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Cutaneous Manifestations of Infection in the Immunocompromised Host

Second Edition

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Preface to the Second Edition

Immunocompromised patients are often some of the sickest patients in the hospital. Dermatologists who focus on inpatient consultations and caring for hospitalized patients are often faced with the gravely ill, severely immunocompromised patient who presents with cutaneous lesions that are a mystery to the primary team and the other involved subspecialty consultants. More often than not these lesions are a sign of an infection, typically one that is potentially life-threatening. Infections in the immunocompromised host often lead to rapid demise, making early recognition of the infectious process crucial to the patient's survival. The dermatologist plays a central role in identifying the pathogenic organism, implementing the appropriate therapy and prolonging or saving a life. That is the crux of this book. We have combed the literature carefully and combined what we have read with our experience in caring for these very sick, complex patients to present the cutaneous manifestations of infection in the immunocompromised host.

This textbook centralizes the available literature on the cutaneous manifestations of infection in the immunocompromised host. The book is a collection of well-documented references (confirmed by biopsy and culture) on specific skin lesions of infection that illustrates cutaneous lesions of routine and rare infectious organisms, demonstrates the evolution of skin lesions over time, – with immune reconstitution or with the recovery of neutrophils – and highlights recognizable patterns of infection and likely causes in different clinical settings (human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS] vs. post solid organ transplantation vs. neutropenia post chemotherapy vs. bone marrow recovery post hematopoietic stem cell transplantation).

We have given particular attention to the pattern of disease produced by routine and opportunistic pathogens to simplify the expanding list of infectious disease possibilities and recognize the most likely organism for a given clinical situation (e.g., fever, pneumonia and rash or fever, meningitis and rash). Starting with the skin lesion (e.g., acral hemorrhagic bullae or subcutaneous nodules), we present an evidence-based tiered differential diagnosis based on a literature review, well-documented case reports and the probability of a specific organism manifesting as a specific pattern of infection in the immunocompromised patient. This approach to skin lesions in the immunocompromised host has resulted in a unique textbook with bold illustrations that can be used as a bedside guide for diagnosis.

The text has been thoroughly updated and expanded since the first edition to reflect emerging trends in infectious organisms that cause disease in each subgroup of immunosuppressed patients. A new chapter discussing the role of viruses in potentiating malignancies in the immunocompromised patient has been added. The collection of images presented here is a rare and precious anthology gathered from our work in the "hospital trenches."

This book is written by dermatologists but intended for all physicians who care for immunocompromised patients, including, but not limited to, internists, transplant surgeons, infectious disease specialists, pediatricians, rheumatologists, and hematologist-oncologists. It is intended to be a diagnostic tool for the clinician, as well as a teaching syllabus for medical students and house staff.

Preface to the First Edition

In 1979, after training in internal medicine at the Hospital of the University of Pennsylvania and in dermatology at Columbia-Presbyterian Medical Center, I began performing an in-hospital dermatology consultation service at Columbia. I relished the challenge of treating the sickest patients with the worst rashes. I was often rewarded for a compulsively complete skin examination by finding the subtle skin clue which was the diagnostic solution to an otherwise complex clinical problem. The patients I treated were usually members of the population of immunocompromised patients, a population whose numbers have increased logarithmically over the past 16 years because of major advances in cancer chemotherapy, transplantation, treatment of autoimmune diseases and the AIDS epidemic.

The major problem in these compromised patients was often infection. The inflammatory response to the invasive organism was altered by either the primary disease or its treatment. Thus, routine pathogens presented in disguise, and the patient became a living culture plate for opportunistic microorganisms, some of which had never been previously described as human pathogens. Skin lesions had to be evaluated not by the morphology alone, but by the clinical setting in which they occurred. There were no atlases or textbooks available to help me in these critical situations. Nor were there teachers or specialists to depend on for dermatology knowledge and advice in the acute care hospital setting, although the infectious disease experts or intensive care specialists, Harold C. Neu and Glenda Garvey, were always willing to share their considerable expertise and wisdom with me. To find out more about cutaneous lesions in the immunocompromised host, I (or more often the dermatology resident doing consults with me for the month) had to search the literature for case reports which were scattered in all general and subspecialty medical journals. Similarly, the care of the compromised host has been managed by all types of physicians: surgeons, internists, primary care physicians, oncologists, rheumatologists and specialists in AIDS, transplantation, infectious disease and dermatology.

This book is a first attempt to centralize the information on cutaneous lesions of infection in the immunocompromised host; to collect well-documented references (by biopsy or culture) on specific skin lesions of infection; to illustrate cutaneous lesions of routine and rare infectious organisms; to demonstrate the evolution of skin lesions over time or with the recovery of neutrophils; to recognize patterns of infection and likely causes in different clinical settings; and to provide a list of pathogens that may cause a particular skin lesion when the host is immunocompromised.

Lastly, and perhaps most importantly, this book will be used to teach. I am fortunate to have studied under some of the best physician-teachers, both as a medical student and house officer at the University of Pennsylvania Medical Center and as a dermatology resident at the Columbia-Presbyterian Medical Center. I can only try to do as well as those from whom I have learned.

Scarsdale, New York — Marc E. Grossman, M.D.

Acknowledgments for the Second Edition

Leonard Harber, M.D., former chairman of the department of dermatology at Columbia Presbyterian Medical Center, gave me my start in 1976 by supporting my idea of a dermatology consultation service in the medical center for Presbyterian and Babies Hospital (later renamed NY Presbyterian Hospital and Children's Hospital of NY). Perhaps the first inpatient consultation service of its kind in dermatology, it morphed under the equally supportive and encouraging department chairman, David Bickers, M.D., into hospitalist dermatology as the field of medical dermatology became established. I am grateful to Dr. Bickers who has indulged all of my academic pursuits and my idiosyncratic teaching methods and for a job in the morning that I love.

Phyllis Della Latta, Director of Clinical Microbiology at Columbia Presbyterian Medical Center, her staff and the laboratory technicians were always available to do their work and show off their results to me and the dermatology residents. It was a special educational experience we all appreciated when I brought all the residents through the microbiology laboratory on consultation rounds to see the microbiologic culprit.

David N. Silvers, M.D., my colleague, friend and Columbia Presbyterian Medical Center dermatopathologist, was always willing to go the distance with deeper cuts, extra cuts, special stains and extra time at the microscope to find the causative "bug." He also provided a counterpoint to my ideas and theories from his own perspective.

Alexis Young, M.D., while a dermatology resident at Columbia worked as a research assistant and fact checker in her spare time.

Special thanks goes to Michele Nunez whose computer skills and organizational talent coordinated the four authors working from New York, San Francisco and Philadelphia to assemble the book and illustrations.

With much thanks to my wife, Leslie, whose vision and guidance created the dermatology practice which allowed me the luxury of this book project.

Scarsdale, NY — Marc E. Grossman, M.D.
2011

Under the expert tutelage of Marc Grossman, M.D., and Paul Schneiderman, M.D., at Columbia University Medical Center, I learned inpatient dermatology. Richard Edelson, M.D., at Yale, unconditionally encouraged my early ideas. With the support of Bruce Wintroub, M.D., and Timothy Berger, M.D., at University of California, San Francisco (UCSF), the modern hospitalist dermatology movement began.

A special thank you to the UCSF dermatology residents, without whom the hospitalist dermatology service at UCSF could not succeed.

Thank you to my parents, Cyril and Mignon, and my brother Keith for their unconditional love and support always.

To my partner in life and love, Ken, and our little Zuri Zev.

San Francisco, CA — Lindy Peta Fox, M.D.
2011

William D. James, M.D., Vice Chair and Director of Clinical Practices and Training Program at the University of Pennsylvania, Department of Dermatology, has inspired us to be the best clinicians we can be and to pursue our interests in medical and infectious dermatology.

We would like to thank the Penn dermatology residents for their hard work and dedication, and for diagnosing and caring for so many challenging and complicated patients.

We are extraordinarily appreciative of the fellows and faculty of the Infection Disease Division of Internal Medicine at the University of Pennsylvania for collaborating and consulting with us and helping to diagnose and treat these challenging patients.

Philadelphia, PA
2011

Carrie Kovarik, M.D.
Misha Rosenbach, M.D.

Acknowledgments for the First Edition

Dermatologic Manifestations of Infections in lmmunocompromised Patients by the late John S. Wolfson, M.D., Arthur J. Sober, M.D., and Robert M. Rubin, M.D., was one of the first published collected series of clinical experience with skin infection in the compromised host. Their outstanding paper was the stimulus for this book. More importantly, Drs. Rubin and Sober established the approach and some of the principles to the diagnosis of skin lesions in the immunocompromised patient. I am grateful to them for allowing me to reproduce parts of their paper (Medicine 1985;64:115–133).

