares of inflammation. Other treatments have included azathioprine, dapsone, cyclosporine, penicillamine, cyclophosphamide, minocycline, and plasma exchange [13]. Biologics, predominantly TNF-α bockers, have been reported to be of therapeutic benefit in small case series and in anecdotal reports [25]. A novel treatment using oral type II collagen as a tolerogen has been described in a child with RP [26]. In a mouse model of spontaneous chondritis, injection of immature dendritic cells pulsed with chick type II collagen was found to delay the onset and decrease the severity of disease. This finding offers hope for a similar treatment in patients with RP [27]. Adjunctive treatments may include airway stent placement, cardiac valve replacement, or surgical repair of aneurysms. Long-term follow-up is indicated because of a propensity for disease persistence, recurrences, and evolution of coexistent diseases.

References

1. Jaksch-Wartenhorst R. Polychondropathia. Wien Arch Int Med. 1923;6:93–100.
2. Pearson CM, Kline HM, Newcomer VD. Relapsing polychondritis. New Engl J Med. 1960;263:51–8.
3. Foidart JM, Abe S, Martin GR, et al. Antibodies to type II collagen in relapsing polychondritis. New Engl J Med. 1978;299:1203–7.
4. Rahkonen O, Savontaus M, Abdelwahid E, Vuorio E, Jokinen E. Expression patterns of cartilage collagens and Sox9 during mouse heart development. Histochem Cell Biol. 2003;120:103–10.
5. Dreiling FJ, Henson MM, Henson Jr OW. Immunolabeling type II collagen in the basilar membrane: a pre-embedding approach. Hear Res. 2002;166:181–91.
6. Hansson AS, Johannesson M, Svensson L, Nandakumar KS, Heinegard D, Holmdahl R. Relapsing polychondritis, induced in mice with matrilin 1, is an antibody- and complement-dependent disease. Am J Pathol. 2004;164:959–66.
7. Terato K, Shimozuru Y, Katayama K, et al. Specificity of antibodies to type II collagen in rheumatoid arthritis. Arthritis Rheum. 1990;33:1493–500.
8. Yoo TJ, Lee MK, Min YS, et al. Epitope specificity and T cell receptor usage in type II collagen induced autoimmune disease. Cell Immunol. 1994;157:249–62.
9. Arnaud L, Mathian A, Haroche J, Gorochov G, Amoura Z. Pathogenesis of relapsing polychondritis: a 2013 update. Autoimmun Rev. 2014;13:90–5.
10. Lang B, Rothenfusser A, Lanchbury JS, et al. Susceptibility to relapsing polychondritis is associated with HLA-DR4. Arthritis Rheum. 1993;36:660–4.
11. Cañas CA, Bonilla Abadía F. Local cartilage trauma as a pathogenic factor in autoimmunity (one hypothesis based on patients with relapsing polychondritis triggered by cartilage trauma). Autoimmune Dis. 2012;2012:453698. doi:10.1155/2012/453698. Epub 2011 Oct 27.
12. O'Hanlan M, McAdam LP, Bluestone R, Pearson CM. The arthropathy of relapsing polychondritis. Arthritis Rheum. 1976;19:191–4.
13. Trentham DE, Le CH. Relapsing polychondritis. Ann Intern Med. 1998;129:114–22.
14. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine. 1976;55:193–215.
15. Michet CJ, McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis: survival and predictive role of early disease manifestations. Ann Intern Med. 1986;104:74–8.
16. Frances C, El Rassi R, Laporte JL, Rybojad M, Papo T, Piette JC. Dermatologic manifestations of relapsing polychondritis. Medicine. 2001;80:173–9.
17. Bhamra K, Weerasinghe R, Steuer A. Epididymo-orchitis as a presenting feature of relapsing polychondritis: a case report. Case Rep Rheumatol. 2011;2011:726038. doi:10.1155/2011/726038. Epub 2012 Jan 4.
18. Fujimoto N, Tajima S, Ishibashi A, Ura-Ishikou A, Manaka I. Acute febrile neutrophilic dermatosis (Sweet's syndrome) in a patient with relapsing polychondritis. Br J Dermatol. 1998;139:930–1.
19. Bernard P, Bedane C, Delrous JL, Catanzano G, Bonnetblanc JM. Erythema elevatum diutinum in a patient with relapsing polychondritis. J Am Acad Dermatol. 1992;26:312–5.
20. Herrera I, Concha R, Molina EG, Schiff ER, Altman RD. Relapsing polychondritis, chronic hepatitis C infection, and mixed cryoglobulinemia. Semin Arthritis Rheum. 2004;33:388–403.

21. Dolev JC, Maurer TA, Reddy SG, Ramirez LE, Berger T. Relapsing polychondritis in HIV-infected patients: a report of two cases. J Am Acad Dermatol. 2004;51:1023–5.

22. Feinerman LK, Johnson WC, Weiner J, Graham JH. Relapsing polychondritis: a histopathologic and histochemical study. Dermatologica. 1970;140:369–77.

23. Kent PD, Michet CJ, Luthra HS. Relapsing polychondritis. Curr Opin Rheumatol. 2003;16:56–61.

24. Valenzuela R, Cooperrider PA, Gogate P, Deodhar SD, Bergfeld WF. Relapsing polychondritis: immunomicroscopic findings in cartilage of ear biopsy specimens. Hum Pathol. 1980;11:19–22.

25. Lekpa FK, Kraus VB, Chevalier X. Biologics in relapsing polychondritis: a literature review. Semin Arthritis Rheum. 2012;41:712–9.

26. Navarro MJ, Higgins GC, Lohr KM, Myers LK. Amelioration of relapsing polychondritis in a child treated with oral collagen. Am J Med Sci. 2002;324:101–3.

27. Sidhu M, Griffiths MM, Bradley DS. Vaccination with collagen-pulsed dendritic cells prevents the onset and reduces the disease severity in the mouse model of spontaneous polychondritis. Clin Exp Immunol. 2009;157:350–8.

40
Graft-Versus-Host Disease

■ Synonyms:	Autologous graft-versus-host disease, graft-versus-host reaction, and cutaneous eruption of lymphocyte recovery syndrome
■ Etiology:	Cytotoxic T cells attack antigens on keratinocytes
■ Associations:	Bone marrow transplantation
■ Clinical:	Erythematous patches and papules progressing in some cases to bullae, associated with fevers, diarrhea, and elevated liver function tests
■ Histology:	Dying keratinocytes within the epidermis and mild perivascular and interface lymphocytic infiltrate
■ IHC repertoire:	CD8 + lymphocyte predominate, decreased epidermal Langerhans cells
■ Staging:	Based upon degree of involvement in the gastrointestinal tract, liver, and skin
■ Prognosis:	Correlated with histologic grade of lesions and overall clinical stage; in general, poor
■ Adverse variables:	Histologic subtype of high-grade GVHD
■ Treatment:	Increased corticosteroids

In 1962, Barnes and Loutit first reported graft-versus-host disease (GVHD) in mice [1]; the condition was later described in humans by Simonsen in 1965 [2]. GVHD is a common consequence of allogeneic bone marrow transplantation. Approximately 3 weeks following complete marrow eradication and the transplantation of allogeneic donor marrow cells, a cutaneous eruption is seen in up to 20–80 % of patients and may result in the death of the patient [3, 4]. The cutaneous manifestations may be the first indication of evolving GVHD.

GVHD is arbitrarily divided into acute and chronic forms. The acute form of the disease ordinarily occurs between 21 and 60 days following bone marrow transplantation. Patients develop maculopapular or scarlatiniform eruptions (Fig. 40.1). In the more severe forms of the disease, bullae may develop and progress to widespread desquamation in a toxic epidermal necrolysis-like pattern. The palms and soles are often involved early in the disease, while the trunk, neck, cheeks, and ears are commonly affected as the disease progresses (Fig. 40.2).

The chronic form of the disease occurs more than 100 days following bone marrow transplantation. The histo-logic features consist of a band-like lymphocytic infiltrate similar to lichen planus in the early chronic phase. Well-developed lesions of chronic GVHD show epidermal atrophy with a thickened basement membrane and dermal fibrosis simulating morphea scleroderma.

FIGURE 40.1. Acute graft-versus-host disease with erythematous macular rash and blister formation.

Figure 40.2. Acral erythematous plaques seen in acute graft-versus-host disease.

Table 40.1 Histologic grading scheme for GVHD

Histologic grade	Histologic features
I	Basal vacuolization, mild lymphocytic infiltrate with exocytosis—nondiagnostic
II	Basal vacuolization, dyskeratotic keratinocytes, mild lymphocytic infiltrate with exocytosis and satellitosis
III	Focal clefting at dermal-epidermal junction due to basal keratinocyte necrosis, mild lymphocytic infiltrate with satellitosis
IV	Epidermis completely separated from dermis, mild lymphocytic infiltrate with exocytosis and satellitosis

GVHD, or a virtually identical process, has been reported in patients receiving autologous blood transfusions [5]. The process is much milder and does not ordinarily lead to adverse consequences, but suggests that even the host's own lymphocytes are capable of causing disease in these immunocompromised patients. The responsible cell is an immunocompetent T cell derived from the bone marrow, be it autologous or allogeneic [6].

