14 Cutaneous Pathology of Emergent and Tropical Infections: Skin, Infectious Pathogens, and Emergent and Tropical Infections

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Introduction to Cutaneous Infections

The skin is often a sentinel for many infectious diseases by being the primary site of involvement, by being the entry site of infectious pathogens, or by demonstrating lesions that result from toxin, inflammatory, or vascular-mediated changes associated with infection. Cutaneous lesions are one of the top medical concerns in travelers returning from tropical regions. According to previous studies (Caumes et al. 1995; Lederman et al. 2008), dermatological disorders were the third most common cause of health problems associated with returning travelers after systemic febrile illness and acute diarrhea. The majority of these lesions develop before the travelers return home and rarely require hospitalization; however, they often lead to medical evaluation.

Healthy and intact skin provides an effective barrier against invasion by microorganisms. Clinical infection usually results from breaks in the skin, loss of local immunity, and disturbances within the normal flora resident on skin surface. The cutaneous flora is relatively simple compared to the diverse variety of microorganisms that inhabits the oral cavity, digestive tract, and female genital tract. The skin flora is mainly composed of aerobic cocci, anaerobic coryneform bacteria, gram-negative bacteria, and yeasts. A major function of this flora is to prevent skin infections, both by providing ecological competition for pathogenic microorganisms and by hydrolyzing lipids of sebum to produce free fatty acids, which are toxic to many bacteria.

Although many pathogens can cause cutaneous infections, the skin has a limited number of responses to inflammatory or infectious processes. In approaching patients with possible infectious rashes or tropical exposures, there are three important steps to help triage the diagnostic possibilities. First, the patient's travel and exposure history needs to be fully obtained; the exposure history should include animal, vector, environment, social behavior, chemical substance, etc. Second, the rash should be accurately defined based on its gross morphology, location, distribution, and associated symptoms. Third, a complete medical history and physical examination needs to be integrated into other clinical information. The underlying immune status of the patient has important implications regarding the differential diagnosis. Immunosuppressed travelers may acquire emergent pathogens at a higher risk. Some infections acquired in the developing countries may have the potential for reactivation or dissemination years later, especially when the patient becomes immunocompromised. There are several factors commonly present among immunocompromised patients that enhance their risk to have cutaneous infections.

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For example, medical interventions with needle punctures and catheters provide a ready route for microorganisms to go through the stratum corneum and enter the bloodstream. Chemotherapy and irradiation can cause hair loss, dryness, and loss of sweat production that disrupt the barrier of healthy skin with these radical changes. When the balance is lost between host defenses and commensal flora on the skin surface or around the hair follicle, the follicles can become inflamed and form a potential entry point of infection. Therefore, cutaneous infections, especially the emergent and tropical infections, pose a substantial threat to immunocompromised patients.

Bacterial Infections

A wide range of bacteria, including mycobacteria, rickettsiae, and spirochetes, can affect the skin and subcutaneous tissue. They represent the largest proportion of pathogens causing emergent and tropical cutaneous infections. A limited number of histopathologic patterns are seen with bacterial infections in the skin, and none of these reaction patterns are specific for any particular pathogens. Definitive diagnosis of most bacterial diseases depends on specific identification of the pathogenic organisms with appropriate cultures or molecular techniques. Cultures from actual biopsies have a higher yield than cultures from aspirates or superficial swabs. An ideal method to maximize the yield of etiologic diagnosis for deeper skin infections is to send half of the biopsy for culture and the other half for hematoxylin and eosin (H&E) and special stains (Maingi and Helm 1998). The location of the bacteria in the skin biopsy is important to note. Gram-positive cocci and coccobacilli, such as staphylococci and corynebacteria, are usually normal flora within the follicles or on the surface of crusted, eroded, or ulcerated conditions. On the contrary, gram-positive cocci in the dermis or subcutaneous tissue indicate a true significant infectious process such as cellulitis, panniculitis, or fasciitis. Special stains, including Gram stain, acid-fast bacillus (AFB) stain, and Warthin–Starry silver stain, may help highlight certain bacteria, but none of them is specific. Immunohistochemical methods are available for the detection of some pathogens, while molecular technique offers a more sensitive and specific method for a definitive identification of etiologic agent. However, many of these applications are available only in research laboratories or in special facilities (Rapini 1991).

The following section describes some of the emerging or tropical pathogens that can cause significant skin infection.

Anthrax

Etiology and Epidemiology

Anthrax is an acute infection caused by *Bacillus anthracis*, a gram-positive rod that is enzootic in many countries, and human infections are usually associated with animal exposure (Godyn et al. 2004). It occurs occasionally among workers through handling infected hides, wool, or hair in wool-scouring mills and tanneries. However, the organism was used as a biological weapon in 2001 through mails intentionally contaminated with white powder containing spores of *Bacillus anthracis*. Before September 2001, cases of anthrax in the United States have been reported infrequently since the 1970s; the last reported case of inhalational anthrax occurred in 1976, while the last reported case of cutaneous anthrax occurred in the summer of 2001 (Tutrone et al. 2002). During the 2001 incidence, 11 confirmed inhalational anthrax with five deaths and 11 cutaneous anthrax with no fatality were identified from October to November (Jernigan et al. 2002; Shieh et al. 2003).

Clinical Features

The majority of natural human infections occur 1–7 days after primary inoculation of the skin with the bacteria from animals or animal products. Only a small proportion (~5 %) of human cases are inhalation anthrax or gastrointestinal disease from eating infected meat. The skin lesion usually starts as a red macule, sometimes pruritic, and evolves through papular and vesicular stages

into hemorrhagic pustule. The pustule eventually ulcerates, and the lesion will be covered by a thick, black eschar (the name anthrax comes from the Greek word for "coal"). The eschar is usually surrounded by marked erythema and edema, which usually is more extensive on the head or neck than on the trunk or extremities. Characteristically, pain is mild or absent. Patients usually are afebrile, but tender regional lymphadenopathy, fatigue, fever, or chills may develop in some cases. The skin lesions usually heal spontaneously in 1–2 weeks, leaving very little scarring. Death from untreated cutaneous anthrax can be as high as 25 % but is near 0 % with appropriate early treatment. The bacteria grow readily in culture media, but the organisms may not be identified correctly if the laboratory is not alerted to the suspicion of anthrax. Confirmatory cultures, serologic assays, and polymerase chain reaction (PCR) testing are available through the public health network (Dauphin et al. 2012).

Histopathology

Histopathologic features can vary according to the stages of infection and sites of biopsy. Cultures and full-thickness punch biopsies should be taken from the edges of both vesicle and eschar, if present. At the site of the eschar, the epidermis is destroyed, and the ulcerated surface is covered with necrotic tissue. There is marked edema of the dermis with variable lymphocytes and neutrophils (Fig. 14.1). Vasculitis, vascular necrosis, and hemorrhage can be observed (Fig. 14.2).

In acute stage of untreated cases, bacilli with characteristic capsule are present in large numbers and can be recognized in sections stained with tissue Gram stain (Fig. 14.3). The organism is best demonstrated when the lesion is in the vesicular stage, so swab exudates for Gram stain and biopsy should be taken for suspect cases. The organisms are usually more abundant in upper dermis, especially in the necrotic tissue toward the ulcerated surface. However, typical bacilli are rarely seen in skin biopsies obtained from a later stage of cases with antibiotic treatment. In general, the longer the duration of illness and treatment course, the less chance of detecting *B. anthracis* organism by culture and special stains. Steiner's silver-impregnation stain appears to be more sensitive than Gram stain for demonstrating these bacilli in cutaneous lesion obtained at a later stage (Fig. 14.4) (Shieh et al. 2003).

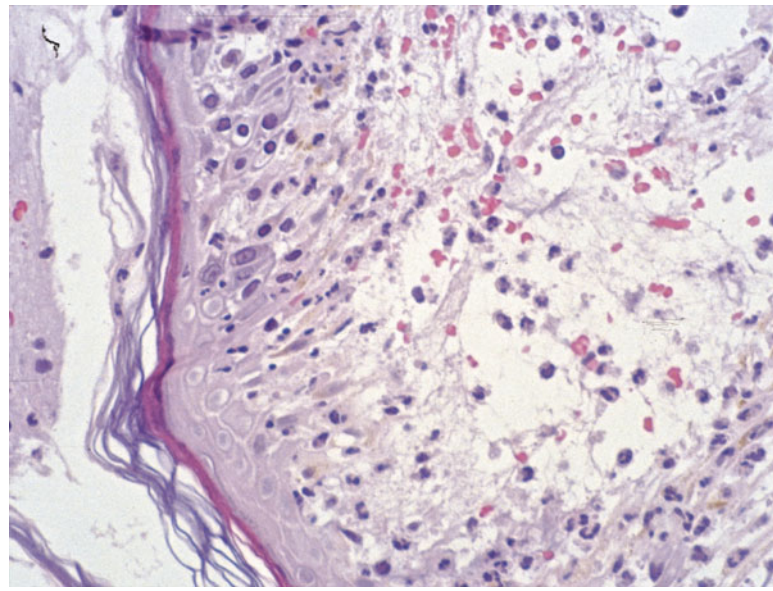

Fig. 14.1 Cutaneous anthrax. Marked edema of the dermis with neutrophils and lymphocytes (H&E, 200× original magnification)

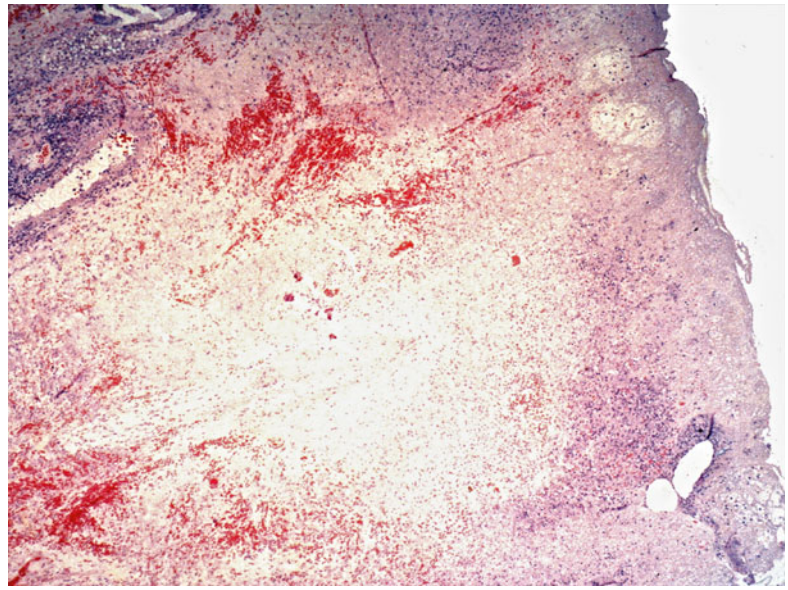

Fig. 14.2 Cutaneous anthrax. Ulceration of epidermis and marked edema, necrosis, and hemorrhage in dermis (H&E, 50× original magnification)

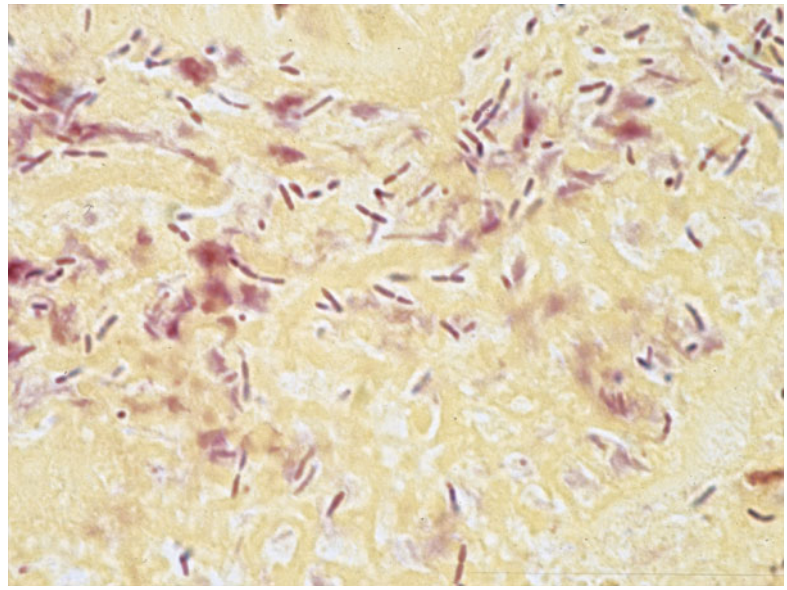

Fig. 14.3 Cutaneous anthrax. Bacilli with characteristic capsule, usually more abundant in upper dermis, especially in the necrotic tissue toward the ulcerated surface (Gram stain, 630× original magnification)

Immunohistochemical assay (IHC) provides a more sensitive and specific way to establish the diagnosis of cutaneous anthrax because of its capability to detect bacterial antigens in tissues regardless of the treatment (Fig. 14.5) (Shieh et al. 2003; Tatti et al. 2006).

Differential Diagnosis

Clinical lesions of anthrax may resemble impetigo, sporotrichosis, orf, arthropod bites, plague, rickettsialpox, scrub typhus, or tularemia. Painful pustules are more typical of impetigo caused by streptococcal or staphylococcal

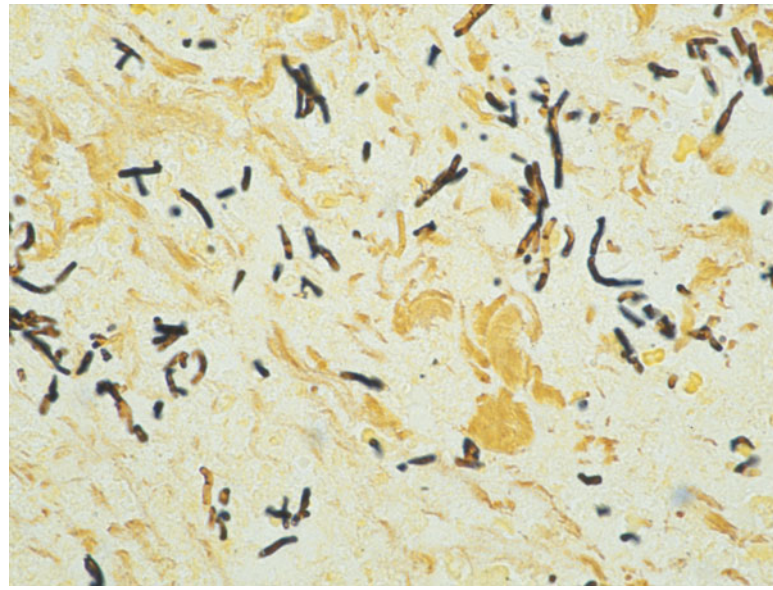

Fig. 14.4 Cutaneous anthrax. Bacilli highlighted by Steiner silver stain (Steiner stain, 630× original magnification)

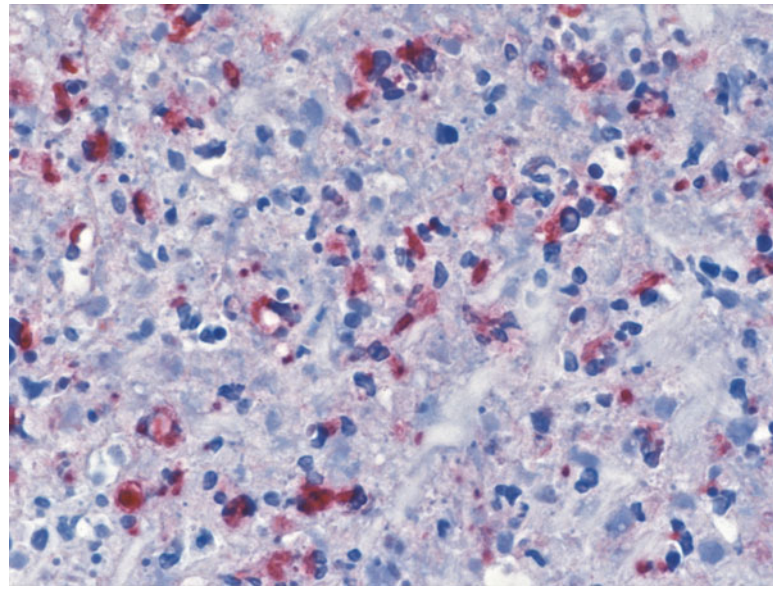

Fig. 14.5 Cutaneous anthrax. Immunostaining of *B. anthracis* antigens in dermis (IHC, 400× original magnification)

infections with prominent neutrophilic infiltrate in epidermis and dermis. Spider and other arthropod bites also are more likely to be painful with prominent eosinophilic infiltrate and vascular necrosis in dermis.

Plague

Etiology and Epidemiology

Plague is caused by *Yersinia pestis*, a small, gram-negative, non-sporing, and nonmotile

bacillus. It is a zoonotic infection that affects a wide variety of rodents, particularly the urban and domestic rats, and the organisms are conveyed from infected rodents to humans by the bites of fleas. Human-to-human transmission rarely occurs in pneumonic plague through inhalation of infectious droplets or other contaminated material. Plague is still endemic in many regions of the world, including India and the Far East, and in Southern and Central Africa. Sporadic outbreaks occur in North Africa and the Middle East, and there are small endemic areas in the United States as well. Occasional cases have been reported elsewhere in travelers from the endemic areas. The potential use of plague as a biological weapon has been of recent interest (Inglesby et al. 2000).

Clinical Features

The incubation period is usually 3 or 4 days, but it may occasionally be longer than 7 days. Following inoculation of the organism by a flea bite, the regional lymph node becomes swollen (the classic presentation of bubonic plague), and systemic dissemination with a severe febrile illness can quickly develop, leading to death within days if untreated. Primary pulmonary infection (pneumonic plague) occurs in some cases, if *Y. pestis* is inhaled, which is almost always fatal within 3 or 4 days. In plague epidemics, mild bubonic infections with no systemic spread and subclinical infections both have been observed. Conversely, a patient may rapidly die of flea-transmitted plague without ever developing a bubo. Clinical cutaneous manifestations of plague are usually nonspecific. Although typically there is no distinct lesion at the site of the initial flea bite, an erythematous plaque may appear, which will become bullous and subsequently crusted like an eschar seen in cutaneous anthrax. Such primary cutaneous lesions may occur in 10 % of patients. The involved regional lymph nodes become painfully swollen several days later. During the bacteremic phase, a macular, erythematous, or petechial rash may develop and sometimes generalized purpuric rash may appear, thus the historic name of "black death." Necrotic lesions that closely resemble ecthyma gangrenosum may develop. Aspiration of a bubo and direct examination of smears and culture confirm the diagnosis. The culture of blood and sputum should also be undertaken if septicemic or pneumonic plague is suspected. Serologic and PCR assays can also confirm the diagnosis.

Histopathology

The histopathologic features of the skin lesions are generally not diagnostic and vary according to the type of lesion associated with their clinical presentation. The purpuric and petechial lesions, especially in those associated with shock, may show vasculitis, vascular necrosis with microthrombi, hemorrhage, and other signs of disseminated intravascular coagulation (Fig. 14.6). The erythematous lesions appear to have a septal panniculitis. The morbilliform rash is associated with a perivascular lymphocytic infiltrate. Giemsa and Gram stain may highlight bacilli with characteristic bipolar staining. Bacilli are usually more abundant in vessels and perivascular areas in biopsy samples obtained at septicemic stage (Fig. 14.7). IHC with a specific anti-*Y. pestis* antibody provides a sensitive method for confirmatory diagnosis because of its capability to detect bacilliform and granular antigens in areas of inflammation and necrotic debris (Fig. 14.8) (Guarner et al. 2002, 2005).

Differential Diagnosis

Plague can mimic many other infectious diseases. Since clinical and histopathologic features of skin lesions are both nonspecific, only definitive serology or cultures allow a confirmed diagnosis of *Y. pestis* infection.

Tularemia

Etiology and Epidemiology

Tularemia is caused by *Francisella tularensis*, a small, gram-negative, pleomorphic coccobacillus. Human infection is usually acquired through direct contact with animal reservoirs harboring the bacteria. The disease can also be transmitted

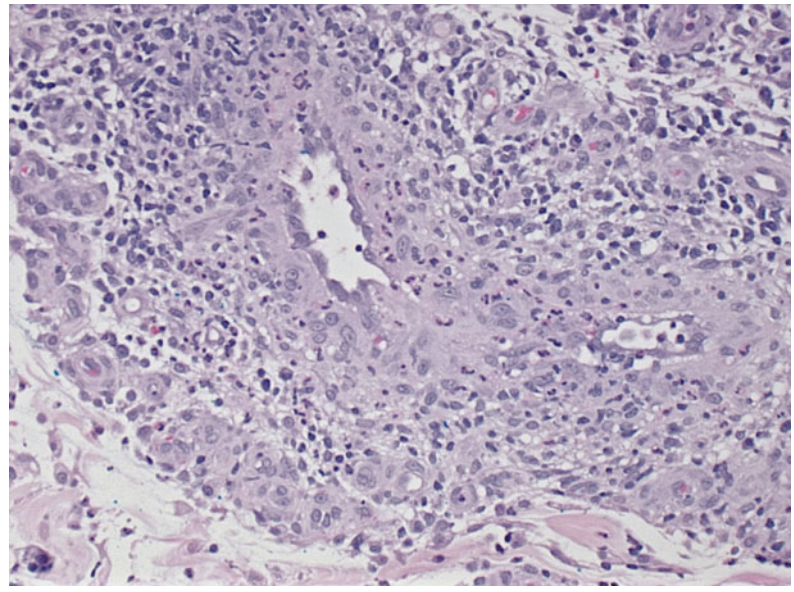

Fig. 14.6 Cutaneous plague. Vasculitis and vascular necrosis with mixed inflammatory infiltrate (H&E, 100× original magnification)

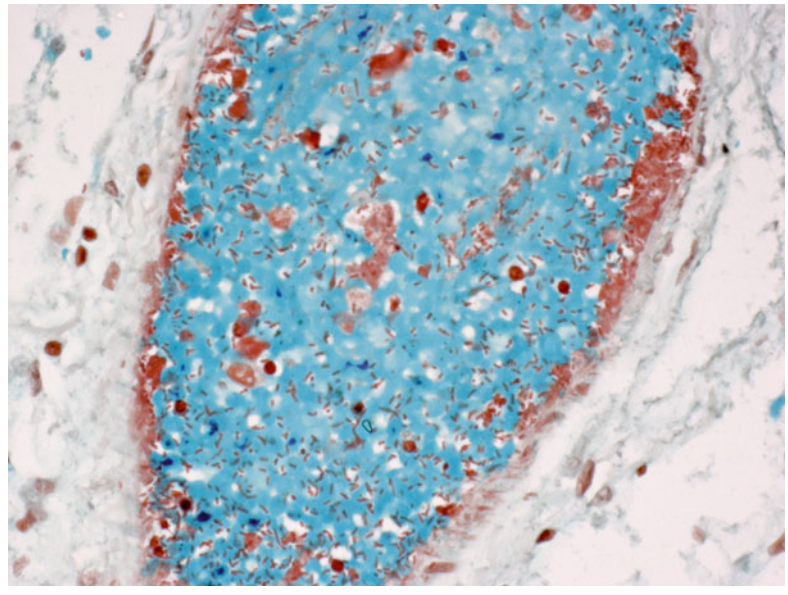

Fig. 14.7 Septicemic plague. Abundant gram-negative bacilli in a dermal vessel (Gram stain, 400× original magnification)

by insects, such as mosquitoes, ticks, deer flies, etc. The disease is endemic in North America and parts of Europe and Asia. The bacterium has several subspecies with varying degrees of virulence. The most important one is *F. tularensis tularensis* (type A), which is found in lagomorphs, such as rabbits and other similar animals in North America, and it is highly pathogenic in humans

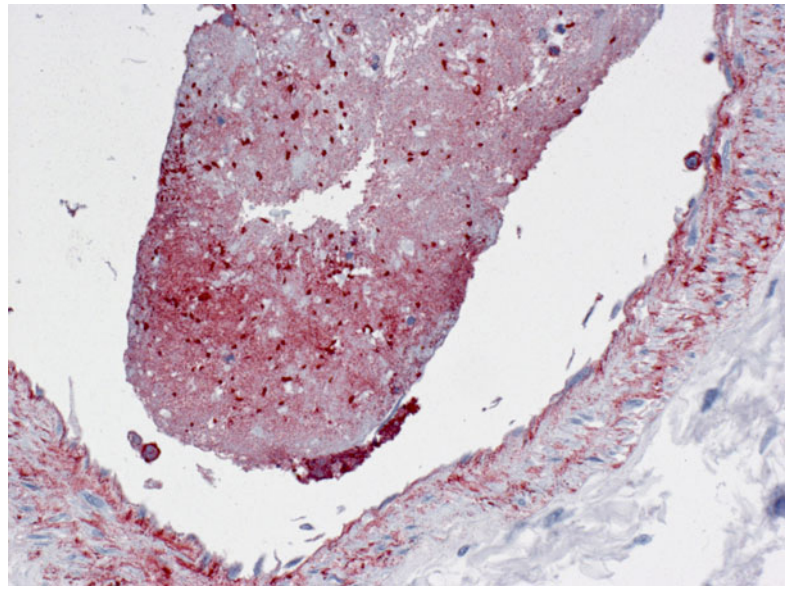

Fig. 14.8 Septicemic plague. Immunostaining of *Y. pestis* antigens in a large vascular thrombus (IHC, 400× original magnification)

and domestic rabbits. *F. tularensis palaearctica* (type B) occurs mainly in aquatic rodents, such as beavers and muskrats in North America, and in hares and small rodents in northern Eurasia. It is less virulent for humans and rabbits (Eliasson et al. 2006).

Clinical Features

The disease can occur as sporadic cases or small epidemics. The usual incubation period is 3–5 days. The characteristic clinical presentation of this disease is the so-called ulceroglandular tularemia, which represents about 80 % of cases (Syrjala et al. 1984). Usually, the finger or hand is the primary site of the inoculation, where a rapidly growing papulonodular lesion develops followed by painful ulceration and necrosis. Tender subcutaneous nodes may form along the lymph vessels that drain the primary lesion. There is considerable swelling of the regional lymph nodes with marked constitutional symptoms. A black eschar appears within 3–5 days after contact. Complete healing of the lesion may take place in 2–5 weeks. Other important forms of tularemia include oculoglandular, oropharyngeal, gastrointestinal, pulmonary, and typhoidal. Mortality of pneumonic tularemia ranges from 30 % to 60 % if untreated. Culture of the organism can confirm the diagnosis but laboratory biosafety is a concern, while serologic diagnosis is safer and more effective. PCR testing also provides a sensitive and rapid method for confirmatory diagnosis (Splettstoesser et al. 2005).

Histopathology

Skin biopsies typically show ulceration, extravasated erythrocytes, and necrosis surrounded by palisading neutrophils. Suppurative granuloma formation eventually develops with central necrosis and nuclear debris (Fig. 14.9). Some of them may appear with caseous necrosis similar to mycobacterial infections. In some cases, only a moderate number of epithelioid cells and a few giant cells are observed. The tender nodes that may be found along lymph vessels show multiple necrotizing granulomas deep in the dermis and extending into the subcutaneous tissue (Fig. 14.10). Organisms are rarely demonstrated with the Gram stain. Steiner or Warthin–Starry silver-impregnation stain may be more sensitive in demonstrating the organisms. IHC with a specific anti-*F. tularensis* antibody provides a sensitive method for confirmatory diagnosis because of its capability to detect bacterial antigens in skin and lymph node biopsies (Fig. 14.11) (Lamps et al. 2004; Asano et al. 2012).

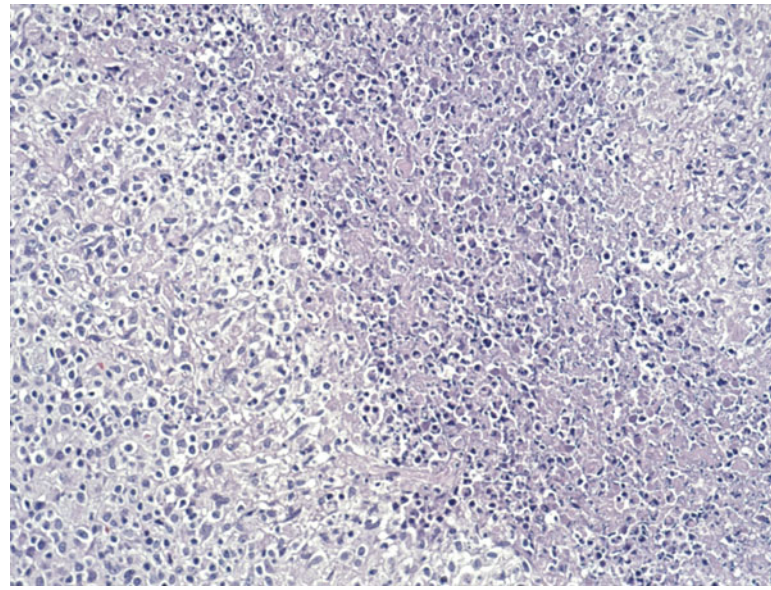

Fig. 14.9 Ulceroglandular tularemia. Suppurative granulomatous inflammation with necrosis and nuclear debris (H&E, 100× original magnification)

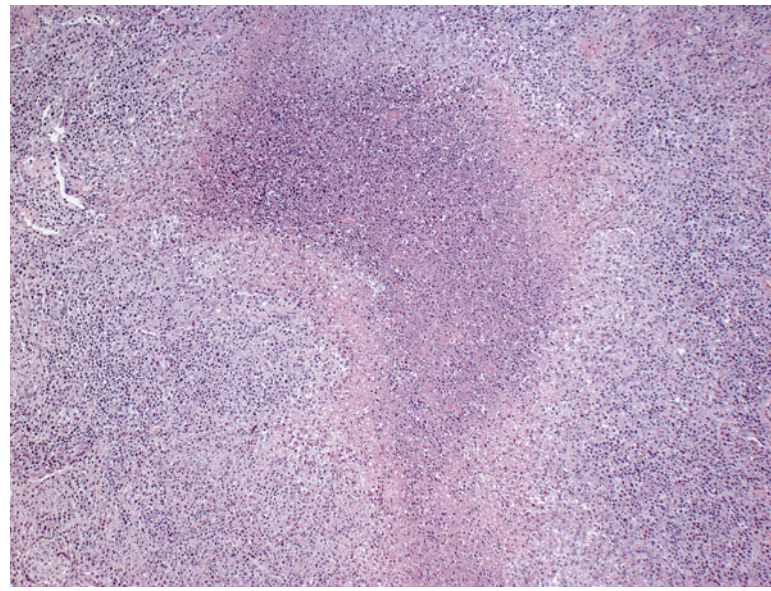

Fig. 14.10 Subcutaneous lymphadenitis of tularemia. Necrotizing granuloma in dermis extending into the subcutaneous tissue (H&E, 50× original magnification)

Differential Diagnosis

A good clinical history and physical findings usually can point toward the diagnosis. Clinical lesions of cutaneous tularemia, especially with eschar formation, may resemble impetigo, anthrax, sporotrichosis, orf, arthropod bites, plague, rickettsialpox, and scrub typhus. Histologically, mycobacterial infections, cat-scratch disease, leishmaniasis, sporotrichosis, and other fungal infections should be considered when prominent granulomatous inflammation is observed.

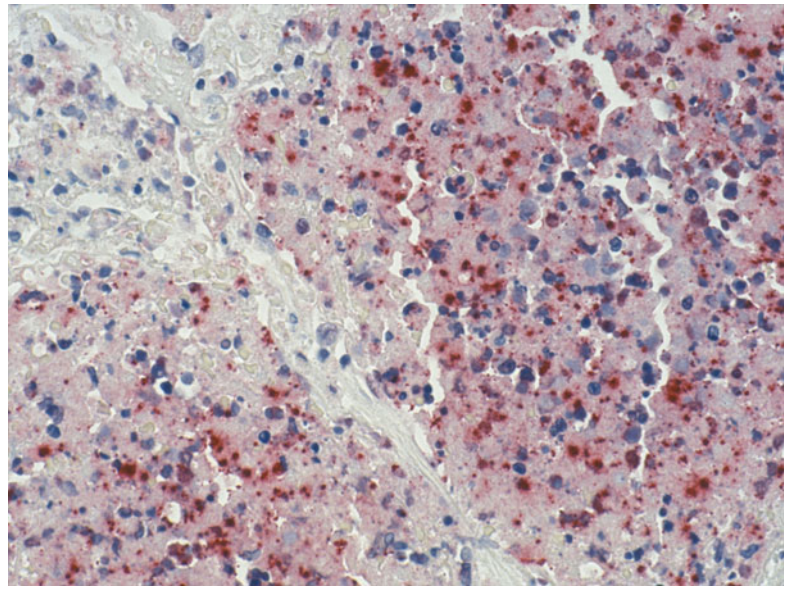

Fig. 14.11 Ulceroglandular tularemia. Immunostaining of *F. tularensis* antigens in areas of necrosis (IHC, 400× original magnification)

Cat-Scratch Disease

Etiology and Epidemiology

Cat-scratch disease is caused by *Bartonella henselae*, a gram-negative bacillus similar to that of bacillary angiomatosis. It is closely related to *Bartonella quintana*, the etiologic agent of louse-borne trench fever. The cat was recognized as the natural reservoir of the disease in 1950. The causative organism was first thought to be *Afipia felis*, but this was disproved by immunological studies demonstrating that cat-scratch fever patients developed antibodies to other organisms, especially *B. henselae* (Bergmans et al. 1995). Kittens are more likely to carry the bacteria in their blood and may therefore be more likely to transmit the disease than adult cats. From many studies, it is believed that a likely pathway of transmission of *B. henselae* from cats to humans may be inoculation with flea feces containing bacteria through a contaminated cat-scratch wound or across a mucosal surface (Murakawa 1997).

Clinical Features

The organism is carried in the blood and oral cavities of cats. The skin lesion develops 2–4 days after a scratch or bite from a cat; it may resemble an insect bite but does not itch. The lesion may appear as macular, papular, or nodular lesions, usually on the forearm or hand. A single or a group of large, tender swelling lymph nodes develops in the drainage area of the scratch 2–3 weeks later. The scratch skin lesion heals in a normal fashion, but the affected lymph nodes may become fluctuant as a result of suppuration (Chian et al. 2002; Pierard-Franchimont et al. 2010). Most cases are mild and resolve spontaneously, but lymphadenopathy may persist for several months after other symptoms disappear. The average duration of lymphadenopathy is 2 months. About one-third of patients develop fever or constitutional symptoms. In immunocompromised patients more severe complications sometimes occur. Other clinical forms of *B. henselae* infections include bacillary angiomatosis, bacillary peliosis, optic neuritis, and acute encephalopathy. Bacillary angiomatosis is primarily a vascular skin lesion more commonly associated with HIV or severe immunocompromised patients. The infection may extend to bone or other areas of the body. The diagnosis may be established by the cat-scratch skin test (Hanger-Rose test).