I am most grateful to the faculty and house staff of Columbia-Presbyterian Medical Center (CPMC) who consulted the dermatology service and allowed us to participate in the care of their patients. I am indebted to the dermatology residents through whose efforts the skin biopsies, couch preparations, cultures, and clinical photographs were obtained. The precise etiologic diagnoses could not have been recorded without the high caliber infectious disease laboratories of Presbyterian Hospital. Jeff Roth, when he was chief resident in dermatology at CPMC, arranged the book contract with the publisher and helped me to get started. He assisted me during the formative phase of the book's development.

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Special praise goes to Deborah Duffy, whose secretarial skills enabled her to transcribe my illegible handwriting into the computer-printed word and continuously organize and reorder the text from the inception of this project.

My colleagues, Paul Schneiderman and Vincent DeLeo, encouraged this project, and my wife, Leslie, and children, Andrea and Julie, sacrificed family time so I could work on it and bring this book to print.

Some figures are reproduced with the kind permission of colleagues:

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Contents

Introduction

The diagnosis of infectious disease complications that occur in the skin of the immunocompromised host poses a formidable challenge to the clinician. The clinician is confounded by the two central characteristics of infection in patients with impaired host defenses: (a) the array of potential pathogens is all inclusive, ranging from rare and exotic fungal or protozoan infections to common bacterial and viral infections; and (b) the clinical presentation and course of even the most common infectious process may be greatly modified or obscured by the impaired inflammatory response associated with the patient's disease or its treatment.

The skin and subcutaneous tissue occupy a central position in any consideration of infection in the immunocompromised host. First, the skin and the mucosal surfaces of the body interface with the environment and are the primary host barriers against infection. These primary barriers assume even greater importance in patients whose secondary host defenses – phagocytosis, cell-mediated immunity, antibody production, etc. – are impaired. Second, the rich blood supply of the skin provides an opportunity for metastatic spread of infection both from the skin as the initial portal of entry and to the skin from other sources. The skin is readily available and easily accessible for examination and biopsy that can provide an "early warning" sign to the clinician that systemic dissemination of infection has occurred. Third, skin infections are common in different immunocompromised patient populations.

The immunocompromised host is an individual with one or more defects in the body's natural defense mechanisms sufficient to predispose that individual to infection. The population of patients at risk has expanded and the etiology of these infections has expanded since the last edition. The principal examples of compromised patients are those with acute leukemia, lymphoma, acquired immune deficiency syndrome (AIDS), solid organ and hematopoietic stem cell transplants, antirejection therapy, graft versus host disease, malignancy receiving aggressive and intensive chemotherapeutic regimens, multiple myeloma, or chronic lymphocytic leukemia, and patients with a variety of autoimmune diseases treated with systemic corticosteroids or other immunosuppressant drugs including the newest tumor necrosis factor (TNF) inhibitors, T-cell depleting therapies, and other immunomodulators. Every immunosuppressive regimen that has been devised to prevent rejection increases infection. Excluded from this text are primary immunodeficiency diseases, hyper-IgE syndrome, chronic granulomatous disease, diabetes mellitus, uremia, alcoholism, severe burns, protein/calorie malnutrition, advanced age, premature birth, and asplenic patients.

The most important factors that predispose to infection are: (a) neutropenia, (b) cellular immune dysfunction, (c) humoral immune deficiency, and (d) damage to the anatomic barriers (skin or mucous membranes). Other risk factors for infection include medical or surgical procedures, irradiation, indwelling catheters and medical devices (such as left ventricular assist devices (LVADS) pre-heart transplantation). Broad-spectrum antibiotics, antimicrobial prophylaxis (such as fluconazole for antifungal prophylaxis or ganciclovir for cytomegalovirus [CMV] prophylaxis), and prolonged hospitalization cause alterations in the normal microbial flora and produce the opportunity to acquire new organisms that may be environmental pathogens or resistant to various antibiotics. Other potential sources of infection besides endogenous flora include contaminated air, water, and food, and direct contact with individuals carrying potential pathogens particularly within the hospital environment. The presence or absence of infection with one or more of the known immunomodulating viruses (CMV, Epstein-Barr virus [EBV], hepatitis B or C, human

immunodeficiency virus (HIV), and perhaps human herpes virus [HHV] 6 and 7) has been known to accentuate the severity of opportunistic infections.

In addition to the classification of skin infections in the immunocompromised host on the basis of microbial etiology (listed in the Table of Contents), these cases can also be categorized on the basis of the pathophysiologic events that have occurred:

1. Infection originating in the skin and typical of that occurring in immunocompetent patients albeit with the potential for more serious consequences
2. Widespread or extensive cutaneous involvement with organisms that usually produce localized or trivial infection in immunocompetent individuals
3. Infection originating in the skin caused by opportunistic organisms that rarely produce disease in immunocompetent patients but which may produce localized or disseminated infection in immunocompromised individuals
4. Disseminated systemic infection metastatic to the skin from a noncutaneous portal of entry

1. *Typical primary skin infection*

Conventional forms of infections originating in the skin such as cellulitis appear to be increased in incidence and severity in immunocompromised patients. These infections are commonly caused by Gram-positive organisms such as Group A *Streptococcus* and *Staphylococcus aureus*. The cutaneous lesions may be indistinguishable from those of other unusual organisms, making diagnosis difficult from clinical assessment alone. Neutropenic patients appear prone to cellulitis caused by *Pseudomonas* and other Gram-negatives or anaerobes. Individuals with leukemia or other diseases or medications affecting cell-mediated immunity may have cellulitis caused by *Cryptococcus neoformans*. This emphasizes the need for skin biopsy, special stains, and cultures for routine appearing skin infections if there is not an adequate response to what appears to be the appropriate antimicrobial therapy.

2. *Unusually widespread cutaneous infection*

Usually minor skin infections in normal individuals such as human papillomavirus and superficial fungal infections are more common, more extensive, and may be associated with serious systemic consequences in immunosuppressed patients. Although single verruca are common in normal individuals, in patients receiving chronic immunosuppressive therapy, warts may be so numerous as to be disfiguring. Warts (condyloma acuminatum) may be so florid with HIV infection as to cause anal blockage. Unusual clinical presentations such as oral condyloma acuminatum may occur in these patients. Warts in immunosuppressed patients are of more than cosmetic significance, as malignant transformation, particularly in sun-exposed areas, has been well documented.

Unusually widespread cutaneous infection may be due to "nonvirulent fungi" in addition to viruses. The fungi include dermatophytes, which have both an increased incidence and an increased severity of infection. In these patients local disease, especially on the extremities, can provide a potential portal of entry for life-threatening bacterial superinfection.

More extensive skin involvement with organisms usually causing limited local infection may occur with herpes simplex, herpes zoster, molluscum contagiosum, human papilloma virus, *Malassezia* species, and scabies.

These common skin diseases may not respond to the usual therapies at all or may require higher doses of medication for prolonged periods or repeated surgical procedures. Dermatophyte infections may be poorly responsive to topical and oral antifungal medications. In many cases, treatment must be continued indefinitely because, when therapy ceases, prompt recurrence may be seen.

3. *Opportunistic primary skin infections*

In most cases, infections follow some form of injury to the skin that has provided the opportunity for these usually nonvirulent microbes to invade. Then with secondary host defenses impaired, significant local or disseminated disease may result. Important causes of localized disease include the fungi *Paecilomyces*, *Penicillium*, *Alternaria*, *Fusarium*, and *Trichosporon*; the atypical mycobacterium; and the alga *Prototheca wickerhamii*. New organisms have appeared in the immunocompromised patient population. These emerging infections have occurred with increasing frequency.

Dissemination and systemic disease followed primary skin infection with *Aspergillus*, *Candida*, and *Rhizopus* species.

Both invasive aspergillosis and disseminated candidiasis with the skin as the primary site of infection have been observed in patients whose skin has been injured by intravenous therapy. Fungal spores of *Rhizopus* contaminating Elastoplast (Beiersdorf UK Limited, Birmingham, United Kingdom) tape used for occlusive dressings resulted in both locally invasive and disseminated infection.