The cutaneous eruption of lymphocyte recovery is a similar process that occurs in patients who have not received a transfusion of blood products. This eruption occurs during the time of bone marrow reconstitution, in patients who have had marrow ablative therapy. Again, several weeks following chemotherapy and radiation therapy, patients develop fevers and a cutaneous eruption indistinguishable from that seen in GVHD. The eruption coincides directly with an increasing lymphocyte count and abates as the marrow fully recovers [7].

The histologic features of each of these entities are similar and differ only in degree. There is a well-recognized grading scheme for evaluating histologic changes of GVHD in the skin (Table 40.1).

In all cases, a mild infiltrate of lymphocytes is present surrounding the vessels of the superficial vascular plexus. Scattered lymphocytes are present within the lower levels of the epidermis, and in grades II–IV, these lymphocytes are present around dying keratinocytes (Figs. 40.3 and 40.4).

The histologic differential diagnosis includes an erythema multiforme-like drug eruption and a viral exanthem.

Widely accepted National Institutes of Health (NIH) consensus criteria were developed in 2005 for the diagnosis of chronic GVHD. Diagnosis requires the presence of at least one diagnostic clinical sign of chronic GVHD (including poikiloderma or esophageal web) or the presence of at least one distinctive symptom (including keratoconjunctivitis sicca) confirmed by biopsy or other relevant tests in the same or another organ. Additionally, other possible diagnoses based upon clinical symptoms must be excluded [8].

A rigorous staging classification has been developed for acute GVHD [9]. Higher-stage disease is associated with increased risk for transplant-related mortality [10].

Patients who develop GVHD have been shown to have a lower risk for relapse of their primary neoplastic disease.
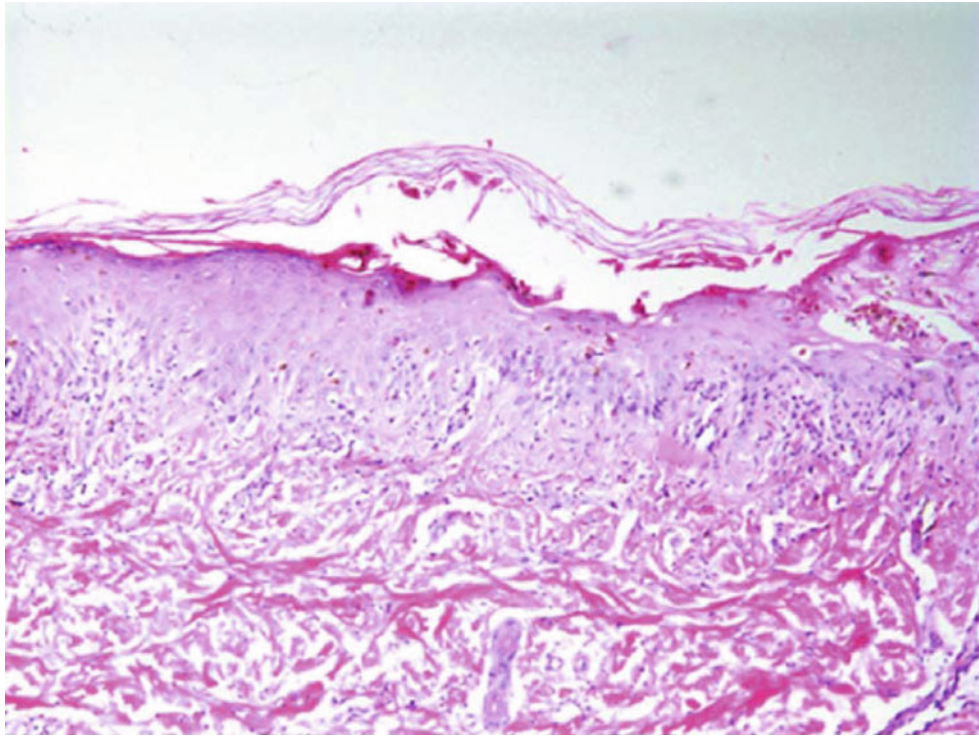
FIGURE 40.3. Medium-power detail of subacute interface dermatitis with epidermal necrolysis.
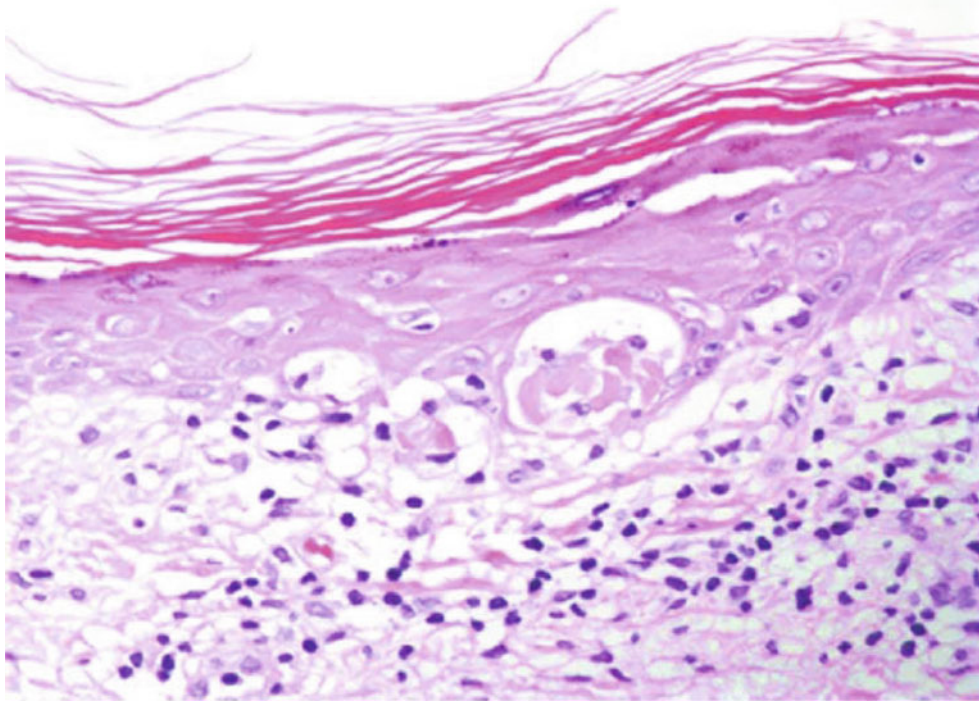
FIGURE 40.4. High-power detail showing clusters of necrotic keratinocytes with adjacent lymphocytes (satellitosis) typical of acute graft-versus-host disease.

References

1. Barnes DW, Loutit JF, Micklem HS. "Secondary disease" of radiation chimeras: a syndrome due to lymphoid aplasia. Ann N Y Acad Sci (Formerly: Annals of the Lyceum of Natural History of New York). 1962;99:374–85.
2. Simonsen M. Graft versus host reactions and their possible implications in man. Bibl Haematol. 1965;23:115–21.
3. Thomas ED, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. Bone marrow transplantation. N Engl J Med. 1975;292:832–43, 895–902.
4. Deeg HJ, Storb R. Graft-versus-host disease: pathophysiological and clinical aspects. Ann Rev Med. 1984;35:11–24.
5. Anderson KC, Weinstein HJ. Transfusion-associated graft-vs.-host disease. N Engl J Med. 1990;323:315–21.
6. Billingham RE. The biology of graft-versus-host reactions. Harvey Lect. 1966–67;62:21–78.
7. Bauer DJ, Hood AF, Horn TD. Histologic comparison of autologous graft-vs.-host reaction and cutaneous eruption of lymphocyte recovery. Arch Dermatol. 1993;129:855–8.
8. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–56.
9. Zhou Y, Barnett MJ, Rivers JK. Clinical significance of skin biopsies in the diagnosis and management of graft-vs-host disease in early postallogeneic bone marrow transplantation. Arch Dermatol. 2000;136:717–21.
10. Storb R, Prentice RL, Buckner CD, Clift RA, Appelbaum F, Deeg J, Doney K, Hansen JA, Mason M, Sanders JE, Singer J, Sullivan KM, Witherspoon RP, Thomas ED. Graft-versus-host disease and survival in patients with aplastic anemia treated by marrow grafts from HLA-identical siblings: beneficial effect of a protective environment. N Engl J Med. 1983;308:302–7.