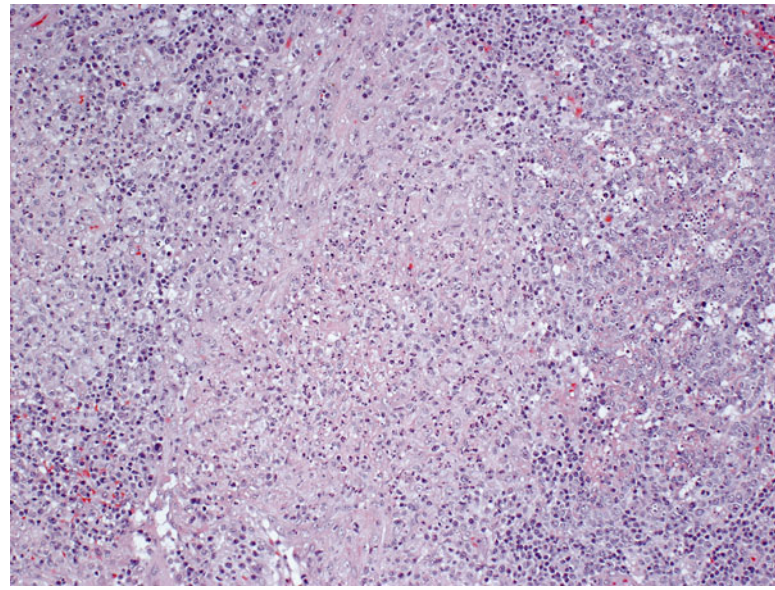

Fig. 14.12 Cat-scratch disease. Variable shapes of necrosis in the dermis (H&E, 100× original magnification)

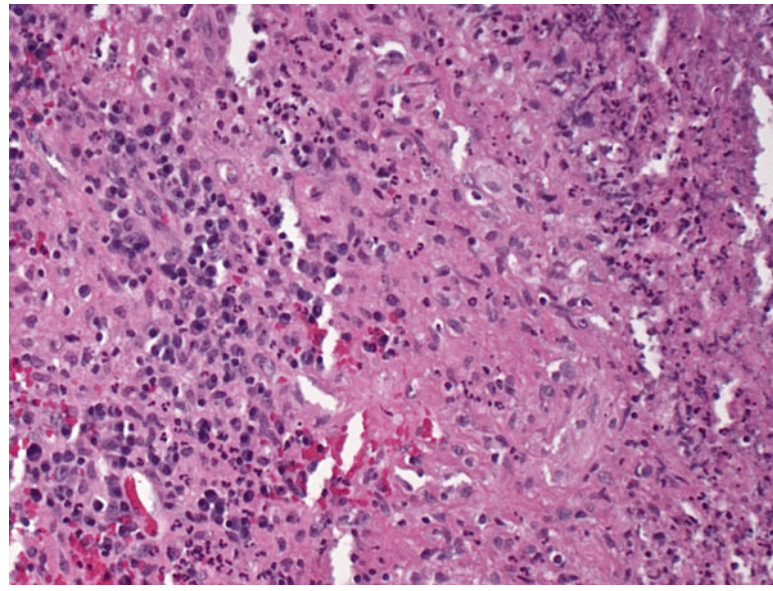

Fig. 14.13 Cat-scratch disease. Lymphohistiocytic and epithelioid cells surrounding the dermal necrosis with palisading arrangement (H&E, 400× original magnification)

The skin test is reliable when performed 1 week after infection; however, it is not readily available and is not standardized. The organism is extremely difficult to culture. Serologic and PCR assays have been used to confirm the diagnosis (Maass et al. 1992; Hansmann et al. 2005).

Histopathology

Biopsies of the primary papular lesion at the site of the scratch show palisading granulomas around necrobiotic foci. Basically, one or several areas of necrosis in the dermis with variable shapes, including round, triangular, or stellate are seen (Fig. 14.12). There are usually several layers of lymphohistiocytic and epithelioid cells surrounding the necrosis, with the innermost layer exhibiting a palisading arrangement (Fig. 14.13). The periphery of the epithelioid cell reaction is surrounded by a zone of lymphocytes, plasma cells, and eosinophils. Scattered multinucleated

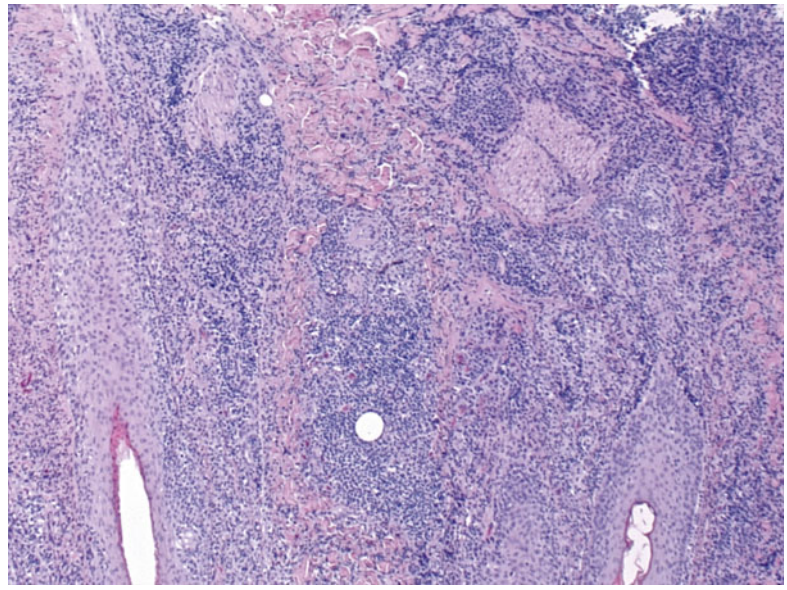

Fig. 14.14 Cat-scratch disease. Lichenoid lymphoplasmacytic infiltrate in dermis (H&E, 50× original magnification)

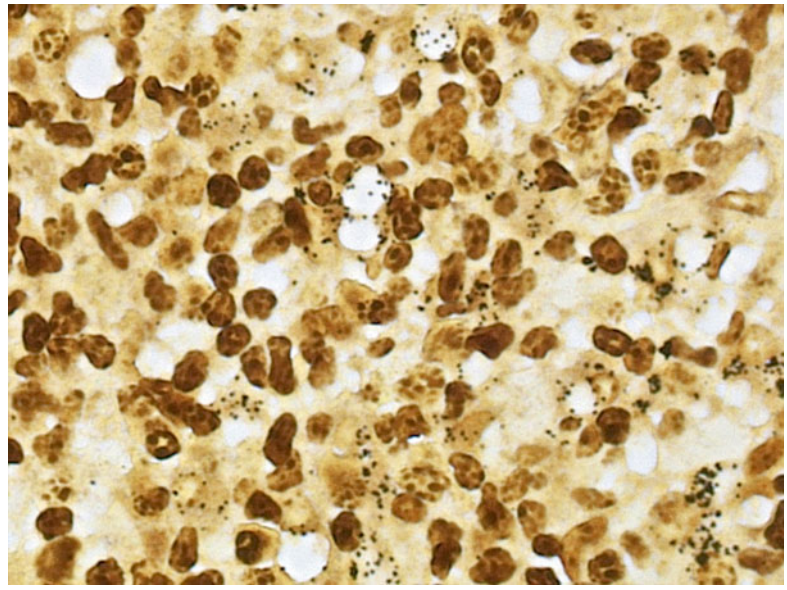

Fig. 14.15 Cat-scratch disease. Small, pleomorphic coccobacilli highlighted by Warthin–Starry silver stain at the periphery of necrosis (Warthin–Starry stain, 400× original magnification)

giant cells may be present. Other microscopic features, such as perivascular or lichenoid lymphoplasmacytic or neutrophilic infiltrates, can also present (Fig. 14.14) (Czarnetzki et al. 1975).

The reaction in the lymph nodes is similar to that observed in the skin, except microabscess formation in the central necrotic areas of the epithelioid granulomas is more commonly present due to the accumulation of numerous neutrophils. As the abscesses enlarge, they become confluent. Warthin–Starry silver-impregnation stain may occasionally demonstrate the small, pleomorphic, gram-negative bacilli at the periphery of central necrosis in involved skin and lymph nodes (Fig. 14.15). IHC is an excellent method to demonstrate the coccobacilli and bacterial antigens in

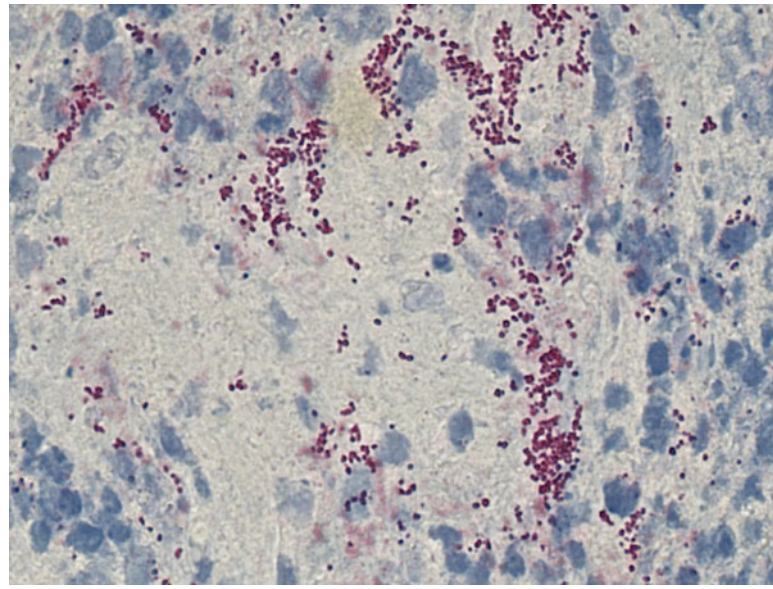

Fig. 14.16 Cat-scratch disease. Immunostaining of *B. henselae* antigens in areas of inflammation and necrosis (IHC, 400× original magnification)

tissues (Fig. 14.16). PCR can be performed on paraffin-embedded skin biopsies to confirm the diagnosis (Maass et al. 1992; Scott et al. 1996).

Differential Diagnosis

The palisading granulomas in the skin lesions of patients with cat-scratch disease need to be differentiated with granulomatous inflammation caused by other infectious agents, such as mycobacteria, fungi, *Leishmania* spp., *F. tularensis*, etc. However, a careful history and the clinical presentations usually allow distinction of cat-scratch disease from other infectious diseases.

Rickettsial and Rickettsia-Like Infections

Rickettsiae are obligate intracellular parasites that are transmitted to humans from infected arthropods. *Rickettsia* species infect and damage endothelial cells, leading to cutaneous and systemic lymphohistiocytic vasculitis, the hallmark and major pathogenetic lesion of vasculotropic rickettsioses. New species and new strains of existing species are being characterized, and there is also reemergence of older organisms. The *Rickettsia* organisms are divided into the spotted fever group and the typhus group. Other rickettsia-like organisms include *Orientia tsutsugamushi* (scrub typhus), *Coxiella burnetii* (Q fever), *Ehrlichia chaffeensis* (ehrlichiosis), and *Anaplasma phagocytophilum* (human granulocytic anaplasmosis). Skin lesions are more commonly seen in infections associated with spotted fever group rickettsiae and *Orientia tsutsugamushi*.

Spotted Fever Group Rickettsioses

Etiology and Epidemiology

There are many diseases caused by spotted fever group rickettsiae depending on the vectors and geographic areas. The more common ones include the following: (1) Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*, (2) Mediterranean spotted fever or boutonneuse fever caused by *R. conorii*, (3) African tick-bite fever caused by *R. africae*, (4) maculatum disease caused by *R. parkeri*, and (5) rickettsialpox caused by *R. akari*. The rickettsial disease of greatest importance in the United States is RMSF (Walker 1995; Chapman et al. 2006b), which is acquired after the bite of infected Dermacentor subspecies ticks. The disease is encountered most commonly in the southeast of the United States

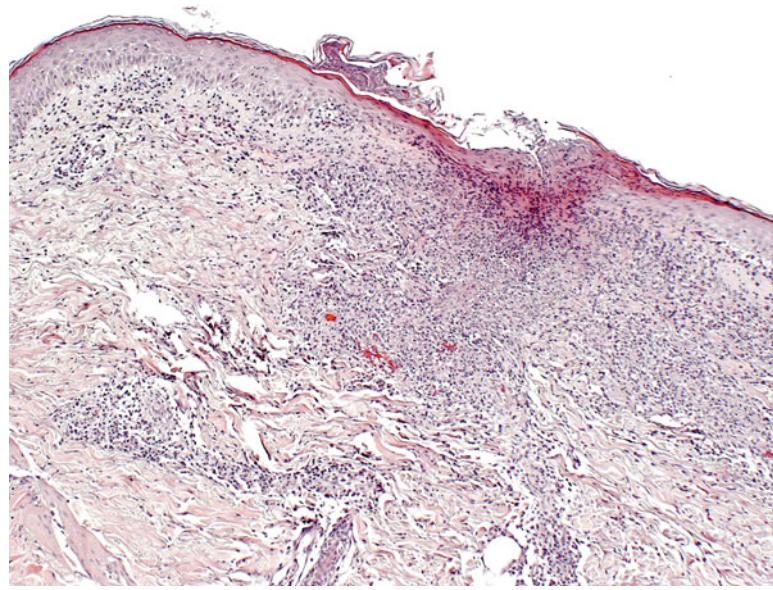

Fig. 14.17 Spotted fever group rickettsioses. Mild to moderate lymphohistiocytic perivascular infiltrate in dermis; acantholysis and focal necrosis in epidermis (H&E, 50× original magnification)

and has been reported even within New York City. Mediterranean spotted fever is widespread in Mediterranean basin, Africa, and Asia (Cascio and Iaria 2006). African tick-bite fever occurs mainly in sub-Saharan Africa and the Caribbean (Althaus et al. 2010). Maculatum disease occurs in North and South America (Paddock et al. 2008). Rickettsialpox is unique because the bacteria is transmitted to humans from a bite by infected mite, not tick. It has been reported from the United States, Ukraine, Croatia, Turkey, and Mexico (Koss et al. 2003).

Clinical Features

The vasculotropic rickettsioses share many similar clinical features. In RMSF, after an incubation period of 1–2 weeks after the tick bite, a short period of malaise and headache is followed by high fever and chills (Walker 1995; Sexton and Kaye 2002). After 3 or 4 days, a maculopapular eruption appears on the wrists and ankles and soon spreads centrally to limbs, trunk, and face. The palms and soles are usually involved. The lesions at first are macular to papular but become purpuric within 2–3 days. The degree of cutaneous involvement is highly variable and sometimes transient; approximately 10–15 % of infected patients do not develop a prominent rash (Sexton and Corey 1992). There may be only petechiae, but in fatal cases widespread ecchymoses are common. Acral gangrene may result from small vessel occlusion. Because the diagnosis may not be made in the beginning and the course may be rapid, mortality exceeds 10 %, despite the effectiveness of antibiotics. Whenever a diagnosis of RMSF is suspected, a search should be made for an eschar indicating the site of a tick bite. Eschar is usually more prominent in Mediterranean spotted fever, African tick-bite fever, and rickettsialpox. Although serologic assay has been used for clinical diagnosis, the titer may not rise in the acute phase up to 10 days. PCR testing is a more sensitive and rapid method to confirm the diagnosis (Dumler and Walker 1994; Chapman et al. 2006a).

Histopathology

The histopathologic features are similar among the vasculotropic rickettsioses. Significant findings are confined mostly within the dermis. The early changes include a mild to moderate mixed lymphohistiocytic infiltrate that surrounds and penetrates into the walls of the dermal vessels (Fig. 14.17). Erythrocyte extravasation (Fig. 14.18) endothelial swelling (Fig. 14.19), and edema are commonly seen. Later (usually after 1 week),

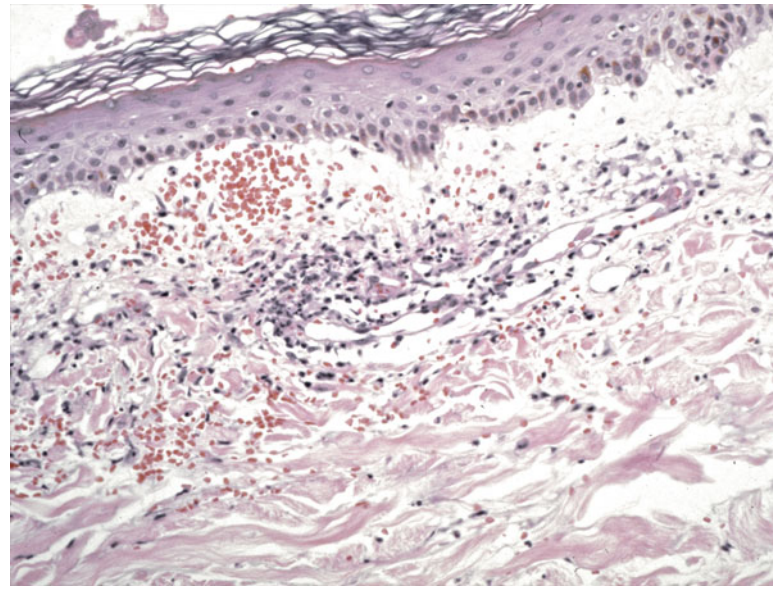

Fig. 14.18 Spotted fever group rickettsioses. Erythrocyte extravasation, edema, and vasculitis in dermis (H&E, 100× original magnification)

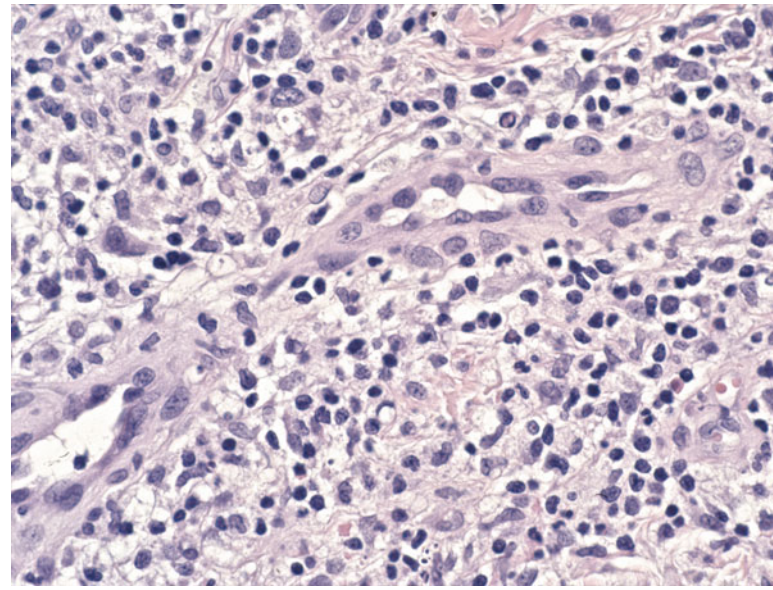

Fig. 14.19 Spotted fever group rickettsioses. Endothelial swelling and lymphohistiocytic perivascular infiltrate in dermis (H&E, 400× original magnification)

vascular damage with leukocytoclastic vasculitis frequently occurs; the infiltrate is predominantly lymphohistiocytic with occasional neutrophilic infiltrate and karyorrhectic nuclear debris. These later lesions are often associated clinically with nonblanching petechiae or hemorrhagic, purpuric rashes. Some of these lesions contain microthrombi and vessel wall necrosis (Fig. 14.20). In the advanced stage there is dermal and epidermal necrosis (Fig. 14.21) (Walker et al. 1987; Kao et al. 1997). The causative organism, which usually measures 0.3 by 1 μm, is too small to be visible by light microscopy using regular stains. IHC can readily demonstrate rickettsial antigen in

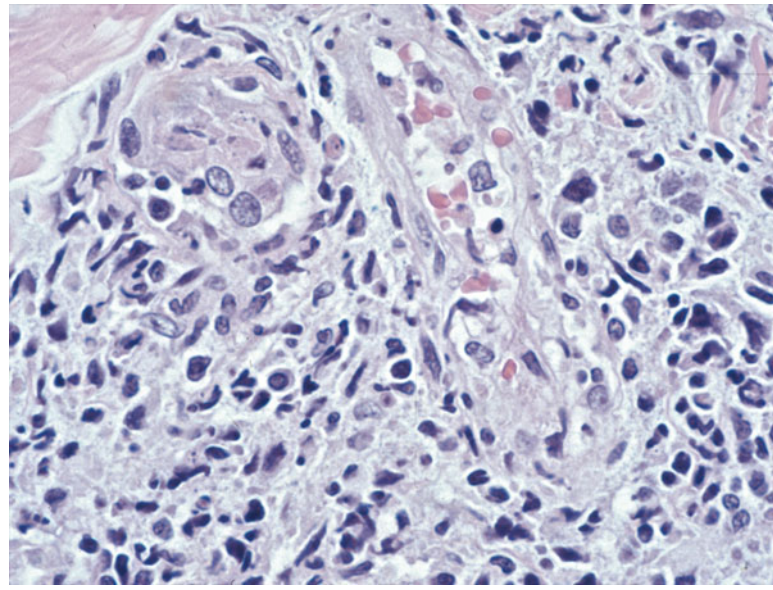

Fig. 14.20 Spotted fever group rickettsioses. Microthrombi and vessel wall necrosis (H&E, 400× original magnification)

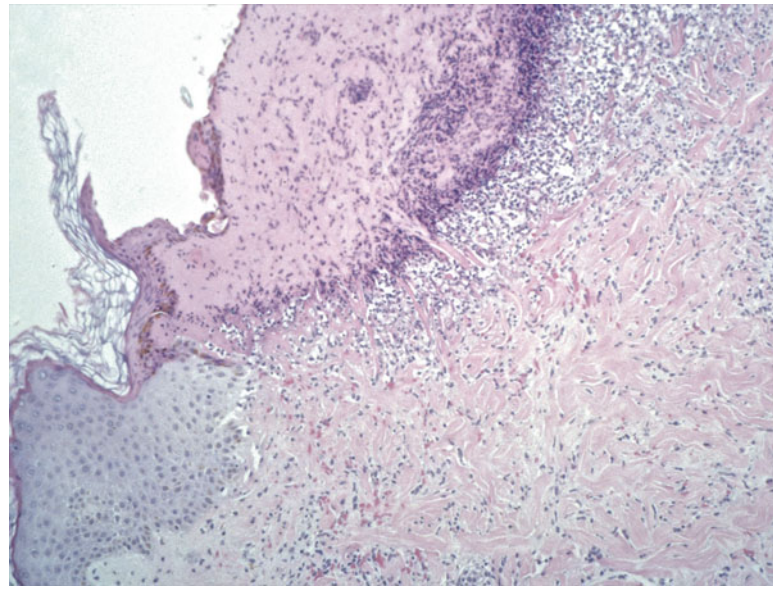

Fig. 14.21 Spotted fever group rickettsioses. Eschar formation with extensive epidermal and dermal necrosis (H&E, 50× original magnification)

endothelial cells in association with perivascular lymphocytic infiltration (Fig. 14.22) (Dumler et al. 1990; Paddock et al. 1999).

Differential Diagnosis

The histologic differential diagnosis includes diseases associated with vascular or capillary inflammation, such as insect bite reaction, drug reaction, septic vasculitis secondary to disseminated intravascular coagulation (DIC), collagen vascular diseases, and many other autoimmune disorders with vasculitis. Many of the lesions can be differentiated by other laboratory or histologic methods, including culture or special stains for specific infectious agents.

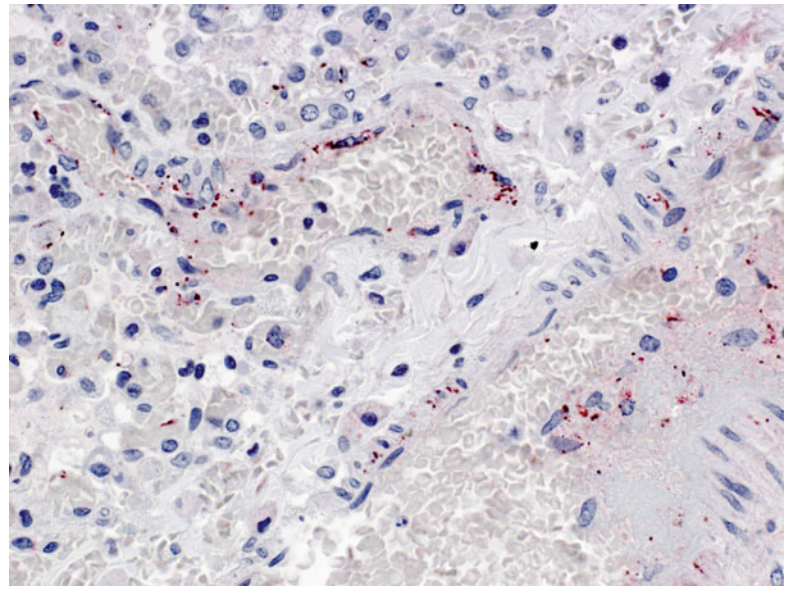

Fig. 14.22 Spotted fever group rickettsioses. Immunostaining of rickettsial antigens in endothelial cells of dermal vessels (IHC, 400× original magnification)

Scrub Typhus

Etiology and Epidemiology

Scrub typhus is caused by *Orientia (formerly Rickettsia) tsutsugamushi* and transmitted from its natural rodent reservoir by the bites of the mites, *Trombicula akamushi* and *T. deliensis*. It is a common disease in endemic areas of Southeast Asia and western Pacific islands. During the Vietnam War, it was the second or third most common cause of fever in American soldiers (Seong et al. 2001).

Clinical Features

Scrub typhus usually presents as an acute febrile illness after an incubation period of about 10 days (6–21 days). Fever, headache, and conjunctivitis accompany the development of the primary skin lesion. The primary eschar lesion is a firm papule surmounted by a vesicle, which dries to form a black crust. The regional lymph nodes are enlarged and tender. A generalized macular or maculopapular eruption develops after about a week and may fade rapidly or persist for 7–10 days. More severe clinical manifestations, such as pneumonitis and myocarditis, can occur and the mortality in cases without treatment can reach 60 % (Lee et al. 2013). In mild or treated cases, the fever subsides and recovery occurs during the second or third week. Serologic and PCR assays have been used for confirmatory diagnosis.

Histopathology

Eschar lesion exhibits ulceration with prominent coagulative necrosis of the epidermis and underlying dermis (Fig. 14.23). A lymphocytic vasculitis of small vessels with microthrombi and vascular necrosis is typically present in the dermis (Fig. 14.24). Various degrees of perivascular infiltrate with lymphocytes and occasional neutrophils are seen. IHC assay can demonstrate the organisms in endothelial cells and macrophages (Allen and Spitz 1945; Park and Hart 1946).

If immunohistochemistry for lymphoma is performed, CD30 positive immunoblasts may be seen raising concern for a CD30 + skin lymphomas (Lee et al. 2009).

Differential Diagnosis

Eschar lesions of scrub typhus may resemble impetigo, anthrax, sporotrichosis, orf, arthropod bites, plague, rickettsialpox, or tularemia. Travel history to endemic areas should raise the index of suspicion.

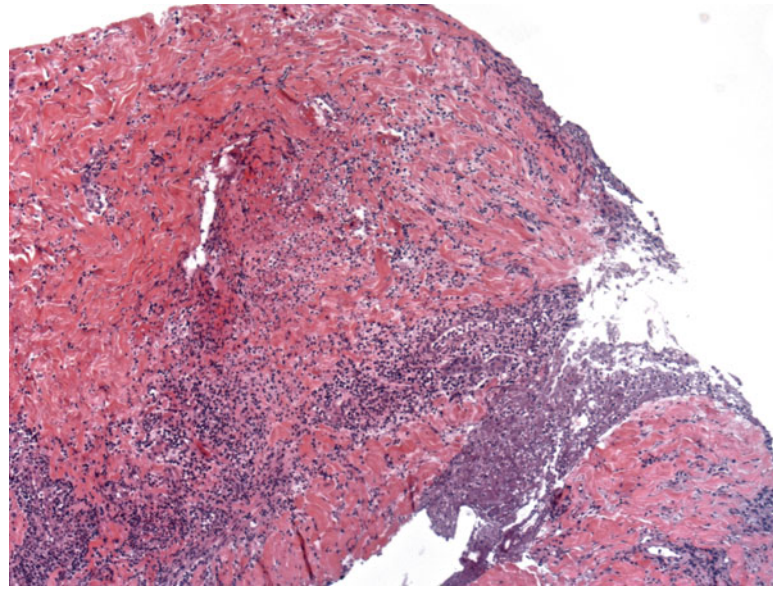

Fig. 14.23 Scrub typhus. Eschar lesion with ulceration and prominent coagulative necrosis in epidermis and underlying dermis (H&E, 50× original magnification)

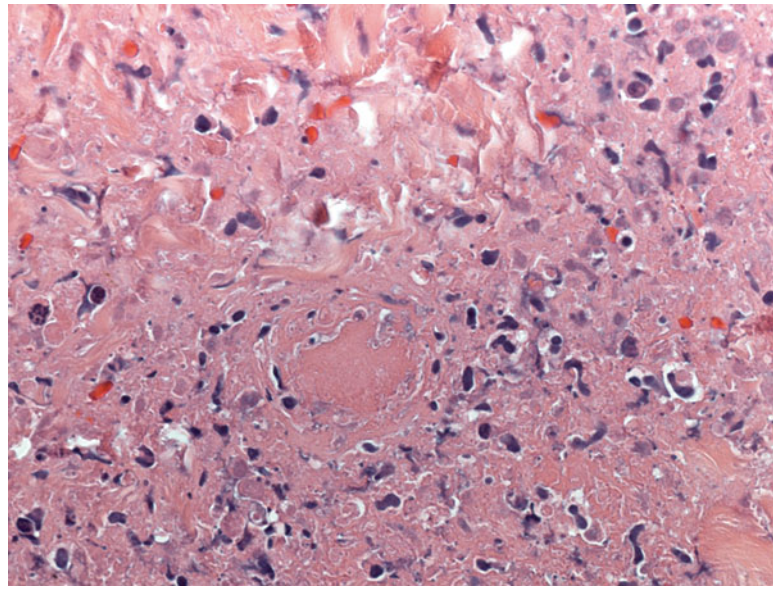

Fig. 14.24 Scrub typhus. Vasculitis of small vessels with microthrombi and vascular necrosis in dermis (H&E, 400× original magnification)

Mycobacterial Infections

The mycobacteria can be divided into two major groups based on their culture growth and biochemical characteristics. The slow growers include *Mycobacterium tuberculosis*, *M. avium complex*, *M. kansasii*, *M. marinum*, and *M. ulcerans*. The rapid growers include *M. fortuitum* and *M. chelonei. M. leprae is* not included in this classification because it cannot be grown in culture. *M. tuberculosis* and *M. leprae* are intracellular parasites usually confined to the tissues of

humans and animals; therefore they are mainly transmitted by exposure to infected hosts. Other mycobacteria are present in soil and water, and the exposure of persons to these bacteria is widespread but usually is not associated with significant clinical disease. Because of the large number of mycobacterial species and wide spectrum of associated illness, only the following are described in this chapter: (1) cutaneous tuberculosis caused by *M. tuberculosis complex*, including BCG; (2) atypical mycobacteria, such as *M. avium complex*, *M. kansasii complex*, *M. Marinum*, *M. ulcerans*, and *M. haemophilum*; and (3) leprosy caused by *M. leprae*.

Cutaneous Tuberculosis

Etiology and Epidemiology

Mycobacterium tuberculosis primarily affects the lungs, but skin and many other organs may also be involved. The incidence of tuberculosis (TB) was decreasing in North America and Europe until the advent of AIDS. It has been estimated that almost 50 % of the earth's population is infected with *M. tuberculosis*, and the infection is responsible for 6 % of all deaths worldwide. The strains with antibiotics resistance have been a growing concern. Majority of individuals who are infected recover completely from their primary TB in the lung, with no further evidence of active disease. However, immunosuppression or any deterioration in health status may allow the bacteria proliferate from their quiescent status within macrophages to cause clinical disease.

In some parts of the world, immunity results from vaccination with bacille Calmette-Guérin (BCG). Skin testing with tuberculin purified-protein derivative is commonly used in patients who have not been vaccinated with BCG as a reliable means of confirming previous mycobacterial infection. Cultures and acid-fast stains of biopsies, sputum, or other fluids are required to make a diagnosis of active disease. When these results are negative, PCR testing may be helpful (Penneys et al. 1993; Degitz 1996).

Clinical Features

Cutaneous TB almost always means long-standing active disease elsewhere, with the rare exception of primary inoculation TB. There are many different types of cutaneous tuberculosis; their clinical features are summarized in Table 14.1 (Beyt et al. 1981; Kakakhel and Fritsch 1989; Sehgal et al. 1989; Inwald et al. 1994; Chong and Lo 1995; Farina et al. 1995; Kothavade et al. 2013).

Histopathology

TB typically causes caseating granulomas, but granulomas do not caseate in some forms, and suppuration or purulence may be more prominent, depending on the stage of lesion and patient's immune status. There are common histopathologic features as well as different patterns among various clinical forms; the features are summarized in Table 14.1 (Figs. 14.25, 14.26, 14.27, 14.28, 14.29, and 14.30) (Kakakhel and Fritsch 1989; Inwald et al. 1994; Jordaan et al. 1994; Farina et al. 1995; Mahaisavariya et al. 2004; Min et al. 2012).

Differential Diagnosis

The differential diagnosis includes other granulomatous conditions, such as atypical mycobacteriosis, leprosy, deep fungal infections, Treponema infections, cat-scratch disease, granuloma inguinale, lymphogranuloma venereum, tularemia, brucellosis, leishmaniasis, and other noninfectious granulomas.