4. *Disseminated infection metastatic to the skin*

Hematogenous dissemination to the skin and subcutaneous tissues from a distant primary site may be the first clinical sign of a widespread life-threatening infection. Three groups of organisms are responsible for this category of cutaneous infection in the immunocompromised host: (a) *Pseudomonas aeruginosa* and to a lesser extent other bacteria; (b) the endemic or endogenous infections such as the so-called geographically restricted fungi *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis* or the parasites in patients from endemic areas such as *Strongyloides stercoralis*; and (c) the opportunistic organisms *Nocardia* species, *Aspergillus* species, *Cryptococcus neoformans*, *Candida* species, *Scedosporium*, hyaline and black molds, and Mucoraceae.

An important aspect of dermatologic diagnosis in the normal host is the gross morphologic appearance of the skin lesion. In the immunocompromised patient, this approach is limited because the variety of organisms causing infection in this population is greater than in normals, and the inflammatory response to the microbe is altered. Even the most banal appearing skin lesion may represent an unusual infection. The physician must consider the "zebras," or the rare infections, as well as the routine ones in disguise. Common entities may assume unusual or bizarre presentations while serious opportunistic infections may be nondescript clinical lesions. The clinician must keep a high index of suspicion that the innocuous skin lesion or the "harmless" laboratory contaminant represents a devastating pathogen in the compromised host. For these reasons, the differential diagnosis of any skin lesion is large and skin biopsy most useful in making a diagnosis.

An infectious process should always be considered in an immunocompromised patient with skin lesions even though fever may not be present. Just as the clinical manifestations of an infectious disease may be unusual, so too may the histologic appearances be bizarre. An inflammatory response may be absent on a skin biopsy specimen. The inability of an immunosuppressed patient to mount an inflammatory response may account for the absence of neutrophils, plasma cells, multinucleated giant cells, or granulomas, usually found with an infection. The pathologist must not be fooled by an unimpressive infiltrate. If the pathologist reads a biopsy specimen as showing panniculitis or vasculitis, the clinician must consider an infectious panniculitis or vasculitis and request appropriate special stains or cultures. Even if a pathogen is identified histologically or by culture from a skin biopsy specimen, the possibility of more than one pathogen or pathologic process should be considered. Complex combined infections may present in the same lesion.

To maximize the chance of identifying the invading organism by skin biopsy, appropriate stains and cultures should be obtained. A wedge excision is preferred, half of which is sent to the pathology laboratory for both routine processing and special stains (for fungi, mycobacteria, and conventional bacteria). The other half is sent to the microbiology laboratory for aerobic and anaerobic bacterial, fungal (at 25°C and 37°C), and mycobacterial culture, and Gram, acid-fast, and fungal stains of touch preparations, ground material from biopsied tissue, or both.

Any unexplained skin lesion in an immunocompromised patient should be biopsied for culture and histologic examination. The skin biopsy is inexpensive, relatively noninvasive, without contraindication, and may avoid the performance of more serious invasive procedures such as open lung biopsies and liver biopsies. Early diagnosis may be made by skin biopsy, as blood cultures and other diagnostic studies (such as antibody tests) may be negative or delayed despite disseminated disease.

1

Subcutaneous and Deep Mycoses

Aspergillosis

Invasive aspergillosis is the most common opportunistic fungal infection in the hematopoetic stem cell transplant patient. Prior to the regular use of antifungal prophylaxis, invasive fungal infections caused by *Candida* were the most common infection, followed by infection by *Aspergillus*.[1] In the 1990s, 90% of *Aspergillus* infections were due to *A. fumigatus*; however *A. flavus*, *A. terreus*, *A. niger*, and *A. versicolor* are all potential causes of invasive aspergillosis. *A. flavus*, followed by *A. niger*, is the most common cause of primary cutaneous disease while *A. fumigatus* more commonly causes disseminated disease.[2] *A. glaucus*, *A. chevalieri*, and *A. ustus* are rare causes of cutaneous disease.[3]

Invasive aspergillosis occurs in the settings of severe or prolonged neutropenia due to cytotoxic therapy for leukemia or lymphoma, high-dose systemic corticosteroids for transplants or collagen vascular disease, a functional neutrophil defect, long-term immunosuppression for graft versus host disease (GVHD), chronic granulomatous disease, neonates, and burn wounds. It is less common, but not infrequently reported, in organ transplant recipients and human immunodeficiency virus (HIV)-positive patients. In HIV-positive patients, low CD4 counts, cytomegalovirus infection, and neutropenia either due to HIV disease, antiretroviral therapy, or ganciclovir are risk factors for cutaneous aspergillosis.[4] Emerging data also implicate polymorphisms in innate immunity genes as a risk factor for *Aspergillus* infection.[5] In patients status post stem cell transplant (SCT), invasive aspergillosis is now more common in the post engraftment phase, often due to immunosuppression for GVHD, than in the neutropenic period.[6]

Aspergillus infection can involve the skin of an immunocompromised patient as either a primary or secondary process. Primary cutaneous aspergillosis is rare in the immunocompetent host and should prompt an evaluation for compromised immune status when the diagnosis is made.[7] In immunocompromised patients, primary cutaneous aspergillosis is classically associated with nosocomially induced infection via contaminated intravenous cannulas, Hickman catheters, non-sterile gauze, adhesive tape, arm boards, or, rarely, in a surgical wound. Occasionally, a clear history of cutaneous injury may not be elicited.[8] Hematogenous dissemination from the skin may occur. Secondary cutaneous aspergillosis is most common in bone marrow transplant recipients and leukemic patients. It arises either from direct invasion of skin from an underlying infected structure such as the nose, sinus, or orbit, or as disseminated lesions from hematogenous spread of infection. In secondary cutaneous aspergillosis, the lungs are usually the initial site of infection.

Aspergillus is a ubiquitous fungus readily isolated from soil, plants, decaying vegetation, food, and water. Nosocomial epidemics of invasive aspergillosis in susceptible patients occur in the hospital environment when large numbers of spores are widely dispersed in the air during construction, renovation, and fire-proofing. This release of spores, coupled with both the interruption of primary host defenses (i.e., the skin and mucosal barrier) and impairment by the underlying disease and chemotherapy of secondary host defenses (i.e., neutrophils and macrophages), allow for nosocomial primary cutaneous aspergillosis to occur.

The lesions of primary cutaneous aspergillosis begin as tender erythematous or purpuric macules or papules that progress to violaceous edematous plaques, often with hemorrhagic bullae. Lesions tend to be large (centimeters) and single or a few grouped lesions if multiple. Lesions then develop dark centers and maintain a peripheral brightly purpuric rim. They may then ulcerate or form black necrotic eschars. The bullous phase of invasive aspergillosis is important to recognize, as potassium hydroxide (KOH) preparation of the hemorrhagic blister roof can provide an

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immediate presumptive diagnosis.[9] Cutaneous aspergillosis should be suspected when a hemorrhagic bulla or necrotizing plaque develops in an immunocompromised host, particularly if the patient is receiving broad-spectrum antibiotic therapy. The initial erythematous phase of invasive aspergillosis can be mistaken for a cellulitis or an irritant contact dermatitis to an arm board or tape. The straight borders of a hemorrhagic bulla would suggest a contact dermatitis in a thrombocytopenic leukemic patient. Erythematous to violaceous, sometimes suppurative, plaques studded with pustules, occasionally mimicking *Candida*, are an emerging clinical presentation of cutaneous aspergillosis.[10-12]

Less common presentations or morphologies of primary cutaneous aspergillosis include otomycosis[13]; nodules[14]; necrotic, zosteriform lesions followed by widespread eschars and death[15]; subcutaneous tumor with mild purple color to the overlying skin[16]; tender nodule with a dusky, necrotic center[7]; ulceration with overlying gray necrosis of the dorsum of the tongue[17]; infiltrated plaque on the nares and nasal skin[18]; retronuchal erythematous swelling[18]; sporotrichoid nodules with a fluctuant ipsilateral mass[19]; and a dehisced surgical wound with black necrotic margins in a heart transplant patient.[20]

Primary cutaneous aspergillosis in HIV-positive patients is most commonly due to *A. fumigatus*.[4] Lesions near catheter insertion sites and under adhesive tape are characteristic. Secondary cutaneous disease is exceptionally rare in this patient group.[4,21] Unusual presentations of *Aspergillus* in HIV-positive patients include Majocchi's granuloma presenting as a red brown plaque with surrounding pustule[22]; a violaceous plaque covered in a yellow-brown crust with adjacent follicular papules[23]; umbilicated papules resembling molluscum contagiosum[24]; nodules, fluctuant papules, deep seated pustules, vesicopustular plaques, and nonhealing ulcers[4]; and penile papules and ulcerated plaques under a condom catheter.[25]