Part VII
Vasculitis and Vasculopathic Disease

41
Systemic Vasculitis

Granulomatosis with Polyangiitis (GPA)

- Synonym: Wegener's granulomatosis
- Etiology: Genetic factors, infectious agents, and environmental factors
- Incidence: Annual incidence of 10–20/million in Europe and North America
- Clinical: Oral ulcers, nasal discharge, pulmonary nodules, infiltrates or cavities, and hematuria
- Distribution: Upper and lower respiratory tract and kidney
- Histology: Necrotizing granulomatous inflammation and necrotizing vasculitis
- Adverse variables: Advanced renal failure, increasing age, a high disease activity score and white blood cell (WBC) count, and low hemoglobin
- Treatment: Corticosteroids, oral cyclophosphamide, methotrexate, azathioprine, and Biologics (FDA approval of rituximab)
- Prognosis: Chronic relapsing and remitting disease
- Mortality rate: 25 % at 5 years

Microscopic Polyangiitis (MPA)

- Synonym: Microscopic polyarteritis
- Etiology: Environmental factors, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)
- Incidence: Annual incidence of 10–20/million in Europe and North America
- Clinical: Nephritis, pulmonary hemorrhage, purpura, neuropathy, arthralgia, and myalgia
- Distribution: The respiratory tract, kidney, skin, nervous system, GI tract, and skeletal muscles
- Histology: Small-vessel necrotizing vasculitis
- Adverse variables: Advanced renal failure, increasing age, a high disease activity score and WBC count, and low hemoglobin
- Treatment: Corticosteroids, oral cyclophosphamide, methotrexate, azathioprine, and Biologics (FDA approval of rituximab)
- Prognosis: Chronic relapsing and remitting disease
- Mortality rate: 25 % at 5 years

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

- Synonyms: Churg-Strauss syndrome and allergic granulomatosis and angiitis
- Etiology: Inflammatory response directed at target antigens
- Incidence: Annual incidence of 0.5–6.8 new cases/million and prevalence of 10.7–13/million [1]
- Clinical: Asthma, eosinophilia, neuropathy, pulmonary infiltrates, and sinus abnormalities
- Distribution: Skin, nose, lungs, GI tract, kidney, heart, and peripheral nervous system
- Histology: Necrotizing granulomatous inflammation with eosinophils and necrotizing vasculitis
- Adverse variables: Vasculitis of extrapulmonary organs
- Treatment: Corticosteroids, oral cyclophosphamide, methotrexate, azathioprine, and Biologics
- Prognosis: Chronic relapsing and remitting disease
- Mortality rate: Dependent upon prognostic factors

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) are three primary systemic vasculitides that affect multiple organ systems via a pauci-immune necrotizing vasculitis of small- to medium-sized blood vessels. Antineutrophil cytoplasmic antibody (ANCA) positivity is a characteristic of most cases of these three diseases; thus, they are commonly called the ANCA-associated vasculitides (AAVs).

In 1990, the American College of Rheumatology (ACR) proposed classification criteria for the systemic vasculitides [2, 3]. At this time, MPA was not yet considered a distinct entity; thus, criteria were not created for its classification. Furthermore, ANCA testing was not widely available at this time; therefore, ANCA serology was not considered in the diagnostic criteria. More recently, the International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC) redefined the vasculitides in 2012 with nomenclature representative of their pathogenesis and clinicopathological characteristics [4]. The CHCC did not use ANCA antigen specificity in the classification of AAVs.

The etiology of GPA is currently unknown; however, genetic factors, infectious agents via molecular mimicry, and environmental factors such as dust inhalation or exposure to silica have been proposed as etiologic agents [5]. The etiology of MPA has not yet been fully elucidated; however, environmental agents such as silica exposure have been proposed as etiologic factors [6]. Additionally, a pathogenic role of anti-myeloperoxidase (MPO) ANCA has been reported [7]. The etiology of EGPA is related to an inflammatory response directed at target antigens. Various environmental agents including infectious triggers, drugs, desensitization, and vaccination have been reported as potential triggers of EGPA. It has also been theorized that the triggering drugs are indirectly involved in the etiology of EGPA; it has been proposed that drugs might be one of several multifactorial agents involved in the process of EGPA [1].

The pathogenesis of the vasculitides is not completely understood; however, ANCA is theorized to contribute to pathogenic mechanisms [7].

The annual incidence of AAVs in Europe and North America is approximately 10–20/million, with a peak age of onset in the 65–74 age range [8]. Although the AAVs are more prevalent in men, they occur at a younger age in females [9].

GPA is a systemic, necrotizing, granulomatous ANCA-associated small-vessel vasculitis with kidney and respiratory manifestations. ANCAs demonstrate a cytoplasmic immunofluorescence pattern (cANCA) and are directed against proteinase 3 (PR3). The initial pathogenic mechanisms of GPA most commonly affect the respiratory tract, resulting in nose, throat, and lung pathology such as sinusitis or cough. The condition may then affect blood vessels and their target organs. A commonly affected organ is the kidney resulting in necrotizing glomerulonephritis. The clinical course of GPA frequently involves relapses; ¼ of patients relapse within 2 years of diagnosis and over ½ relapse within 5 years [10]. Individuals with localized forms of GPA relapse more often than individuals with systemic GPA with renal involvement [11]. Additionally, chronic

nasal carriage of *Staphylococcus aureus* is associated with a greater risk of relapse [12].

MPA may affect blood vessels of the kidney, lungs, skin, gastrointestinal tract, nerves, and skeletal muscles; clinical findings of MPA frequently include glomerulonephritis, pulmonary hemorrhage, palpable purpura, peripheral neuropathy, arthralgias, myalgias, and abdominal pain. Individuals commonly demonstrate pANCA positivity. Antibodies directed against PR3 may be present but less frequently than antibodies directed against MPO.

EGPA is characterized by allergic rhinitis/asthma, atopy, pulmonary infiltrates, and peripheral eosinophilia. The development of allergic rhinitis/asthma characterizes the first phase of EGPA which is then followed by the second phase, eosinophilia, and subsequently the third phase characterized by vasculitis. The vasculitic phase most frequently affects the skin and peripheral nervous system. EGPA is variable in terms of its presentation and course; some individuals will not experience all three phases or progress from one phase to the next. Clinical manifestations of EGPA include peripheral neuropathy, ENT abnormalities, skin lesions, lung infiltrates, and cardiomyopathy. The presence of MPO-ANCAs is present in about 30–38% of patients [1]. Furthermore, ANCA status has also been reported to influence the clinical characteristics of EGPA patients; a study of 383 patients in the French Vasculitis Study Group cohort demonstrated that ANCA-positive patients had more frequent ENT symptoms, peripheral neuropathy, and/or renal involvement but less frequent cardiac symptoms than the ANCA-negative patients [13].

The AAVs are currently considered chronic diseases with periods of remission and relapse.

The histology of GPA is characterized by necrotizing granulomatous inflammation frequently involving the upper and lower respiratory tract and necrotizing vasculitis predominately affecting small- to medium-sized vessels [4]. Histologic features of MPA include a necrotizing vasculitis predominately affecting small-sized vessels (Fig. 41.1a–c); necrotizing arteritis of small- and medium-sized arteries may also be present [4]. EGPA is characterized by necrotizing granulomatous inflammation with eosinophils often involving the respiratory tract and necrotizing vasculitis predominately affecting small- to medium-sized vessels [4].

The American College of Rheumatology published a traditional format for classification of Wegener's granulomatosis in 1990 which includes four criteria, of which two must be met for diagnosis of GPA: (1) nasal or oral inflammation (development of oral ulcers or purulent or bloody nasal discharge); (2) abnormal chest x-ray showing nodules, fixed infiltrates, or cavities; (3) urinary sediment with microhematuria (>5 RBCs/HPF) or the presence of red cell casts; and (4) granulomatous inflammation on biopsy within the wall of an artery or in the perivascular or extravascular area [2].

The nomenclature of MPA has been defined by the Chapel Hill Consensus Conference as a non-granulomatous, necrotizing, pauci-immune, predominately small-vessel vasculitis frequently causing pulmonary capillaritis and necrotizing glomerulonephritis [4]. The presence of small-vessel (arterioles, venules, capillaries) vasculitis is the definitive diagnostic criterion of MPA and helps to differentiate it from polyarteritis nodosa (PAN). Additionally, the absence of granulomatous inflammation and sparing of the upper respiratory tract differentiate MPA from GPA.

The American College of Rheumatology published a traditional format for classification of EGPA which includes six symptoms: asthma, eosinophilia (>10% on differential WBC count), mononeuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy containing a blood vessel with extravascular eosinophils [3].

Treatment for the AAVs should be tailored based upon the severity of the disease, with more severe cases requiring more aggressive treatments. Severe disease is defined as organ-threatening or life-threatening and includes features such as rapidly progressive glomerulonephritis, pulmonary hemorrhage, mesenteric ischemia, scleritis, and nervous system involvement. Limited disease is non-organ and nonlife-threatening and includes mild renal or pulmonary involvement [11].

The goal of treatment for the AAVs is aimed at inducing remission and instituting maintenance treatment. For induction of remission, corticosteroids are considered the predominant treatment; once remission is achieved, steroids are tapered to minimize relapse. Daily oral cyclophosphamide in combination with high-dose corticosteroids is considered effective at inducing remission in the majority of patients [14]. For maintenance therapy, low-dose corticosteroids may be used; for most individuals, maintenance treatment is utilized for approximately 2 years [15]. Methotrexate and azathioprine have also been used successfully for maintenance therapy. The optimal time period of maintenance therapy should be individualized for each patient and should reflect the risks of relapse vs. the risk of immunosuppression.

Within the past decade, the development of biologic therapies such as Rituximab, a monoclonal anti-CD20 antibody that targets B cells, has demonstrated efficacy in both inducing remission and maintaining remission for severe AAVs [11, 16].