Atypical Mycobacteriosis

Etiology and Epidemiology

There are many different Mycobacterium species that may infect humans besides *M. tuberculosis* and *M. leprae*. Common organisms include *M. marinum* ("swimming pool granuloma") (Bonamonte et al. 2013), *M. ulcerans* (Buruli ulcer in Central Africa), *M. avium-intracellulare* (MAI, especially with AIDS) (Cole and Gebhard 1979), and *M. fortuitum* and *M. chelonei* (rapid growers) (Kothavade et al. 2013). Unlike *M. tuberculosis*, which is transmitted from person to person, nontuberculosis mycobacteria are abundant in nature, in soil and water, and contact is frequent in most zones of the world. These skin infections may be acquired by direct inoculation into the skin or by hematogenous spread from

Table 14.1 Clinical and histopathologic features of various cutaneous tuberculosis

Disease	Clinical features	Histopathologic features
Primary inoculation	Rare crusted ulcer with regional adenopathy following infection of the skin by laboratory accidents, trauma, performance of autopsies, or tattooing	Variable epidermal ulceration. Diffuse mixed infiltrate with many neutrophils in early phase. Variable granulomatous components with epithelioid cells and multinucleated giant cells. Caseation more prominent in later stage. Acid-fast bacilli often present, particularly in areas of necrosis
Miliary	Rare papulopustular eruption as a result of widespread hematogenous dissemination owing to poor immunity or steroid treatment	Similar as the above. In severe form, microabscess at center of the papule with abundant neutrophils, cellular debris, and numerous acid-fast bacilli. In mild form, acid-fast bacilli less appreciable
TB cutis orificialis	Mucosal ulcers in patients with poor immunity	Similar as primary inoculation
Scrofuloderma	Nodular swelling or ulceration resulting from direct extension of underlying bone or lymph node TB	Similar as primary inoculation. Central abscess formation or ulceration more prominent
TB verrucosa cutis	Solitary purulent verrucous plaque seen in patients with high immunity	Hyperkeratosis, papillomatosis, acanthosis. Sometimes neutrophilic microabscesses in the epidermis. Diffuse mixed infiltrate in the dermis with prominent neutrophils. Tuberculoid granulomas, sometimes with caseation. Acid-fast bacilli may or may not present
Lupus vulgaris	Reddish brown apple jelly patches or plaques, usually on the head or neck, resulting from reactivation in a patient with good immunity	Secondary changes in the epidermis common, such as epidermal atrophy, hyperplasia, or ulceration. Tuberculoid granulomas in the superficial dermis with minimal or no caseation. Abundant Langhans-type giant cells. Acid-fast bacilli usually absent
Tuberculids (hypersensitivity reactions to active TB elsewhere)	Papulonecrotic tuberculid: multiple erythematous or crusted papules, usually on the limbs in a symmetrical distribution	Papulonecrotic tuberculid: lymphocytic or neutrophilic vasculitis. Fibrinoid necrosis of vessels with microthrombi frequently observed. Wedge of dermal necrosis. Acid-fast bacilli negative
	Lichen scrofulosorum: lichenoid papules, sometimes follicular or annular, mostly on the trunk	Lichen scrofulosorum: superficial dermal granulomas with or without caseation. Often around follicles or sweat ducts. Acid-fast bacilli negative

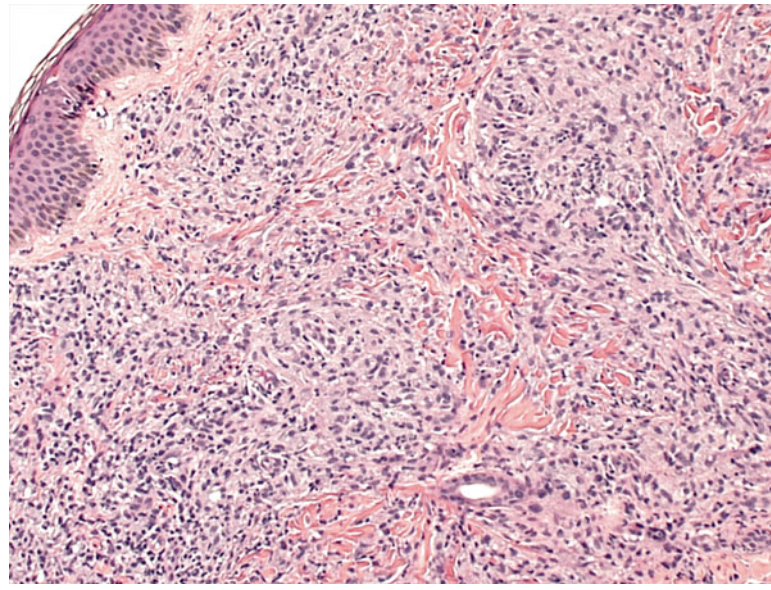

Fig. 14.25 Cutaneous tuberculosis. Diffuse mixed inflammatory infiltrate in dermis with variable epithelioid cells and multinucleated giant cells (H&E, 200× original magnification)

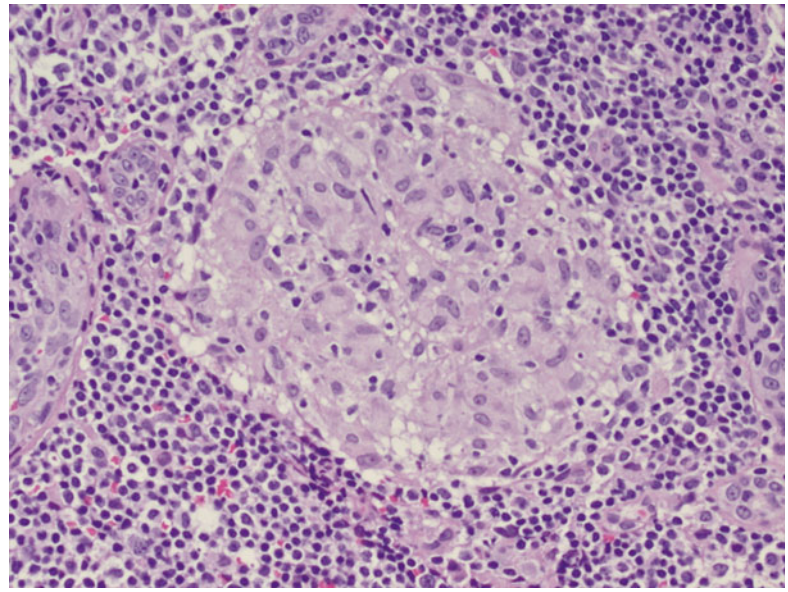

Fig. 14.26 Cutaneous tuberculosis. Noncaseating granuloma with epithelioid cells and lymphohistiocytic infiltrate (H&E, 400× original magnification)

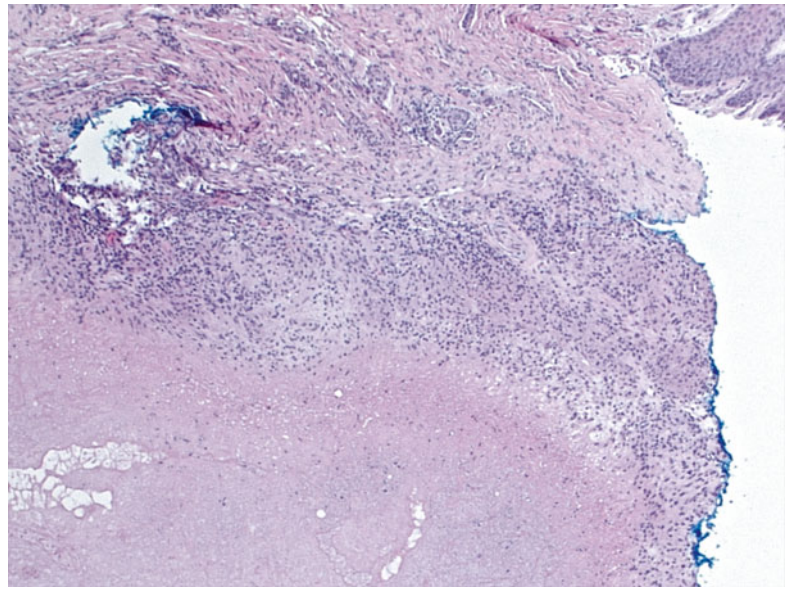

Fig. 14.27 Scrofuloderma. Prominent epidermal ulceration, abscess formation, and caseating necrosis in dermis (H&E, 50× original magnification)

other visceral foci (Dodiuk-Gad et al. 2007). Increased use of immunosuppression in medicine such as those for organ transplant and cancer chemotherapy and the pandemic of HIV/AIDS have resulted in many more mycobacterial skin infections (Mahaisavariya et al. 2003; Lee et al. 2010).

Clinical Features

Clinical lesions are variable, including solitary or multiple erythematous nodules, abscesses, ulcers, verrucous plaques, cysts, or sinus tracts. Sometimes lesions spread in a sporotrichoid pattern. In most cases, an infection is clinically

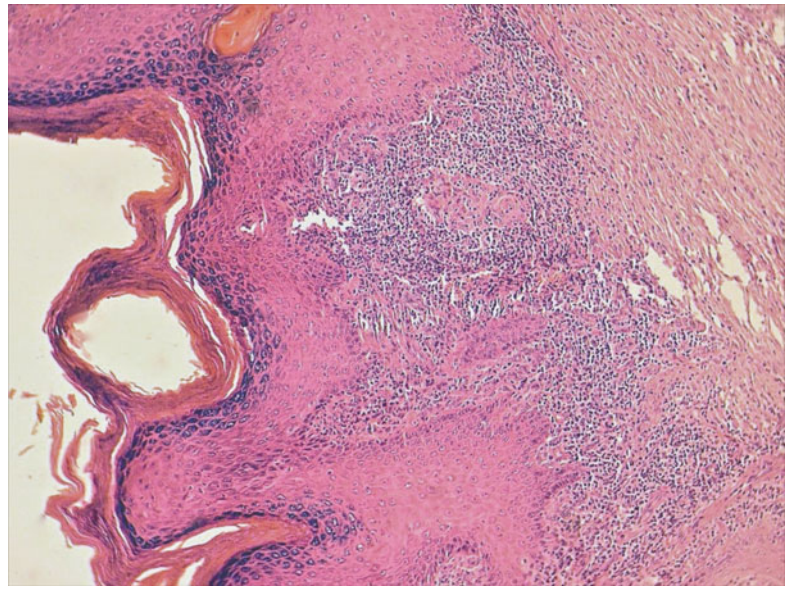

Fig. 14.28 Tuberculosis verrucosa cutis. Hyperkeratosis, papillomatosis, acanthosis, and neutrophilic microabscesses in epidermis. Diffuse mixed infiltrate in dermis with prominent neutrophils (H&E, 50× original magnification)

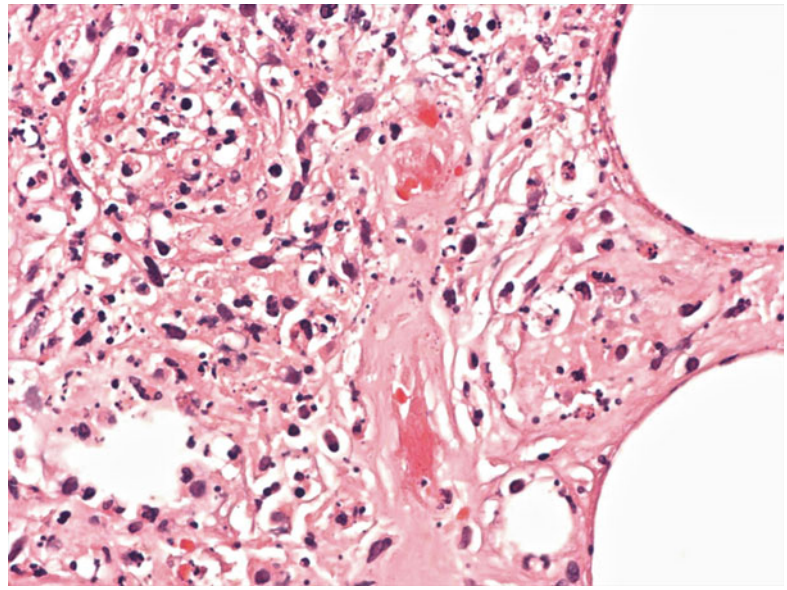

Fig. 14.29 Papulonecrotic tuberculid. Lymphocytic or neutrophilic vasculitis, fibrinoid necrosis of vessels with microthrombi (H&E, 400× original magnification)

appreciable, but some cases of prurigo nodularis and other chronic skin disorders have been found to be related to mycobacterial infection only when the skin lesions are tested by culture, biopsy, or molecular techniques. Their clinical features are summarized in Table 14.2 (Eckman 1981; Dodiuk-Gad et al. 2007; Elston 2009). Multiple PCR assays have been established for the detection of a variety of mycobacterial organisms (Cook et al. 1994).

Histopathologic Features

The histopathologic picture in atypical mycobacterioses is just as variable as the clinical picture

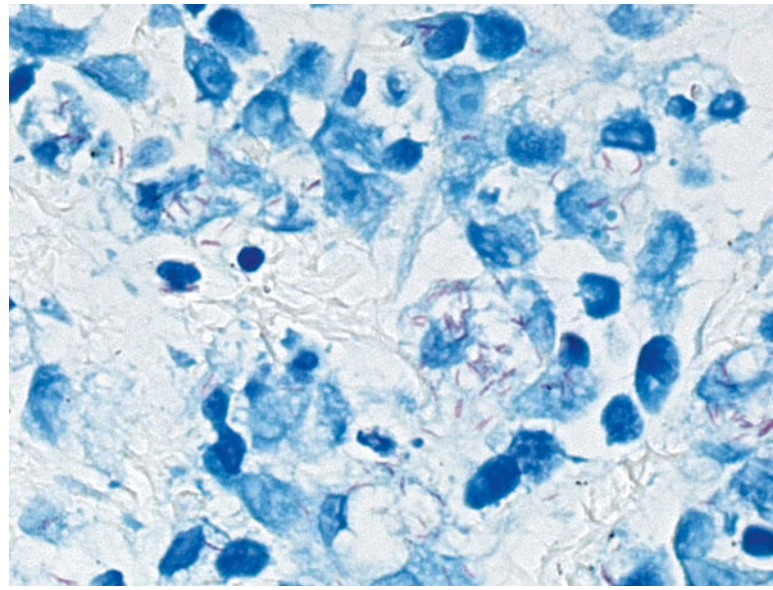

Fig. 14.30 Cutaneous tuberculosis. Acid-fast bacilli in areas of lymphohistiocytic inflammation and necrosis (Ziehl–Neelsen acid-fast stain, 630× original magnification)

Table 14.2 Clinical and histopathologic features of various atypical mycobacteriosis

Disease	Clinical features	Histopathologic features
M. avium-intracellulare infection	Hematogenously borne lesions in skin and subcutis in patients with HIV/AIDS or other immunosuppressing diseases	Granulomatous or mixed acute and chronically inflammatory, as with tuberculosis. Sometimes may resemble lepromatous leprosy. Abundant acid-fast bacilli in areas without necrosis
M. marinum infection	Infections contracted through minor abrasions incurred while bathing in contaminated swimming pools or in ocean or lake water. Solitary indolent, dusky red, hyperkeratotic, papillomatous papules, nodules, or plaques. Fingers, knees, elbows, and feet most commonly affected	Early lesions: a nonspecific inflammatory infiltrate composed of neutrophils, monocytes, and macrophages. Acid-fast bacilli usually present Older lesions: a few multinucleated giant cells and small epithelioid cell granulomas with occasional necrosis. Marked hyperkeratosis with an acute inflammatory infiltrate and ulceration in epidermis. Acid-fast bacilli usually not appreciable
Buruli ulcer (*M. ulcerans* infection)	Endemic in West and Central Africa, Central America, China, and South Australia. Organism identified in nature, near inland water and rivers. Infections directly implanted or via an aquatic insect bite. Palpable cutaneous nodule usually on the extremities, buttocks, trunk, or face; progresses to painless ulceration with extensive undermining of the epidermis and extension of the necrosis down to fascia and even bone	Begins as a subcutaneous nodule exhibiting dermal collagen and fat necrosis with deposition of fibrin and extracellular clumps of acid-fast bacilli. Extensive ulceration with a variable degree of neutrophil infiltration and thrombosis of vessels. Variable nonspecific granulation tissue or a granulomatous reaction throughout the lesion
Other atypical Mycobacterioses: *M. chelonei*, *M. fortuitum*, *M. abscessus*, *M. haemophilum*	Commonly iatrogenic, associated with medical injections through unsterile contaminated needles and cannulae	Usually a mixed acute (neutrophilic) and chronic (granulomatous) inflammatory response, with various numbers of acid-fast bacilli

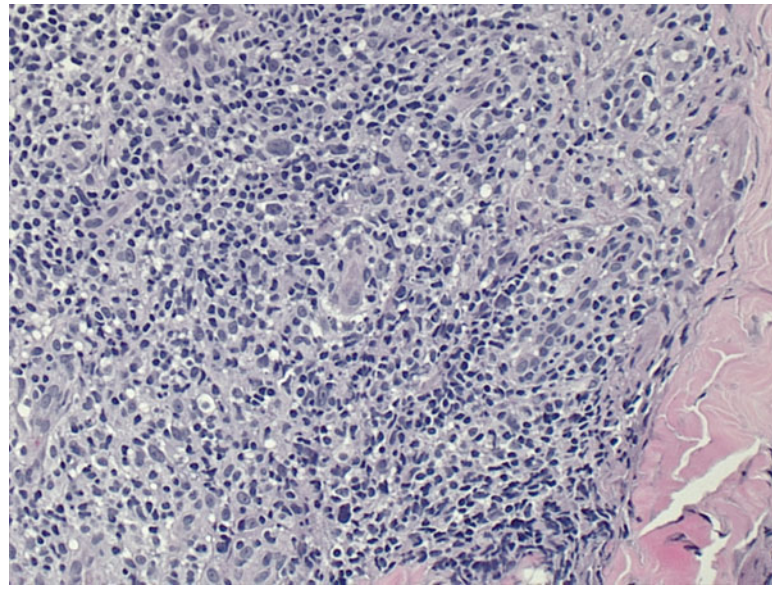

Fig. 14.31 *Mycobacterium marinum* infection. Mixed inflammatory infiltrate composed of neutrophils, monocytes, and macrophages in early lesion (H&E, 400× original magnification)

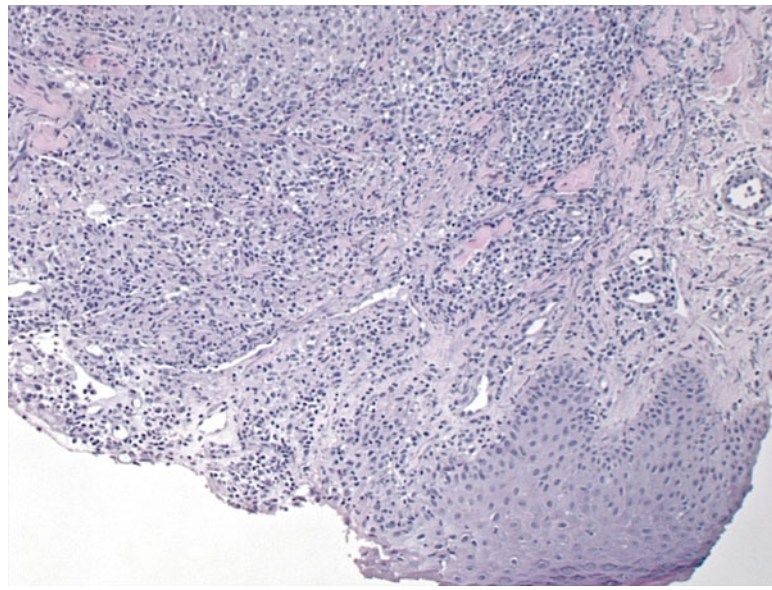

Fig. 14.32 *Mycobacterium marinum* infection. Epidermal ulceration, dense mixed inflammatory infiltrate, and scattered small epithelioid cell granulomas with multinucleated giant cells and occasional necrosis in later lesion (H&E, 100× original magnification)

and may present nonspecific acute and chronic inflammation, suppuration, and abscess formation or tuberculoid granulomas with or without caseation. Coagulative necrosis is more prominent in the case of *M. ulcerans*. The epidermis may be hyperplastic or ulcerated. Fibrosis and granulation tissue may be prominent. The presence or absence of acid-fast bacilli depends on the tissue reaction. In suppurative lesions, numerous acid-fast bacilli often can be found. Various modifications of the Ziehl–Neelsen acid-fast stain or Fite stain may reveal the AFB. The AFB are most frequently found in microabscesses or within vacuoles in the sections rather than within multinucleated giant cells. The features are summarized in Table 14.2 (Hayman and McQueen 1985; Travis et al. 1985; Hanke et al. 1987; Hayman 1993; Mahaisavariya et al. 2004; Song et al. 2009; Min et al. 2012) (Figs. 14.31, 14.32, 14.33, 14.34, and 14.35).

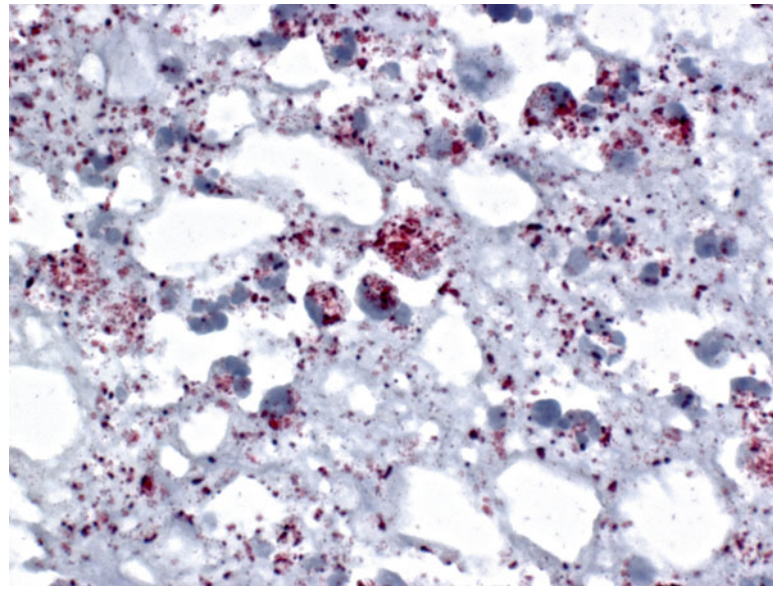

Fig. 14.33 *Mycobacterium marinum* infection. Abundant immunostaining of mycobacteria in areas of lymphohistiocytic inflammation and necrosis (IHC, 630× original magnification)

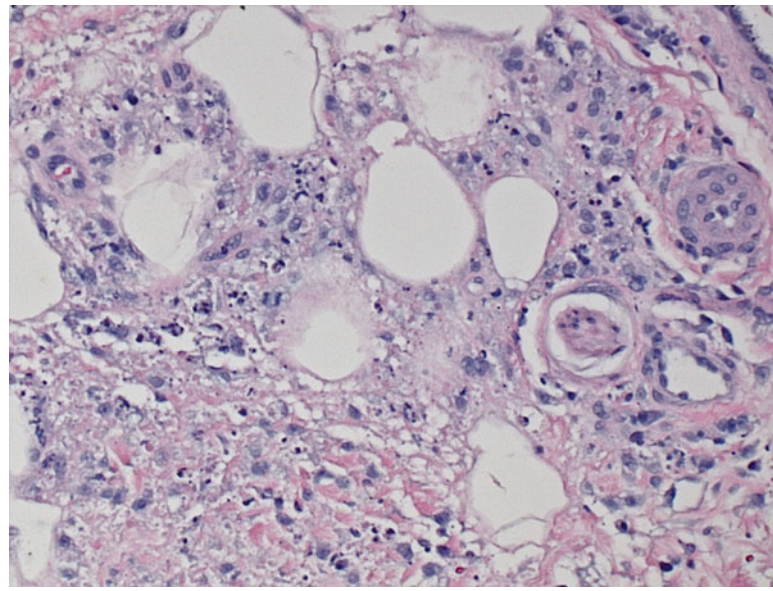

Fig. 14.34 *Mycobacterium haemophilum* infection. Lymphohistiocytic inflammation and necrosis in dermis (H&E, 400× original magnification)

Differential Diagnosis

Other diseases associated with granulomas as described with cutaneous tuberculosis.

Leprosy (Hansen Disease)

Etiology and Epidemiology

Hansen disease, caused by *M. leprae*, affects millions of people worldwide. The disease is endemic in many tropical and subtropical countries but is declining in prevalence as a result of multidrug therapy (Noordeen 1995; Declercq 2001; Britton and Lockwood 2004). The Indian subcontinent, Southeast Asia, sub-Saharan countries in Africa, and Brazil comprise the areas most affected at present. In the United States, it occurs mainly in immigrants from endemic areas,

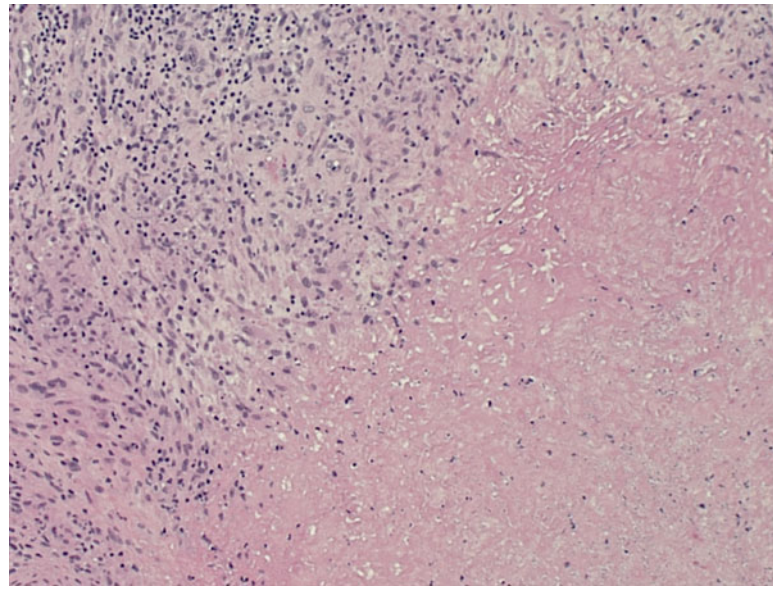

Fig. 14.35 *Mycobacterium ulcerans* infection. Prominent coagulative necrosis in dermis (H&E, 100× original magnification)

but some cases have been reported in Texas and Louisiana, perhaps from armadillo exposure. Leprosy affects multiple organs of the body, but clinical disease is most apparent in the skin, eyes, and peripheral nerves. Neuropathies may result in deformities of the distal extremities. The mode of transmission of leprosy is largely unknown; however, the bacilli may be inhaled from the nasal excretion of a multibacillary patient or possibly implanted from organisms in the soil. Direct person-to-person infection through skin contact occurs rarely. After inhalation, it is likely that bacilli pass through the blood to peripheral and cutaneous nerves, where infection and host reaction occurs.

Clinical Features

Leprosy is divided into several types in the Ridley–Jopling classification system based on the immune status of the patient (Ridley and Jopling 1966; Skinsnes 1973). Patients with lepromatous leprosy are anergic, and they tend to develop widespread cutaneous lesions. Lepromatous leprosy initially has cutaneous and mucosal lesions, with neural changes occurring later. The lesions usually are numerous and are symmetrically arranged. Although they are less likely to have hypoesthesia in the lesions, the peripheral nerves may still be enlarged with consequent neuropathies. Lepromatous lesions include hypopigmented or erythematous macules, infiltrated erythematous nodules or plaques, leonine (lionlike) facies with a loss of eyebrows and eyelashes, and diffuse macular involvement of the skin resulting in a smooth surface. A distinctive variant of lepromatous leprosy, the histoid type, is characterized by the occurrence of well-demarcated cutaneous and subcutaneous nodules resembling dermatofibromas. It frequently follows incomplete chemotherapy or acquired drug resistance, leading to bacterial relapse.

The skin lesions of tuberculoid leprosy are scanty, dry, erythematous, hypopigmented papules, or plaques with sharply defined edges. The tuberculoid form occurs in those with intact immunity, and patients tend to develop one or a few lesions with prominent hypoesthesia and palpable thickened peripheral nerves. In borderline leprosy, combined features of tuberculoid and lepromatous disease are seen. The lesions are less numerous and less symmetrical than lepromatous leprosy lesions and often display some central dimples. Indeterminate leprosy represents early disease in patients living in populations where

leprosy is prevalent; it is difficult to establish a definite diagnosis in some of these patients. The earliest detectable skin lesion may present as one or a few hypopigmented macules with variable loss of sensation. Any part of the body may be affected and the disease may heal spontaneously or may evolve into one of the other forms.

There are three types of reactional leprosy, and they usually occur as a result of a change in the patient's immune status, with or without treatment (Skinsnes 1973; Rea and Modlin 1991; Ottenhoff 1994; Pardillo et al. 2007). The type I reaction (lepra reaction) is called a reversal reaction when the patient is under treatment and has shifted toward the tuberculoid spectrum with greater immunity. On the contrary, it is considered as a downgrading reaction when untreated patients shift toward the lepromatous spectrum. Type I reactions involve swelling of previously existing cutaneous and neural lesions with associated constitutional symptoms. Type II reactions (erythema nodosum leprosum) occur most commonly in lepromatous leprosy and less frequently in borderline lepromatous leprosy. Clinically, the reaction has a greater resemblance to erythema multiforme than to erythema nodosum. Tender new red plaques and nodules develop on normal skin. The eruption is widespread and is accompanied by fever, malaise, arthralgia, and leukocytosis. This type of reaction involves immune complexes. Type III reactions (Lucio phenomenon) occur only in patients with the diffuse form of lepromatous leprosy. Hemorrhagic plaques occur on the legs, arms, or buttocks. These may ulcerate eventually. There are usually no constitutional symptoms.

Histopathology

The histopathologic findings vary in different forms and are summarized in Table 14.3 (Figs. 14.36, 14.37, 14.38, 14.39, 14.40, 14.41, and 14.42) (Ridley 1974; Modlin and Rea 1988; Fine et al. 1993). The Fite stain is recommended because the conventional AFB stain methods,

Table 14.3 Clinical and histopathologic features of various types of leprosy

Type	Clinical features	Histopathologic features
Lepromatous	Cutaneous and mucosal lesions with multiple erythematous or hypopigmented smooth patches, plaques, or nodules, sometimes leonine facies with a loss of eyebrows and eyelashes	Diffuse dermal infiltrate of foamy macrophages with grenz zone separating the macrophages from the epidermis; numerous acid-fast bacilli, often in clumps or in endothelial cells
Tuberculoid	Hypopigmented scaly or annular patches or plaques, smaller in number than lepromatous, more hypoesthesia in the lesions	Tuberculoid (epithelioid) granulomas without grenz zone; granulomas often linear, following nerves; Langhans giant cells typically absent; acid-fast bacilli rare or absent
Borderline	Features intermediate between lepromatous and tuberculoid	Histology in between lepromatous and tuberculoid
Indeterminate	Early hypopigmented or erythematous macules	Perivascular and perineural lymphohistiocytic inflammation. Few or no acid-fast bacilli
Lepra reaction (type I reaction)	Acute redness or pain in previously existing lesions with associated constitutional symptoms	Histology as in borderline leprosy
Erythema nodosum leprosum (type II reaction)	Acute onset of erythematous nodules in new sites not previously involved with associated constitutional symptoms	Lepromatous leprosy plus leukocytoclastic vasculitis
Lucio phenomenon (type III reaction)	Occurs exclusively in diffuse lepromatous leprosy with acute onset of hemorrhagic plaques or ulcers and no associated constitutional symptoms	Similar to type II, with greater tendency of endothelial proliferation leading to vascular obliteration, thrombosis, necrosis, and ulceration; dense aggregates of acid-fast bacilli in vascular walls and the endothelium

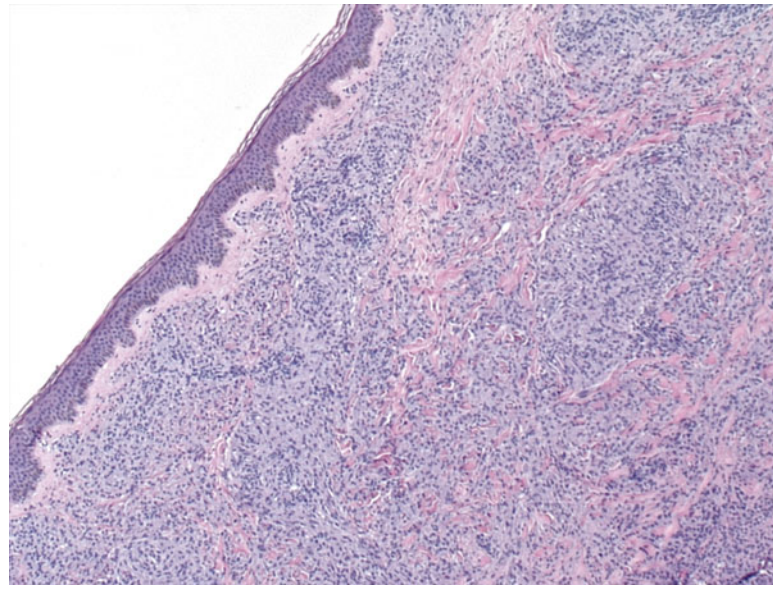

Fig. 14.36 Lepromatous leprosy. Diffuse dermal infiltrate of lymphocytes and macrophages with grenz zone separating the infiltrate from the epidermis (H&E, 50× original magnification)

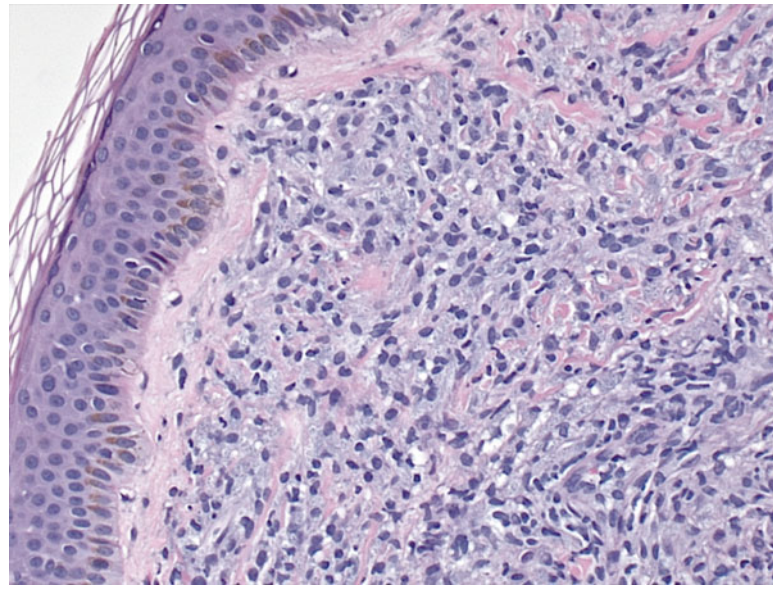

Fig. 14.37 Lepromatous leprosy. Dermal infiltrate with abundant foamy macrophages underneath the narrow grenz zone (H&E, 400× original magnification)

such as Ziehl–Neelsen stain, do not work as well (Fig. 14.39). Immunostaining for AFBs can enhance the ability to diagnose lesions containing few bacilli (Fig. 14.40). In situ hybridization and PCR analysis of specimens are more sensitive and are available at a few specialized laboratories (Fleury and Bacchi 1987; de Wit et al. 1991; Nishimura et al. 1994).

Differential Diagnosis

These include other granulomatous conditions, such as cutaneous tuberculosis, atypical mycobacteriosis, deep fungal infections, Treponema infections, cat-scratch disease, granuloma inguinale, lymphogranuloma venereum, tularemia, brucellosis, leishmaniasis, and other noninfectious granulomas.