Skin manifestations of secondary or disseminated aspergillosis are uncommon and occur in less than 10% of patients with invasive aspergillosis. However, cutaneous lesions may be the presenting sign of disseminated disease.[26] They appear as erythematous macules, papules, or nodules that become purpuric, hemorrhagic, necrotic, or ulcerate[27,28]; a hemorrhagic bulla; or subcutaneous nodules or abscesses. Other presentations include a cellulitic plaque on the leg with erythematous, firm, subcutaneous nodules within the plaque and violaceous firm nodules on the axilla and elbow[29]; verrucous lesions in addition to typical erythematous to violaceous papules and nodules with central necrosis[28]; extension from underlying sinus infection to overlying skin presenting with vegetative plaques with crusts on the nares, hemorrhagic bullae overlying the eyelid, and hemorrhagic plaques on the face[28]; or linear suppurative and ulcerative nodules.[30] Transmission of invasive aspergillosis from an infected donor to a host, who presented with *Aspergillus* endocarditis and periorbital and skin lesions, has been reported.[31]

Skin biopsy specimens from *Aspergillus* infected patients demonstrate acute angle, regularly septate, dichotomously branching hyphal elements that may be angioinvasive. The histopathologic differential diagnosis includes several other opportunistic fungi including *Fusarium*, *Scopulariopsis*, *Pseudallescheria*, and *Penicillium* which appear identical to *Aspergillus* in tissue. In primary cutaneous disease, the inflammatory infiltrate is superficial or superficial and deep. In secondary cutaneous aspergillosis, the infiltrate is in the deep dermis and subcutaneous fat; intravascular thrombosis with masses of hyphae may be seen.[3] While a skin biopsy is needed to prove invasive disease, isolation in culture of the organism from tissue specimens is needed for definitive identification of the fungus.

Enzyme linked immunoassay (ELISA) testing for the galactomannan antigen may aid in the diagnosis of invasive aspergillosis. Galactomannan is a carbohydrate component of the *Aspergillus* cell wall that is released during hyphal growth. It requires angioinvasion of the organism to be detected and can be tested in serum, brocheoalveolar lavage fluid, or cerebral spinal fluid. The sensitivity of the test ranges from 65% to 90% and the specificity is ≥90%; thus, a negative result rules out disease while a positive result requires a second positive to confirm true infection. False negatives occur if patients are tested while on antifungal agents or if there is limited angioinvasion. False positives occur with loss of integrity of gastrointestinal mucosa (mucositis, neonates, GVHD, cytotoxic chemotherapy) or with the use of piperacillin-tazobactam.[32] The β-D-glucan assay is a nonspecific marker for invasive fungal infection as it detects the β-D-glucan component of the cell wall of various fungi including *Aspergillus*, *Fusarium*, *Trichosporon*, and *Candida*. Its sensitivity is 70% while its specificity is 87–94%.[32] It is not as widely used as the galactomannan ELISA.

Primary cutaneous aspergillosis has a more favorable prognosis than secondary or disseminated disease. Surgical excision in addition to systemic antifungal therapy may be beneficial for primary cutaneous aspergillosis. Systemic treatment is with antifungal therapy such as amphotericin B, itraconazole, voriconazole, or an echinocandin. Fluconazole is not an effective treatment for aspergillosis.

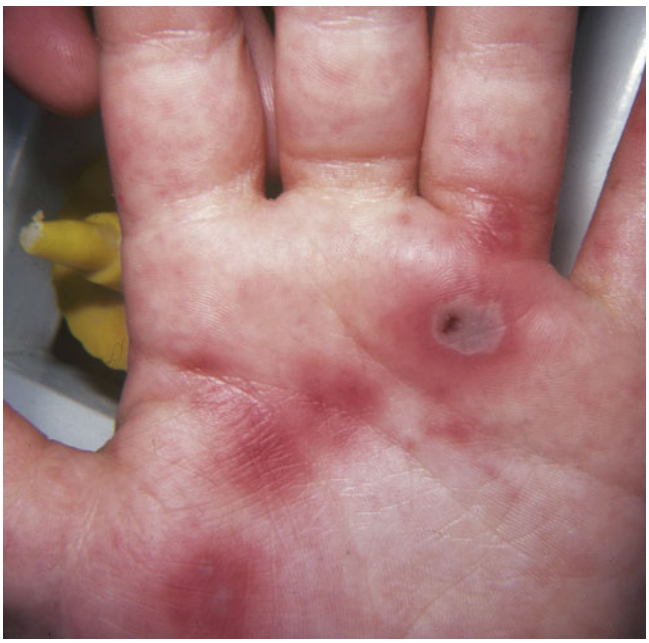

Figure 1.1. Purpuric papules and a gray flat bullae due to *Aspergillus flavus* on the palm of a 7-year-old with acute lymphocytic leukemia (ALL) on the 15th day of chemotherapy, febrile with an absolute neutrophil count of 60 on triple antibiotics

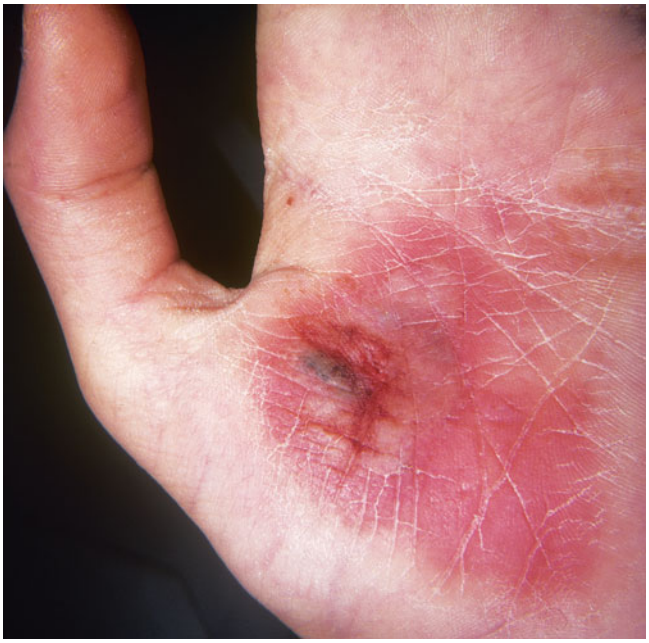

Figure 1.3. A 4 × 6-cm erythematous patch with a central hemorrhagic bulla on the palm of a 13-year-old with ALL on her 11th day of antibiotics for *Staphylococcus aureus* sepsis and osteomyelitis with an absolute neutrophil count of 42