The prognosis of the AAVs has significantly increased since the 1960s with the introduction of cyclophosphamide and corticosteroids. Despite the increased prognosis, a prospective cohort of 535 patients with GPA and MPA treated with conventional regimens demonstrated that these individuals are at increased risk of death compared to an age- and sex-matched population [17]. It is noteworthy to report that the study reported a cause of death within the first year from either infection (48%) or active vasculitis
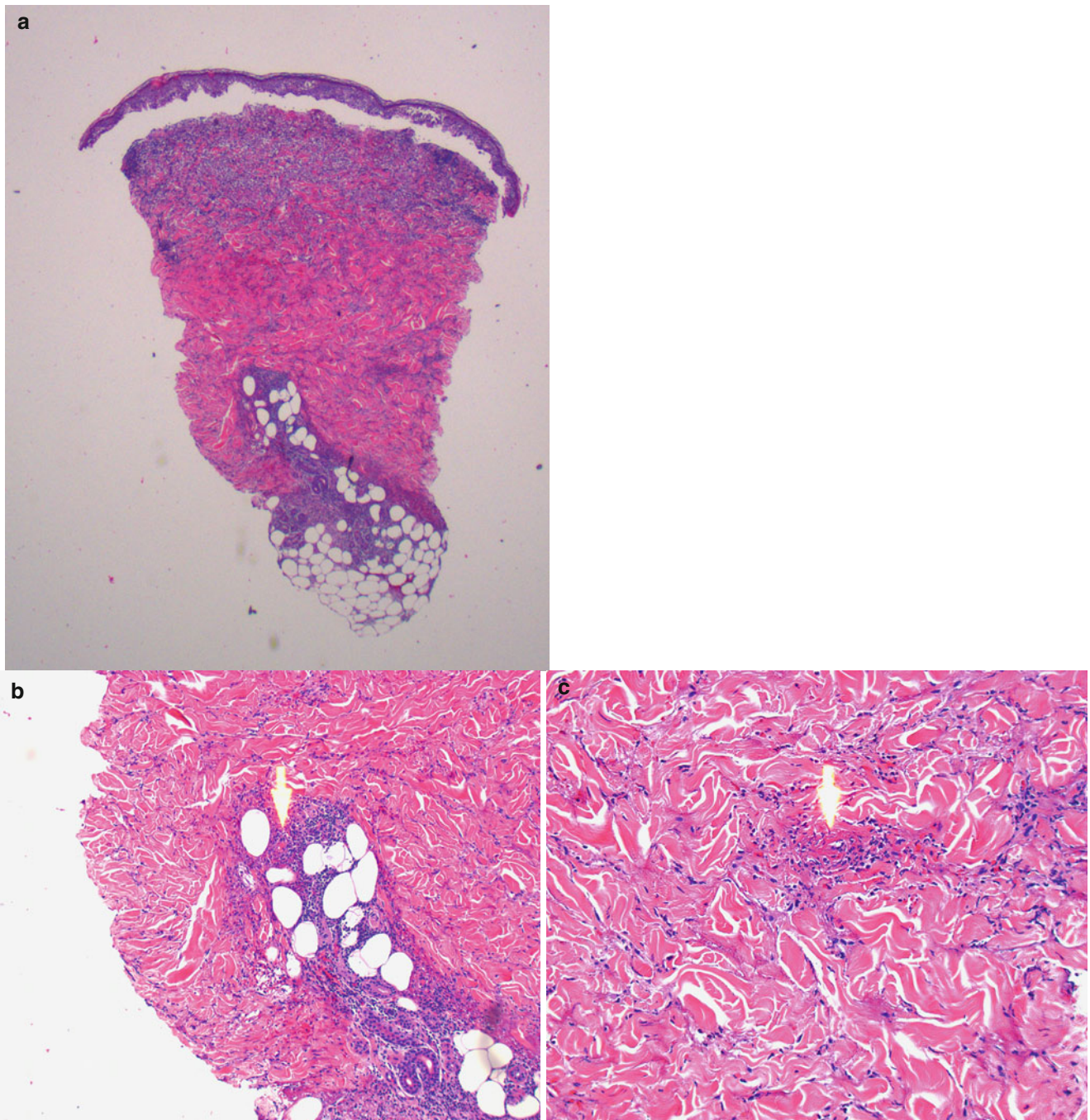
Figure 41.1. (**a**) Low-power photomicrograph depicting dermo-epidermal separation (vesicle) and "busy" dermis due to leukocytoclasia with extravasated erythrocytes. (**b**) Medium-power photomicrograph depicting deeper component of inflammation seen in perivascular locations. (**c**) High-power photomicrograph depicting destruction of vessel (note rounded silhouette) with extravasated erythrocytes, leukocytoclasia, and pink fibrin vascular deposits.

(19 %) as opposed to a cause of death after the first year as cardiovascular disease (26 %), malignancy (22 %), or infection (20 %). They reported that the main predictive factors of poor outcome at presentation were advanced renal failure, increasing age, a high disease activity score and WBC count, and low hemoglobin [17].

The French Vasculitis Group Study produced a five-factor score that predicts risk of death in individuals with EGPA. The five factors include impaired renal function (serum creatinine > 140 µmol/L), proteinuria (>1 g/24 h), gastrointestinal hemorrhage, infarction, or pancreatitis, CNS involvement, and cardiomyopathy. Individuals with

none of the above factors have a mortality rate of 11.9 % at 5 years as opposed to individuals with two or more factors having a mortality rate of 46 % at 5 years [18]. A more recent retrospective study of 383 patients with EGPA in the French Vasculitis Study Group cohort reported cardiomyopathy, older age, and diagnosis during or prior to 1996 as independent risk factors for death; furthermore, a lower eosinophil count at diagnosis was predictive of relapse [13]. Additionally, they reported the influence of ANCA status on the long-term outcome of EGPA patients; ANCA positivity was associated with more frequent vasculitis relapses but a lower mortality rate. Furthermore, they stated that although EGPA relapses remain frequent, mortality has decreased since 1996.

References

1. Mouthon L, Dunogue B, Guillevin L. Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). J Autoimmun. 2014;48–49:99–103.
2. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990;33(8):1101–7.
3. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094–100.
4. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11.
5. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014;13(11):1121–5.
6. Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ, et al. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. J Am Soc Nephrol. 2001;12(1):134–42.
7. Chen M, Kallenberg CG. ANCA-associated vasculitides--advances in pathogenesis and treatment. Nat Rev Rheumatol. 2010;6(11):653–64.
8. Watts RA, Lane SE, Bentham G, Scott DGI. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum. 2000;43(2):414–9.
9. Abdou NI, Kullman GJ, Hoffman GS, Sharp GC, Specks U, McDonald T, et al. Wegener's granulomatosis: survey of 701 patients in North America. Changes in outcome in the 1990s. J Rheumatol. 2002;29(2):309–16.
10. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis. 2008;67(7):1004–10.
11. Stone JH. Limited versus severe Wegener's granulomatosis: Baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2003;48(8):2299–309.
12. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med. 1994;120(1):12–7.
13. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270–81.
14. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983;98(1):76–85.
15. Lally L, Spiera R. Current landscape of antineutrophil cytoplasmic antibody-associated vasculitis: classification, diagnosis, and treatment. Rheum Dis Clin North Am. 2015;41(1):1–19.
16. Jones RB, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211–20.
17. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011;70(3):488–94.
18. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore). 1996;75(1):17–28.

42
Calciphylaxis (Calcific Uremic Arteriolopathy)

■ Synonyms:	Calcifying panniculitis, subcutaneous calcific arteriolopathy, uremic small-artery disease with medial calcification and intimal hyperplasia, and metastatic calcinosis cutis
■ Etiology:	Multifactorial, including hyperphosphatemia, hypercalcemia, hyperparathyroidism, hypoalbuminemia, rapid weight loss, and obesity
■ Associations:	Chronic renal insufficiency
■ Histopathology:	Subcutaneous vascular calcification, thrombosis, and necrosis
■ Evaluation:	Serum blood urea nitrogen, creatinine, calcium, phosphate, albumin, parathyroid hormone, quantitative and functional proteins C and S, skin biopsy, possible soft tissue radiographic evaluation for subcutaneous calcification, and arterial large-vessel evaluation in distal variant
■ Treatment:	Reduction of calcium and phosphorous levels, treatment of secondary hyperparathyroidism, sodium thiosulfate, and hyperbaric oxygen

Calciphylaxis is a syndrome of subcutaneous vascular calcification resulting in painful ulcers on the legs, thighs, or abdomen. The disease develops almost exclusively in patients with end-stage renal disease and is frequently fatal due to infectious complications. Calciphylaxis was described in 1962 by Hans Selye. He made rats hypercalcemic with "sensitizers" vitamin D or parathyroid hormone. "Challengers" were then administered. These included skin injury by hair-plucking or injections of various sorts. Injured areas calcified and became ulcerated. Injection of "challengers" intravenously resulted in systemic necrotic lesions associated with tissue calcification [1]. The concept of calciphylaxis has been imperfectly applied to cutaneous ulcerations that develop in patients with end-stage renal disease due to vascular calcification and subsequent occlusion. While this clinical scenario has some parallels with Selye's experiments, his experimental subjects were not uremic, and the calcifications were not vascular. Therefore, "calciphylaxis" does not accurately describe the syndrome. Because this disease does not conform to the model of calciphylaxis as described by Selye, many advocate eliminating that label in favor of "calcific uremic arteriolopathy."