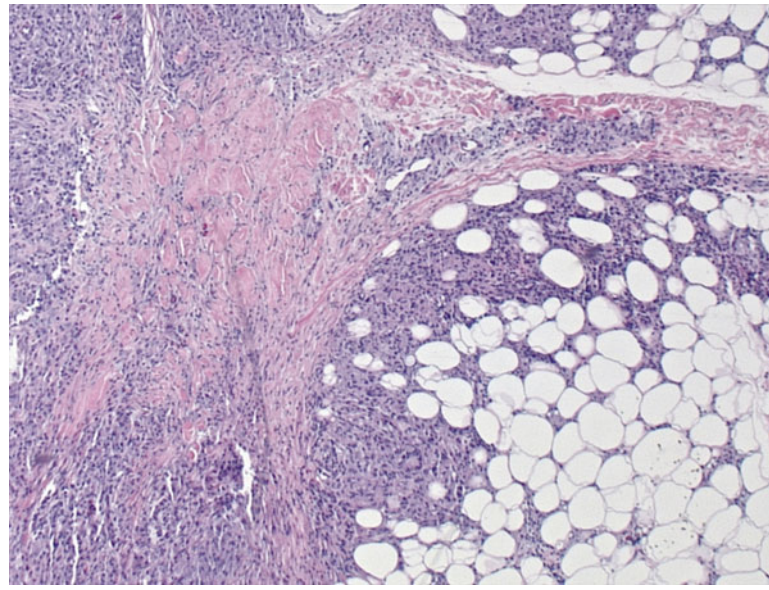

Fig. 14.38 Lepromatous leprosy. Diffuse infiltrate of lymphocytes and macrophages in deep dermis and subcutaneous tissue with scattered multinucleated cells (H&E, 50× original magnification)

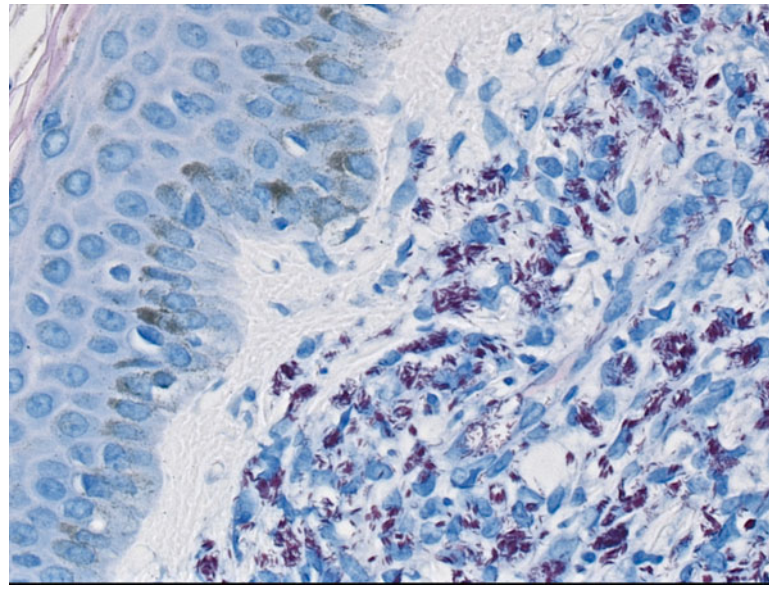

Fig. 14.39 Lepromatous leprosy. Abundant acid-fast bacilli highlighted by Fite acid-fast stain in dermis (Fite stain, 630× original magnification)

Treponemal Diseases

The venereal and nonvenereal treponemal diseases are caused by motile bacteria of the family Spirochaetaceae. Accurate recognition of spirochetal infection requires correlation of the patient's travel and medical history to a detailed knowledge of the clinical and histologic expression of each pathogen. The pathogenic treponemes measure 6–20 by 0.10–0.18 μm, are coiled with regular periodicity, have a high degree of DNA sequence homology, and react with silver stains in dark-field and biopsy material (Hook and Marra 1992). The nonvenereal treponematoses include endemic syphilis, yaws, and pinta (Antal et al. 2002). The use of polymerase chain reaction (PCR)

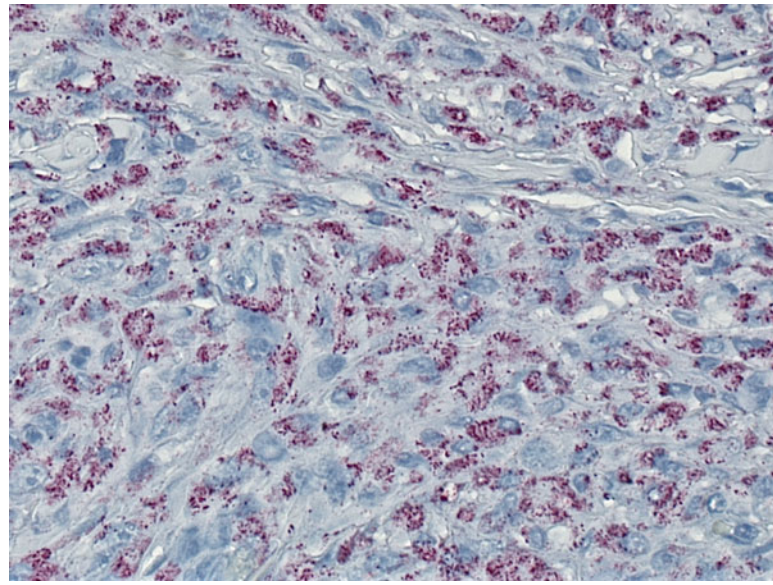

Fig. 14.40 Lepromatous leprosy. Abundant immunostaining of *M. leprae* in foamy macrophages (IHC, 400× original magnification)

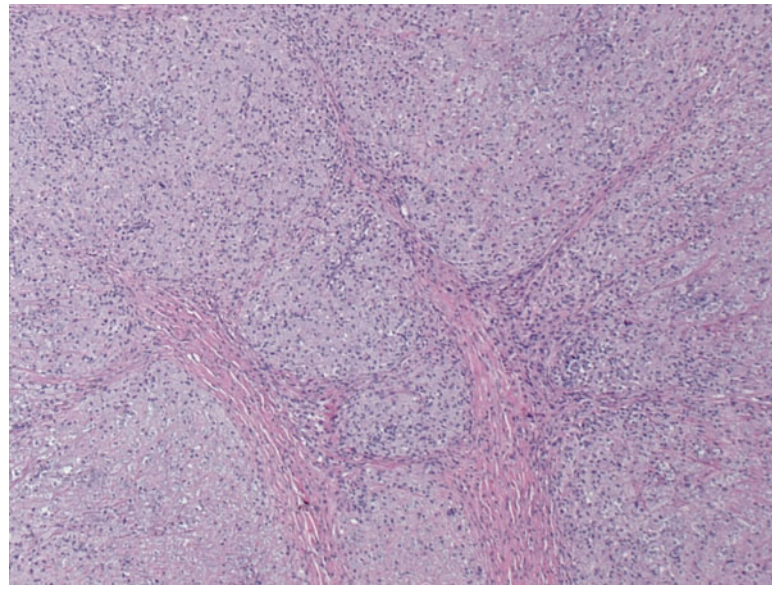

Fig. 14.41 Tuberculoid leprosy. Linear epithelioid granulomas following distribution of nerves (H&E, 50× original magnification)

methodologies and restriction polymorphism analysis has allowed the identification of at least 27 distinct strains of pathogenic treponemal species (Centurion-Lara et al. 2006). Many studies suggest that these organisms have evolved from a common ancestor to cause different diseases in the modern era.

Venereal Syphilis

Etiology and Epidemiology

Venereal syphilis, caused by Treponema pallidum, has afflicted humanity since at least the fifteenth century. It was a significant cause of morbidity and mortality in the early twentieth century, although its incidence in the developed

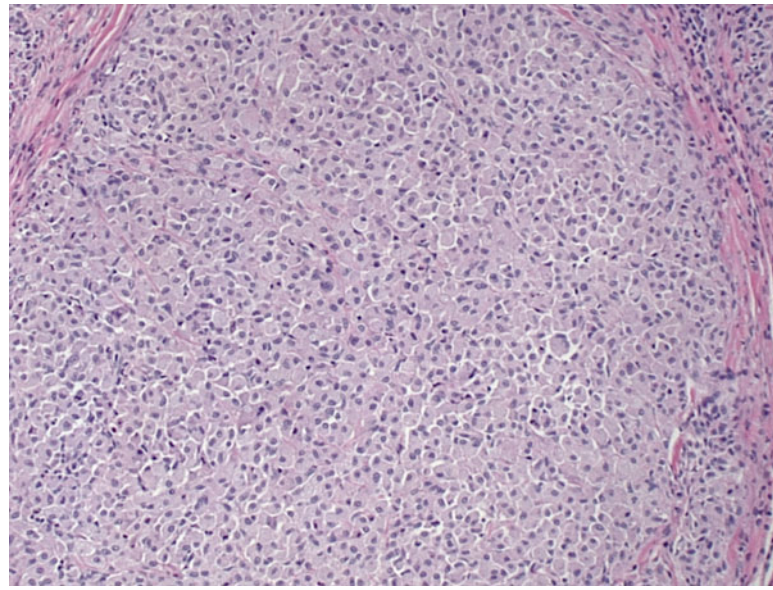

Fig. 14.42 Tuberculoid leprosy. Epithelioid granulomas with no conspicuous Langhans giant cells (H&E, 200× original magnification)

world has diminished due to public health programs and the advent of antibiotics (Goh 2005). Recently, the incidence of venereal syphilis has been steadily increasing, in part reflecting the epidemic of human immunodeficiency virus infection, with which venereal syphilis is linked epidemiologically. In 1990, the incidence was 20 per 100,000 in the United States and 360 per 100,000 in parts of Africa. New diagnoses of syphilis increased eightfold in the United Kingdom between 1997 and 2002. By 2003, more than 60 % of all reported cases of syphilis were believed to occur in men who have had sex with men (Heffelfinger et al. 2007).

Clinical Features

Spread of *T. pallidum* usually occurs by contact between an infectious lesion and disrupted epithelium, either at sites of trauma occurred during sexual intercourse or at sites of concurrent chancroid and other genital sores. Primary syphilis is defined by a skin lesion, or chancre, in which organisms are identified. It typically arises three weeks after exposure at the inoculation site and is classically a painless, brown-red, indurated, round papule, nodule, or plaque 1–2 cm in diameter. Lesions may be multiple or ulcerative, and the regional lymph nodes may be enlarged (Goh 2005; Lautenschlager 2006; Bjekić et al. 2012).

Secondary syphilis occurs after hematogenous dissemination of organisms, resulting in widespread disease with constitutional symptoms. Fever, malaise, and generalized lymphadenopathy can occur; a disseminated eruption of red-brown macules, papules, papulosquamous lesions, and pustules may appear (Noppakun et al. 1987; Lawrence and Saxe 1992). Lesions may be follicular-based, annular, or serpiginous, particularly in recurrent attacks of secondary syphilis. Other cutaneous manifestations include alopecia and condylomata lata, the latter comprising confluent gray papules in anogenital areas and pitted hyperkeratotic palmoplantar papules, or in severe cases, ulcerative lesions of lues maligna may develop. Shallow, painless ulcers sometimes are seen in mucosal surfaces (Lautenschlager 2006; Arias-Santiago et al. 2009; Pföhler et al. 2011; Sezer et al. 2011; Villaseñor-Park et al. 2011).

Primary- and secondary-stage lesions may resolve without therapy or go unnoticed by the patient, who then develops into a latent phase, consisting of an early and late stage. The Centers for Disease Control and Prevention bases its

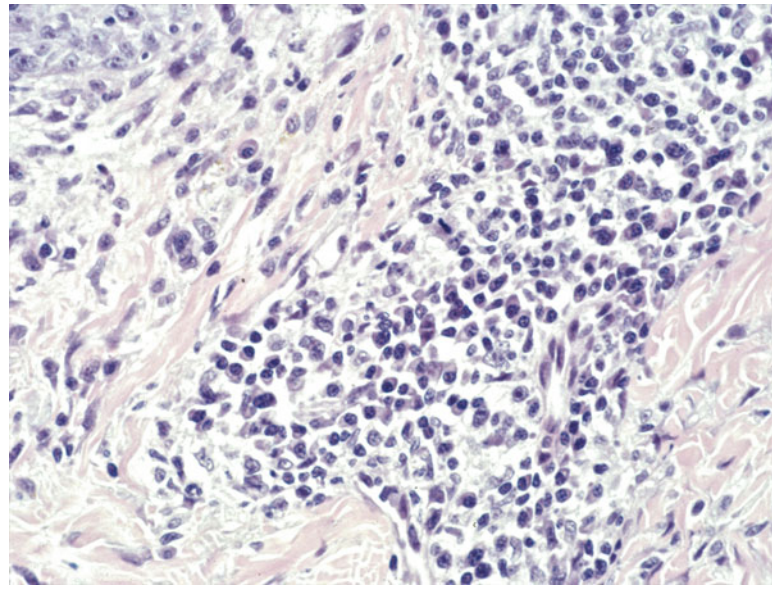

Fig. 14.43 Cutaneous syphilis. Typical feature with perivascular infiltrate composed of lymphoid cells, especially prominent plasma cells (H&E, 400× original magnification)

distinction on whether the duration of the infection is less or more than 1 year: the early (infectious) latent stage if less than a year and the late (noninfectious) latent stage if more than year.

After a variable period of latency, the patient enters the tertiary stage. Tertiary syphilis can present as gummatous skin and mucosal lesions, as well as involves cardiovascular and neurologic systems (Schoutens et al. 1996; Chudomirova et al. 2009). Skin lesions are solitary or multiple and consist of superficial nodular and deep gummatous subtypes. Superficial nodular type has smooth, atrophic centers with raised, serpiginous borders; deep gummatous type appears as ulcerative subcutaneous swellings. Congenital syphilis arises through transplacental infection and affects more than 50 % of infants born to mothers with primary or secondary syphilis, roughly 40 % of those born to mothers in the early latent stage, and only 10 % of those born to mothers with late latent infections (Sanchez 1992). Most HIV-infected patients exhibit a normal serologic response to *T. pallidum* infection; however, in some HIV-positive patients, both treponemal (FTA-ABS, MHA-TP, HATTS) and nontreponemal (VDRL, RPR) test results for syphilis have been reported as negative (Terry et al. 1988). The diagnosis of syphilis in seronegative HIV-infected patients depends on dark-field microscopy, fluorescent antibody, and histopathology with conventional silver-impregnation stains or IHC (Guarner et al. 1999).

Histopathology

Cutaneous syphilis presents as a perivascular infiltrate composed of lymphoid cells, especially prominent plasma cells (Fig. 14.43). The late secondary and tertiary stages also show infiltrates of epithelioid histiocytes and occasional giant cells. In all stages, endothelial swelling and proliferation are apparent.

Primary Syphilis

The primary syphilitic chancre presents a variety of histopathology, depending on the location of lesion that is biopsied. The epidermis at the periphery of the syphilitic chancre reveals changes comparable to those observed in lesions of secondary syphilis, mainly acanthosis, spongiosis, and exocytosis of lymphocytes and neutrophils (Fig. 14.44). Toward the center, the epidermis becomes thinned, edematous, and permeated by inflammatory cells (Fig. 14.45). In the center, the epidermis may be absent. The papillary dermis is edematous, and a dense dermal perivascular and interstitial lymphohistiocytic and plasmacellular

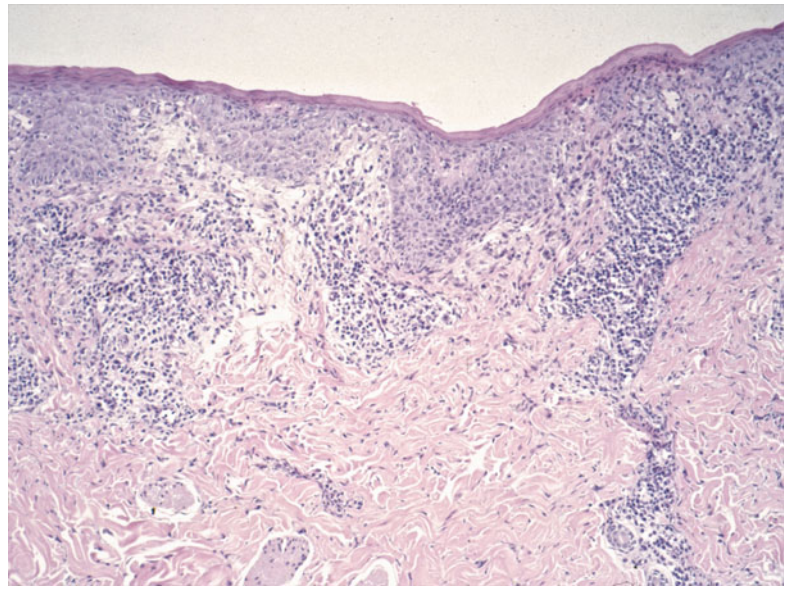

Fig. 14.44 Primary syphilis. Acanthosis, spongiosis, dermal edema, and exocytosis of lymphocytes and neutrophils at the periphery of the chancre (H&E, 50× original magnification)

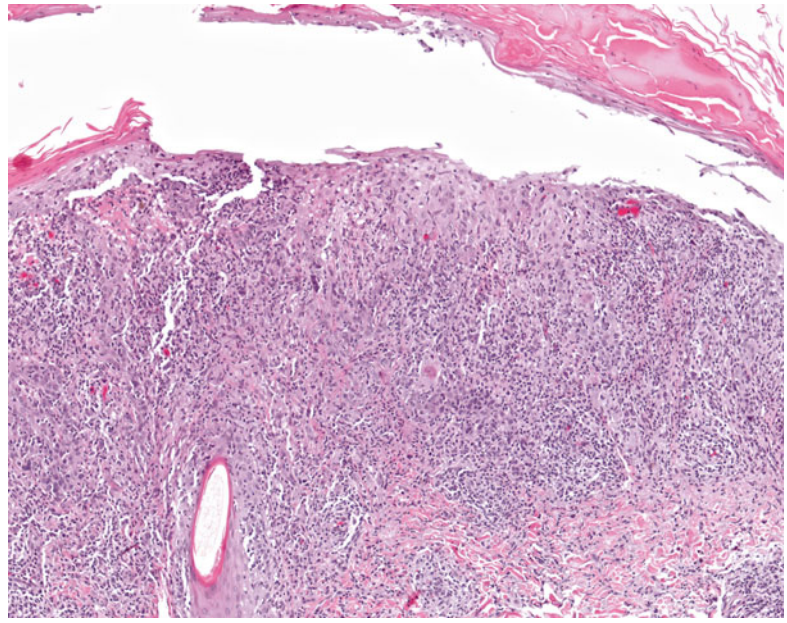

Fig. 14.45 Primary syphilis. Thinned and ulcerated epidermis with inflammatory infiltrate toward the center of chancre (H&E, 50× original magnification)

infiltrate is present (Fig. 14.43). Neutrophils are often admixed. Endarteritis obliterans characterized by endothelial swelling and mural edema may be observed (Engelkens et al. 1991b). With silver-impregnation stains or IHC techniques, spirochetes are usually seen within and around blood vessels and along the dermal–epidermal junction (Figs. 14.46 and 14.47). Warthin–Starry silver stain and Steiner silver stain must be interpreted with caution in evaluating biopsy specimens because other cellular structures and artifacts may resemble *T. pallidum*.

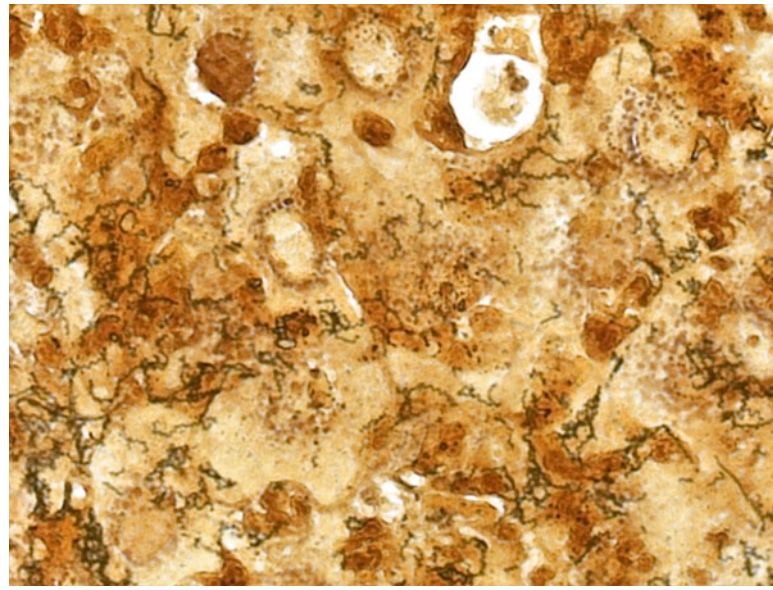

Fig. 14.46 Primary syphilis. Abundant spirochetes highlighted by Warthin–Starry silver stain along the dermal–epidermal junction (Warthin–Starry stain, 630× original magnification)

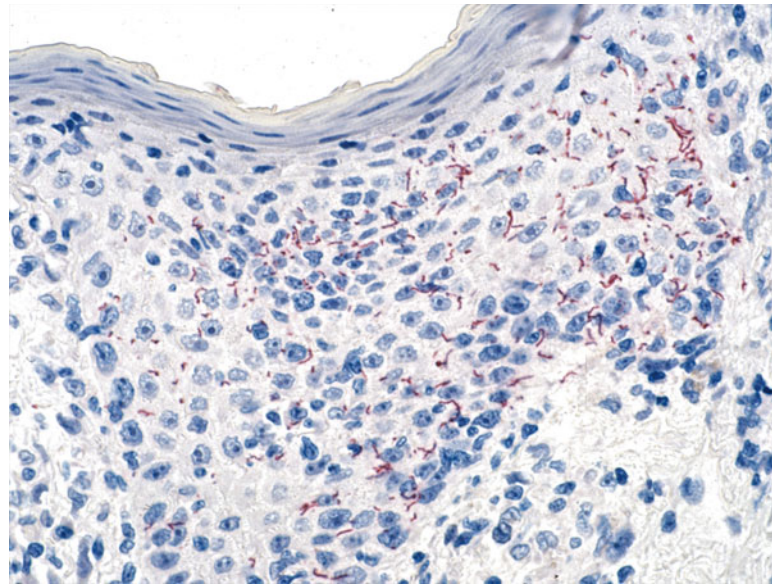

Fig. 14.47 Primary syphilis. Abundant immunostaining of *T. pallidum* in epidermis and dermal–epidermal junction (IHC, 400× original magnification)

Secondary Syphilis

In secondary syphilis, skin biopsies generally reveal variable epithelial changes in the macular, papular, and papulosquamous eruptions (Jeerapaet and Ackerman 1973; Abell et al. 1975; Cochran et al. 1976; Engelkens et al. 1991b). There is considerable histologic overlap among the various clinical forms of secondary syphilis; however, epidermal changes are least pronounced in the macular type and most pronounced in papulosquamous lesions. Biopsies generally reveal psoriasiform hyperplasia, often with spongiosis and basilar vacuolar alteration and often with edema of the papillary dermis (Fig. 14.48).

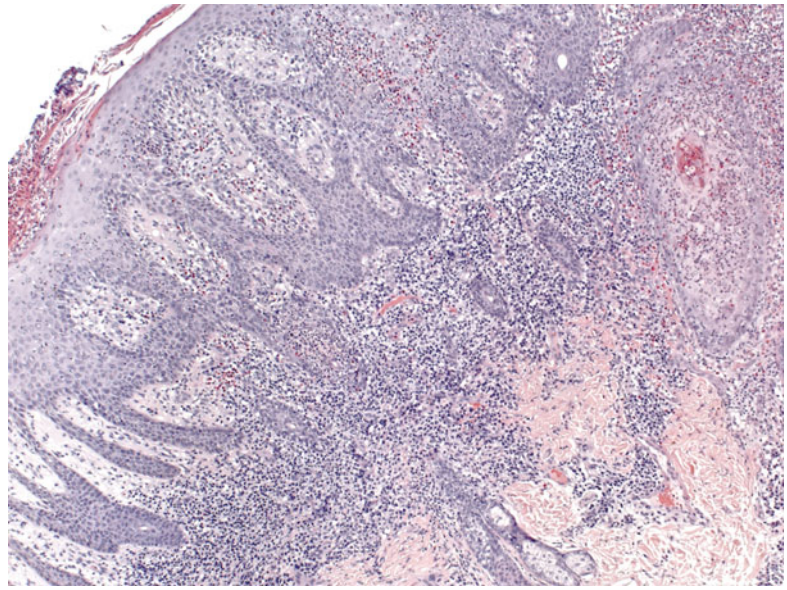

Fig. 14.48 Secondary syphilis. Psoriasiform hyperplasia, spongiosis, edema of the papillary dermis, and dense dermal inflammatory infiltrate (H&E, 50× original magnification)

Exocytosis of lymphocytes, spongiform pustulation, and parakeratosis also may be observed. Patchy or confluent parakeratosis may be present, sometimes accompanied by intracorneal neutrophilic abscesses. Ulceration is not a feature, except in patients with lues maligna. The dermal changes include marked papillary dermal edema and a perivascular and/or periadnexal infiltrate that may be lymphocyte predominant, lymphohistiocytic, histiocytic predominant, or frankly granulomatous and that is of greatest intensity in the papillary (Sezer et al. 2011). Atypical lymphoid forms, representing a type of lymphomatoid hypersensitivity, may suggest the possibility of mycosis fungoides or non-Hodgkin lymphoma. Plasma cells are inconspicuous or absent in 25 % of patients. Eosinophils are usually absent. Endothelial cell swelling and mural edema are seen in only 50 % of patients, and mural necrosis is rare. Silver stains show spirochetes in only one-third of patients and are best visualized within the epidermis and around the superficial blood vessels (Poulsen et al. 1986).

Tertiary Syphilis

Tertiary syphilis includes a wide spectrum of clinical manifestations, including nodular tertiary syphilis confined to the skin; benign gummatous syphilis principally affecting skin, bone, and liver; cardiovascular syphilis; neurosyphilis; and syphilitic hepatic cirrhosis. In nodular tertiary syphilis, granulomas are small and limited to the dermis, in which scattered, nested epithelioid cells are admixed with a few multinucleated giant cells and lymphoplasmacytic cells (Fig. 14.49). Granulomas may be absent and necrosis is usually inconspicuous. The vessels may show endothelial swelling. Benign gummatous syphilis shows granulomatous inflammation with central zones of acellular necrosis in involved organs. In cutaneous lesions, blood vessels throughout the dermis and subcutaneous fat exhibit endarteritis obliterans, with variable angiocentric plasma cell infiltrates (Schoutens et al. 1996; Wu et al. 2000; Rocha et al. 2004; Chudomirova et al. 2009).

Differential Diagnosis

Lesions of chancroid caused by *Haemophilus ducreyi* are the most difficult to differentiate clinically from a syphilitic chancre. The characteristic histopathology of chancroid is one of dense lymphohistiocytic infiltrates with a paucity of plasma cells and a granulomatous vasculitis. An epidermal reaction pattern similar to the syphilitic chancre is observed, namely, psoriasiform epidermal hyperplasia and spongiform

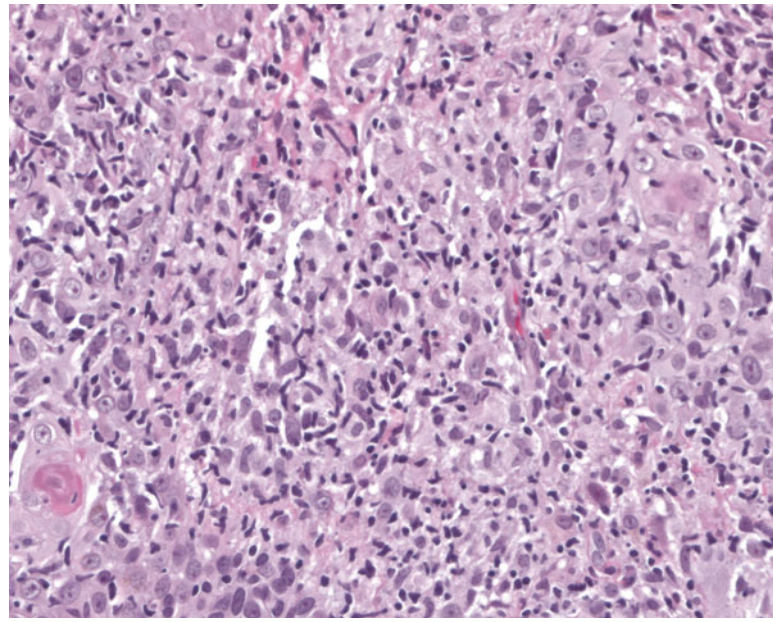

Fig. 14.49 Tertiary syphilis. Small granulomas limited to the dermis with scattered, nested epithelioid cells admixed with lymphoplasmacytic cells and occasional multinucleated cells (H&E, 400× original magnification)

pustulation. A Giemsa, Alcian blue, or periodic acid–Schiff stain reveals coccobacillary forms between keratinocytes and along the dermal–epidermal junction. Spirochetes may coinfect chancroid lesions.

The differential diagnosis of lesions of secondary syphilis includes other causes of lichenoid dermatitis including lichen planus, a lichenoid hypersensitivity reaction, pityriasis lichenoides and connective tissue disease, sarcoidosis, psoriasis, and psoriasiform drug eruptions.

The differential diagnosis of lesions of tertiary syphilis depends on the involved organ system. The cutaneous lesions need to be differentiated with other granulomatous diseases.

Nonvenereal Treponematoses

Yaws

Etiology and Epidemiology

Yaws is caused by *T. pallidum pertenue*, which is indistinguishable microscopically from *T. pallidum subspecies pallidum* but has been shown to be genetically distinctive by molecular methods (Noordhoek et al. 1989; Wicher et al. 2000). Yaws is spread by casual contact between primary or secondary lesions and abraded skin. The infection classically affects the buttocks, legs, and feet of children and is most prevalent in warm, moist tropical climates (Engelkens et al. 1991a). Despite only minor sequence variation between the organisms, there are distinct differences between disease expressions and host immunologic responses of yaws and syphilis (Noordhoek et al. 1990). Infants born to mothers with yaws do not produce IgM antibodies, and no spirochete is found in their organs. These findings strongly support the dermotropic nature of *T. pallidum pertenue*, as opposed to organotropic property of *T. pallidum subspecies pallidum*.

Clinical Features

Primary yaws usually starts as an erythematous papule, or mother yaws, roughly 21 days after inoculation. The lesion enlarges peripherally to form a 1–5-cm nodule, with an amber crust and adjacent satellite pustules. Lesions heal as pitted, hypopigmented scars. Fever, arthralgia, or lymphadenopathy may develop during the course.

Secondary yaws is characterized by involvement of skin, bones, joints, and cerebrospinal fluid. Skin lesions, or daughter yaws, resemble the mother yaw but are smaller and more numerous.

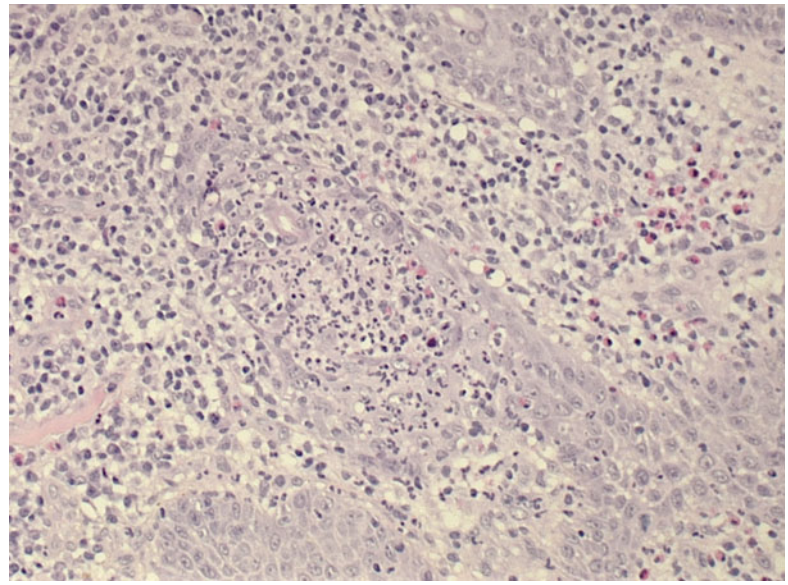

Fig. 14.50 Primary yaws. Epidermal acanthosis, papillomatosis, spongiosis, and neutrophilic exocytosis with microabscesses (H&E, 200× original magnification)

Although periorificial lesions may resemble venereal syphilis, a circinate appearance may mimic fungal infection. A morbilliform eruption or condylomatous vegetations involving the axillae and groin may occur. Macular, hyperkeratotic, and papillomatous lesions may be seen on palmoplantar surfaces and may cause the patient to walk with a painful, crablike gait (crab yaws). Papillomatous nail fold lesions may give rise to pianic onychia. Bone lesions consist of painful, sometimes palpable periosteal thickening of arms and legs (Engelkens et al. 1991a; Antal et al. 2002).

Skin manifestations in tertiary yaws include subcutaneous abscesses, coalescing serpiginous ulcers, keratoderma, keloids, and palmoplantar hyperkeratosis. The bone and joint involvements include osteomyelitis, hypertrophic or gummatous periostitis, and chronic tibial osteitis. Obstructive hypertrophy of the nasal maxillary processes produces the rare but characteristic goundou. Another otorhinolaryngologic complication, termed gangosa, consists of nasal septal or palatal perforation.

Histopathology

Primary lesions show epidermal acanthosis, papillomatosis, spongiosis, and neutrophilic exocytosis with microabscesses (Fig. 14.50). A diffuse dermal infiltrate of plasma cells, lymphocytes, histiocytes, and granulocytes is seen. Prominent eosinophils can also be present in some cases (Fig. 14.51). Unlike syphilis, little or no endothelial proliferation is present. Secondary lesions may resemble condylomata lata in their epidermal changes but differ with a diffuse dermal infiltrate. The ulcerative lesions of tertiary yaws histologically resemble those of late syphilis. Spirochetes are demonstrated in primary and secondary lesions by dark-field examination and silver stains. Unlike *T. pallidum*, which can also been found in the dermis, *T. pertenue* is almost entirely seen in epidermis (Hasselmann 1957).

Differential Diagnosis

The distinction of yaws from syphilis is based on clinical features, although localization of the organism in a skin biopsy may be helpful.

Other Nonvenereal Treponematoses

These diseases are rare and confined to small endemic areas (Antal et al. 2002). Pinta is caused by *T. carateum*, and the involvement is usually confined to the skin with hypopigmentation being the only significant sequela. Pinta is endemic to Central America and is not observed outside the Western Hemisphere. It affects all age groups with a mild

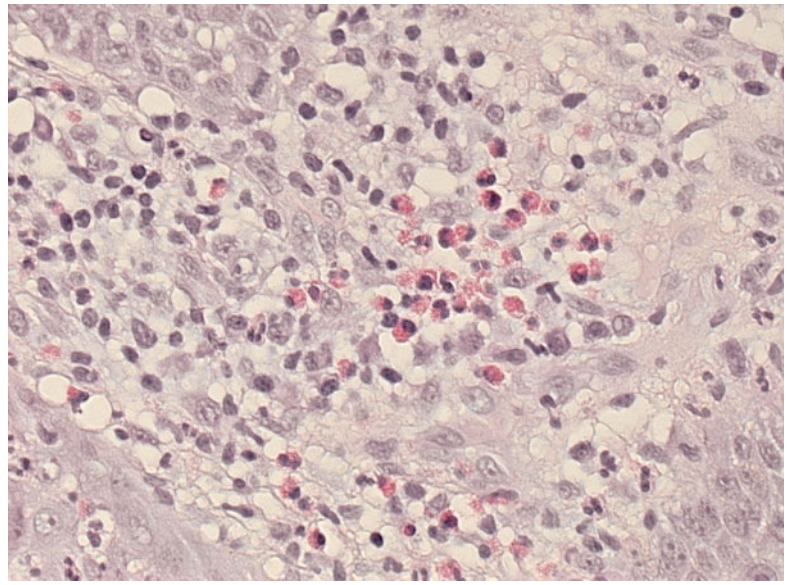

Fig. 14.51 Primary yaws. Diffuse dermal infiltrate of plasma cells, lymphocytes, histiocytes, and granulocytes with prominent eosinophils in some cases (H&E, 400× original magnification)

clinical course and is declining in incidence. Transmission appears to be from lesion to skin, usually between family members. Endemic syphilis, or bejel, is thought to affect about 2.5 million people. It is caused by *T. pallidum endemicum*, and the disease is largely confined to the arid Arabian peninsula and the southern border of the Sahara Desert. Children are the principal reservoir for a disease spread by skin-to-skin contact or via fomites such as communal pipes or drinking vessels. The rare primary-stage skin lesions usually go unnoticed, or appear as stomatitis at the angles of the lips. These painless lesions may resolve spontaneously but are usually followed by papulosquamous and erosive papular lesions of the trunk and extremities that are similar to yaws (Engelkens et al.1991c).