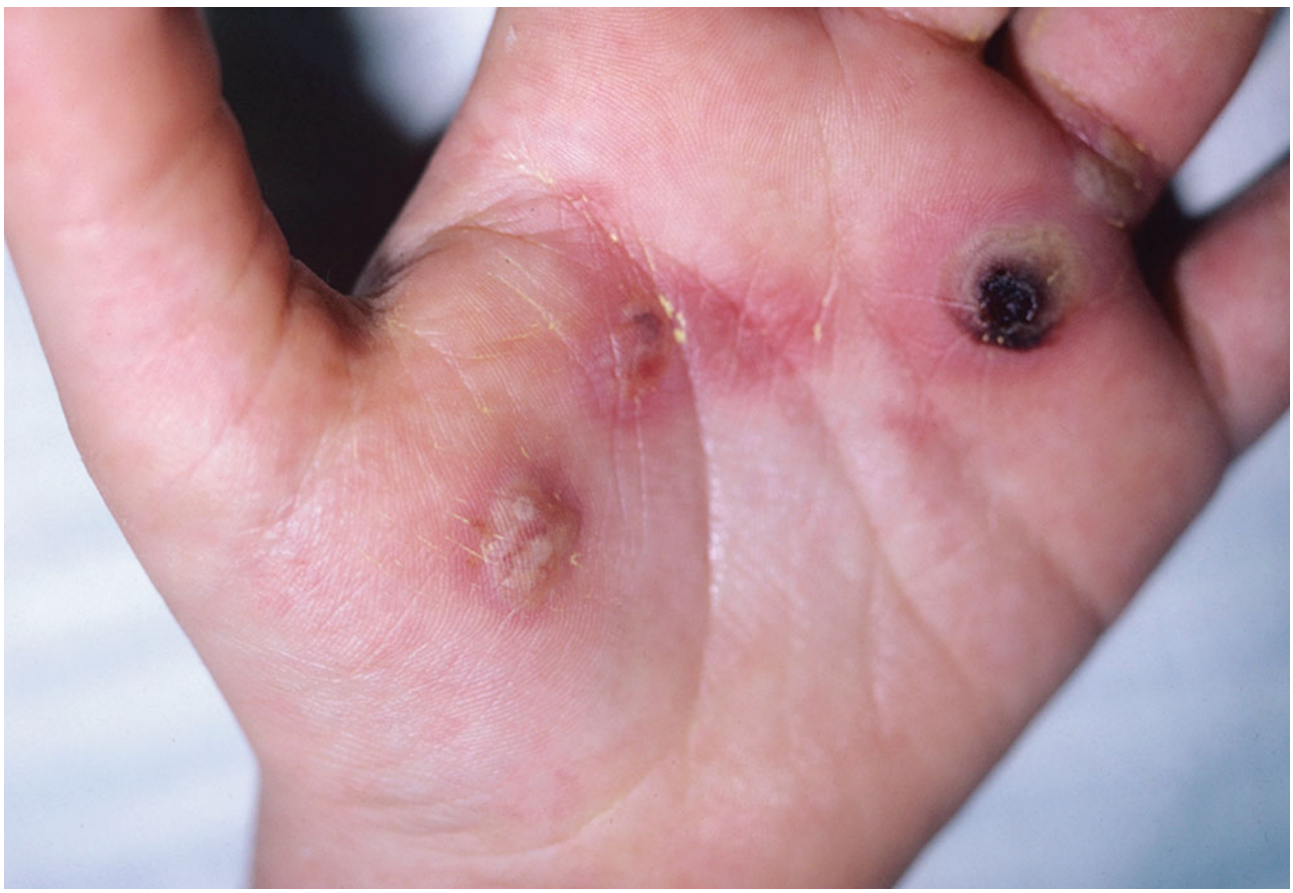

Figure 1.2. Forty-eight hours later, the papules became pustular and the bullae developed a gray-black necrotic base

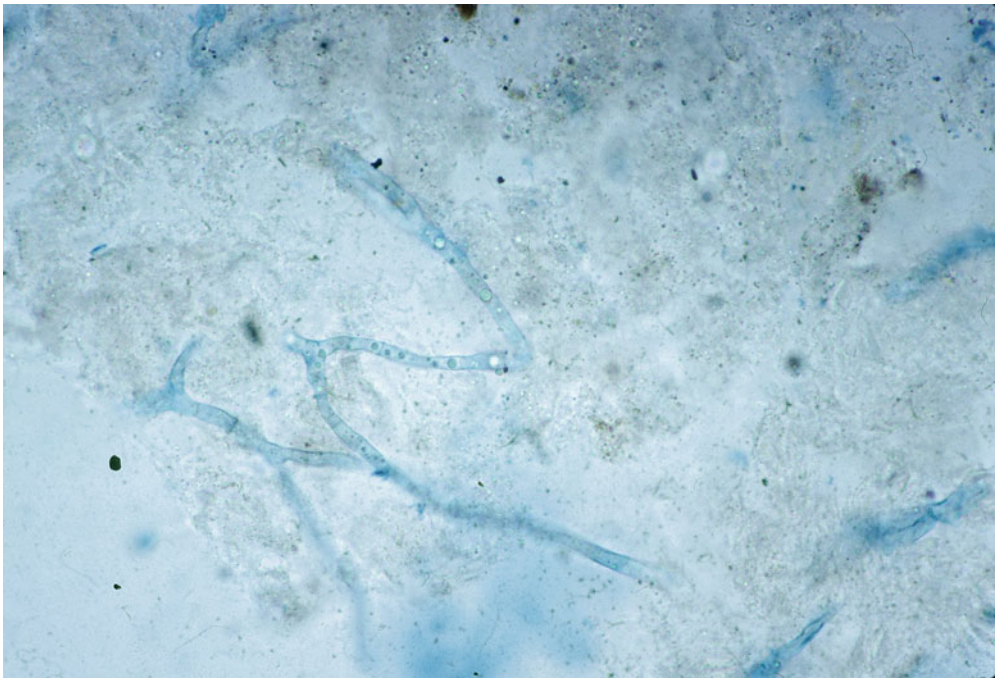

Figure 1.4. A wet mount of a blister with potassium hydroxide and Parker blue-black ink, which stains the *Aspergillus* hyphae. The characteristic broad hyphae dichotomously branched with acute angles are present. Fungal cultures confirmed the diagnosis of aspergillosis

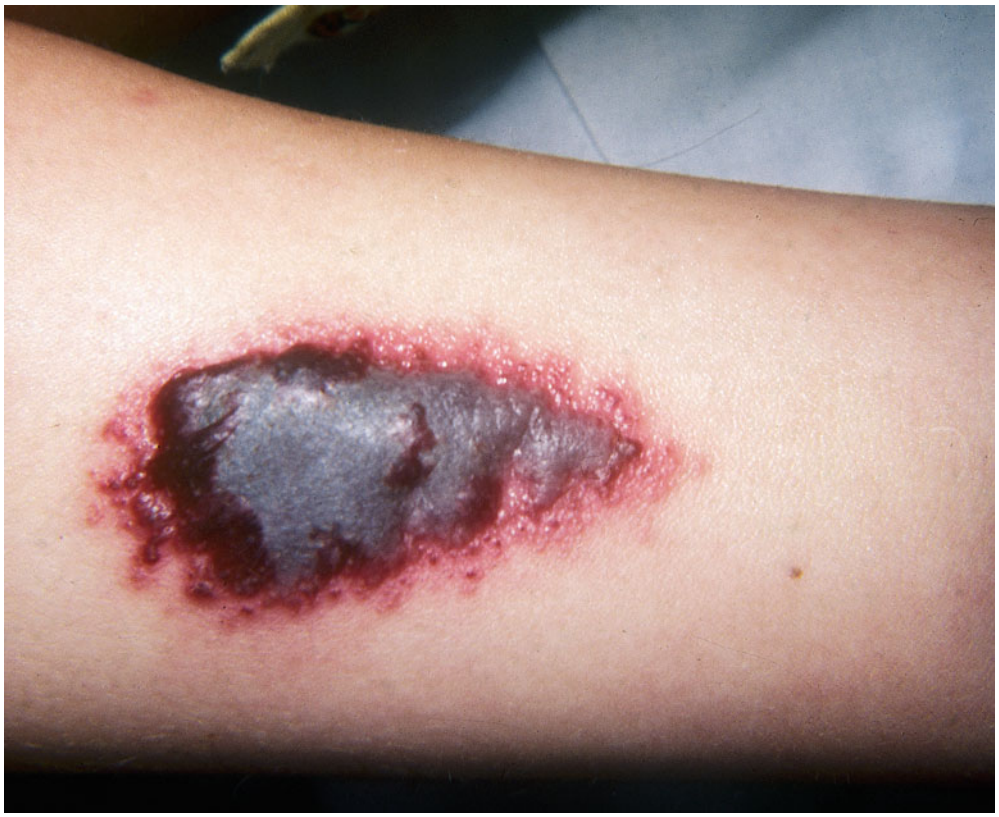

Figure 1.5. A hemorrhagic bulla with linear vesicular borders on the forearm of a 9-year-old with ALL. Potassium hydroxide (KOH) preparation, biopsy, and culture demonstrated *Aspergillus fumigatus*

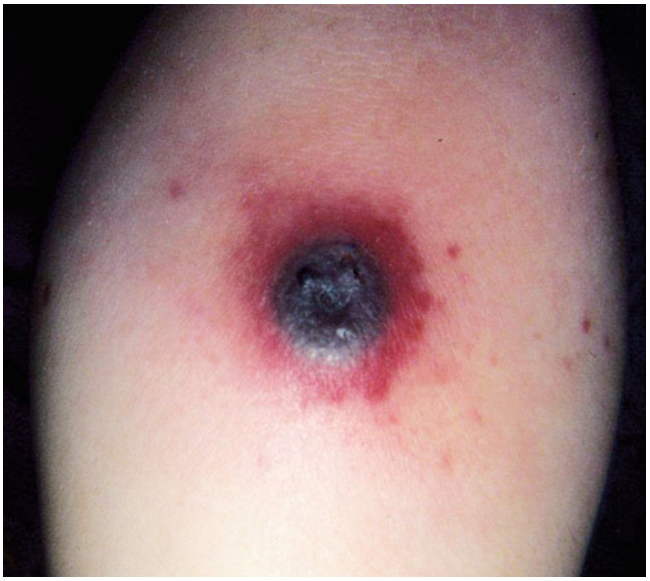

Figure 1.6. A 3×3-cm hemorrhagic nodule with a black necrotic eschar was surgically excised from a 7-year old with ALL. A touch preparation of the biopsy revealed typical hyphae of *Aspergillus*. *A. flavus* was confirmed by culture