The pathogenesis of calciphylaxis is likely multifactorial. The precise process has remained elusive. Most patients

developing calciphylaxis have end-stage renal disease, but some have milder renal insufficiency. Other cases have occurred in association with primary hyperparathyroidism, alcoholic liver disease, malignancy, and connective tissue disease [2]. Most earlier literature on the subject regarded the disease as a form of metastatic calcification due to secondary hyperparathyroidism of end-stage renal disease. This view is not supported by data that show that only one third of patients with calciphylaxis have an elevated calcium phosphate product. Additionally, the calcium phosphate products of calciphylaxis patients and a control group of patients with end-stage renal disease without skin lesions are similar [3]. Evidence of hyperparathyroidism is often lacking in patients with calciphylaxis, and treatment by parathyroidectomy results in clinical improvement in only a subset of patients. A group of patients with calciphylaxis has been described in which low turnover of renal bone disease is present, with low intact parathyroid hormone levels and a low calcium phosphate product, favoring other inciting factors [4].

Earlier descriptions of calciphylaxis attribute its cause to metastatic calcification resulting from an elevated calcium phosphate product and secondary hyperparathyroidism. However, the data do not support that contention. Vascular

calcification, the hallmark of calciphylaxis, is a complex process regulated by many factors. Medial arterial calcification is a feature characteristic of both diabetes mellitus and end-stage renal disease. This calcification involves a phenotype switch of the vascular myofibroblast to one of an osteoprogenitor (osteogenic transdifferentiation), a process influenced by osteotropic hormones and inhibitors. In pathologic states, the end result is vascular calcification. Local paracrine control of the process involves bone morphogenetic proteins (BMP) 2 and 7 among others, pyrophosphate, matrix metalloproteinases, parathyroid hormone-related peptide, osteopontin, osteoprotegerin, Pit-1 (a sodium-dependent phosphate cotransporter), fetuin-A, and matrix Gla protein (MGP), all of which respond to various metabolic and inflammatory stimuli (summarized in Fig. 42.1) [5–8]. Much of the process of osteogenic transdifferentiation is mediated by the transcription factor nuclear factor κB (NFκB). The receptor activator of NFκB is RANK at its ligand is RANKL. The activation process potentiates the phenotype switch from vascular smooth muscle to osteoprogenitor. Its activation can be inhibited by osteoprotegerin and bisphosphonates and enhanced by corticosteroids, PTH, vitamin D3, and an inflammatory setting [8].

Osteopontin inhibits calcium crystal growth and increases osteoclast function, thus inhibiting calcification [7]. MGP is an inhibitor of vascular calcification. Warfarin, which is a risk factor for calciphylaxis, inhibits gamma-carboxylation of MGP, rendering it nonfunctional, theoretically tipping the balance toward vascular calcification [9]. Parathyroid hormone-related peptide is an endogenous inhibitor of vascular calcification that is suppressed by vitamin D3, another mechanism by which vascular calcification may occur [10]. The activity of Pit-1, a sodium-dependent phosphate cotransporter, is enhanced by exposure to calcium and phosphorous, as it may occur in patients with chronic renal insufficiency. Pit-1 transports phosphorous into vascular smooth muscle cells, causing mineralization of matrix vesicles that provide nuclear elements for mineralization of the extracellular matrix. Intracellular phosphorous also induces phenotypic switching toward an osteoprogenitor cell [6]. Osteoprotegerin inhibits vascular calcification by inhibiting the RANKL-RANK-NFκB cascade [8].

In addition to vascular calcification, tissue calcification due to precipitation of calcium phosphate may occur in calciphylaxis. Such calcification is normally suppressed by mineralization inhibitors, such as fetuin-A, a circulating glycoprotein, and tissue pyrophosphates. Fetuin-A production may be suppressed by vitamin D, another factor favoring calcification in some patients with end-stage renal disease [5]. Matrix metalloproteinases, which can be associated with the catabolic state of rapid weight loss, partially digest elastic tissue, which then avidly binds calcium. This process may contribute to the pathogenesis of calciphylaxis in patients with recent weight loss [11]. Fetuin-A, pyrophosphates, and matrix metalloproteinases also have parallel effects on vascular mineralization homeostasis [7]. Additional factors promoting calcification include BMP-2, calcium, phosphate, hyperglycemia, increased blood urea nitrogen, and inflammatory setting via pro-inflammatory cytokines and those inhibiting calcification include BMP-7 and vitamin K [7]. While the above observations do not elucidate a specific pathogenesis of calciphylaxis, they indicate that vascular and tissue calcification is induced in a certain metabolic milieu. Many of the forces that favor this process are found in patients with renal disease.
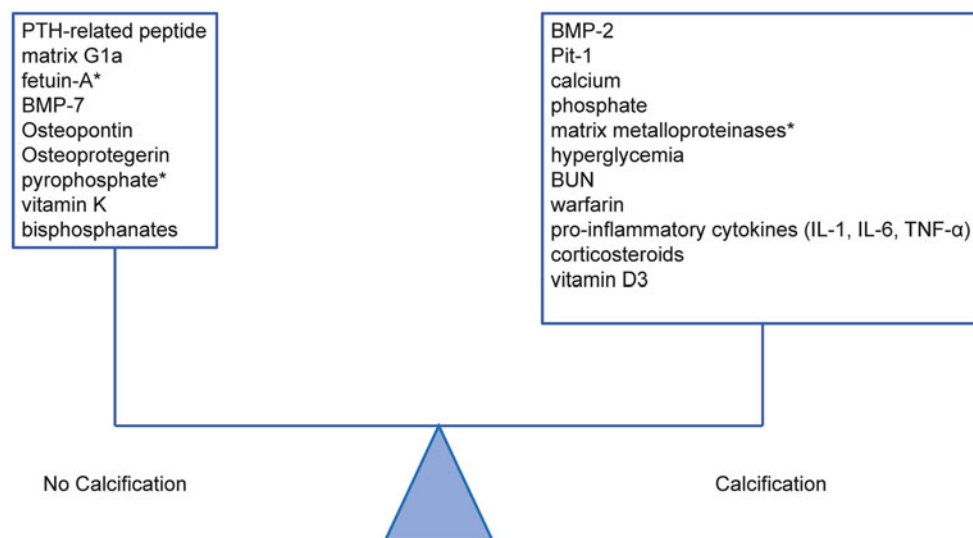
FIGURE 42.1. Vascular calcium homeostasis. * Parallel effects in tissue.

In addition to metabolic factors that may be involved in the pathogenesis of calciphylaxis, there may also be physical factors. Obesity is known to be a risk factor for the development of disease, and it is noted that skin lesions tend to occur in areas of greatest adipose tissue deposition, such as the abdomen, hips, and thighs. With fixed subcutaneous fibrous septa, there may be considerable tensile stress that compromises blood flow in these areas, predisposing to vascular stasis, associated ischemia, and dystrophic lesions [12]. Another predisposing factor may be reduced cutaneous oxygen tension. Patients with calciphylaxis have been shown to have reduced transcutaneous oxygen tension in multiple body regions, in areas with and without ulcers [13]. This phenomenon may be explained by background vascular calcification of subcutaneous vessels that precedes the onset of clinical lesions. This has been referred to as the "primary lesion" of calciphylaxis [12]. It is in this background setting that patients are susceptible to developing ischemic necrosis and tissue calcification. Hypercoagulable states such as protein C or S deficiency and functional impairment may further contribute to precipitation of the disease [14].

Risk factors for calciphylaxis tend to be those that induce a metabolic or physical state favoring vascular and tissue calcification in an already susceptible patient with renal insufficiency. In addition to those factors, the influence of vascular stasis as may be seen in obesity, hypotension, and hypercoagulable states may contribute to precipitation of lesions of calciphylaxis. The risk factors for the development of calciphylaxis are summarized in Table 42.1 [7, 8, 15].

TABLE 42.1. Risk factors for calciphylaxis

Renal insufficiency
Obesity
Female gender
Caucasian
Hypotensive episode
Recent period of rapid weight loss
Diabetes mellitus/hyperglycemia
Hypoalbuminemia
Increased parathyroid hormone level
Increased calcium phosphate product
Hypercoagulable state
   Protein C or S deficiency or functional impairment
   Antithrombin III deficiency
   Antiphospholipid antibody syndrome
   Cryofibrinogenemia
Medication use
   Warfarin
   Albumin infusions
   Vitamin D
   Calcium carbonate
   Aluminum
   Methotrexate
   Corticosteroids
   Iron

Patients with calciphylaxis usually present with painful indurated plaques or nodules of the abdomen, thigh, and hips, which frequently ulcerate (Figs. 42.2 and 42.3). Livedo reticularis, purpura, and bullae may also be seen. Disease localized to the breast or penis has been described [9, 16]. There is also a distal form of the disease in which patients present with acral ischemia resembling that of peripheral arteriosclerotic disease. A distinguishing feature is that peripheral pulses are generally intact. These patients are reported to have higher survival rates than those with proximal disease [17].

In addition to cutaneous involvement in calciphylaxis, myopathy may develop secondary to skeletal muscle involvement. This usually occurs in areas of skin involvement and may result in rhabdomyolysis. Other less common areas of involvement are the heart, joints, lungs, pancreas, eyes, and gastrointestinal tract [9].