Viral Infections

Many viral infections have prominent skin manifestations. Certain characteristic skin lesions suggest a specific viral illness and the diagnosis can be confirmed by appropriate laboratory testing, such as cell culture, serology, electron microscopy, and PCR-based molecular assays. Viruses are obligatory intracellular organisms that need to use the metabolic machinery of the host cells for replication. Viral infection of the host cells induces alterations of cellular functions, inflammatory responses, and apoptosis that lead to the manifestations of viral illness. Viruses attach themselves to specific receptors on the surface before entering a host cell; therefore, virus infection is a receptor-mediated, species-type-specific, and cell-type-specific process. Viral infections of the skin are of increased significance and frequency in immunocompromised patients. Some of the common skin diseases, such as those caused by herpes simplex virus, herpes zoster virus, or enteroviruses will not be discussed in this chapter.

Acquired Immunodeficiency Syndrome

Etiology and Epidemiology

Acquired immune deficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV). AIDS was first recognized in the United States in 1981 and is the advanced form of infection with the HIV virus. Early HIV infection may not cause recognizable disease for a long period after the initial exposure. AIDS is considered one of the most devastating public health problems in recent history. AIDS can

be transmitted in several ways, and the risk factors for HIV include sexual contact, vertical transmission in pregnancy, exposure to contaminated blood or blood products, and needle sticks among healthcare professionals or drug abusers.

Clinical Features

HIV infects predominantly CD4+ cells, mainly T-helper cells, and leads to a profound alteration of immune system function that predisposes patients to numerous opportunistic infections, malignancies, and neurologic diseases. HIV itself produces cutaneous lesions shortly after exposure. More than 50 % of patients report cutaneous symptoms of acute HIV infection, approximately 2–6 weeks following HIV exposure. These usually present as a macular or morbilliform rash involving the trunk. Pruritic papular eruption is the most common cutaneous manifestation in HIV-infected patients (Kaplan et al. 1987; Hevia et al. 1991; Zalla et al. 1992; Ray and Gately 1994).

Several skin diseases occur almost exclusively in HIV-infected individuals, such as oral hairy leukoplakia, bacillary angiomatosis, and Kaposi's sarcoma. Approximately 25 % of HIV-infected individuals may be affected with oral hairy leukoplakia. These are white, verrucous, confluent plaques most commonly located on the lateral aspects of the tongue, which do not scrape off with a tongue depressor. EBV infection plays an important role in production of this lesion, although HPV and Candida are also frequently present (Ficarra et al. 1988; Scully et al. 1998; Patton 2013). Bacillary angiomatosis is a systemic infections caused by *Bartonella henselae* or *B. quintana*. Patients may have palpable painful subcutaneous nodules, which may resemble Kaposi's sarcoma or hemangioma but resolve with appropriate antibiotic therapy (Plettenberg et al. 2000; Grilo et al. 2009). Kaposi's sarcoma is the most common AIDS-associated cancer in the United States. Over 95 % of all Kaposi's sarcoma lesions have been associated with HHV-8 infections (Kemény et al. 1996). Skin lesions of Kaposi's sarcoma typically present with asymptomatic reddish-purple patches that may progress to raised plaques or nodules. One-third of patients also experience oral cavity lesions characterized by red-to-purple plaques or nodules (Ball 2003; Grayson and Pantanowitz 2008; O'Donnell et al. 2010).

Gradual deterioration of the immune system makes HIV-infected patients susceptible to many cutaneous viral diseases, such as those caused by herpesviruses (HSV, VZV, EBV, CMV) and human papillomavirus. Patients with HIV are also subject to fungal, protozoa, and arthropod infections that produce mucocutaneous lesions.

Histopathology

The histopathologic finding of the acute exanthema of HIV infection is nonspecific and mainly shows a dense perivascular infiltrate of lymphocytes in the dermis. Epidermal changes are usually mild, but may include spongiosis, vacuolar change, and keratinocyte apoptosis. The papular eruption of AIDS may show nonspecific perivascular eosinophils with mild folliculitis, although occasional epithelioid cell granulomas have also been reported (Smith et al. 1993a, b).

The lesions of oral hairy leukoplakia show irregular keratin projections, parakeratosis, and acanthosis (Fig. 14.52). Vacuolar change of superficial keratinocytes is a characteristic finding within the epithelium (Ficarra et al. 1988).

Skin biopsies of bacillary angiomatosis show single or multinodular proliferations of capillaries in the dermis accompanied by an inflammatory infiltrate that includes variable numbers of neutrophils, eosinophils, and mononuclear cells (Fig. 14.53). Leukocytoclasia and edema are frequently observed. Characteristic extracellular deposits of palely hematoxyphilic granular material containing dense masses of short bacilli can be observed and further highlighted with Warthin–Starry silver staining. These bacilli may also be delineated as gram-negative bacilli by modified Gram stains such as the Brown–Hopps stain (LeBoit et al. 1989; Cockerell 1990; Cockerell et al. 1991).

Differential Diagnosis

The acute exanthema of HIV infection can mimic many other skin lesions. Since there is no specific histopathologic finding to suggest the etiologic diagnosis, other confirmatory laboratory tests must be performed when there is a high index of suspicion.

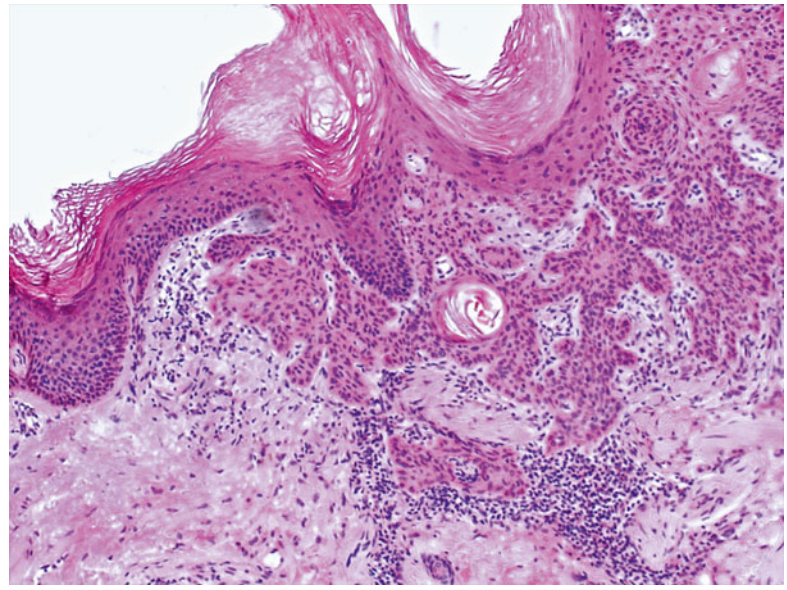

Fig. 14.52 Oral hairy leukoplakia. Irregular keratin projections, parakeratosis, acanthosis, and mild to moderate inflammatory infiltrate in dermis (H&E, 100× original magnification)

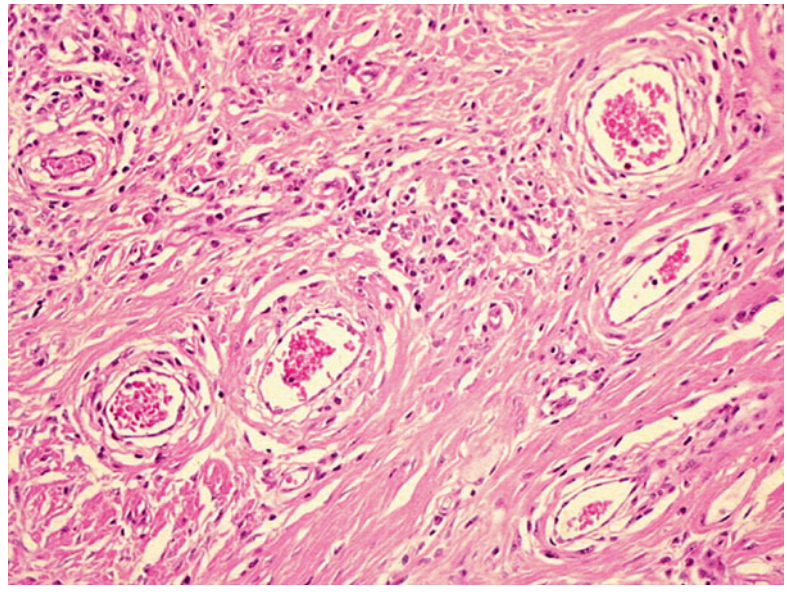

Fig. 14.53 Bacillary angiomatosis. Proliferations of capillaries in dermis accompanied by an inflammatory infiltrate, including variable numbers of neutrophils, eosinophils, and mononuclear cells (H&E, 200× original magnification)

Poxvirus Infections

The Poxviridae are double-stranded DNA viruses with two subfamilies that can infect both vertebrate and invertebrate animals. Four genera of poxviruses may infect humans: (1) orthopoxviruses such as variola (smallpox), monkeypox, and vaccinia, which are ovoid and 300 by 250 nm in diameter; (2) parapoxviruses such as those cause orf (ecthyma contagiosum) and milker's nodule, which are cylindrical and 260 by 160 nm in diameter; (3) Molluscipoxvirus, mainly molluscum contagiosum virus, which has an oval bullet shape and is 275 by 200 nm in diameter; and (4) Yatapoxviruses, such as tanapox, which is somewhat similar to the parapoxviruses.

These are complex DNA viruses that replicate in the cytoplasm and are adapted to proliferation in keratinocytes. Spread is primarily by direct contact with infectious material from an infected individual or animal or via fomites, although variola is spread via aerosolized droplets.

After the eradication of smallpox (Bhattacharya 2008), the most common poxvirus infections in humans are vaccinia (in Indian subcontinent), orf, and molluscum contagiosum; however, monkeypox (in West and Central African rain forest countries) and some unusual parapoxvirus infections have become emerging diseases with public health concern.

Monkeypox

Etiology and Epidemiology

Monkeypox virus belongs to the genus *Orthopoxvirus*. It is a zoonotic pathogen that causes a febrile rash disease in humans (Di Giulio and Eckburg 2004). It was first identified as a pathogen of laboratory macaque monkeys in 1958, but the first human cases were not reported until 1970, in Democratic Republic of the Congo. More than 400 cases in humans were reported between 1970 and 1995, and sporadic cases continue to be reported in several health districts within Democratic Republic of the Congo (Levine et al. 2007). Several studies showed that a variety of African mammals had serological evidence of previous infections with an Orthopoxvirus, and some of these species could serve as a natural reservoir for monkeypox virus in its endemic range. Humans and monkeys were possibly infected incidentally and did not readily transmit infection to others (Fleischauer et al. 2005). The first reported outbreak in the United States occurred in 2003 in several midwestern states (Centers for Disease Control and Prevention CDC 2003; Reed et al. 2004). Most of the patients became sick after having contact with pet prairie dogs infected with monkeypox virus, through contact with imported rodents from Ghana.

Clinical Features

Monkeypox has a mean incubation period of approximately 12 days, with a range of 7–17 days. The signs and symptoms of monkeypox in humans are similar to those of smallpox, but usually milder. Clinical manifestations often start with several days of high fever, general malaise, muscle aches, and headache followed by the development of a maculopapular rash. Similar to smallpox, the rash appears first on the mucosa of oropharynx, the face, and the forearms and spreads to the trunk and legs. The lesions usually develop through several stages before crusting and detaching. Within 1–2 days of appearance, the rash becomes vesicular and then pustular. The illness typically lasts for 2–4 weeks. The main distinguishing characteristic between monkeypox and smallpox is the prominent involvement of lymph nodes in monkeypox. Generalized or regional lymphadenopathy can appear and usually develops concurrently with or shortly after the onset of the prodromal fever. The involved lymph nodes are 1–2 cm in diameter and are firm with tenderness. Most of the monkeypox cases resolve spontaneously within 2–4 weeks. However, a small number of patients, especially in pediatric population, may present with a more severe course with respiratory distress or neurologic deterioration. Complications reported from African outbreaks include deforming scars, bronchopneumonia, secondary bacterial infection with septicemia, respiratory failure, ulcerative keratitis, blindness, and encephalitis (McCollum and Damon 2013). PCR assays have been developed to provide a rapid confirmatory diagnosis as well as speciation (Putkuri et al. 2009).

Histopathology

The skin lesion shows a spectrum of changes corresponding to the progression of disease (Stagles et al. 1985). At early stage, a mildly acantholytic epidermis with spongiosis and ballooning degeneration of basal keratinocytes is seen (Fig. 14.54). The changes progress to marked acantholysis and full-thickness necrosis of epidermis later (Fig. 14.55). A mixed inflammatory cell infiltrate is usually present around the vascular areas, eccrine glands, and follicles in the epidermis and dermis. Viral cytopathic effect is present with multinucleated syncytial keratinocytes with eosinophilic intracytoplasmic inclusions (Fig. 14.56). IHC demonstrates viral

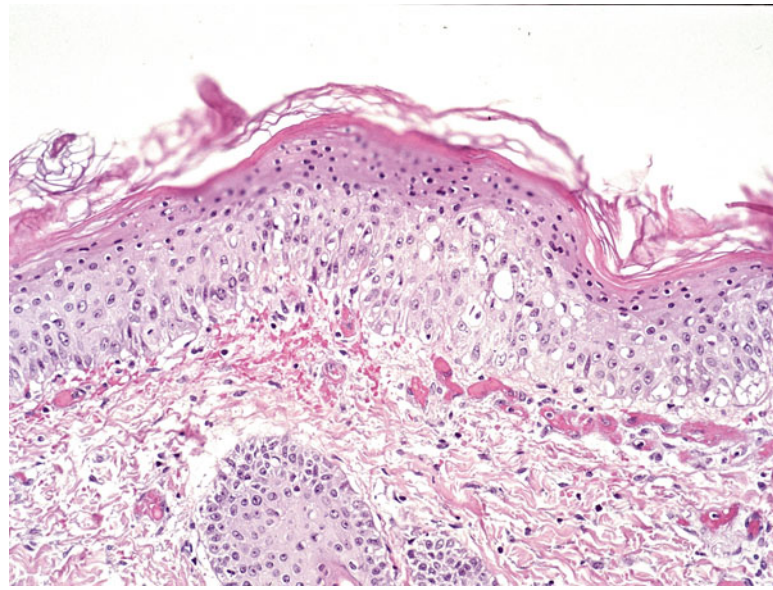

Fig. 14.54 Monkeypox. Epidermis with mild acantholysis, spongiosis, and ballooning degeneration of basal keratinocytes at early stage of infection (H&E, 100× original magnification)

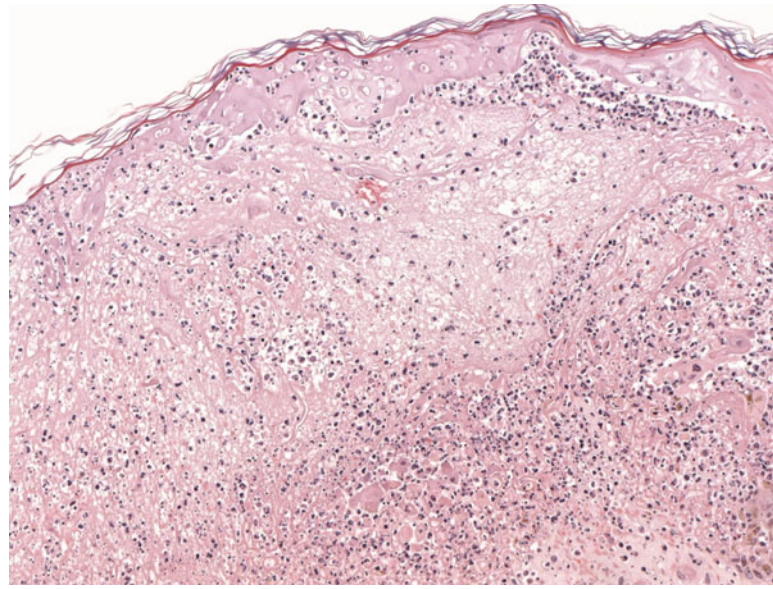

Fig. 14.55 Monkeypox. Marked acantholysis and full-thickness necrosis of epidermis at later stage of infection (H&E, 50× original magnification)

antigens within the infected keratinocytes and dermal adnexa (Fig. 14.57) (Guarner et al. 2004).

Differential Diagnosis

Skin lesions of monkeypox have to be differentiated from other vesicular pustular rash illnesses, such as varicella, impetigo, erythema multiforme, enteroviral infections, disseminated herpes simplex, and molluscum contagiosum.

Parapoxvirus Infections

Etiology and Epidemiology

Parapoxviruses infect many vertebrates, such as cows, sheep, goats, and red squirrels worldwide

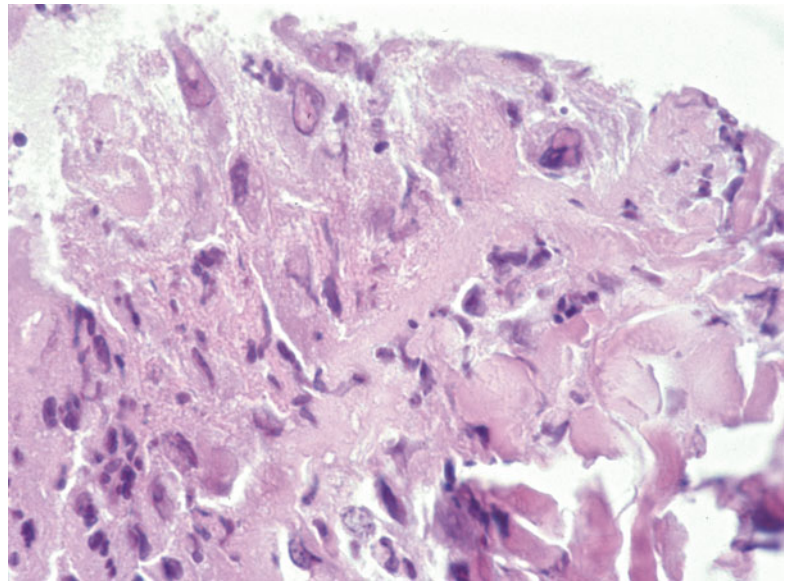

Fig. 14.56 Monkeypox. Viral cytopathic effect in keratinocytes with eosinophilic intracytoplasmic inclusions (H&E, 630× original magnification)

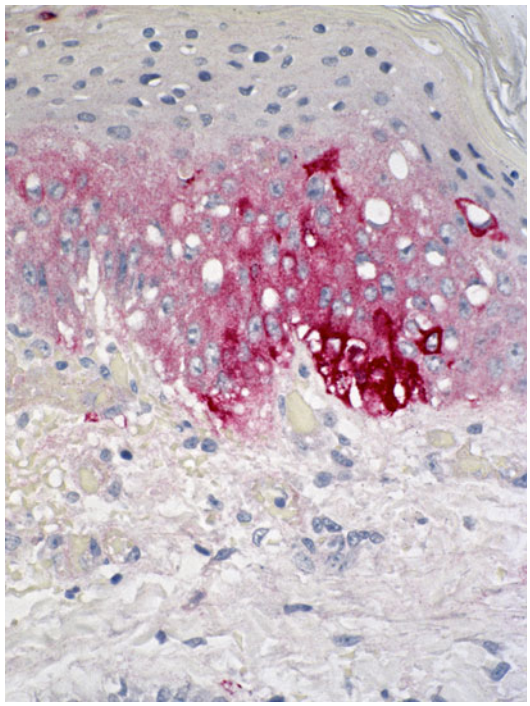

Fig. 14.57 Monkeypox. Immunostaining of *orthopoxvirus* antigens in the infected keratinocytes (IHC, 400× original magnification)

(Hessami et al. 1979). They cause skin lesions with a wide spectrum of clinical presentations that vary in size and location. Orf and Milker's nodule are the two most common human infections caused by parapoxvirus. There are many emerging parapoxviruses identified in the past decade because of increasing awareness and availability of molecular assays (Tondury et al. 2010).

Clinical Features

Orf virus is widespread in sheep and goats. Human lesions are caused by direct inoculation of infected material and are more common among shepherds, veterinary surgeons, and other individuals with exposure to animals. Butchers, meat porters, and cooks are sometimes infected from infected carcasses. There is an incubation period of 5–6 days, after which a small, firm, red, or reddish-blue papule enlarges to form an umbilicated hemorrhagic pustule or bulla. In the fully developed lesion, which is usually 2 or 3 cm in diameter but may be as large as 5 cm, the central crust is surrounded by a grayish to violaceous ring further encircled by a zone of erythema. The lesions are usually solitary or few in number and are located most commonly on the fingers, hands, or forearms. There may be tenderness and associated lymphangitis and regional lymphadenitis with mild fever. Spontaneous recovery usually occurs within 3–6 weeks (Leavell et al. 1968; Johannessen et al. 1975).

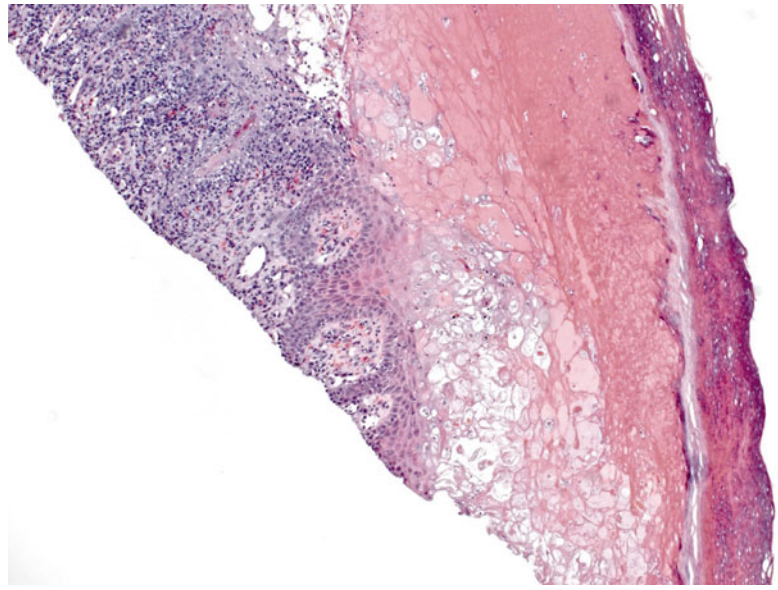

Fig. 14.58 Orf. Prominent parakeratosis, marked inter- and intracellular edema, vacuolization, ballooning degeneration, epidermolysis, and focal necrosis in epidermis (H&E, 50× original magnification)

Milker's nodule is caused by a parapoxvirus that most commonly leads to infection of the teats and mouths of cattle. Milkers, farmers, and veterinarians with a direct exposure to these lesions are accidental hosts. After an incubation period of about 5 days to 2 weeks, flat, red papules are formed. Within a week they appear as reddish-blue, firm, slightly tender nodules. The epidermis becomes opaque and grayish, and soon after, a crust develops centrally. As with orf, central umbilication is usually present. Many cases develop lymphangitis, but there are rarely any constitutional symptoms. Lesions resolve over 4–6 weeks without scarring. In contrast to orf, lesions are usually multiple. The most common sites of involvement are the hands and fingers. Rarely, a more widespread papulovesicular eruption of the hands, arms, legs, and neck may develop (Kuokkanen et al. 1976; Groves et al. 1991).

Histopathology

Parapoxvirus infections share some common histopathologic features. The epidermis usually shows prominent parakeratosis, marked inter- and intracellular edema, vacuolization, ballooning degeneration, epidermolysis, and focal necrosis (Fig. 14.58). Keratinocytes with eosinophilic cytoplasmic and intranuclear inclusions can be observed (Fig. 14.59). A dense infiltrate is present in the dermis that consists mainly of histiocytes at the center with lymphocytes and plasma cells at the periphery. There are usually very few neutrophils. The dermis may contain many newly formed, dilated capillaries with perivascular mononuclear infiltrate (Leavell et al. 1968; Evins et al. 1971; Groves et al. 1991). IHC is a useful ancillary assay that can highlight the parapoxviruses in skin biopsies to establish the diagnosis (Fig. 14.60) (Sanchez et al. 1985).

Differential Diagnosis

Each of the parapoxvirus infections must be distinguished from the others by clinical history and number of lesions. Other acute inflammatory infections that may resemble parapoxvirus infections include primary tuberculosis, sporotrichosis, pyogenic granulomas, anthrax, impetigo, arthropod bites, plague, rickettsialpox, scrub typhus, and tularemia. These lesions can usually be differentiated by histopathologic examination. Arthropod bites reaction, if persistent, raise a differential of T cell lymphoma and T cell pseudolymphoma. If immunohistochemistry for lymphoma is performed, CD30 positive immunoblasts may be seen raising concern for a CD30 + skin lymphomas (Rose et al. 1999).

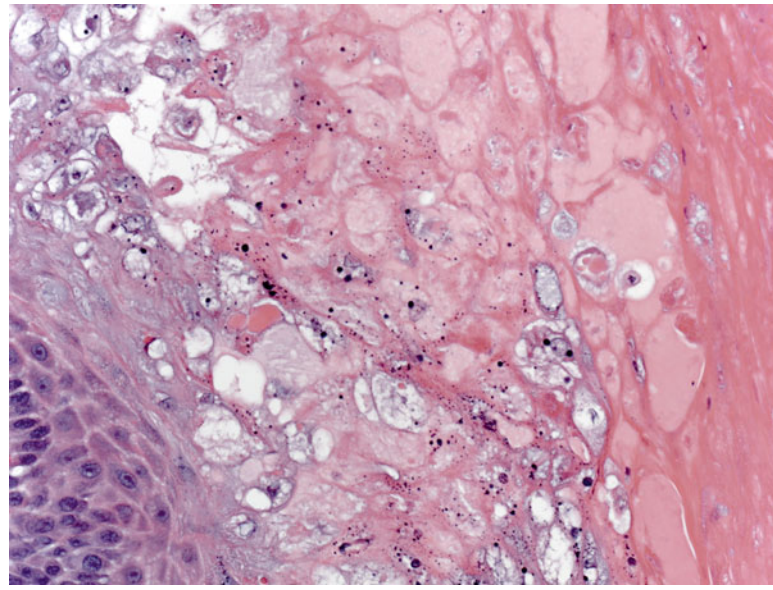

Fig. 14.59 Orf. Keratinocytes with vacuolization, ballooning degeneration, and eosinophilic cytoplasmic and intranuclear inclusions (H&E, 630× original magnification)

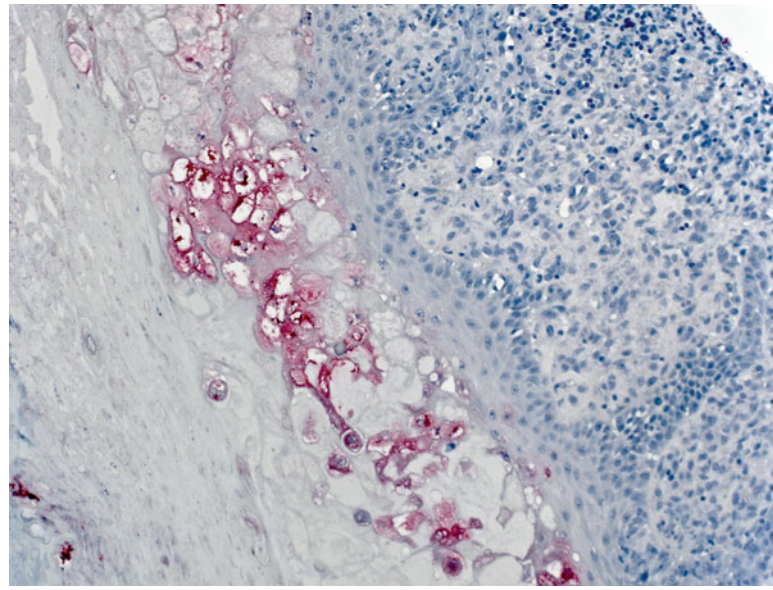

Fig. 14.60 Orf. Immunostaining of *parapoxvirus* antigens in the infected keratinocytes (IHC, 200× original magnification)

Viral Hemorrhagic Fevers

Etiology and Epidemiology

Although viral hemorrhagic fevers (VHF) are generally regarded as emerging diseases, they have existed for many years in different parts of the world. This designation does not mean to imply that they are newly recognized, but rather that the human exposure to the causative viruses has been increasing to an alarming level. These viruses are maintained in different species of reservoir in nature, such as insect, arthropod, or animal populations. They are transmitted from these reservoir populations to humans by direct

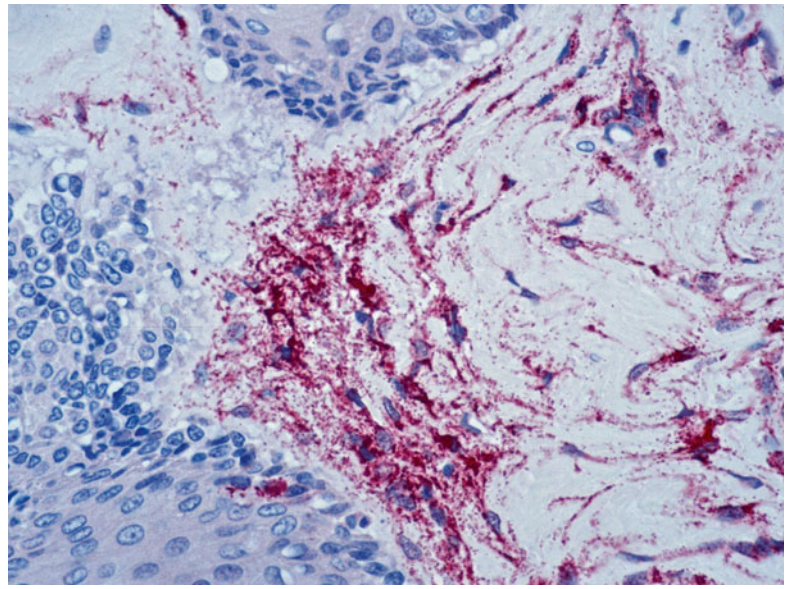

Fig. 14.61 Ebola hemorrhagic fever. Immunostaining of *Ebola* virus antigens in dermis, usually with no prominent inflammation (IHC, 400× original magnification)

or indirect exposure. Hemorrhagic fevers are usually endemic or linked to specific locations. The incidence and prevalence varies widely due to many factors, such as the reservoir and human population density, mode of transmission, environmental changes, geoclimateric alterations, and virulence of viruses (Guerrant et al. 2011; Singh and Ruzek 2013).

The viruses that cause hemorrhagic fevers are found most commonly in tropical locations; however, some of them can exist in cooler climates. Typical disease vectors include rodents, ticks, or mosquitoes, but person-to-person transmission in health-care settings or through sexual contact can also occur. The major viruses causing hemorrhagic fever belong to the following four families: (1) Filoviridae, such as Ebola virus and Marburg virus; (2) Arenaviridae, such as Lassa virus (Lassa HF), Junin virus (Argentinian HF), Machupo virus (Bolivian HF), and Guanarito virus (Venezuelan HF); (3) Flaviviridae, such as yellow fever virus and dengue virus; and (4) Bunyaviridae, such as Rift Valley fever virus (RVF), Crimean–Congo hemorrhagic fever virus (CCHF), and hantavirus (HF with renal syndrome and hantavirus pulmonary syndrome).

Since dengue virus infection has a much higher incidence with a more profound public health impact than other hemorrhagic fever viruses, it will be discussed in more detail later.

Clinical Features

The incubation period of these VHFs varies from 3 days to 3 weeks. The clinical symptoms and signs are nonspecific and usually start as flulike illness with fever, headache, backache, and generalized muscle and joint pain. These symptoms may be accompanied by nausea, vomiting, diarrhea, and abdominal pain. Hemorrhagic manifestations can appear early as petechiae, purpura, subconjunctival hemorrhage, or mucosal bleeding in oral cavity and gastrointestinal tract. Case fatality varies widely according to the different family of viruses, ranging from 15 to >90 %.

Histopathology

There is no specific histopathologic finding in skin biopsies of VHFs. Occasionally, mild perivascular lymphocytic infiltrate and subtle endothelial hyperplasia may be seen, but they do not provide any diagnostic value. IHC assay is a sensitive method for diagnosis of Ebola virus infection in skin biopsies; (Fig. 14.61) (Zaki et al. 1999) however, the sensitivity for other VHFs using skin biopsy as test sample is generally very low.

Differential Diagnosis

The petechial or purpural lesions should be differentiated with meningococcemia, bacterial sepsis, RMSF, and other forms of vasculitis and within the category of VHF itself.

Dengue Fever

Etiology and Epidemiology

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are caused by arthropod-borne viruses in the Flaviviridae family. They are single-stranded RNA viruses with four antigenically distinct members in the subgroup. Dengue viruses are transmitted by mosquitoes of the genus *Aedes* (e.g., *A. aegypti* and *A. albopictus*). The principal vector, *A. aegypti*, is found worldwide in the tropics and subtropics. Dengue virus infection has been reported in over 100 countries and has become one of the world's major emerging infectious diseases. About 100 million cases of DF, 250,000 cases of DHF, and 25,000 fatal cases are estimated to occur annually. DF is diagnosed in an increasing proportion of febrile travelers returning from the tropics, ranging from 2 % in the early 1990s to 16 % more recently. In some case series, DF now presents as the second most frequent cause of hospitalization (after malaria) in travelers returning from the tropics. There are now small endemic areas of disease in the United States as well. The majority of DHF cases are reported from Asian countries, where it is a leading cause of hospitalization and death among children. In the American tropics, DHF was once a rare disease but has been reported with a significantly increasing incidence since the 1980s, especially in the Caribbean, Central America, and South America (McBride and Bielefeldt-Ohmann 2000; Halstead 2008; Whitehorn and Farrar 2010).

Clinical Features

The incubation period is 2–8 days after a mosquito bite. The onset of the infection usually starts with abrupt fever, chills, headache, conjunctival injection, severe bone pain ("break bone fever"), generalized myalgias, arthralgias, and cutaneous exanthem. The exanthem is morbilliform and central in distribution. Petechiae and thrombocytopenia may be seen with initial infections, although hemorrhagic manifestations are seen more commonly in DHF. Hemorrhagic manifestations include petechiae, purpura, and bleeding of the gums, nose, and GI tract. Uncomplicated DF resolves within 5–7 days, whereas DHF carries mortality rate as high as 20 %. According to WHO criteria, the diagnosis of DHF is made based on the combination of hemorrhagic manifestations, with platelet count $<100{,}000/mm^3$, and objective evidence of plasma leakage, shown by either increased packed cell volume >20 % during the course of illness or hematocrit >45 % and clinical signs of plasma leakage, such as pleural effusion, ascites, or hypoproteinemia.