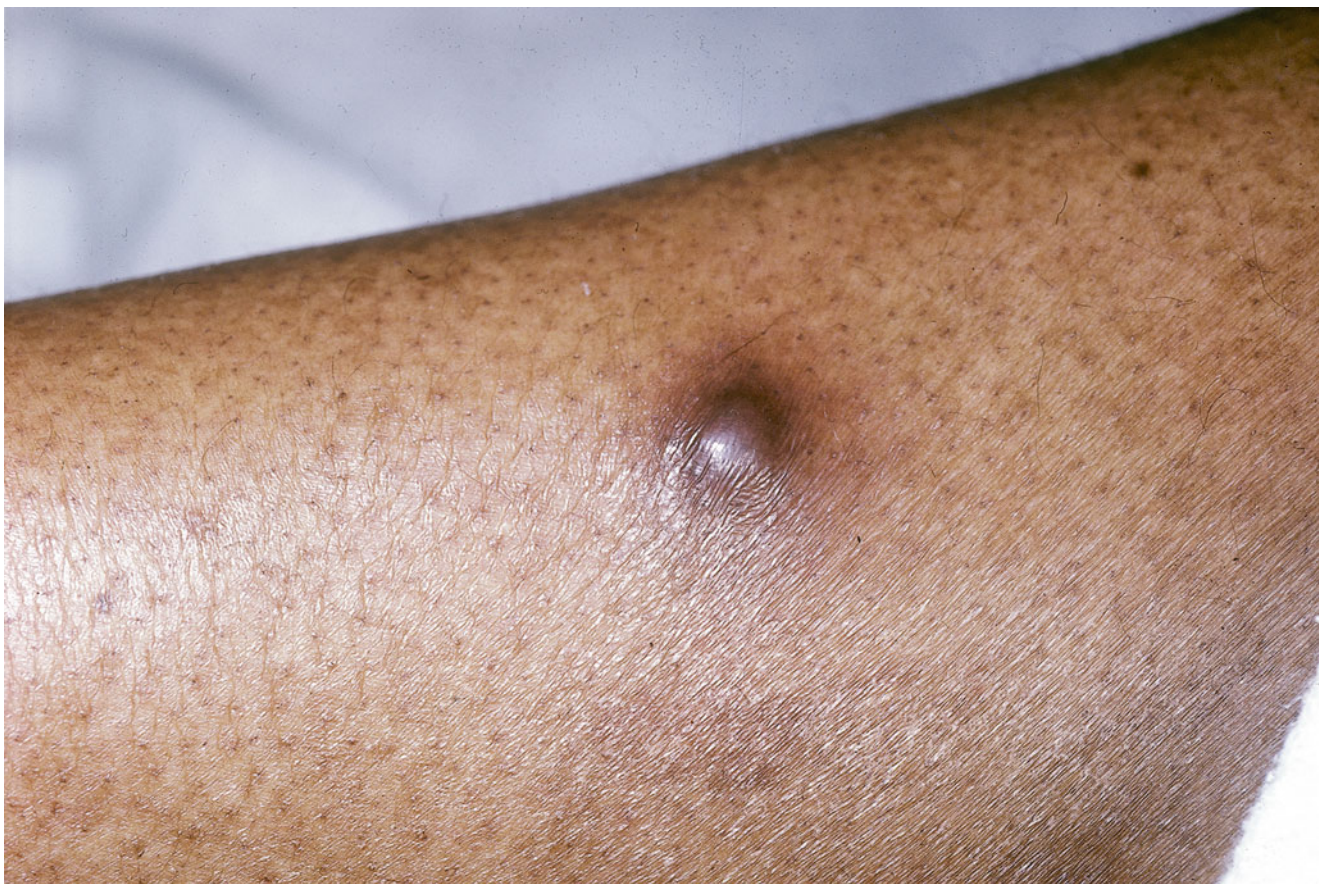

Figure 1.7. Four months after cardiac transplantation, a new nontender subcutaneous nodule was noted on the anterior thigh of a 50-year-old man. An "iceberg lesion" was surgically excised and *A. flavus* was demonstrated on biopsy and culture. After a negative workup, this was felt to be primary cutaneous aspergillosis

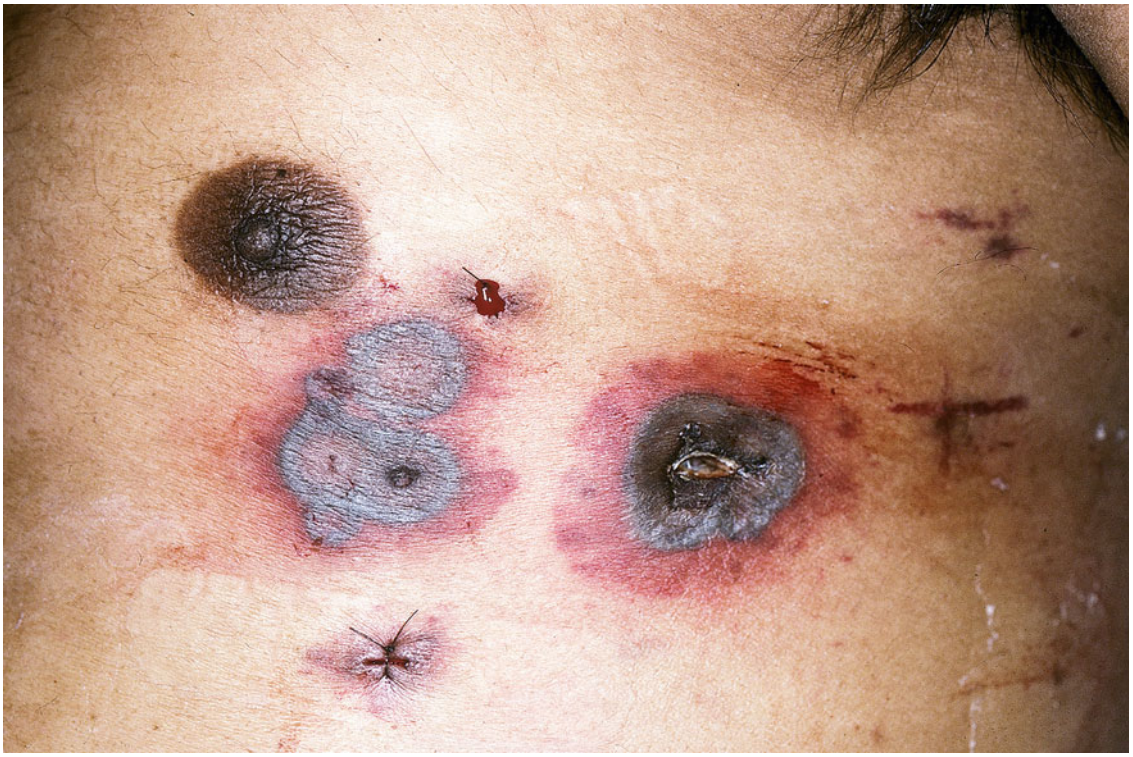

Figure 1.8. *A. flavus* infection developed during chemotherapy where a chest tube had been in a 24-year-old with Hodgkin's disease