Histopathologic features of calciphylaxis are vascular calcification and varying degrees of necrosis and

FIGURE 42.2. Reticulated and stellate pattern of ulceration with eschar formation on the legs.

FIGURE 42.3. Later-stage deep ulceration of the thigh with peripheral eschar.
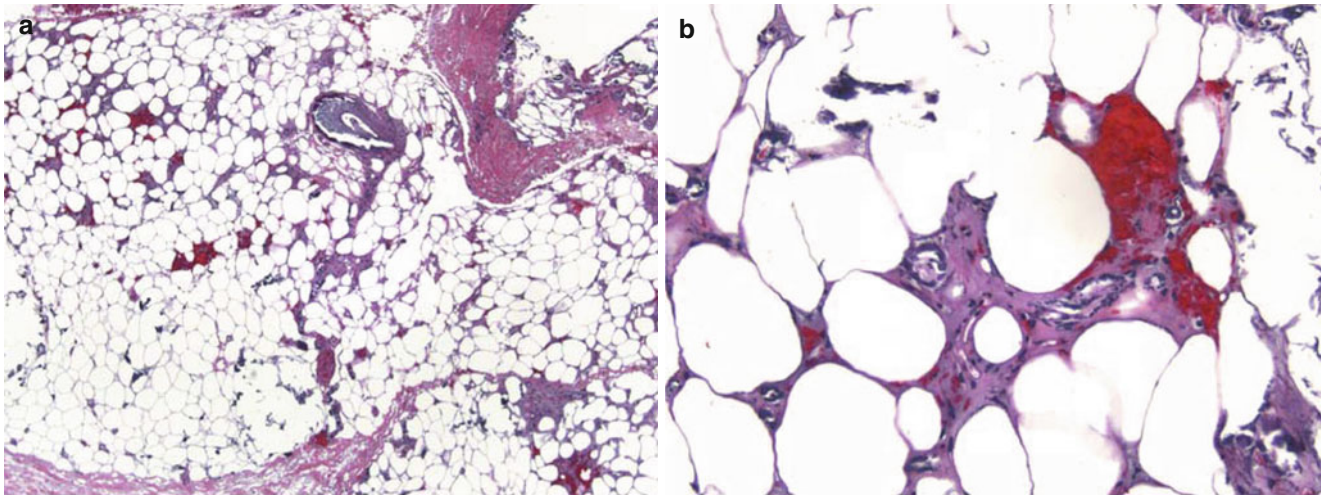
FIGURE 42.4. (**a**) Subcutaneous vascular and interstitial calcification. (**b**) Stippled vascular and lipocyte calcification.

inflammation, depending on timing and location of the biopsy specimen. Calcification occurs in small- to medium-sized venules, arterioles, and capillaries in the subcutaneous tissue and, in some instances, the dermis (Fig. 42.4a, b) [17, 18]. Calcification of subcutaneous septa and adipocytes may also occur [12]. The inflammatory infiltrate consists of lymphocytes, neutrophils, and occasional eosinophils. Early lesions devoid of necrosis may have a dermal inflammatory infiltrate. The subcutaneous component is predominantly septal. Calcifications are usually readily seen but occasionally require histochemical staining with von Kossa or alizarin red. Use of both may confer greater sensitivity in diagnosis. Perieccrine calcifications may be the sole finding in a small number of specimens. Vascular thrombi are seen in approximately 50 % of cases. Necrosis is variable [18]. Subcutaneous calciphylaxis-like calcifications have been reported in biopsy specimens from patients with nephrogenic systemic fibrosis. This finding was not accompanied by clinical evidence of calciphylaxis [19]. These calcifications may correspond to the "primary lesion" of calciphylaxis that represents the setting in which clinical lesions develop. A netlike pattern of calcification is seen frequently in patients with calciphylaxis, reported to have an almost 90 % specificity for the disease [20]. The histologic differential diagnosis of subcutaneous calcifications includes pancreatic panniculitis and Mönckeberg's medial calcific sclerosis. Pancreatic panniculitis has diffuse subcutaneous necrosis with "ghost" cells and an infiltrate of neutrophils, without vascular calcification. Mönckeberg's medial calcific sclerosis occurs as an incidental finding in cutaneous biopsy specimens from the leg and correlates with underlying arteriosclerotic disease.

The differential diagnosis of calciphylaxis depends upon the distribution of lesions but may include warfarin necrosis, primary hyperoxaluria, peripheral arteriosclerotic disease, vasculitis, emboli, cryoglobulinemia, and cryofibri-

TABLE 42.2. Diagnostic evaluation of suspected calciphylaxis

1. Serum calcium, phosphate, blood urea nitrogen, creatinine, glucose
2. Serum albumin
3. Serum intact parathyroid hormone
4. Hypercoagulation evaluation, including proteins S and C
5. Exclude infection
6. Skin biopsy of indurated plaque or ulcer margin
7. Evaluation for large-vessel arterial disease (in distal subset)
8. Consider radiographic evaluation of soft tissue for subcutaneous calcifications

nogenemia. The diagnosis of calciphylaxis in the right clinical setting is usually apparent. However, some evaluation is indicated for confirmation and, perhaps more importantly, to gather data that will help direct management. A diagnostic evaluation is suggested in Table 42.2.

Treating calciphylaxis is far more challenging than establishing the diagnosis. Treatment is directed at reversing metabolic derangements favoring calcification. In early series, the focus of treatment was parathyroidectomy. Literature favoring parathyroidectomy reported higher survival rates in surgically treated patients, but these were uncontrolled studies with limited follow-up [17]. Use of parathyroidectomy is likely to be beneficial only in cases with striking elevations in parathyroid hormone. Cinacalcet, a calcimimetic useful in managing hyperparathyroidism, has been shown to decrease the incidence of calciphylaxis approximately threefold in patients with ESRD and moderate to severe secondary hyperparathyroidism in the Evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events (EVOLVE) trial and may be used as an alternative to surgery [21]. The incidence of calciphylaxis appears be increasing, and this may be, in part, due to a switch from aluminum-containing phosphate binders to those

containing calcium. In the patient with calciphylaxis, calcium-containing phosphate binders should be changed to non-calcium ones such as sevelamer. In a pilot study, lanthanum carbonate as a non-calcium phosphate binder induced remission of calciphylaxis in four patients [22]. Increased frequency of dialysis from three to five times a week with a low-calcium bath has been advocated to reduce calcium burden [23]. This requires careful monitoring for hypocalcemia. While the use of vitamin D would be expected to worsen disease based on Selye's model, it has a theoretical advantage of suppressing parathyroid hormone levels while limiting gastrointestinal absorption of calcium and phosphorous in the patient with secondary hyperparathyroidism [23]. Hyperbaric oxygen has been reported to be of benefit in healing of cutaneous ulcers [24]. Even oxygen administration by nasal cannula may increase cutaneous oxygen tension in patients with calciphylaxis [9]. Bisphosphonates have been found to suppress experimental calciphylaxis, and intravenous treatment with the bisphosphonate, pamidronate, was reported to result in dramatic disease resolution in a case report [25, 26]. In a case series of 172 patients, intravenous sodium thiosulfate, which may solubilize tissue calcium deposits, was found to be associated with complete resolution or marked clinical improvement in approximately 50 % of patients [27]. Another case report noted good response to low-dose tissue plasminogen activator in a patient with calciphylaxis, history of deep venous thrombosis, low protein C and antithrombin III, and elevated fibrinogen levels, suggesting that this is a therapy to consider in calciphylaxis patients with evidence of a hypercoagulable state [28]. A summary of possible therapeutic tools in calciphylaxis is given in Table 42.3.

The prognosis in calciphylaxis has been poor, with most patients succumbing to sepsis because of extensive cutaneous ulceration. Severe debilitation from comorbidities also contributes to a poor outcome. While the disease has a grave prognosis, elucidation of the pathways of metabolic control of vascular and tissue calcification gives hope for effective management and treatment of these patients in the future.