Histopathology

The morbilliform eruption appears similar to other viral exanthems with mild to moderate perivascular infiltrate of lymphocytes and slight spongiosis. Skin biopsies of hemorrhagic dengue show abundant extravasated erythrocytes. Occasionally, endothelial hyperplasia and thrombosis may be seen in vessels. None of the histopathologic changes are specific and there was no apparent correlation between histopathologic features and prognosis (Thomas et al. 2007; Saadiah et al. 2008; Saleem and Shaikh 2008). Although IHC with specific anti-dengue virus antibody can demonstrate viral antigens in endothelial cells or circulating monocytes (Fig. 14.62), the sensitivity is too low in skin biopsies to be a useful diagnostic method (Boonpucknavig et al. 1979; de Andino et al. 1985; Saadiah et al. 2008).

Differential Diagnosis

The differential diagnosis varies depending on which type of skin eruption is present. For the morbilliform eruption, scarlet fever, measles, rubella, toxoplasmosis, syphilis, drug eruption, and the acute HIV seroconversion reaction must be distinguished. For petechiae or purpura, meningococcemia, bacterial sepsis, RMSF, other hemorrhagic fever viruses, and other forms of vasculitis have to be considered.

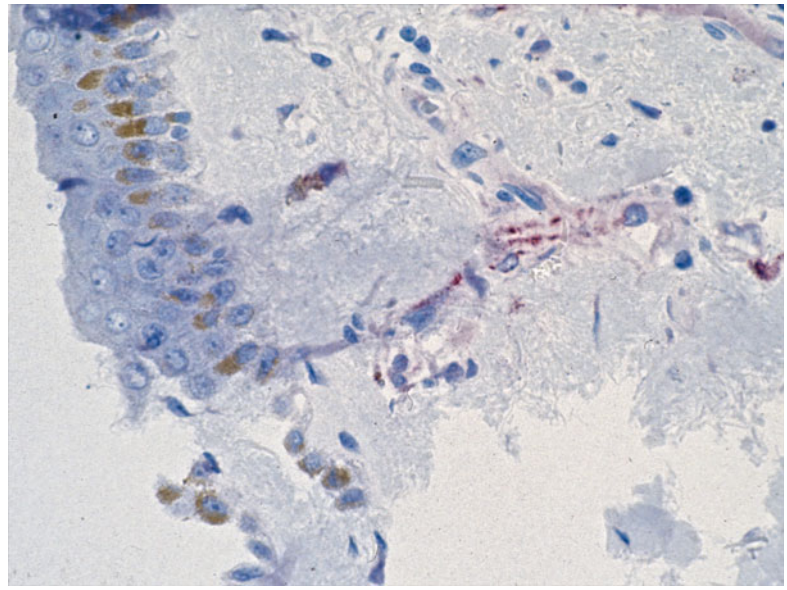

Fig. 14.62 Dengue hemorrhagic fever. Immunostaining of *dengue* virus antigens in endothelial cells (IHC, 400× original magnification)

Parasitic Infections

Protozoal Diseases

Protozoa may cause cutaneous lesions as a primary, secondary, or incidental infection. Leishmaniasis is the most common form of protozoal dermatitis and affects millions of people in the tropical and subtropical belts of the world. Free-living ameba such as *Acanthamoeba* species and *Balamuthia mandrillaris* have become emerging organisms associated with both immunocompromised and immunocompetent patients. Many protozoal infections can cause cutaneous immune reactions without the presence of organisms in the skin.

Leishmaniasis

Etiology and Epidemiology

Leishmaniasis is caused by the protozoon *Leishmania* with a wide spectrum of clinical illness, including cutaneous, mucosal, or visceral diseases. Leishmaniasis is one of the most common infectious diseases globally with a prevalence of 12 million cases and annual incidence of more than two million cases worldwide. The disease is more prevalent in countries with warmer climate, such as those around the Mediterranean coast, North Africa, South America, Central America, and Central Asia. There are many species of *Leishmania*, but most cases seen in travelers returning from tropical areas are due to *L. tropica*, *L. major*, and *L. aethiopica* (Grevelink and Lerner 1996; Choi and Lerner 2001; Weina et al. 2004; Rastogi and Nirwan 2007; Pavli and Maltezou 2010).

Leishmania spp. have both flagellar (promastigote) and aflagellar (amastigote) stages during their life cycle. The organisms are present at the elongated motile promastigote stage with an anterior flagellum in sandfly or in artificial culture media. Human infection is transmitted by the bite of the sandfly, usually at night and outdoors. After the promastigotes have entered the skin of the human host via the bite of infected sandflies, they transform into amastigotes, which primarily affect cells of mononuclear phagocytic system in its vertebrate host. If the host response to *Leishmania* spp. is confined to the skin, cutaneous lesions develop; however, if dissemination of the protozoa occurs, internal organs will become involved. The amastigote is round or oval, 2–3 μm in diameter, with no protruding flagellum. The nucleus and kinetoplast stain deeply with the Romanovsky stains, giving the organism its characteristic appearance. The infection is commonly zoonotic; one species of *Leishmania* may be associated with

Table 14.4 Etiologic organisms and histopathologic features of various types of cutaneous leishmaniasis

Type	New World parasites	Old World parasites	Histopathologic features
Localized acute cutaneous leishmaniasis	*L. b. braziliensis* *L. b. guyanensis* *L. b. panamensis* *L. m. mexicana* *L. m. amazonensis* *L. donovani chagasi*	*L. major* *L. tropica* *L. aethiopica* *L. infantum*	A dense and diffuse lymphohistiocytic infiltrate throughout the dermis with varying numbers of organisms. Amastigotes (Leishman–Donovan bodies) with dull blue-gray, round to oval bodies measuring 2–4 μm in diameter are seen in the cytoplasm of the histiocytes. Typical organisms also show a round basophilic nucleus and a rod-shaped paranuclear kinetoplast. These intracellular bodies stain red or dark blue with Giemsa stain but not with PAS or GMS stains. A granulomatous reaction containing epithelioid cells and multinucleated giant cells develops at later stages
Diffuse acute cutaneous leishmaniasis	*L. m. amazonensis* *L. mexicana* *L. m. pifanoi*	*L. aethiopica*	Similar as those seen in localized acute cutaneous leishmaniasis except for more abundant Leishman–Donovan bodies and a relative lack of accompanying lymphocytes. Eosinophils are prominent in the rare ulcerated lesions
Chronic cutaneous leishmaniasis (Leishmaniasis recidivans)	*L. braziliensis*	*L. tropica*	The histopathologic hallmark is a dense, diffuse, or nodular infiltrate composed of epithelioid cell granulomas within the superficial and deep dermis. The granulomas made up of epithelioid histiocytes and Langerhans giant cells surrounded by lymphocytes and plasma cells
Mucocutaneous leishmaniasis	*L. b. braziliensis*		In the early edematous phase, parasites are scant, a lymphohistiocytic infiltrate with admixed plasma cells in the superficial and deep dermis is present. At proliferative phase, parasites become obvious and granulomas can be seen. In necrotizing phase, areas of necrosis with numerous neutrophils and abundant Leishman–Donovan bodies are present
Post-kala-azar dermal leishmaniasis	*L. donovani chagasi*	*L. donovani* *L. tropica* *L. infantum*	The amount of epidermal melanin is decreased. Dermis shows superficial perivascular lymphocytic infiltrate with admixed plasma cells without evidence of granuloma formation
Visceral leishmaniasis	*L. donovani chagasi*	*L. donovani* *L. infantum* *L. tropica*	The cutaneous lesions, if present, are nonspecific and consist of a perivascular lymphohistiocytic infiltrate within the superficial dermis

one or many natural vertebrate hosts, which provide the reservoir of infection. Humans are usually accidental hosts (Ryan et al. 2012).

Clinical Features

Leishmaniasis used to be classified into a cutaneous, mucocutaneous, and visceral form; however, this simplistic classification has been abandoned in favor of a classification that recognizes the overlap in the clinical spectrum of various types of leishmaniasis (Sangueza et al. 1993; Pearson and Sousa 1996; Samady et al. 1996). Each form of leishmaniasis is associated with a different type of *Leishmania* spp. and has a specific predilection for a geographic location. These different forms include (1) localized acute cutaneous leishmaniasis; (2) diffuse acute cutaneous leishmaniasis; (3) chronic cutaneous leishmaniasis, including leishmaniasis recidivans (lupoid leishmaniasis); (4) mucocutaneous leishmaniasis; (5) post-kala-azar dermal leishmaniasis; and (6) visceral leishmaniasis. Because of the wide spectrum of clinical manifestations and complexity of host–vector–parasite relationship associated with these different forms, a detailed description of each form is beyond the scope of this chapter. The causative organisms and main histopathologic features are summarized in Table 14.4. The following

description will only focus on the most common form of skin involvement, i.e., localized acute cutaneous leishmaniasis. This form usually affects the exposed parts of the body, such as face, scalp, and arms. It appears initially as a painless, erythematous papule which enlarges over a period of 4–12 weeks to a nodule or a plaque measuring up to 2 cm in diameter. Ulceration is common. After several months the lesion spontaneously regresses, starting from the center and progressing outward. The end stage is represented by a scar accompanied by hypo- or hyperpigmentation. New World leishmaniasis commonly presents with a single lesion, while Old World leishmaniasis with multiple lesions (Goihman-Yahr 1994; Samady et al. 1996; Salman et al. 1999; Scarisbrick et al. 2006). The diagnosis of leishmaniasis depends on isolation or identification of the organism from tissue (Sharquie et al. 2002; Gazozai et al. 2010). Species-specific PCR assays have been developed to provide a rapid confirmatory diagnosis, especially in lesions that organisms cannot be identified in histologic sections (Safaei et al. 2002).

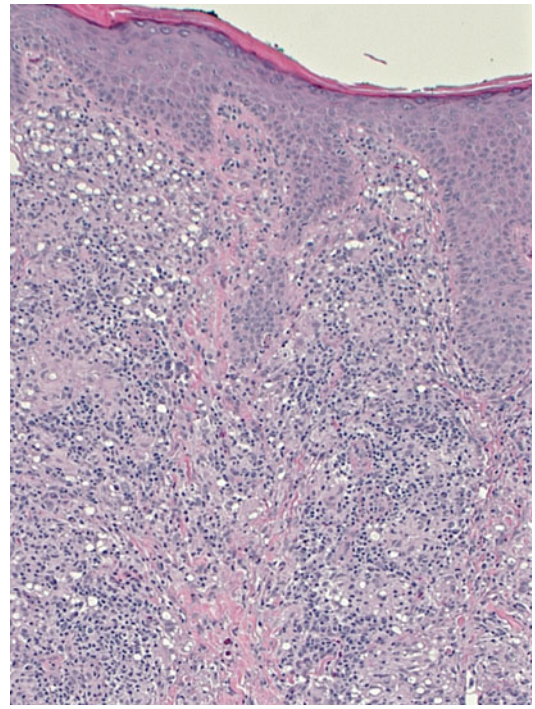

Fig. 14.63 Leishmaniasis. Dense and diffuse lymphohistiocytic infiltrate throughout the dermis (H&E, 100× original magnification)

Histopathology

The characteristic histopathologic change is a dense and diffuse lymphohistiocytic infiltrate throughout the dermis with varying numbers of organisms (Fig. 14.63). Eosinophils and neutrophils are rare and more commonly seen in ulcerated lesion. In routine H&E sections, amastigotes (Leishman–Donovan bodies) with dull blue-gray, round to oval bodies measuring 2–4 μm in diameter are seen in the cytoplasm of the histiocytes (Fig. 14.64). Typical organisms also show a round basophilic nucleus and a rod-shaped paranuclear kinetoplast, a specialized mitochondrial structure containing extracellular DNA (Fig. 14.65). These intracellular bodies stain red or dark blue with Giemsa stain but not with PAS or GMS stains. Organisms vary in number depending on the stage of the lesion and the immunologic status of the host. They are more abundant in early lesions and in immunocompromised hosts. Extracellular distribution can be observed when there are numerous organisms. As the lesions progress, the number of both organisms and histiocytes tend to gradually reduce. A granulomatous reaction containing epithelioid cells and multinucleated giant cells develops (Fig. 14.66); caseous necrosis is notably absent. The epidermal changes are nonspecific and consist of hyperkeratosis, parakeratosis, and epidermal atrophy or hyperplasia. Ulceration can be seen in some cases (Kurban et al. 1966; Gutierrez et al. 1991; Peltier et al. 1996; Botelho et al. 1998; Mehregan et al. 1999).

IHC with specific anti-*Leishmania* antibodies is a useful assay that can highlight *Leishmania* in skin biopsy samples to establish the diagnosis (Fig. 14.67) (Kenner et al. 1999). It is also a valuable tool for identifying organisms in unusual histopathological manifestations of leishmaniasis. Extracellular parasites can be noted in the connective tissue or in capillary lumens. Furthermore, immunolocalization of the antigens provides insightful information to understand the pathogenesis of leishmaniasis.

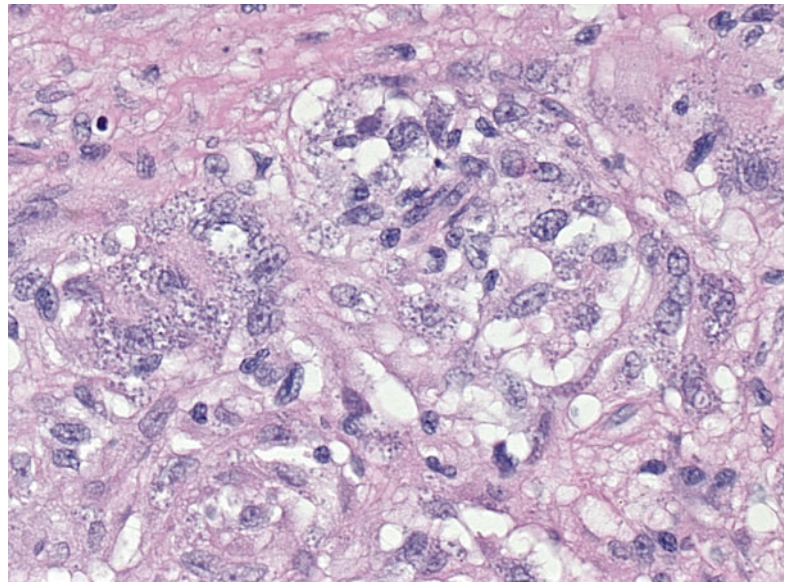

Fig. 14.64 Leishmaniasis. Amastigotes (Leishman–Donovan bodies) with dull blue-gray, round to oval bodies in the cytoplasm of the histiocytes (H&E, 400× original magnification)

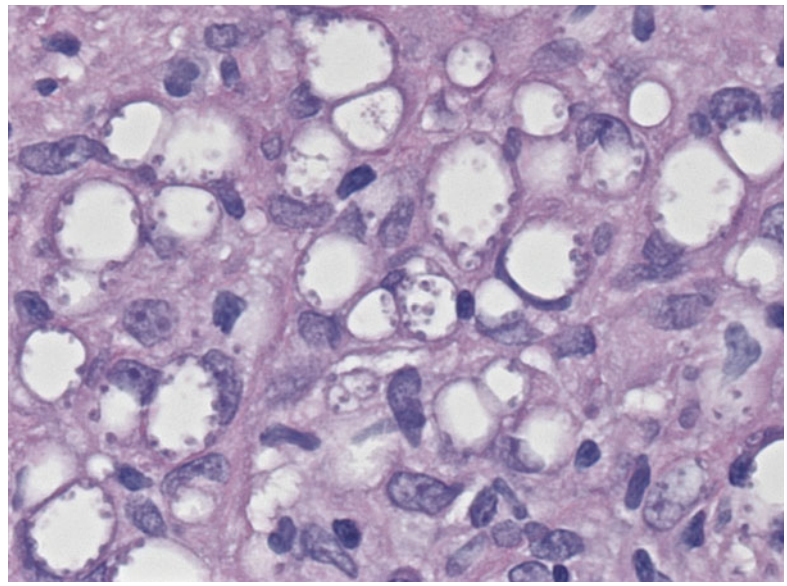

Fig. 14.65 Leishmaniasis. Amastigotes with a round basophilic nucleus and a rod-shaped paranuclear kinetoplast (H&E, 630× original magnification)

Differential Diagnosis

The morphology of intracytoplasmic amastigotes can appear similar to organisms of histoplasmosis, toxoplasmosis, and Chagas disease. *Histoplasma capsulatum* does not exhibit a kinetoplast and does stain with PAS and GMS. *Toxoplasma gondii* and *Trypanosoma cruzi* rarely cause skin lesions.

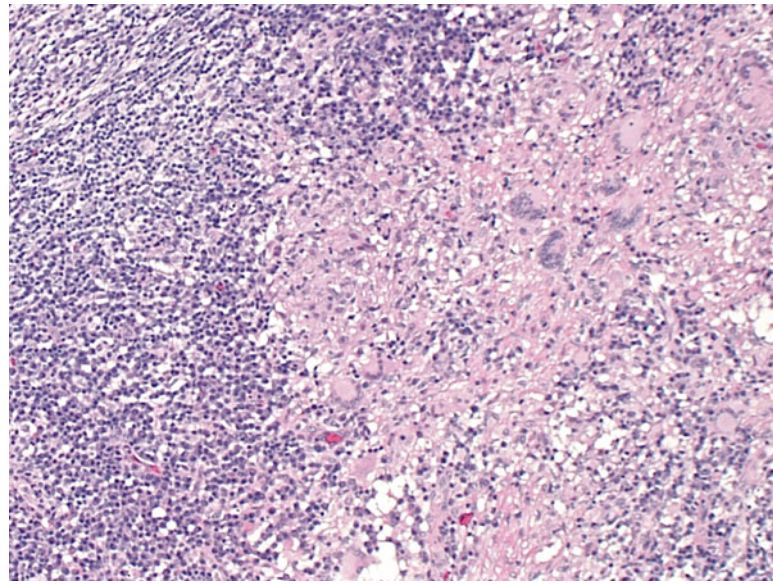

Fig. 14.66 Leishmaniasis. A granulomatous reaction containing epithelioid cells and multinucleated giant cells at later stage of infection (H&E, 100× original magnification)

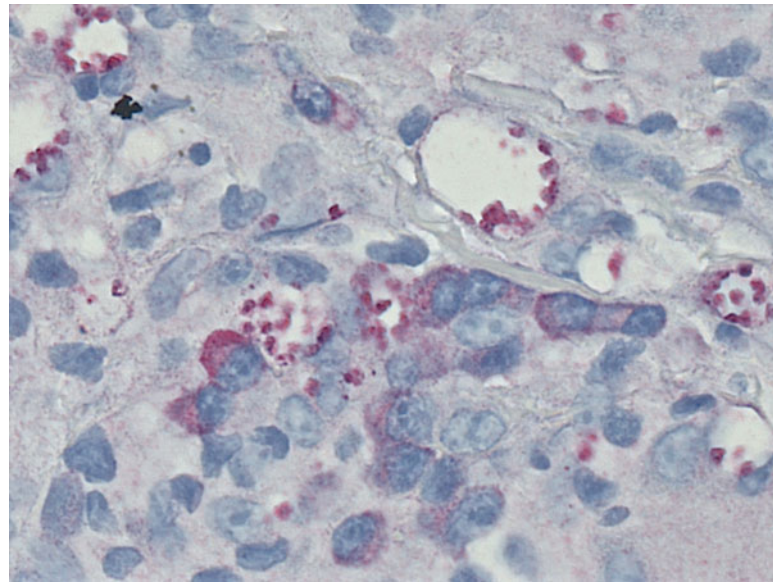

Fig. 14.67 Leishmaniasis. Immunostaining of leishmanial antigens in histiocytes (IHC, 630× original magnification)

Free-Living Amebic Infections

Free-living amebae are important causes of disease in humans and animals. These organisms are commonly found in soil and water throughout the world. Species that are able to tolerate temperatures above 37 °C are most likely to cause human disease.

Cutaneous Acanthamebiasis

Etiology and Epidemiology

Among the free-living amebic organisms capable of producing cutaneous lesions, acanthamebiasis recently surfaced as the most common one, especially among HIV, organ transplant, and other immunocompromised patients (Helton et al.

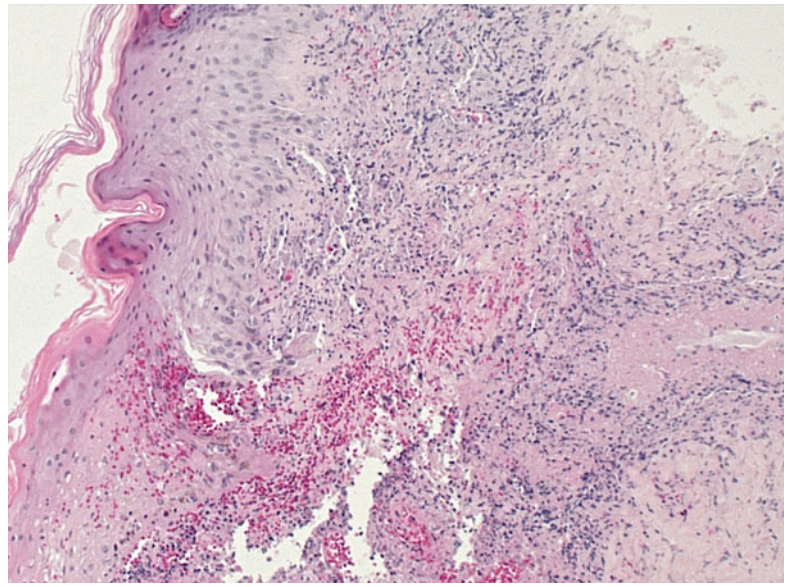

Fig. 14.68 Acanthamebiasis. Diffuse perivascular inflammatory infiltrate composed mainly of neutrophils and histiocytes admixed with extensive tissue necrosis, sometimes evolving into abscess formation (H&E, 50× original magnification)

1993; Tan et al. 1993; Deluol et al. 1996). *Acanthamoeba* spp. can be isolated from soil, dust, air, natural and treated water, etc. These organisms can also be found in nasal and pharyngeal mucosa of healthy individuals. They have a worldwide distribution with many species that can cause skin infections. Most infections are caused by three or four genotypes; T4 is the most common genotype in the environment and causes most cases of corneal and cutaneous infections. Multiplication occurs in the trophozoite stage by binary fission. *Acanthamoeba* spp. exists in two forms. The amebic cysts, measuring 12–20 μm in diameter, are resistant to desiccation and transform to trophozoites only in a favorable environment. Trophozoites, measuring between 15 and 45 μm in size, represent the infectious and invasive form of the organism. Both cyst and trophozoite stages exist in nature and can be identified in tissue sections. Transmission occurs via the respiratory mucosa or contamination of skin lesions. The organisms can infect other organs through hematogenous spread.

Clinical Features

The cutaneous lesions in acanthamebiasis are nonspecific and may present as macules, papules, nodules, or chronic nonhealing ulcers. The ulcers are poorly demarcated with elevated borders that may form eschar and eventually heal. The lesions are usually multiple as well as multifocal and may appear in crops involving the trunk, face, and extremities. Disseminated form has been reported in transplant patients. The skin may serve either as the initial port of entry or may become secondarily involved via hematogenous spread (Gullett et al. 1979; Wortman 1996; Galarza et al. 2009).

Other clinical diseases caused by acanthamebic infection include granulomatous amebic encephalitis, pneumonitis, keratitis, and osteomyelitis. Clinical laboratory diagnosis can be made by culture, DFA, or PCR assays.

Histopathology

The skin biopsies usually demonstrate multifocal or diffuse perivascular inflammatory infiltrate composed mostly of neutrophils and histiocytes admixed with extensive tissue necrosis, sometimes evolving into abscess formation (Fig. 14.68). A predominant neutrophilic infiltrate may be present in the pustules, acute ulcers, or abscesses. Leukocytoclastic vasculitis with fibrin deposits within the vessel wall and vascular necrosis can also be observed. Lobular panniculitis with necrotizing vasculitis has been reported

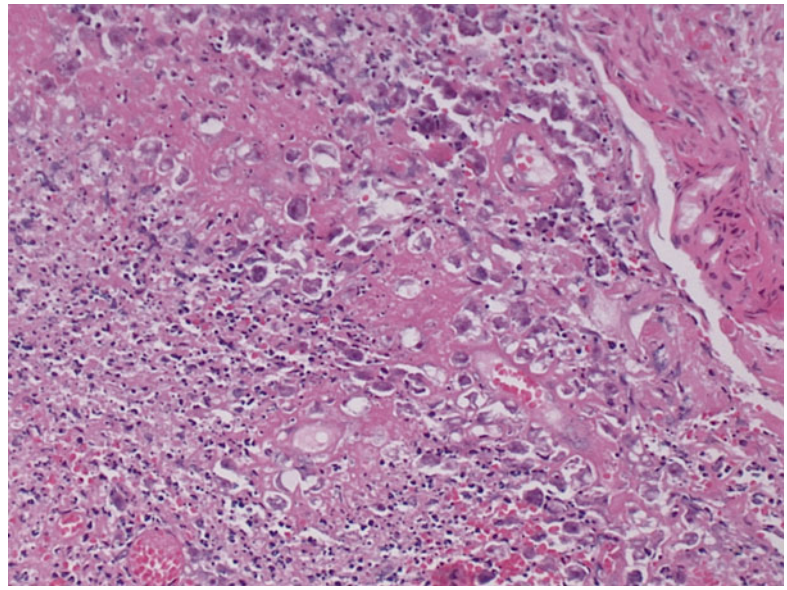

Fig. 14.69 Acanthamebiasis. Variable numbers of amebic organisms throughout the skin lesion, often more abundant in perivascular areas (H&E, 200× original magnification)

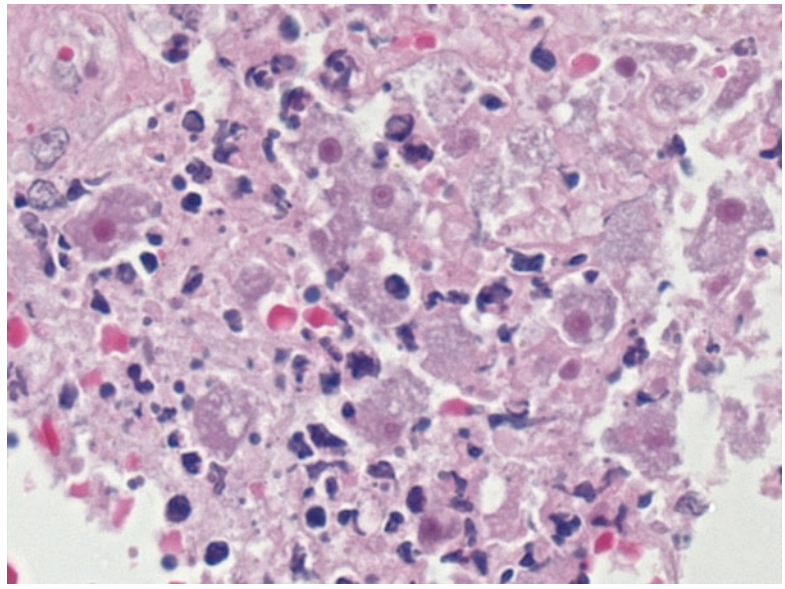

Fig. 14.70 Acanthamebiasis. Round trophozoites with projecting acanthopodia, vacuolated cytoplasm, and a centrally placed large nucleus with a single prominent nucleolus (karyosome) mixed within the inflammatory infiltrate (H&E, 630× original magnification)

in cases with deep dermal and subcutaneous lesions. Skin lesions in severely immunocompromised hosts show an altered tissue response with lack of giant cells and only poorly formed granulomas (Helton et al. 1993; Rosenberg and Morgan 2001; Galarza et al. 2009).

Variable numbers of amebic organisms are seen throughout the skin lesion and often more abundant in perivascular areas (Fig. 14.69). The round trophozoites usually present with projecting acanthopodia, vacuolated cytoplasm, and a centrally placed large nucleus with a single prominent nucleolus (karyosome) mixed within the inflammatory infiltrate (Fig. 14.70). Despite often being numerous, the trophozoite forms are relatively inconspicuous and can be missed easily, because their morphology closely resembles macrophages. The cyst forms display a double

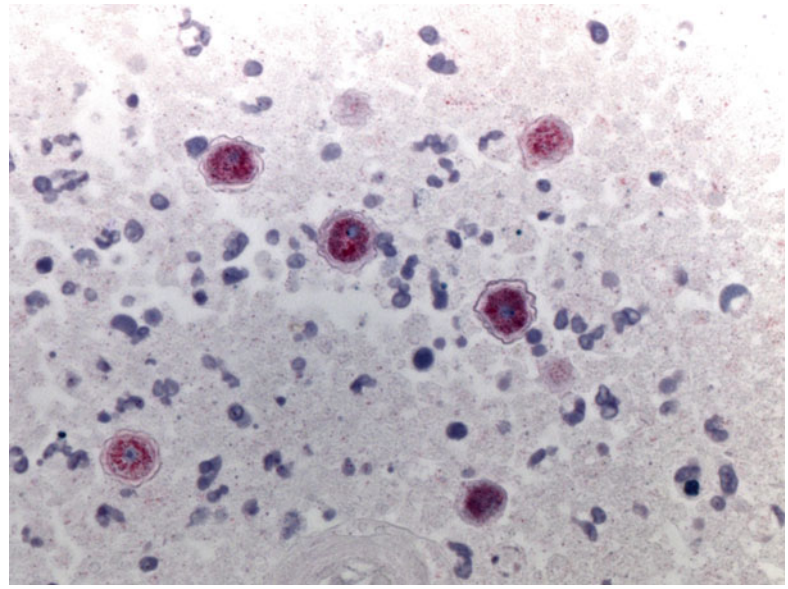

Fig. 14.71 Acanthamebiasis. Immunostaining of antigens in amebic cysts with outer wavy and wrinkled wall (IHC, 630× original magnification)

wall, with the outer wall wavy and wrinkled in appearance and the inner wall shallow and scalloped surrounding the cytoplasm (Fig. 14.71). The cyst walls can be highlighted with PAS and GMS. The genus and species cannot be determined by morphologic features. IHC is a useful ancillary assay to help highlight the amebic organisms in tissue samples, especially amid abundant macrophages with similar morphology (Fig. 14.71) (Guarner et al. 2007).

Differential Diagnosis

In immunocompromised hosts, *Acanthamoeba* infection must be differentiated from other skin lesions caused by many parasitic, fungal, bacterial, and viral infections. Most of these can be ruled out by clinical history, biopsy, direct examination, culture, or molecular testing of material from the lesion. *Entamoeba histolytica* produces painful ulcers that are seen most often in the perineal or perianal areas rather than on the face or extremities. The trophozoites of *E. histolytica* have similar size range with *Acanthamoeba* species, but they have a smaller nucleus with a vaguely perceptible karyosome. No cyst form of *E. histolytica* is present in tissue. *Acanthamoeba* cysts may be confused with *Blastomyces dermatitidis*; the yeast is slightly smaller with no prominent karyosome and has characteristically thick cell walls with broad-based budding.

Cutaneous *Balamuthia mandrillaris* Infection

Etiology and Epidemiology

B. mandrillaris, formerly referred to as leptomyxid ameba, is the only known species of this genus and was originally isolated from the brain of a mandrill baboon (Visvesvara et al. 1993). *B. mandrillaris* is found in the environment and can infect human beings through skin wounds or by inhaling the dust containing the organisms. Though *B. mandrillaris* infects animals and humans worldwide, it has only rarely been isolated from the soil and water, presumptively because it does not grow on conventional culture media. The life cycle consists of the trophozoite and cyst stages, both of which are infectious. *B. mandrillaris* trophozoites have a mean diameter of 30 μm (range 12–60 μm) and are uninucleate. Cysts have a mean diameter of 15 μm (range 12–30 μm) with a wavy and irregular outer wall that is composed of three layers. On H&E-stained slides, the organism cannot be reliably differentiated from *Acanthamoeba* (Lobo et al. 2013).

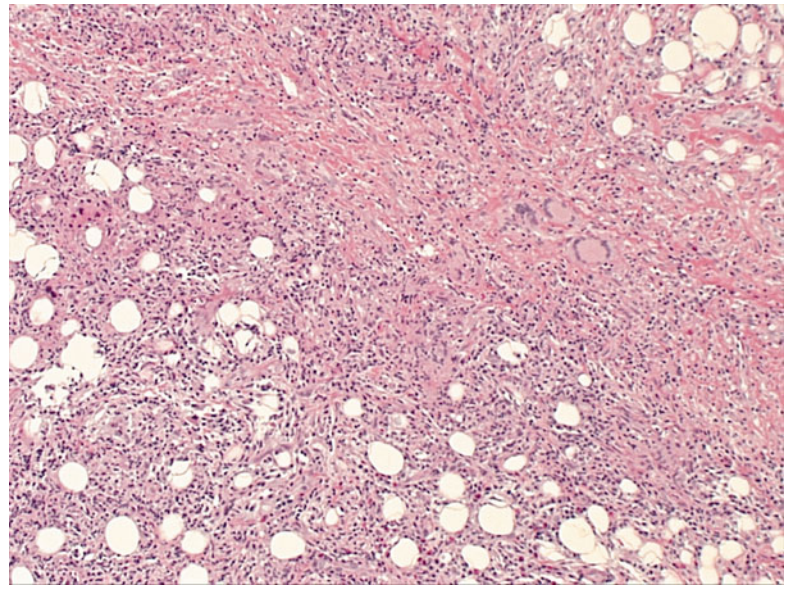

Fig. 14.72 *Balamuthia mandrillaris* infection. Diffuse inflammatory infiltrate in dermis and subcutaneous tissue with a mixture of neutrophils, lymphocytes, histiocytes, and scattered multinucleated giant cells (H&E, 50× original magnification)

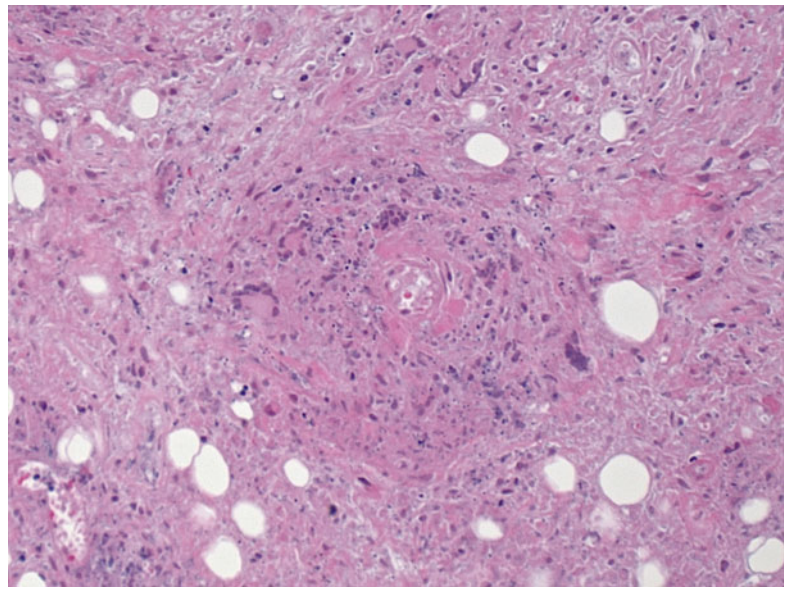

Fig. 14.73 *Balamuthia mandrillaris* infection. Perivascular inflammatory infiltrate, vasculitis, and vascular necrosis in dermis (H&E, 400× original magnification)

Clinical Features

Balamuthia can cause disease in both immunocompetent and immunocompromised hosts. Subacute or chronic granulomatous meningoencephalitis is the most common clinical presentation with a high mortality rate (Bravo et al. 2011). Balamuthiasis also sometimes manifests with skin lesions, particularly common in Peruvian patients (Martinez et al. 2010). These skin lesions are usually solitary and nodular and often appear on the central face, although other locations such as the lower face, abdomen, and extremities have been reported. Balamuthia skin lesions frequently precede CNS involvement. Clinical laboratory diagnosis can be made by DFA or PCR assays (Qvarnstrom et al. 2006).