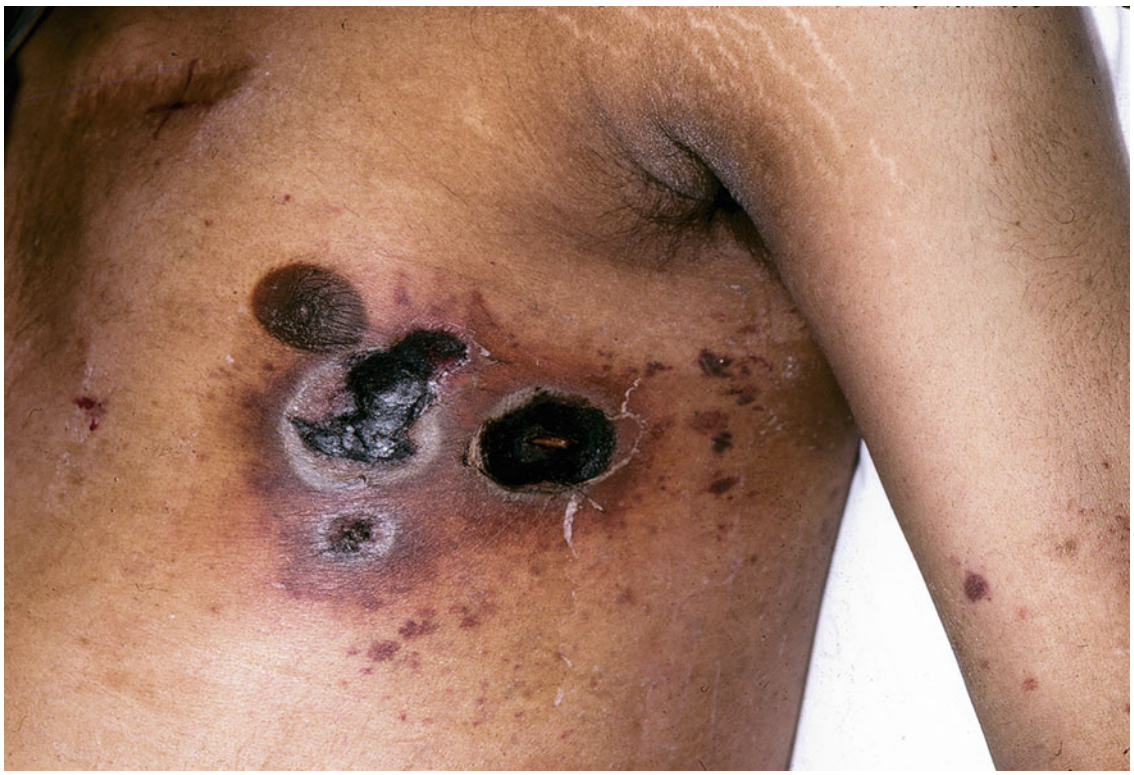

Figure 1.9.–1.11. Several days later, the purpuric hemorrhagic plaques became necrotic black eschars

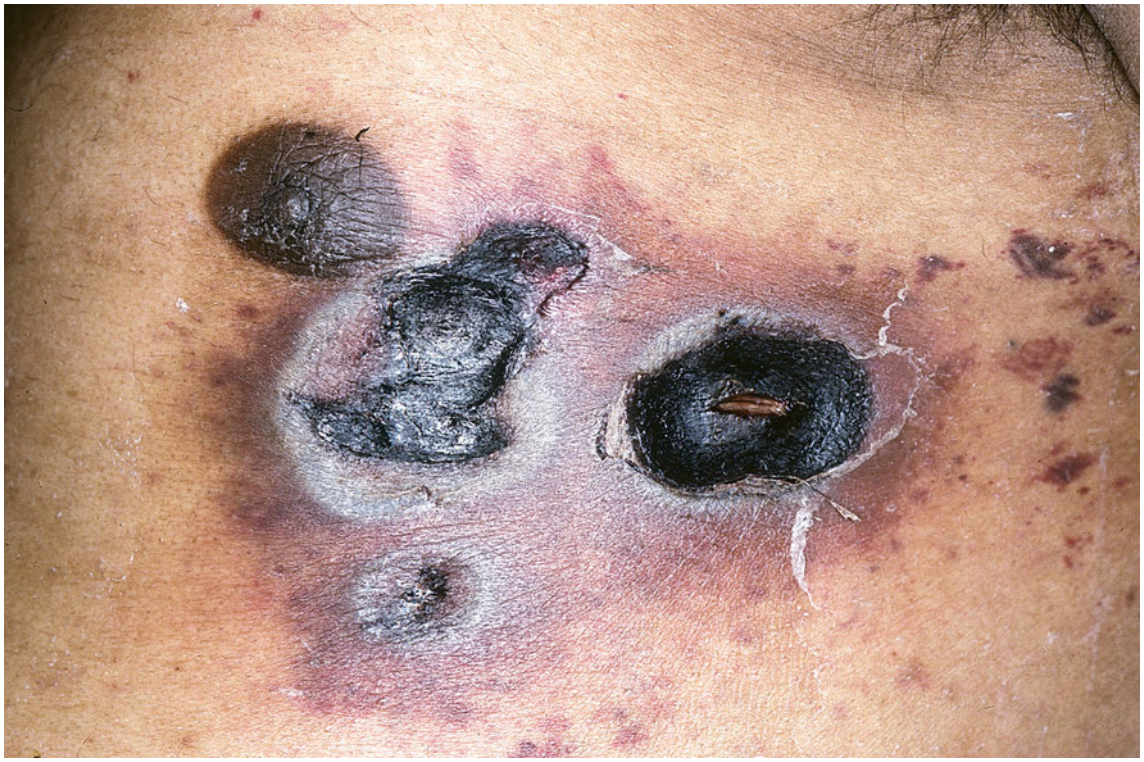

Figure 1.10.

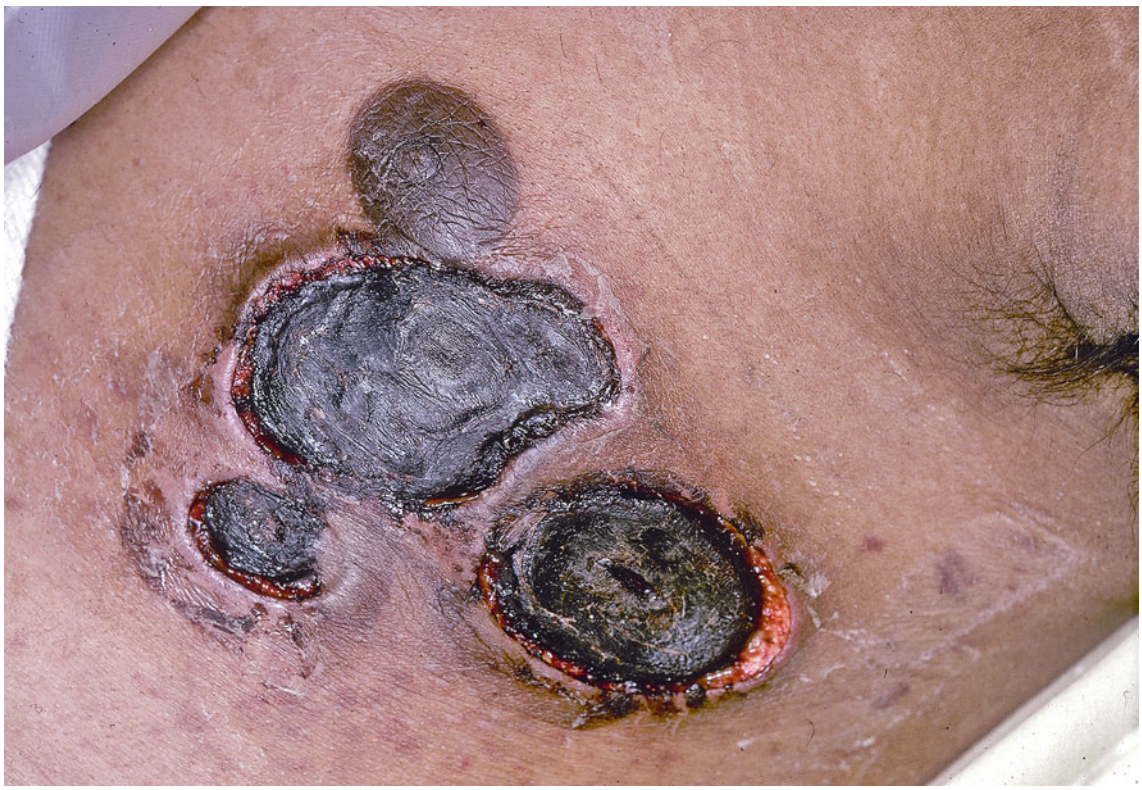

Figure 1.11.