TABLE 42.3. Management of calciphylaxis

1. Eliminate calcium-containing phosphate binders and other oral calcium intake
2. Avoid excessive calcium phosphate product
3. Low-calcium dialysate
4. Increased frequency of dialysis
5. Consider cinacalcet therapy for those with secondary hyperparathyroidism
6. Consider parathyroidectomy in cases with severe secondary hyperparathyroidism
7. Consider sodium thiosulfate
8. Hyperbaric oxygen, consider oxygen by nasal cannula
9. Weight loss in obese patients
10. Optimize nutritional status
11. Serum glucose control in diabetics
12. In patients on warfarin, attempt switch to a different anticoagulant
13. Gentle wound debridement
14. Consider low-dose tissue plasminogen activator and bisphosphonates based on anecdotal reports
15. Pain management

References

1. Selye H. Calciphylaxis. Chicago: University of Chicago Press; 1962.
2. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. Clin J Am Soc Nephrol. 2008;3:1139–43.
3. Llach F. Calcific uremic arteriolopathy (calciphylaxis): an evolving entity? Am J Kidney Dis. 1998;32:514–8.
4. Mawad HW, Sawaya BP, Sarin R, Malluche HH. Calcific uremic arteriolopathy in association with low turnover uremic bone disease. Clin Nephrol. 1999;52:160–6.
5. Vattikuti R, Towler DA. Osteogenic regulation of vascular calcification: an early perspective. Am J Physiol Endocrinol Metab. 2004;286:E686–96.
6. Giachelli CM. Vascular calcification mechanisms. J Am Soc Nephrol. 2004;15:2959–64.
7. Schlieper G, Schurgers L, Brandenberg V, Reutlingsperger C, Floege J. Vascular calcification in chronic kidney disease: an update. Nephrol Dial Transplant. 2016;31:31–9. pii: gfv111. [Epub ahead of print]. Review.
8. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor κB. J Am Acad Dermatol. 2008;58:458–71.
9. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. Semin Dial. 2002;15: 172–86.
10. Jono S, Nishizawa Y, Shioi A, Morii H. 1,25-Dihydroxyvitamin D3 increases *in vitro* vascular calcification by modulating secretion of endogenous parathyroid hormone-related peptide. Circulation. 1998;98:1302–6.
11. Munavalli F, Reisenauer A, Moses M, Kilroy S, Arbiser JL. Weight loss-induced calciphylaxis: potential role of matrix metalloproteinases. J Dermatol. 2003;30:915–9.
12. Janigan DT, Hirsch DJ, Klassen GA, MacDonald AS. Calcified subcutaneous arterioles with infarcts of the subcutis and skin ("calciphylaxis") in chronic renal failure. Am J Kidney Dis. 2000;35:588–97.
13. Wilmer WA, Voroshilova O, Singh I, Middendorf DF, Cosio FG. Transcutaneous oxygen tension in patients with calciphylaxis. Am J Kidney Dis. 2001;37:797–806.
14. Mehta RL, Scott G, Sloand JA, Francis CW. Skin necrosis associated with acquired protein C deficiency in patients with renal failure and calciphylaxis. Am J Med. 1990;88:252–7.
15. Weenig RH, Sewell LD, Davis MDP, McCarthy JT, Pittlekow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol. 2007;56:569–79.
16. Karpman E, Das S, Kurzrock EA. Penile calciphylaxis: analysis of risk factors and mortality. J Urol. 2003;169:2206–9.
17. Hafner J, Keusch G, Wahl C, et al. Uremic small-artery disease with medial calcification and intimal hyperplasia (so-called calciphylaxis): a complication of chronic renal failure and

benefit from parathyroidectomy. J Am Acad Dermatol. 1995;33:954–62.

18. Mochel MC, Arakaki RY, Wang G, Kroshinsky D, Hoang MP. Cutaneous calciphylaxis: a retrospective histopathologic evaluation. Am J Dermatopathol. 2013;35:582–6.

19. Edsall LC, English JC, Patterson JW. Calciphylaxis and metastatic calcification associated with nephrogenic fibrosing dermopathy. J Cutan Pathol. 2004;31:247–53.

20. Shmidt E, Murthy NS, Knudsen JM, et al. Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. J Am Acad Dermatol. 2012;67:1296–301.

21. Floege J, Kubo Y, Chertow GM, Parfrey PS. The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. Clin J Am Soc Nephrol. 2015;10:800–7.

22. Chan MR, Ghandour F, Murali NS, Washburn MJ, Astor BC. Pilot study of the effect of lanthanum carbonate (Fosrenol®) in patients with calciphylaxis: a Wisconsin Network for Health Research (WiNHR) study. J Nephrol Ther. 2014;4(3):1000162.

23. Don BR, Chin AI. A strategy for the treatment of calcemic uremic arteriolopathy (calciphylaxis) employing a combination of therapies. Clin Nephrol. 2003;59:463–70.

24. An J, Devaney B, Ooi KY, Ford S, Frawley F, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. Nephrology. 2015;20:444–50.

25. Price PA, Omid N, Than TN, Williamson MK. The amino bisphosphonate ibandronate prevents calciphylaxis in the rat at doses that inhibit bone resorption. Calcif Tissue Int. 2002;71:356–63.

26. Monney P, Nguyen QV, Perroud H, Descombes E. Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. Nephrol Dial Transplant. 2004;19:2130–2.

27. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol. 2013;8:1162–70.

28. Sewell LD, Weenig RH, Davis MDP, McEvoy MT, Pittelkow MR. Low-dose tissue plasminogen activator for calciphylaxis. Arch Dermatol. 2004;140:1045–8.

43
Kawasaki Disease

■	Synonym:	Mucocutaneous lymph node syndrome
■	Etiology:	Unknown
■	Associations:	None
■	Histology:	Coronary arteritis; skin-nonspecific with dermal edema and perivascular lymphocytes
■	Evaluation:	Throat culture, serologic testing for viral infections, urinalysis, complete blood count with differential, electrocardiogram, transthoracic echocardiography in younger patients, and magnetic resonance angiography in older patients
■	Treatment:	Intravenous gamma globulin and aspirin and systemic steroids in refractory cases
■	Prognosis:	Good with treatment and 1–2 % sudden cardiac death due to coronary arteritis

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, was first described in Japan in the late 1960s as an illness characterized by persistent fever, conjunctivitis, mucous membrane changes, acral erythema with desquamation, and cervical adenopathy, associated with coronary arteritis [1, 2]. While earlier descriptions of the disease were limited to Asia and Hawaii, the disease is now known to occur worldwide. The disease is primarily one of young children, with 85 % of cases occurring in children under 5 years. It is uncommon in children less than 6 months. There have been some epidemiologic investigations linking KD to freshly cleaned carpets, humidifier use, and living near a body of water, but these associations have not been observed consistently [3].

The etiology of KD is unknown. There are seasonal peaks in the winter and spring months, with occasional epidemics. There are only rare cases of the disease occurring in infants less than 3 months, suggesting protection via passive maternal antibodies. These findings have suggested an infectious agent, yet extensive investigations have failed to detect one. IgA plasma cells have been found in early and subacute lesions of Kawasaki vasculitis, suggesting the possibility of an immune response to a gastrointestinal or respiratory tract pathogen [4]. Furthermore, the IgA response is oligoclonal rather than polyclonal, favoring an antigen-driven response over nonspecific B-cell activation [5]. Synthetic versions of these antibodies bind to intracytoplasmic inclusion bodies in ciliated respiratory epithelium of children with KD, suggesting a potential viral etiology [6]. Acute KD is associated with upregulation of T-helper cell type 17 cytokines and downregulation of regulatory T cells (Treg), as is seen in rheumatoid arthritis and systemic lupus erythematosus, suggesting an autoimmune-like process [7]. The incidence of KD is greater in the Asian population and in siblings and parents of those with the disease, suggesting a genetic predisposition [3]. Several immune function gene single nucleotide polymorphisms (SNPs) have been shown to confer susceptibility to KD, including *CD40*, *FCGR2A*, *CASP3*, and *ITPKC* genes, the latter two of which may indicate risk of coronary artery involvement [6].

Patients with KD present with persistent fever despite antibiotics, conjunctival congestion, oral dryness, redness, fissuring of the lips, strawberry tongue, and mucosal erythema (Figs. 43.1 and 43.2). These findings are accompanied by acral erythema and edema, followed by desquamation in the convalescent stage (Fig. 43.3). The acral erythema spreads to a truncal exanthem within 3–5 days (Fig. 43.4). Cervical adenopathy is also a relatively constant feature. Other symptoms may include diarrhea, arthralgia or arthritis, and aseptic meningitis [2]. A feature found in the majority of patients, but not emphasized in early descriptions, is perineal erythema and subsequent desquamation (Fig. 43.5) [8]. Small sterile pustules have

FIGURE 43.1. Conjunctival injection (Courtesy of Nancy Esterly, MD).

FIGURE 43.2. Lip and tongue erythema and edema (Courtesy of Nancy Esterly, MD).

FIGURE 43.3. Acral edema and erythema (Courtesy of Nancy Esterly, MD).

FIGURE 43.4. Morbilliform exanthem (Courtesy of Nancy Esterly, MD).

FIGURE 43.5. Inguinal and genital accentuation of exanthem with minute pustules (Courtesy of Nancy Esterly, MD).

also been described in some patients with KD, occurring symmetrically on erythematous skin on the buttocks, axillae, genitalia, and extensor surfaces [9].

Diagnostic criteria for Kawasaki disease are as follows [3].

43.1 Diagnostic Criteria for Kawasaki Disease

The presence of fever for at least 5 days, 4 of the 5 criteria below, and the lack of another known disease process to cause the illness:

1. Bilateral conjunctival injection
2. Changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected, fissured lips, and strawberry tongue

3. Polymorphous rash
4. Changes of the extremities: peripheral edema, peripheral erythema, and periungual desquamation
5. Cervical adenopathy

Strict use of these criteria will miss cases of KD, so-called "atypical" or "incomplete" KD. These are patients in whom coronary arteritis is present, in association with persistent fever and fewer than four other diagnostic criteria. Vigilance for these cases is mandated because of the potential for disastrous consequences in untreated coronary arteritis. In cases of suspected KD, imaging of the coronary vessels is indicated. In young children, transthoracic echocardiography can be used to diagnose coronary artery changes with high specificity, but in older children and in adults, visualization of the vessels is more difficult. Coronary X-ray angiography has been the mainstay of evaluation. However, magnetic resonance angiography has been shown to be comparable to X-ray angiography [10]. Laboratory findings may include elevated erythrocyte sedimentation rate and C-reactive protein (CRP), leukocytosis with left shift, pyuria, proteinuria, or anemia. In addition to traditional biomarkers for diagnosis and disease activity, recent investigations suggest that complement system factor B and C5a may be useful in diagnosis [11]. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is elevated in patients with KD relative to febrile controls and may correlate with subtle cardiac involvement [12]. In cases of suspected KD, a suggested diagnostic evaluation is given.