Histopathology

The skin lesions caused by *B. mandrillaris* are similar to those caused by *Acanthamoeba* species with a broader spectrum. The inflammatory responses can range from an acute or neutrophilic infiltrate to a lymphocytic or granulomatous response (Fig. 14.72). Perivascular inflammatory infiltrate, vasculitis, and vascular necrosis are observed (Fig. 14.73). Unlike CNS

infection, cysts and trophozoites of *B. mandrillaris* are not readily appreciable (Pritzker et al. 2004; Guarner et al. 2007). IHC is a useful ancillary assay to help highlight the antigens of *B. Mandrillaris* in skin biopsy samples for etiologic diagnosis.

Differential Diagnosis

Similar to cutaneous Acanthamebiasis, the skin infection caused by *B. mandrillaris* must be differentiated from other infectious skin lesions. Most of these can be ruled out by clinical history, biopsy, direct examination, culture, or molecular testing of material from the lesion.

Helminthic Diseases

Skin lesions caused by endemic helminth infections are still prevalent in many tropical rural regions. These lesions can occasionally be seen in the United States and Europe as imported cases. Skin biopsies taken from such lesions are usually sent to a parasitologist for consultation; however, because such specimens usually demonstrate a limited spectrum of specific morphologic criteria, any pathologist should be able to arrive at a precise etiologic diagnosis with information on patient's travel or exposure history. The life cycles of these helminth worms may be complex, but humans can only be infected in three manners: (1) ingestion of eggs or larvae, (2) skin penetration of larvae, or (3) a bite or sting of an insect vector.

When a suspected helminth structure is seen microscopically, the first differential diagnosis should be the possibility of plant material, insect, or other foreign bodies. Plant cells can usually be recognized by their rigid and refringent cell walls with prominent glycogen granules. Intact insect cuticles are thick, chitinous, and pigmented with elaborate appendages. Nevertheless, a partially destroyed worm or helminth egg can be confused with plant material or insect, and the distinction between these materials can be very difficult. Once the helminth structures are determined, a taxonomic differentiation should be made to further categorize the organisms in the order of roundworms (nematodes), tapeworms (cestodes), or flukes (trematodes). The main morphologic features of differentiation are summarized in Table 14.5 (Chiodini et al. 2001; Satoskar et al. 2009).

Onchocerciasis

Etiology and Epidemiology

Onchocerciasis is caused by the filarial nematode *Onchocerca volvulus*. The cutaneous lesion is a chronic dermatitis accompanied by progressive keratitis, uveitis, and loss of vision (river blindness). It is transmitted by black flies of the genus *Simulium*, which breed in fast-flowing rivers. Onchocerciasis is endemic in the savannahs and rain forests of subequatorial Africa and in Yemen, Central America, and the Amazon basin of South America (Gibson et al. 1989).

Clinical Features

The adult worms live in the deep dermis and subcutis and become clinically apparent as asymptomatic subcutaneous nodules. These nodules are discrete, movable, ranging in size from 0.5 to 2.0 cm, and often located close to the bony prominences. The adult worms do not cause any detrimental host response; on the contrary, their progeny, consisting of numerous microfilariae, can provoke intense inflammatory changes in the dermis and the aqueous humor of the eyes. Endemic onchocercal dermatitis is predominantly papular and lichenoid and intensely itchy. The appearance of skin lesions varies according to their duration; they can be spotty and depigmented ("leopard skin"), scaly and atrophic ("lizard skin"), or thickened and hyperkeratotic ("elephant skin"). Inguinal lymphadenopathy and lymphedema of the groin ("hanging groin") may occur in advanced disease (Edungbola et al. 1987; Gibson et al. 1989; Murdoch et al. 1993; Somo et al. 1993; Abanobi et al. 1994). Onchocerciasis acquired by travelers to endemic regions can be seen up to 2 years later as an itchy rash with marked peripheral eosinophilia. In the eyes, keratitis, iridocyclitis, chorioretinitis, and optic atrophy can occur, leading to eventual blindness.

Histopathology

The cutaneous nodules show a chronic inflammatory infiltrate and fibrosis at their peripheries.

Table 14.5 Main morphologic features for differentiation of helminths

Helminth	Nematode		Trematode		Cestode
Stage in cutaneous lesion	Adult	Larva	Adult or larva	Ova	Larva
Common species	*Dracunculus*, *Onchocerca*, *Wuchereria*, *Brugia*, *Mansonella*, *Loa Loa*, *Dirofilaria*	*Ankylostoma*, *Onchocerca*, *Mansonella*, *Gnathostoma*	*Schistosoma*, *Fasciola*	*Schistosoma*, *Paragonimus*, *Fasciola*	*Cysticercus*, *Sparganum*
Size and shape	2 mm to 35 cm, round and slender	500 μm in length; no more than 10–30 μm in cross section	Variable size; leaf shaped	Variable sizes up to 140 μm in greatest diameter, round or elliptical shells	1–10 cm, rounded cysts
Detailed structures	Nonsegmented body with a true collagenous epicuticle surrounding a coelomic cavity that contains their sexually differentiated reproductive organs, as well as a digestive tract with a distinct proximal esophageal segment and with both buccal and anal openings	No sexual differentiation; tiny, basophilic, dot-like nuclei.	Nonsegmented body with a syncytial, noncollagenous tegument with spines or tubercles; ventral sucker plates; a primitive gut ending in two blind bifurcations (ceca); hermaphroditic or sexually dimorphic reproductive organs with prominently granulated vitellaria Larvae: smaller with no true cuticle; syncytial, noncollagenous tegument; larger and more distinct nuclei than roundworm larvae		Hyaline wall containing an inwardly protruding embryo lined by a noncollagenous syncytial tegument with a brush border; scolex or scolices possess arrays of sucker plates and shark tooth-shaped hooklets

Their centers consist of dense fibrous tissue containing long, tangled, and coiled worms of both sexes (Fig. 14.74). The transverse and diagonal sections of adult worms measure from 125 to 450 μm in transverse diameter and up to 500 mm in length in females and 42 mm in males. Adult worms are embedded in dense granulation tissue and in mixed inflammatory cells, including macrophages and multinuclear giant cells of the foreign body type (Fig. 14.75). Microfilariae are occasionally observed within lymphatic vessels of the cutaneous lesions. Their size ranges from 5 to 9 μm in diameter and from 220 to 360 μm in length. In early, untreated onchocercal dermatitis, many undulating microfilariae are present within the upper dermis with minimal inflammatory response around intact microfilariae. Their number decreases greatly with time and may be

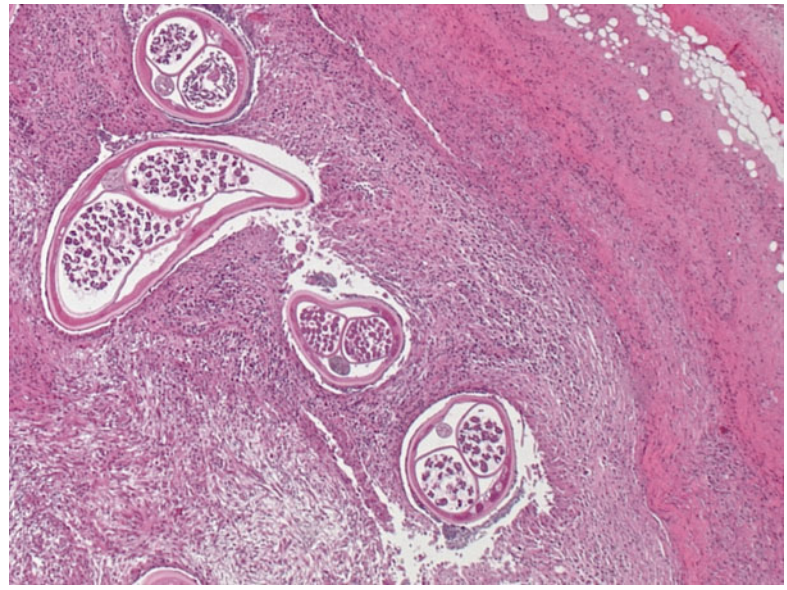

Fig. 14.74 Onchocerciasis. Chronic inflammatory infiltrate, fibrosis, and dense fibrous tissue containing long, tangled, and coiled worms of both sexes (H&E, 50× original magnification)

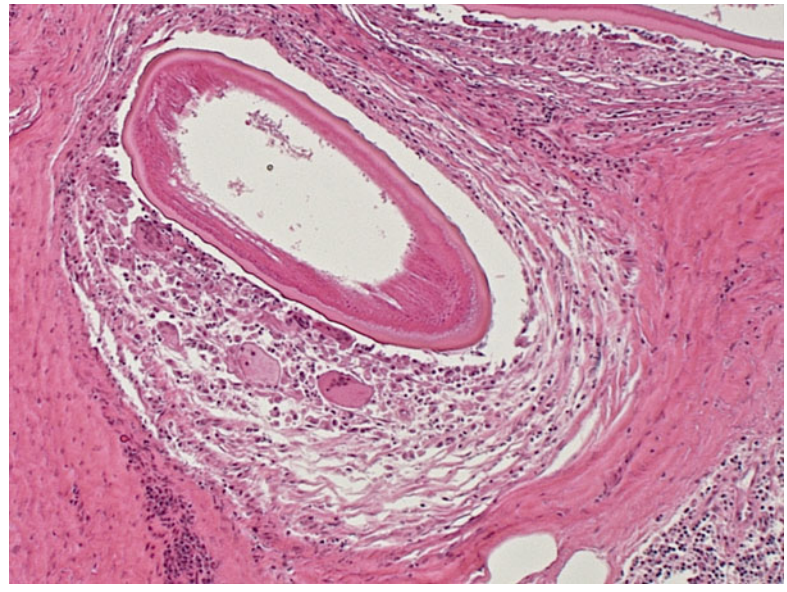

Fig. 14.75 Onchocerciasis. Adult worms embedded in dense granulation tissue and mixed inflammatory cells, including macrophages and multinuclear giant cells (H&E, 200× original magnification)

difficult to find in old lesions. In early infections, reactive changes in the dermis are minimal, but, in the course of years, mixed inflammatory cells including eosinophils accumulate around the vessels, and, ultimately, fibrosis of the dermis results, especially in the perivascular areas (Fig. 14.76). Hyperorthokeratosis, parakeratosis, epidermal hyperplasia (in the late-stage flattening

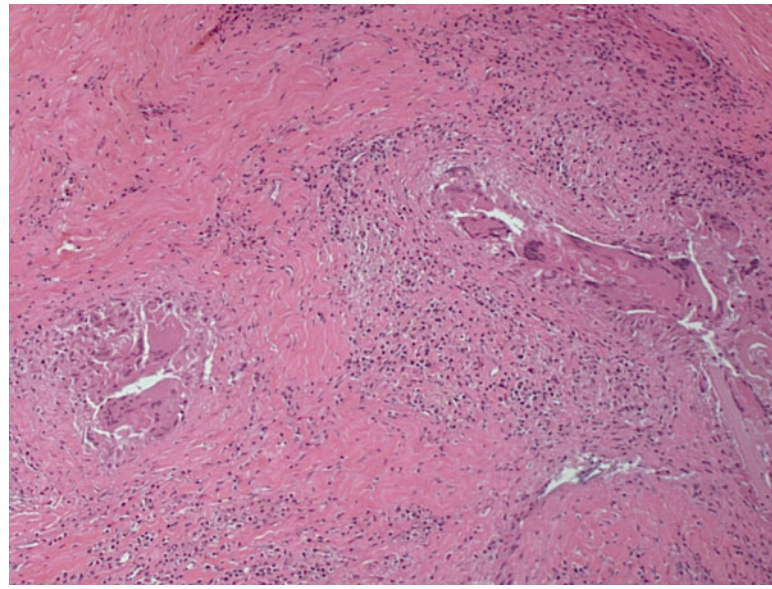

Fig. 14.76 Onchocerciasis. Mixed inflammatory cells including eosinophils around the vessels and diffuse fibrosis of dermis, especially in the perivascular areas (H&E, 50× original magnification)

of the epidermis), tortuosity of dermal vessels, and pigment incontinence are other features of long-standing onchocercal dermatitis (Benitez Soto 1947; Bonucci et al. 1979; Langham and Richardson 1981; Taylor et al. 1987).

Schistosomiasis

Etiology and Epidemiology

Schistosomiasis is a widespread chronic endemic infection by sexually dimorphic trematodes of the genus *Schistosoma.* The disease affects 180–200 million people in more than 80 countries, thereby making it the most important trematode pathogenic to humans worldwide. Human skin lesions can be caused by animal schistosomes or one of the schistosome species, most commonly *Schistosoma mansoni*, *S. haematobium*, or *S. japonicum. S. mansoni* is common in the Caribbean islands and in northeastern South America; *S. japonicum* is found in Eastern Asia; and *S. haematobium* is common in the Middle East and in Africa. The infection is usually acquired through exposure to skin-penetrating cercariae, a stage in the life cycle of the parasite. The cercariae emerge from a freshwater snail which functions as an obligate intermediate host to the fluke. The cercariae burrow through the skin and migrate to venous plexuses in various organs, where they mature into adult worms. *S. mansoni* and *S. japonicum* can cause portal hypertension and esophageal varices through lesions in the liver, and *S. haematobium* may lead to hematuria and hydronephrosis with involvement in the bladder. In Africa, mixed infections with both *S. mansoni* and *S. haematobium* are not uncommon (Secor and 2006; Meltzer and Schwartz 2013).

Clinical Features

The cutaneous manifestations of schistosomiasis can be divided into three types depending on the life cycle of the trematode. A pruritic, maculopapular erythematous skin rash called swimmers' itch (*dermatitis schistosomica)* occurs after penetration of the human skin by human or nonhuman cercarial larvae. This rash is self-healing within hours or days. Cercariae of nonhuman *Schistosoma* species exposed to human tissue always die at an early developmental stage (El-Mofty and Cahill 1964; El-Mofty and Nada 1975). More rarely, a similar rash occurs soon after exposure to cercariae of any of the major human-adapted schistosomes. This rash is usually mild and is seen more frequently in adult

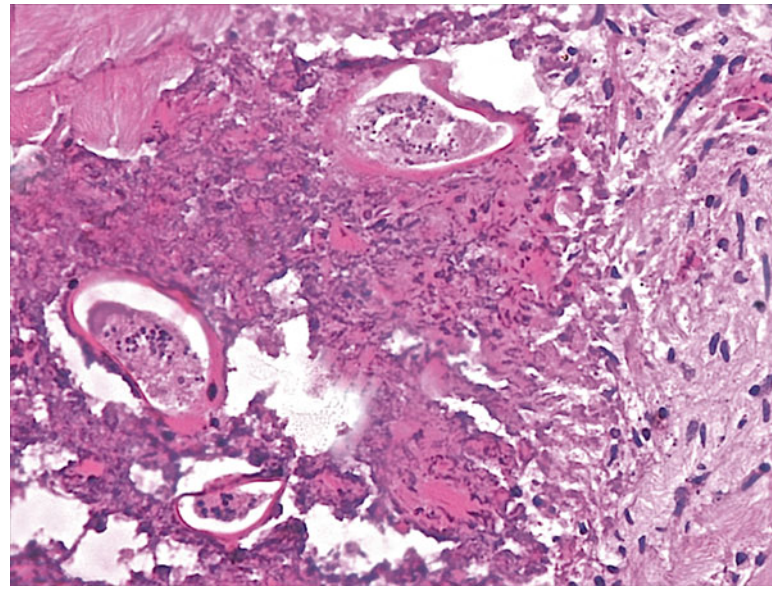

Fig. 14.77 Schistosomiasis. Necrotizing granulomatous inflammation in dermis with complete or degenerated schistosomal ova located in the center of necrosis (H&E, 630× original magnification)

travelers to the tropics than in residents of the endemic zone. The initial skin penetration of cercariae is followed by full-scale systemic reactions including fever, urticaria, and sometimes purpura known as Katayama syndrome in Japan and Yangtze fever in China (Marotto et al. 1995; Rocha et al. 1995; Doherty et al. 1996). This usually occurs within a few weeks due to release of numerous eggs into the blood stream by adult female worms. Another rare type of skin lesions is due to ectopic deposition of eggs within the dermis (known as *bilharziasis cutanea tarda*) by established schistosome worms during the chronic phase of infection (MacDonald and Morrison 1976; Wood et al. 1976). These lesions are most commonly seen in *S. haematobium* infection and presents as papular, verrucous, ulcerative, or granulomatous lesions in the genital or perianal skin.

Histopathology

The skin lesion of swimmers' itch is rarely biopsied. The chronic lesion of Bilharziasis cutanea tarda represents the main persistent cutaneous pathology of schistosomiasis. The histopathologic features comprise a palisading, necrotizing granulomatous inflammation within the dermis with complete or degenerated schistosomal ova located in the center of necrosis (Fig. 14.77). These ova are usually surrounded by histiocytes, lymphocytes, plasma cells, and occasional multinucleated giant cells. Prominent eosinophils can be observed in some lesions as part of the inflammation. Calcification of the eggs surrounded by fibrosis is a common finding in older lesions. The overlying epidermis often reveals pseudopapillomatous hyperplasia (Uthman et al. 1990; Kick et al. 2000).

The ova measure up to 120 μm in greatest dimension and possess a chitinous outer shell that stains positively with PAS. The presence and position of a spine on the shell of the ova allow their classification within the tissue. The spine of *S. mansoni* ova is on the lateral aspect, whereas *S. haematobium* ova have a spine in the apical position, and *S. japonicum* ova have no prominent spine. However, the morphology of these ova is often too distorted to discern the characteristic spines in paraffin-embedded sections. *S. mansoni* and *S. japonicum* eggs are acid fast by the Ziehl–Neelsen method, while *S. haematobium* eggs are negative.

Differential Diagnosis

Acute cercarial dermatitis should be differentiated from other allergic and pruritic skin lesions based on clinical evaluation and serologic testing. Patients with chronic skin lesions due to deposition of schistosome eggs usually also excrete eggs in the feces or urine or present with clinical evidence of urinary or hepatointestinal schistosome pathology.

Fungal Infections

The primary cutaneous fungal pathogens can be divided into two groups according to their nature and locations of the lesions they produced: those tend to cause superficial infections and those mainly cause deep infections. Another group of cutaneous fungal pathogens are more commonly seen in immunocompromised patients. These infections only involve the skin secondarily as part of systemic disease. The basic histopathologic pattern of cutaneous fungal infection is relatively uniform within each of these three groups because of similar host responses.

The degree of inflammatory response varies according to the host immune status. For example, infections with organisms causing superficial dermatomycoses, such as the dermatophytes, *Candida* species, or *Malassezia furfur*, are generally characterized by hyphae or pseudohyphae and sometimes yeast cells in the keratin layer of the epidermis and in follicles. The intensity of the tissue reaction in the epidermis and follicular epithelium ranges from no response to a mild or moderate lymphocytic infiltrate with chronic spongiotic-psoriasiform pattern. These organisms are usually not found in the dermis except in the case of follicular rupture.

Deep cutaneous fungal infections are clinically more significant because of their detrimental local or systemic consequence. These infections typically demonstrate a mixed dermal inflammatory infiltrate associated with pseudoepitheliomatous hyperplasia and occasionally with dermal fibrosis. Deep cutaneous fungal infections have also been associated with traumatic wound or iatrogenic injection. These rare instances are caused by environmental fungi that penetrate into host tissue due to breakdown of cutaneous barrier.

The laboratory diagnosis of fungal infections relies on culture, histopathologic evaluation, and other ancillary tests, such as special stains, IHC, ISH, and PCR assays.

Multiple special stains have been used to highlight certain fungal elements. These techniques can be helpful especially when the overall histologic pattern is suspicious for a fungal infection, but fungi are not conspicuous on routine H&E-stained sections. These special stains include periodic acid–Schiff (PAS), Grocott's methenamine silver impregnation (GMS), Gram, Fontana–Masson, mucicarmine, Alcian blue, India ink, and acid-fast stains. Immunohistochemical assays with relevant antibodies, in situ hybridization with pertinent probes, and PCR assays with specific primers have been developed to provide more sensitive and specific diagnosis for fungal infections in tissue samples.

It is beyond the scope of this chapter to describe these fungal infections individually in detail; the epidemiologic, clinical, morphologic, and histopathologic features of primary deep fungal infections and secondary cutaneous infections are summarized in Table 14.6 (Figs. 14.78, 14.79, 14.80, 14.81, 14.82, 14.83, 14.84, 14.85, 14.86, 14.87, 14.88, 14.89, 14.90, 14.91, 14.92, 14.93, 14.94, 14.95, 14.96, 14.97, 14.98, 14.99, and 14.100) (Chapman and Daniel 1994; Symposium 2002; Dismukes et al. 2003; Kauffman et al. 2011).

Table 14.6 Clinical, epidemiological, and histopathologic features of deep and secondary dermatomycoses

Disease	Etiology and epidemiology	Clinical features	Fungal size and morphology	Histopathologic features
Alternariosis (Figs. 14.78 and 14.79)	*Alternaria* species; ubiquitous saprophytic fungi in natural soil and plants	Exogenous form: ulcers and warty and granulomatous plaques. Endogenous form: deep dermis and subcutis involvement by hematogenous spread in immunocompromised patients	5–7 μm septate hyphae with variable branching and brown pigmentation; 3–10 μm round to oval spores, often with double contours	Suppurative and granulomatous dermatitis or panniculitis
Aspergillosis (Fig. 14.80)	*Aspergillus* species; *A. fumigatus* is the most common human pathogen of the genus; ubiquitous saprophytes found in soil, air, and decaying organic matter	Leading cause of opportunistic infection among immunocompromised patients, especially those with leukemia and solid organ or bone marrow transplant recipients	2–4 μm septate hyphae with dichotomous branching at 45° angle	Primary infection: granulomatous infiltrate. Secondary infection: angioinvasion, ischemic necrosis, and hemorrhage
Blastomycosis, North American (Figs. 14.81 and 14.82)	*Blastomyces dermatitidis*; in acidic soil of wooded areas near Mississippi and Ohio River valleys, South America, Europe, and Africa	Cutaneous infection occurs from hematogenous spread in 70 % of patients with disseminated blastomycosis; primary cutaneous infection is rare with ulcerated verrucous plaque at the inoculation site followed by lymphangitis and nodules spreading in a sporotrichoid distribution	5–15 μm thick-walled spores with single broad-based buds	Pseudoepitheliomatous hyperplasia with intraepidermal microabscesses. Suppurative granulomatous dermal infiltrate with giant cells
Candidiasis (Figs. 14.83 and 14.84)	Mainly *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*; C. albicans is part of the normal flora of the GI tract, oral cavity, and vagina	Clinical forms: acute mucocutaneous, chronic mucocutaneous, and disseminated	3–7 μm yeast cells; hyphae 3–5 μm wide; pseudohyphae with chains of cells formed by repeated budding of blastoconidia	Subcorneal pustules, pustules in dermis, variable acute and chronic dermal infiltrate with occasional granulomas
Chromoblastomycosis	*Fonsecaea pedrosoi* (most common), *Phialophora verrucosa*, *Cladophialophora carrionii*, *Fonsecaea compacta*, *Rhinocladiella aquaspersa*, endemic in decaying wood or soil in tropical and subtropical regions	Erythematous papule that subsequently develops into one or multiple coalescing warty papules or plaques, typically occur on an extremity.	6–12 μm thick-walled, dark brown spores, often in clusters; some cells possess central septation and cross walls (*Medlar bodies*, *sclerotic bodies*)	Hyperkeratosis and epidermal hyperplasia, often with a pseudoepitheliomatous pattern, overlying a suppurative and granulomatous dermatitis

(continued)

Table 14.6 (continued)

Disease	Etiology and epidemiology	Clinical features	Fungal size and morphology	Histopathologic features
Coccidioidomycosis (Fig. 14.85)	*Coccidioides immitis* and *C. posadasii*, endemic in the arid and semiarid regions of the southwestern United States and northern Mexico, also occurs in parts of Central and South America	Clinical forms: pulmonary, cutaneous inoculation, and systemic; primary cutaneous infection shows verrucous plaques often associated with lymphangitis and lymphadenitis	20–80 µm thick-walled sporangia spores with granular cytoplasm; 1–4 um endospores in spherules	Primary inoculation: mixed dermal infiltrate with granulocytes, lymphocytes, and occasional histiocytic giant cells Systemic: acanthosis and formation of intraepidermal microabscesses with granulomas
Cryptococcosis (Figs. 14.86 and 14.87)	*Cryptococcus neoformans and C. gattii*; in soil contaminated with bird and bat excreta	Skin involvement variable with papules, pustules, nodules, plaques, and cellulitis; most common systemic fungal infection in AIDS patients	5–15 µm spore with wide capsule in gelatinous reaction. 2–4 µm spore in granulomatous reaction	Gelatinous reaction with many spores Granulomatous reaction with fewer spores
Eumycetoma (Fig. 14.88 and 14.89)	*Madurella mycetomatis:* the most prevalent dematiaceous fungal agent. Many other etiologic fungi. Endemic in equatorial Africa, the Middle East, India, and Mexico; etiologic agents usually associated with woody plants and soil	Inoculation into skin after trauma; localized infection of skin, subcutis, fascia, and bone; tumefactive nodules, ulceration, and draining sinuses with extrusion of sclerotia (grains, granules) in exudates; bone involvement often extensive	0.5–2.0 mm sulfur granules composed of 4–5 µm thick septate hyphae	Aggregate of microorganisms (grain) in a microabscess surrounded by granulation tissue and fibrosis; numerous neutrophils with granulomatous inflammation
Histoplasmosis, African	*H. capsulatum* var. *duboisii*, endemic in Central and West Africa and on the island of Madagascar	Localized form: chronic illness involving the skin, bone, and lymph nodes Disseminated form: involves the liver, spleen, and other organs in addition to the features of the localized form and often fatal	8–15 µm ovoid spores in macrophages and free in tissue	Granulomatous dermal infiltrate with focal suppuration
Histoplasmosis, classic (Figs. 14.90 and 14.91)	*H. capsulatum* var. *capsulatum*, worldwide in soil containing bird excreta, common in Southeastern and Midwestern United States, Central America, parts of Southeast Asia, and the Mediterranean basin	Clinical forms: pulmonary, cutaneous inoculation, and systemic. Primary cutaneous infection presents as a chancriform ulcer with associated regional lymphadenopathy	2–4 µm round, narrow-necked budding spores with clear halo in the cytoplasm of large histiocytes	Suppurative granulomatous infiltrate in ulcerative skin lesions, neutrophils and eosinophils in oral lesions; histiocytes contain variable numbers of organisms
Hyalohyphomycosis (Figs. 14.92 and 14.93)	*Fusarium*, *Acremonium*, *Paecilomyces*, *Scedosporium*, *and Trichoderma* species; ubiquitous saprophytic organisms found in soil	Cutaneous infection may develop as a complication of ulcers, surgical trauma, and burns; disseminated infection may arise after pulmonary inhalation or as a result of spread of cutaneous disease	Septate, 2–4 µm-diameter hyalinized hyphae with branching at an acute angle	Cutaneous plaques, ulceration, and subcutaneous abscesses

Disease	Etiology and epidemiology	Clinical features	Fungal size and morphology	Histopathologic features
Lobomycosis (keloidal blastomycosis)	*Lacazia loboi*; endemic in South America near Amazon and Orinoco Rivers	Slowly growing cutaneous and subcutaneous keloidal nodules and plaques that occur on the cooler regions of the body, such as the ears, face, arms, and legs	6–12 μm thick double wall spherical spores with single or multiple budding, often in chains or beaded appearance	Atrophic epidermis with dermal macrophage and giant cells; nodules with numerous intracellular organisms and fibroblastic proliferation
Paracoccidioidomycosis (South American blastomycosis)	*Paracoccidioides brasiliensis*; endemic in the humid mountain forests of South and Central America	Cutaneous infection typically developed by dissemination from primary pulmonary infection; acneiform papules or nodules slowly develop into crusted plaques with well-defined, raised borders	6–20 μm thick-walled, refractile yeasts with narrow-necked, single or multiple buds	Similar to North American blastomycosis
Penicilliosis (Fig. 14.94)	*Penicillium marneffei*; endemic in Southeast Asia; the third most common opportunistic infection after tuberculosis and cryptococcosis in AIDS patients in northern Thailand	Significant cause of disseminated infection in HIV-infected patients residing or traveling to endemic area. Papular skin eruptions progress to necrotic cutaneous ulcers and abscesses, generalized lymphadenopathy, and hepatosplenomegaly, which can be fatal	Resembles *H. capsulatum*, except yeast cells multiply by binary fission rather than by budding	Granulomatous inflammation with foci of suppuration or necrosis
Phaeohyphomycosis (Figs. 14.95 and 14.96)	The most common fungi in this group are *Exophiala jeanselmei* and *Wangiella dermatitidis*; others include *Cladophialophora bantiana*, *Bipolaris spicifera*, *Exophiala* species, *Wangiella dermatitidis*, *Ramichloridium obovoideum*, and *Chaetomium atrobrunneum*	Subcutaneous pseudocysts, ulcerated and verrucous lesions	Loosely arranged, septate, occasionally branching pigmented hyphae varying from 2 to 25 μm diameter, budding spores often producing chains	Deep, coalescing, suppurative granulomas with multinucleated giant cells, fibrous encapsulation of cystlike lesions, pseudoepitheliomatous hyperplasia and intradermal neutrophilic microabscesses at the surface of nodules or verrucous plaques
Rhinosporidiosis (Fig. 14.97)	*Rhinosporidium seeberi*; highest prevalence in India and Sri Lanka, also reported in Americas, Africa, and Europe	Large polypoid growths usually involve the nasal (70 %), ocular, nasopharyngeal mucosa or skin	Sporangia up to 300 μm; 7–12 μm endospores within sporangia	Hyperplastic epithelium with papillomatosis, deep invagination with pseudocysts, submucosal infiltrate of neutrophils, lymphocytes, histiocytes, plasma cells, and multinucleated giant cells

(continued)

Table 14.6 (continued)

Disease	Etiology and epidemiology	Clinical features	Fungal size and morphology	Histopathologic features
Sporotrichosis (Figs. 14.98 and 14.99)	*Sporothrix schenckii*, saprophytic mold in soil, wood, and decaying vegetative matter; widely distributed in the United States, Central and South America, Australia, Asia, and South Africa	Clinical forms: lymphocutaneous, fixed cutaneous, and disseminated. Inoculation into skin with trauma, cutaneous and subcutaneous nodules with frequent involvement of lymphatics	4–6 μm round to oval spores, cigar-shaped forms; single or uncommon multiple buds, rare branching, nonseptate hyphae	Cutaneous lesions: epidermal hyperplasia with intraepidermal abscesses, suppurative granulomatous dermal infiltrate, occasional asteroid bodies Subcutaneous nodules: central zone of neutrophils surrounded by zones of epithelioid macrophages and round cells
Zygomycosis (mucormycosis) (Fig. 14.100)	Order Mucorales: *Rhizopus*, *Mucor*, *Absidia*, *Rhizomucor*, *Apophysomyces*, and *Cunninghamella bertholletiae* Order Entomophthorales: *Conidiobolus* and *Basidiobolus*; ubiquitous saprophytic organisms found in soil and on decomposing organic material	Clinical forms: rhinocerebral, pulmonary, GI, cutaneous, and disseminated	8–30 μm hyphae with pauciseptation and branching at haphazardly arranged angles. Variably thin, often collapsed or twisted walls	Angioinvasion with thrombosis, infarction, necrosis, and variable, mild, neutrophilic infiltrate

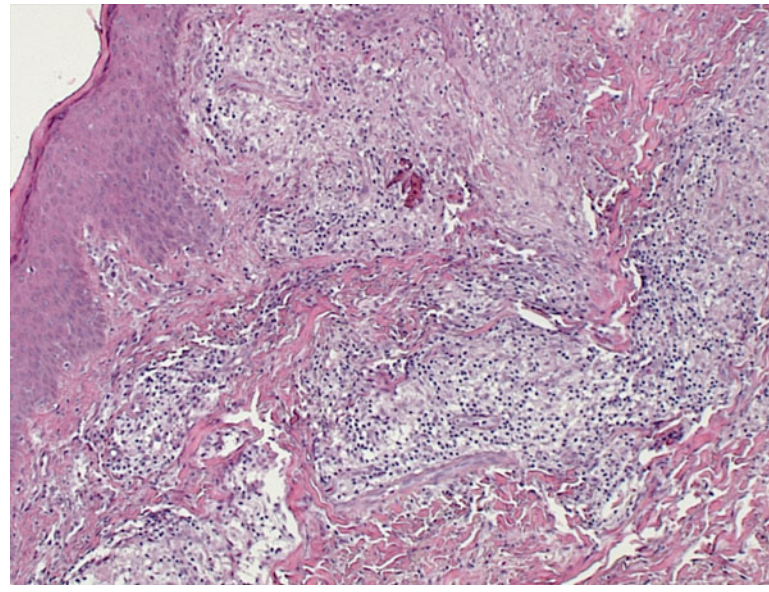

Fig. 14.78 Alternariosis. Suppurative and granulomatous inflammation in dermis, sometimes extending into subcutaneous tissue (H&E, 50× original magnification)

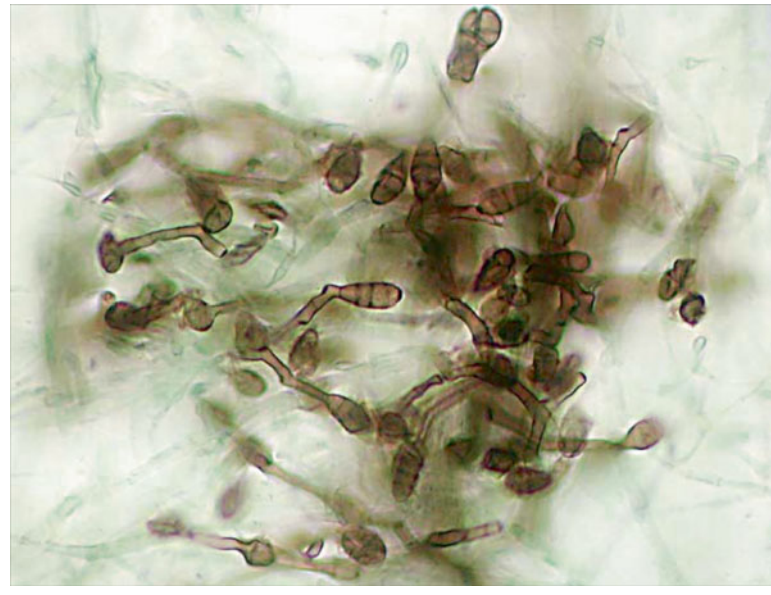

Fig. 14.79 Alternariosis. Septate hyphae with variable branching and brown pigmentation and round to oval spores, often with double contours (Grocott's methenamine silver stain, 1,000× original magnification)