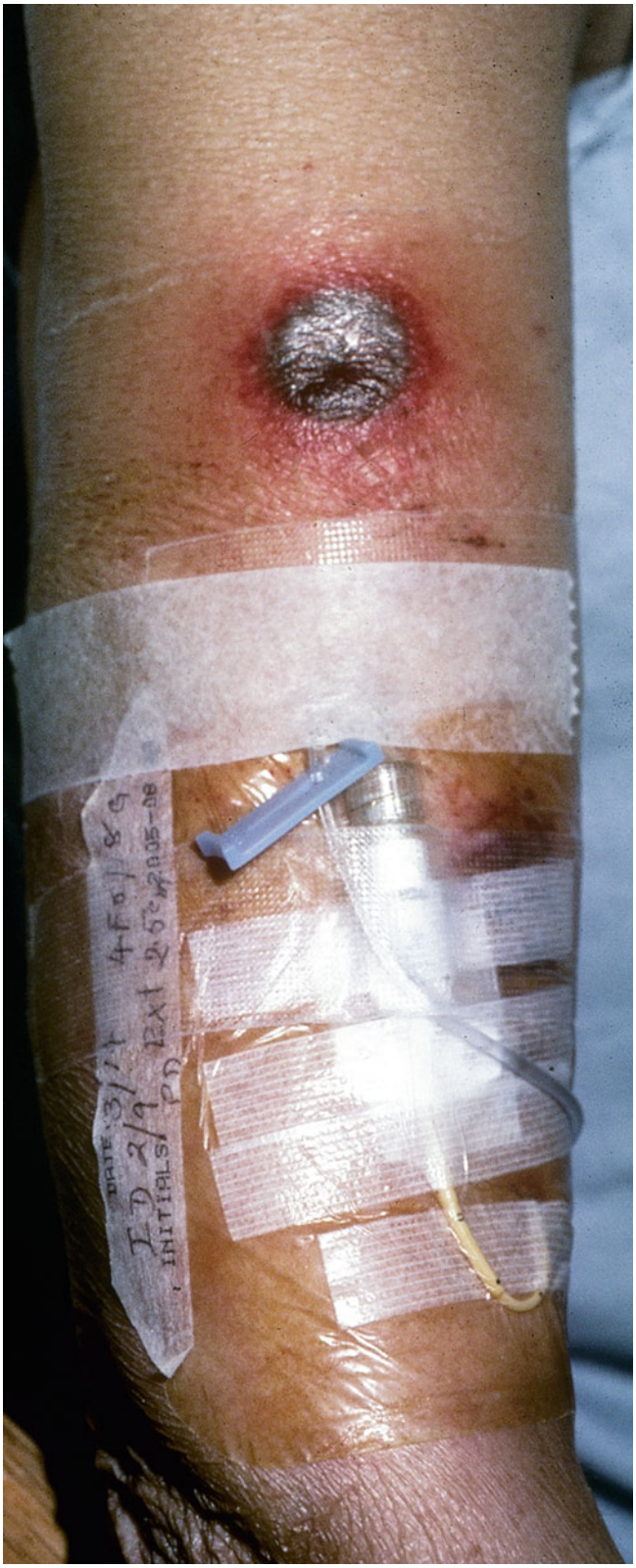

Figure 1.12. A 73-year-old with neutropenic fever post chemotherapy for AML developed a hemorrhagic necrotic bulla above the peripherally inserted central catheter (PICC) line on her arm due to *Aspergillus flavus*

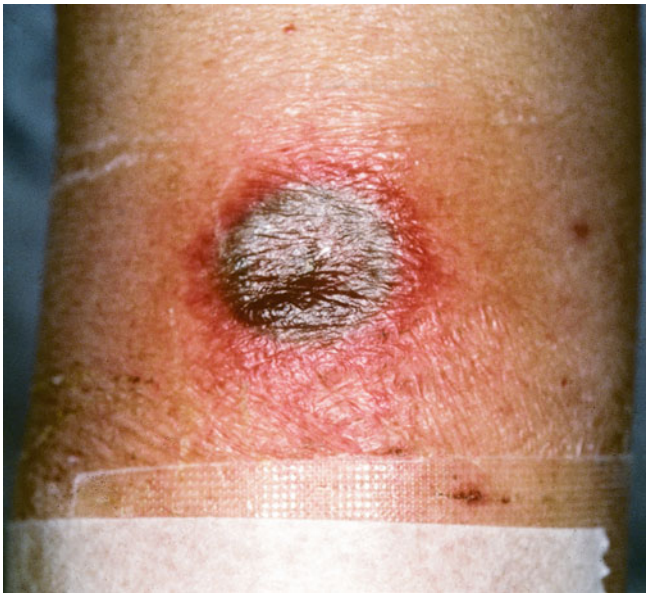

Figure 1.13. Close-up of the black necrotic bulla

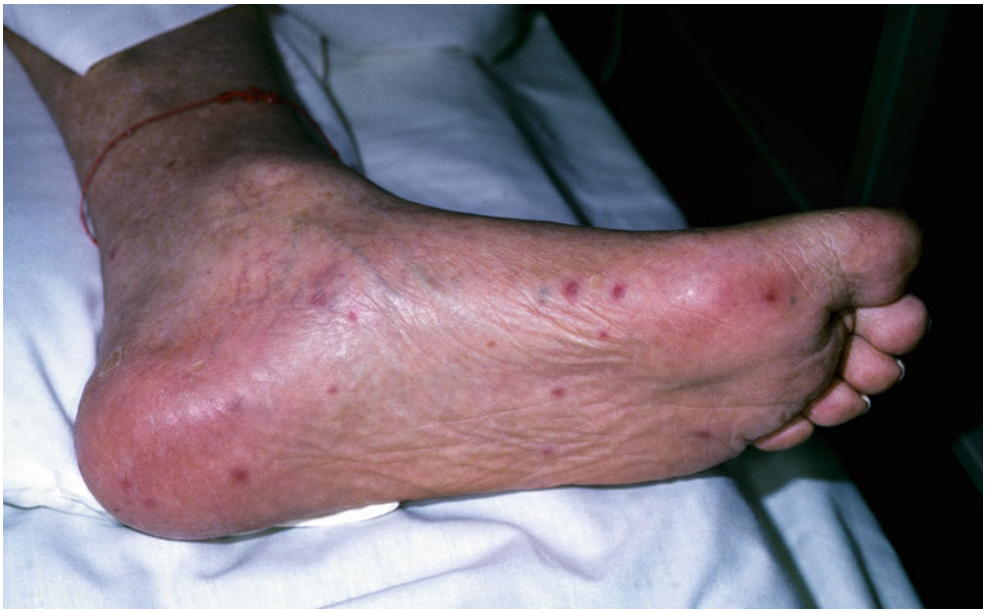

Figure 1.14. Fatal disseminated *A. fumigatus* in multiple myeloma. Purpuric papulonodules developed on the palms and soles

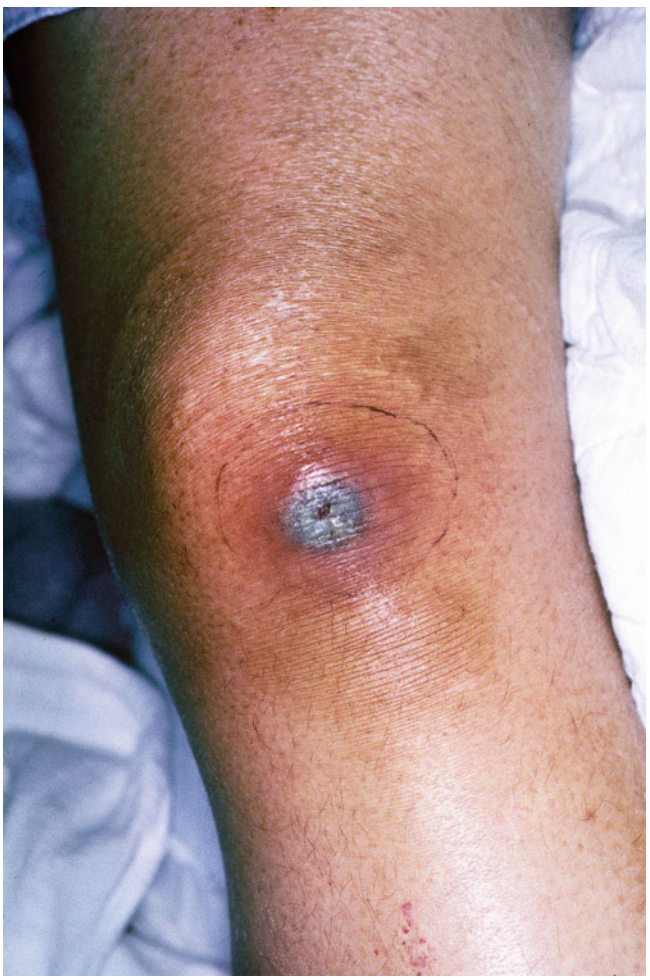

Figure 1.15. A 44-year-old man with peripheral T cell lymphoma developed neutropenic fevers post chemotherapy and a hemorrhagic necrotic knee bulla due to *Aspergillus* species