43.2 Diagnostic Evaluation in Suspected Kawasaki Disease

1. Complete blood count and differential
2. Throat and nasal cultures
3. Nasopharyngeal swab for adenovirus and rapid direct fluorescent antigen test
4. Urinalysis
5. Erythrocyte sedimentation rate and C-reactive protein
6. Electrocardiogram
7. Echocardiogram or magnetic resonance angiography
8. Blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT)

The principal differential diagnosis of KD includes scarlet fever, Staphylococcal scalded skin syndrome, toxic shock syndrome, and adenovirus infection. A summary of important features of each is given in Table 43.1.

The typical pathologic finding in KD is that of a vasculitis, occurring most commonly in the coronary arteries but also occurring in renal, iliac, femoral, and mesenteric arteries. A neutrophilic necrotizing arteritis occurs early in the disease, begins at the luminal surface, and may progress to transmural involvement. This process generally resolves within 2 weeks but may be complicated by large aneurysms which are at risk for thrombosis and rupture. A second form of vasculitis beginning in the first 2 weeks of disease begins in the adventitial layer but can progress to involve the entire thickness of the vessel. The infiltrate is composed of lymphocytes, plasma cells, and eosinophils. A closely related process is luminal myofibroblastic proliferation forming a concentric mass which may more insidiously cause luminal narrowing and delayed cardiac morbidity. These recent pathologic observations suggest a potential benefit for ongoing immunomodulatory therapy, although to date, this has not been investigated [6]. Biopsy specimens of the skin in KD do not have specific findings, but in those with sterile pustules, the location is subcorneal [9].

The mainstay of the treatment of KD is intravenous gamma globulin (IVIG), with aspirin, given before the seventh day of onset. A comparison of treatment with aspirin alone versus aspirin with IVIG reveals a striking reduction in the development of coronary aneurysms in the IVIG group and greater resolution of existing coronary lesions over time in the same group [14]. Treatment with IVIG is generally given using 2 g/kg as a single infusion [3]. High-dose aspirin is recommended early on in the disease to prevent thrombotic events, 80–100 mg/kg per day, divided in four doses, for up to 14 days, and then 3–5 mg/kg as a single daily dose for 7 weeks or longer [15]. Lower doses of 30–50 mg/kg per day are given in Japan [16]. Aspirin does not reduce aneurysm formation [17]. Approximately 80 % of patients will become afebrile within 48 h of IVIG treatment. An additional dose of 1 g/kg is commonly given in those not responding to the first dose. Forty percent of nonresponders will respond to the second dose [16]. This second dose decreases the risk of cardiac complications [18]. A number of risk stratification scores have been developed to predict refractory disease. These factors include age, gender, duration of illness, white blood cell and neutrophil count, hematocrit, platelet count, C-reactive protein (CRP), AST, ALT, total bilirubin, sodium, and albumin. In those high-risk patients, coronary complications have been shown to be decreased when initial therapy includes systemic steroids in addition to IVIG [16]. Treatment options for those refractory to two doses of IVIG include additional doses of IVIG, pulse methylprednisolone, infliximab, cyclosporine, cyclophosphamide, and plasmapheresis [3, 19]. In patients treated with systemic steroids, conversion from parenteral to oral therapy should take place once the patient has defervesced and is showing clinical improvement. A 15-day oral steroid taper should commence once the CRP returns to normal [16].

The principal complication of KD is coronary artery disease. Sudden death occurs in 1–2 % of patients in the acute phase of the disease, and coronary aneurysms

TABLE 43.1. Differential diagnosis of Kawasaki disease

	Kawasaki disease	SSSS	Scarlet fever	Toxic shock syndrome	Adenovirus [13]
Age group	>3 months, <5 years	<3 months most common but any age	2–10 years most common	Menstruating women, uncommon in children	Usually <10 years
Conjunctival involvement	+, injection	+, purulent	–	+/–, injection	Usually present
Strawberry tongue	+	–	+, white early on	+/–	rare
Lip involvement	+	–	–	–	–
Acral	+	+, but part of diffuse involvement	–	+, but part of diffuse involvement	–
Perineal	+	+, but part of diffuse involvement	+/–	+/–	–
Bullae	–	+	–	–	–
Other	Cervical adenopathy, may have aseptic meningitis, pyuria	May be able to culture *Staphylococcus aureus*	+Throat culture, group A *Streptococcus*, truncal exanthem accentuated in skin folds, "sandpaper" texture on skin	+Culture for *Staphylococcus aureus*, sometimes group A *Streptococcus*, from primary site of infection, scarlatiniform eruption, rhabdomyolysis, liver dysfunction, thrombocytopenia	May have exudative pharyngitis and conjunctivitis

develop in 25 % of patients with the disease; 55 % eventually regress, but some are complicated by stenosis or occlusion [20]. Patients with giant aneurysms (those greater than 8 mm in diameter) are at considerably higher risk for complications [3]. Lifelong follow-up is warranted in those with cardiac abnormalities. A recent study evaluating optical coherence tomography (OCT), a technique with ten times the resolution of intravascular ultrasound, during routine coronary angiography being performed as follow-up in KD patients, showed potentially improved diagnostic benefit by revealing areas of intimal hyperplasia in angiographically normal coronary artery segments [21]. Persistent coronary lesions tend to occur in patients with persistently elevated indices of inflammation, such as C-reactive protein, serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule-1 [22]. This potential functional relationship may have implications for long-term treatment. Recurrent skin peeling has been described in patients with a history of KD, without any other evidence of disease reactivation. Some of these episodes have been associated with respiratory tract infections [23].

Kawasaki disease may resemble several bacterial toxin-mediated diseases and, less likely, viral infections. Early diagnosis is important because of the ability to dramatically decrease the risk of complications with IVIG treatment.

References

1. Kawasaki T. Mucocutaneous lymph node syndrome: clinical observation of 50 cases. Jpn J Allerg. 1967;16:178–222 (in Japanese).

2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54:271–6.

3. Burns JC, Glode MP. Kawasaki syndrome. Lancet. 2004; 364:533–44.

4. Rowley AH, Eckerly CA, Hans-Martin J, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. J Immunol. 1997;159:5946–55.

5. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J Immunol. 2001;166:1334–43.

6. Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. Nat Rev Rheumatol. 2015;11:475–82. doi:10.1038/nrrheum.2015.54. [Epub ahead of print]. Review.

7. Guo MMH, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015;70:310–8.

8. Friter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. Arch Dermatol. 1988;124:1805–10.

9. Kimura T, Miyazawa H, Watanabe K, Moriya T. Small pustules in Kawasaki disease: a clinicopathological study of four patients. Am J Dermatopathol. 1988;10:218–23.

10. Greil GF, Stuber M, Botnar RM, et al. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. Circulation. 2002;105:908–11.

11. Zou QM, Li XH, Song RX, et al. Early decreased plasma levels of factor B and C5a are important biomarkers in children with Kawasaki disease. Pediatr Res. 2015;78:205–11. doi:10.1038/pr.2015.81 [Epub ahead of print].

12. Parthasarathy P, Agarwal A, Chawla K, Tofighi T, Mondal TK. Upcoming biomarkers for the diagnosis of Kawasaki disease: a review. Clin Biochem. 2015. pii: S0009-9120(15) 00067-3. doi:10.1016/j.clinbiochem.2015.02.013. [Epub ahead of print]. Review.

13. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: use of clinical features and a rapid direct fluorescent antigen test. Arch Pediatr Adolesc Med. 2000;154:453–6.

14. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315:341–7.

15. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:645S–87.

16. Research Committee of the Japanese Society of Pediatric Cardiology; Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease. Guidelines for medical treatment of acute Kawasaki disease: report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int. 2014;56(2):135–58.

17. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997;131:888–93.

18. Miura M, Ohki H, Tsuchihashi T, et al. Coronary risk factors in Kawasaki disease treated with additional gammaglobulin. Arch Dis Child. 2004;89:776–80.

19. Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as novel therapy for refractory Kawasaki disease. J Rheumatol. 2004;31:808–10.

20. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. Circulation. 1996;94:1379–85.

21. Dionne A, Ibrahim R, Gebhard C, et al. Coronary wall structural changes in patients with Kawasaki disease: new insights from optical coherence tomography (OCT). J Am Heart Assoc. 2015;4:e001939. doi:10.1161/JAHA.115.001939.

22. Mitani Y, Sawada H, Hayakawa H, et al. Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: association between inflammation and late coronary sequelae in Kawasaki disease. Circulation. 2005;111:38–43.

23. Michie C, Kinsler V, Tulloh R, Davidson S. Recurrent skin peeling following Kawasaki disease. Arch Dis Child. 2000;83:353–5.

Index