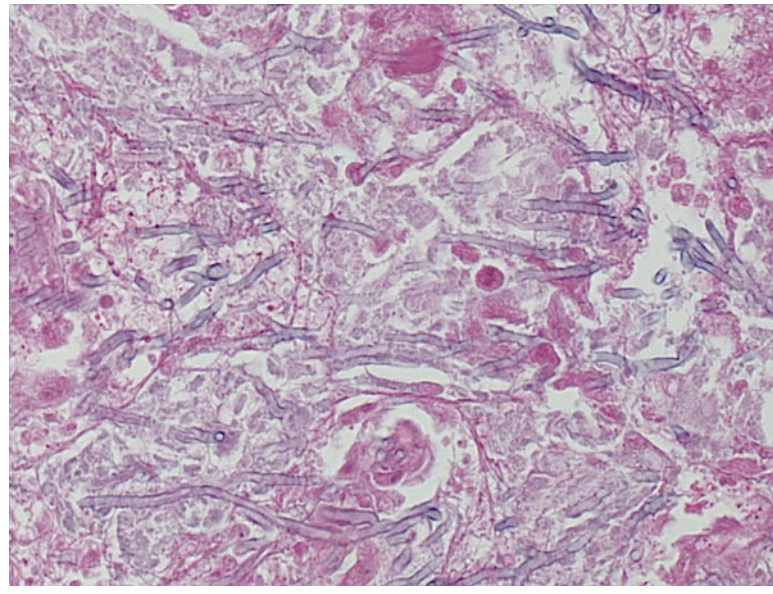

Fig. 14.80 Aspergillosis. Septate hyphae with dichotomous branching at 45° angle in areas of granulomatous infiltrate or in areas with angioinvasion and ischemic necrosis (H&E, 630× original magnification)

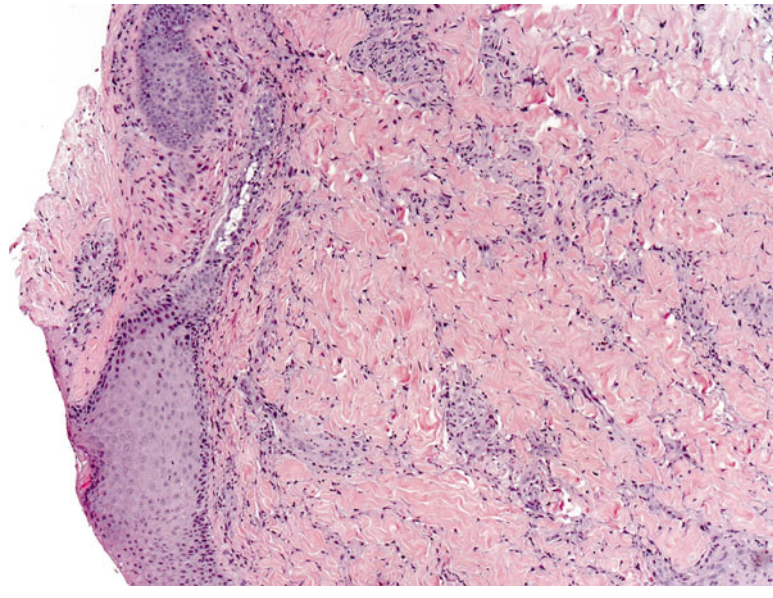

Fig. 14.81 Blastomycosis. Pseudoepitheliomatous hyperplasia with intraepidermal microabscesses and granulomatous dermal infiltrate (H&E, 50× original magnification)

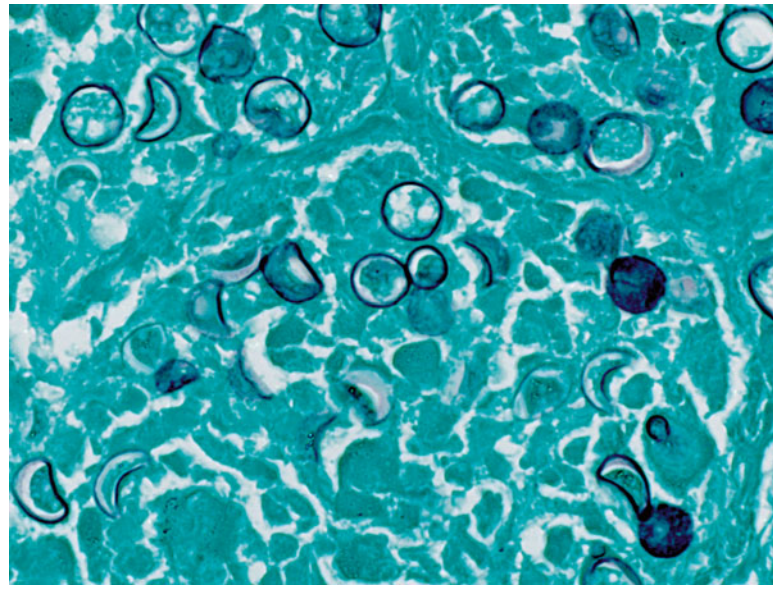

Fig. 14.82 Blastomycosis. Thick-walled spores with single broad-based buds in areas of inflammation (Grocott's methenamine silver stain, 1,000× original magnification)

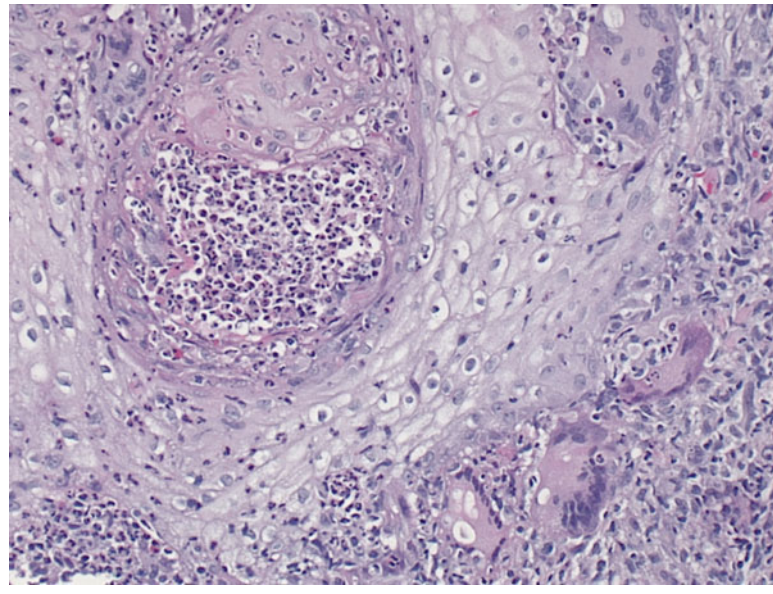

Fig. 14.83 Candidiasis. Pustules beneath stratum corneum and in dermis, variable acute and chronic dermal infiltrate with granulomas (H&E, 400× original magnification)

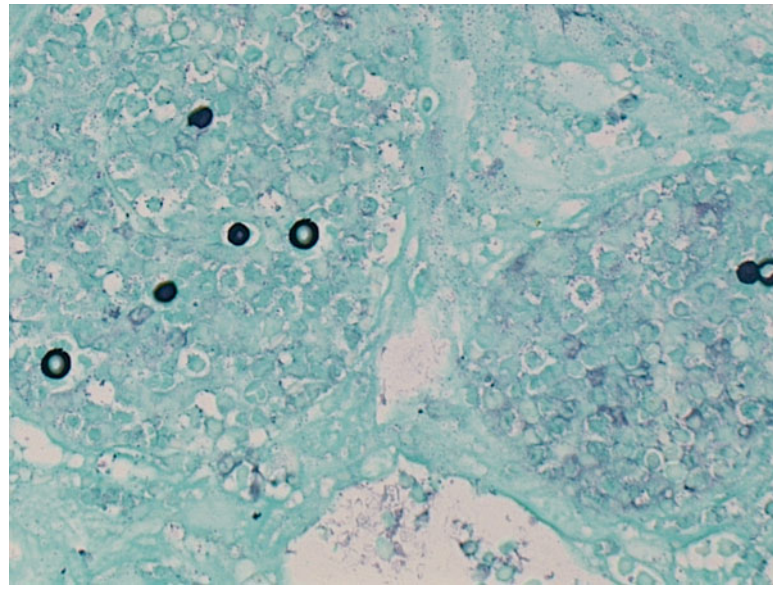

Fig. 14.84 Candidiasis. Yeast cells with budding of blastoconidia (Grocott's methenamine silver stain, 630× original magnification)

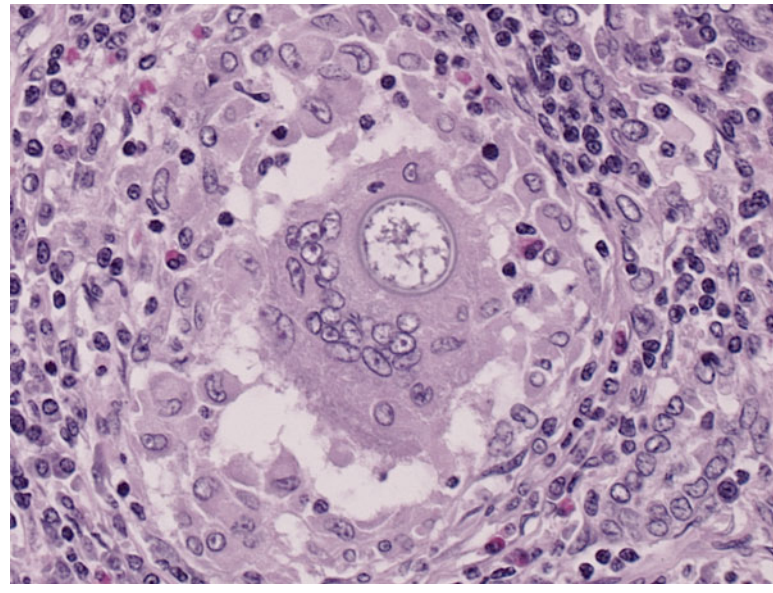

Fig. 14.85 Coccidioidomycosis. Spherule with thick wall, granular cytoplasm, and endospores in a multinucleated giant cell surrounded by mixed infiltrate of granulocytes, lymphocytes, and plasma cells (H&E, 630× original magnification)

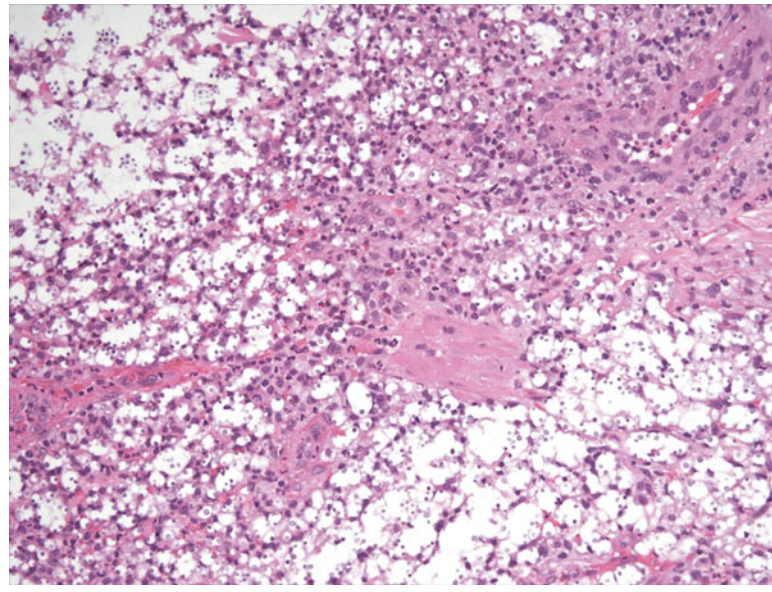

Fig. 14.86 Cryptococcosis. Gelatinous reaction in dermis with mixed inflammatory infiltrate and many yeasts (H&E, 200× original magnification)

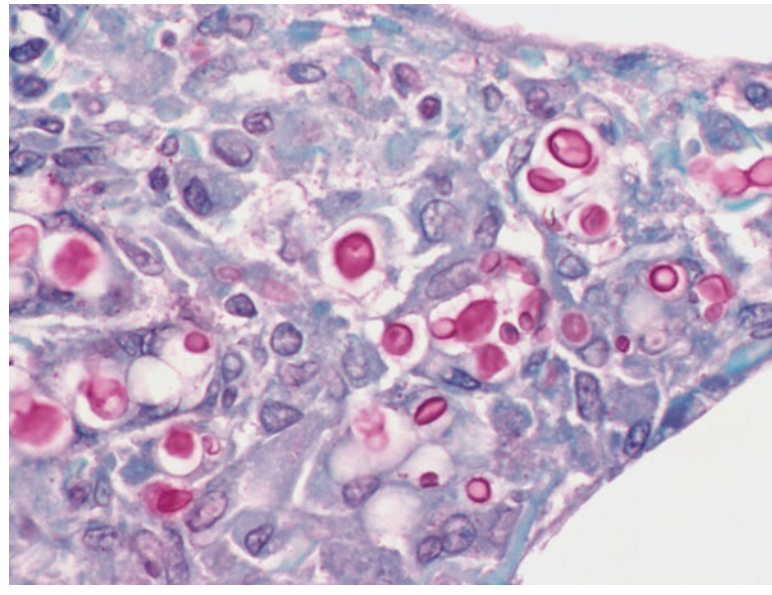

Fig. 14.87 Cryptococcosis. Yeast cells with wide capsule in dermal gelatinous reaction (Mucicarmine stain, 1,000× original magnification)

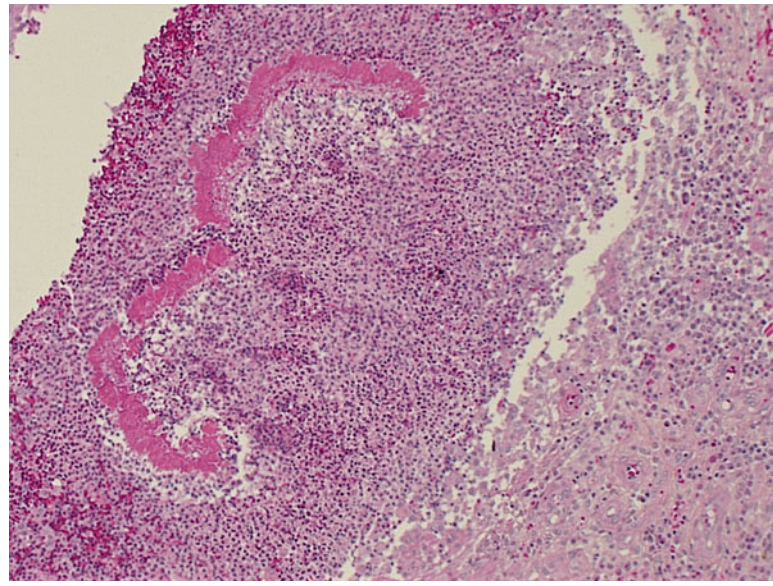

Fig. 14.88 Eumycetoma. Aggregate of microorganisms in a microabscess surrounded by granulation tissue, fibrosis, numerous neutrophils, and granulomatous inflammation (H&E, 50× original magnification)

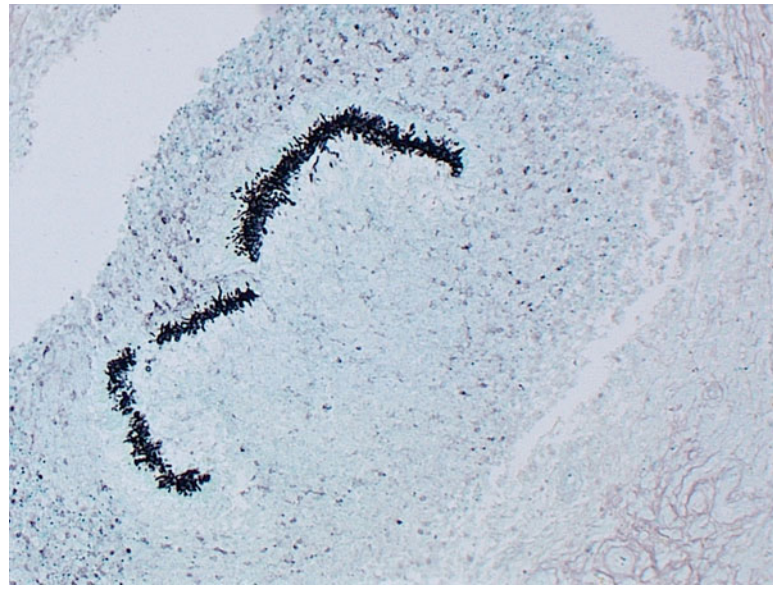

Fig. 14.89 Eumycetoma. Numerous septate hyphae in microabscess (Grocott's methenamine silver stain, 50× original magnification)

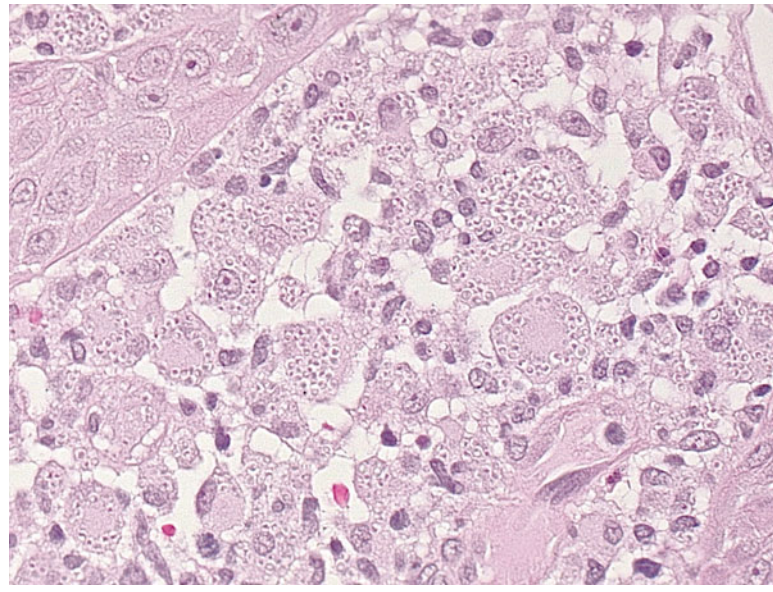

Fig. 14.90 Classic histoplasmosis. Suppurative granulomatous inflammation with abundant yeasts in large histiocytes (H&E, 630× original magnification)

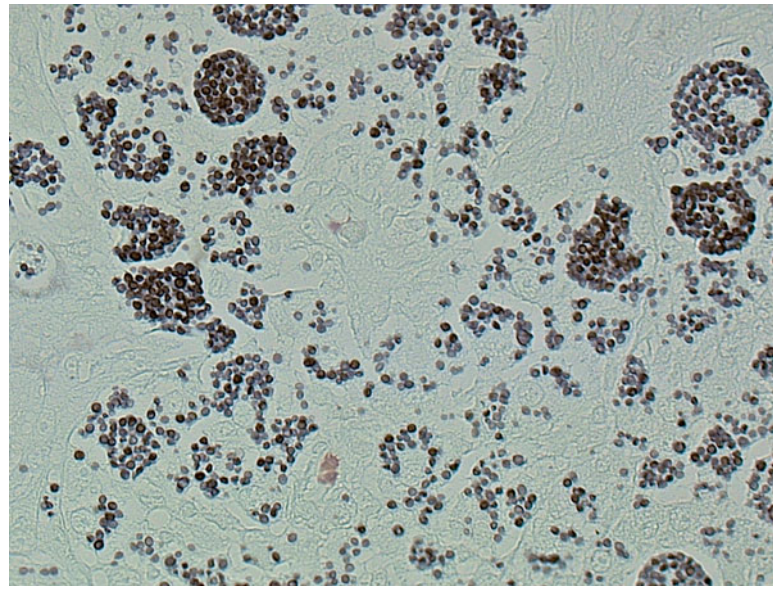

Fig. 14.91 Classic histoplasmosis. Small round, narrow-necked budding yeasts with clear halo in the cytoplasm of histiocytes (Grocott's methenamine silver stain, 630× original magnification)

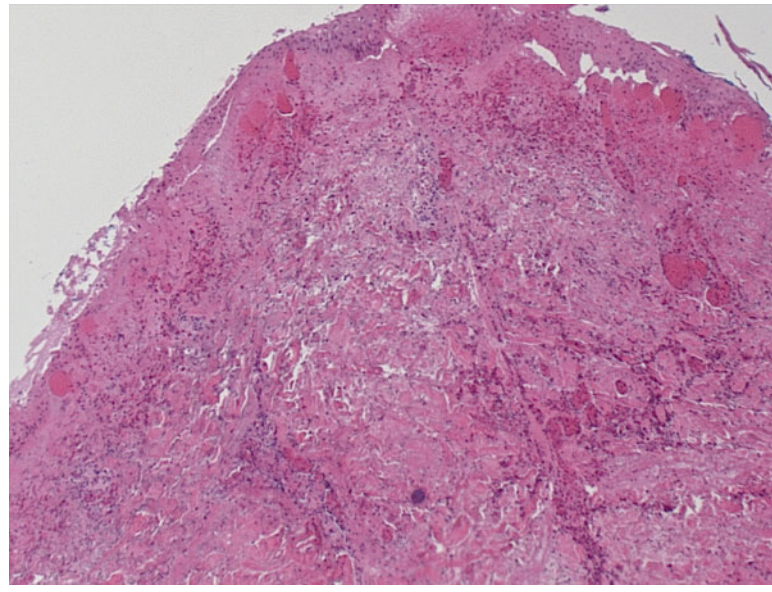

Fig. 14.92 Hyalohyphomycosis. Ulceration, dermal hemorrhage, mixed inflammatory infiltrate, and subcutaneous abscesses (H&E, 50× original magnification)

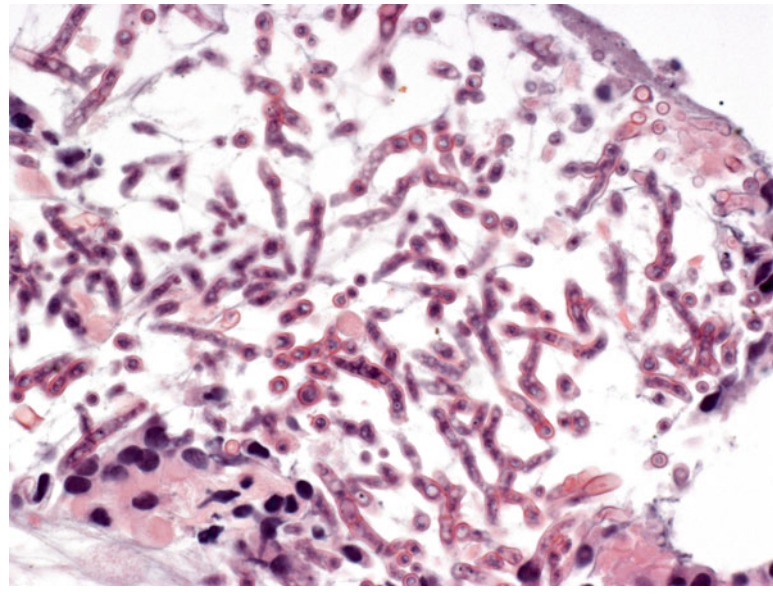

Fig. 14.93 Hyalohyphomycosis. Septate, hyalinized hyphae with branching at an acute angle and many intercalated spores (H&E, 200× original magnification)

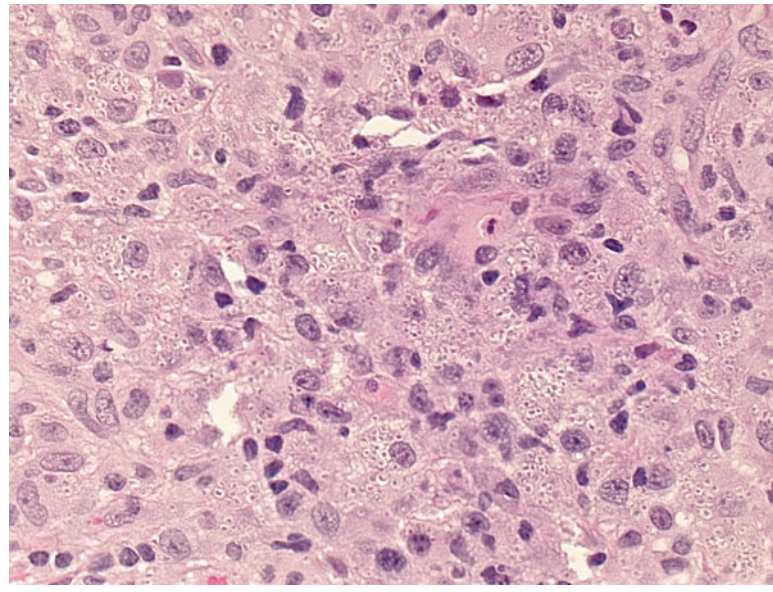

Fig. 14.94 Penicilliosis. Granulomatous inflammation and small round yeasts with clear halo in the cytoplasm of large histiocytes (H&E, 630× original magnification)

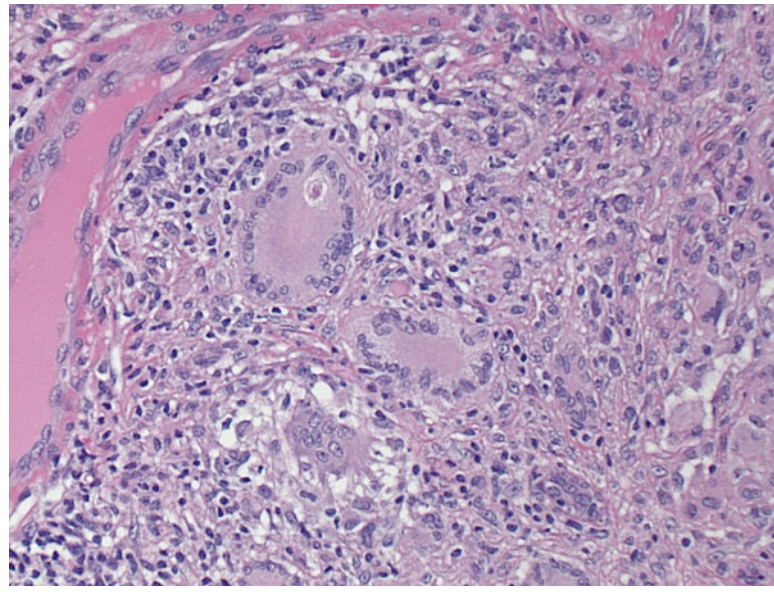

Fig. 14.95 Phaeohyphomycosis. Coalescing, suppurative granulomas with multinucleated giant cells in dermis (H&E, 400× original magnification)

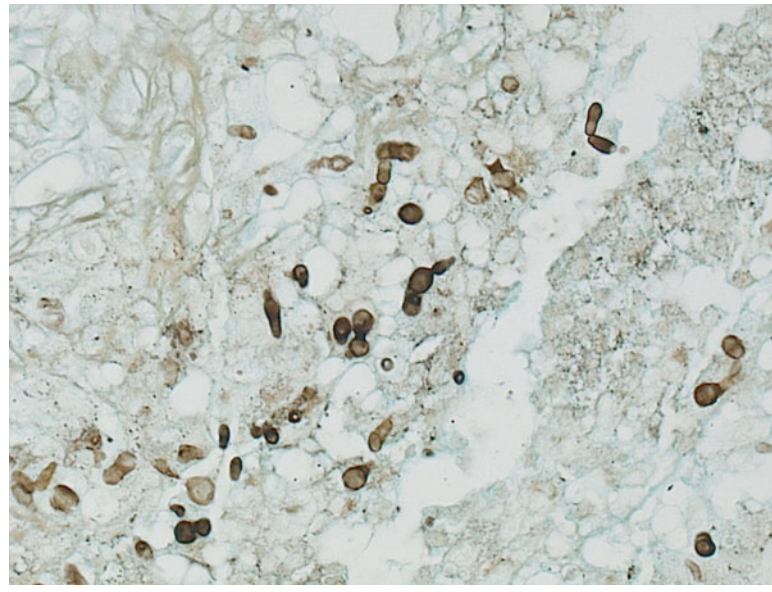

Fig. 14.96 Phaeohyphomycosis. Loosely arranged, septate, occasionally branching pigmented hyphae with budding spores in chains (Grocott's methenamine silver stain, 630× original magnification)

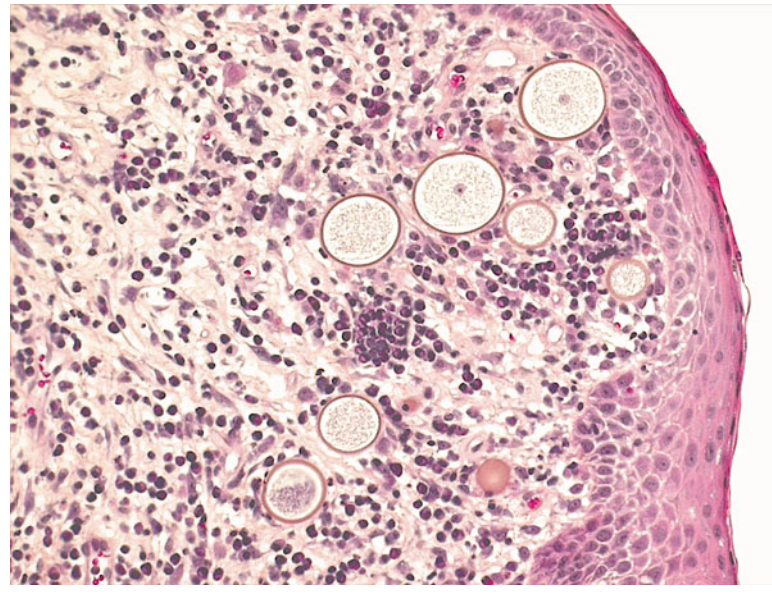

Fig. 14.97 Rhinosporidiosis. Hyperplastic epithelium and mixed inflammatory infiltrate in dermis with multiple various-sized sporangia containing endospores (H&E, 400× original magnification)

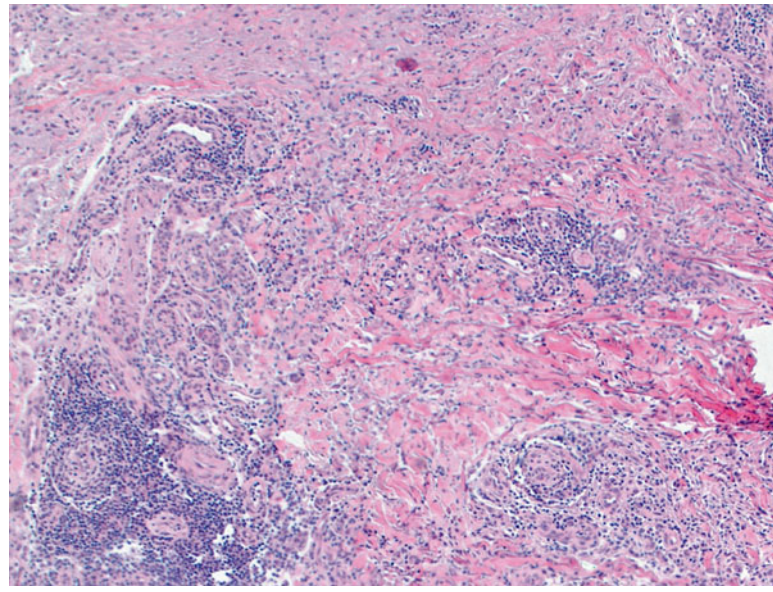

Fig. 14.98 Sporotrichosis. Intraepidermal abscesses and suppurative granulomatous inflammation in dermis (H&E, 50× original magnification)

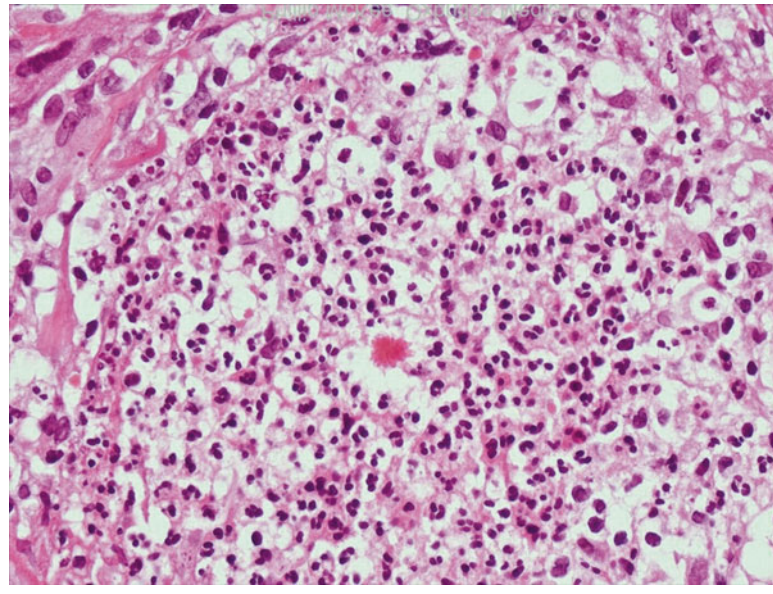

Fig. 14.99 Sporotrichosis. Suppurative granulomatous inflammation in dermis with occasional asteroid bodies (H&E, 400× original magnification)

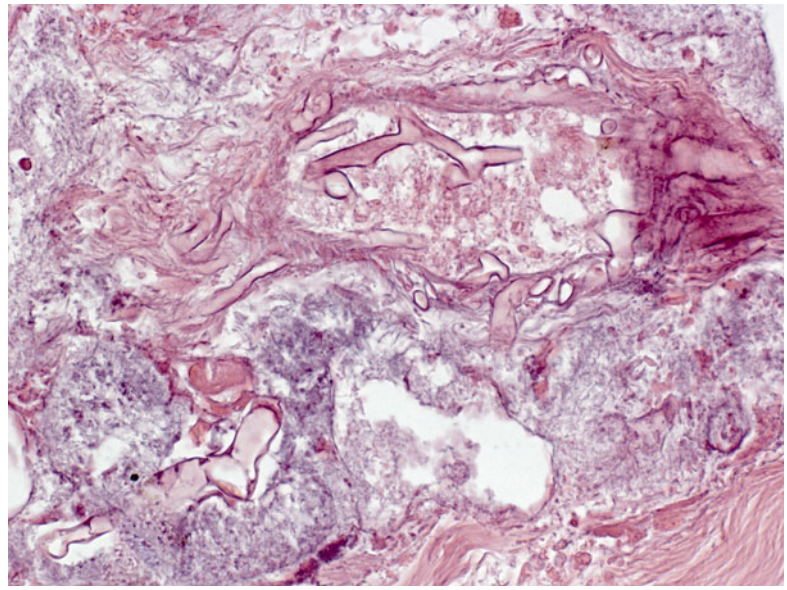

Fig. 14.100 Zygomycosis (mucormycosis). Thrombosis, infarction, and necrosis caused by angioinvasion of hyphae with pauciseptation and branching at haphazardly arranged angles (H&E, 630× original magnification)

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