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Chapter 12

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# Dermatologic manifestations of systemic infections

## INTRODUCTION

The skin is the largest and most visible organ of the body. In addition to its role as a barrier separating the body from the external environment and its role in temperature regulation, the skin has a complex immune system that recognizes and attacks foreign antigens and microbes.

The skin may be affected by systemic infections in three ways:

- by direct involvement by the infectious agent;
- by specific reaction to an infection; and
- by nonspecific reaction to an infection.

In addition, there are a number of inflammatory dermatoses that can mimic skin infections.

## DIRECT INVOLVEMENT OF THE SKIN BY AN INFECTIOUS AGENT DURING A SYSTEMIC INFECTION

### Viral infections

#### Chickenpox

Viral infection of the skin as part of a systemic infection is well demonstrated by chickenpox. After an incubation period of 14–21 days the patient develops 1–2 days of fever and malaise. This is followed by crops of unilocular vesicles, which quickly become pustular, appearing over 2–4 days. After the acute infection the virus persists in dorsal root nerve ganglion cells and on reactivation of the residual latent virus, herpes zoster or shingles develops.

#### Hand, foot and mouth disease

Hand, foot and mouth disease is caused most commonly by coxsackievirus A16 and enterovirus 71.[1] It occurs predominantly in children in both sporadic and epidemic forms. After an incubation period of 5–7 days the patient develops painful stomatitis with oral vesicles that ulcerate. Small, thin-walled vesicles may later develop on the fingers and toes. Onychomadesis is a rare complication due to nail matrix arrest leading to nail shedding from the proximal portion.[2] Disease related to coxsackievirus infection is generally mild and self-limiting; however, cardiopulmonary failure and neurologic sequelae may follow enterovirus 71 infection.[3] Viral particles can be identified in the vesicles on electron microscopy.

### Bacterial infections

#### Gonococcal infection

In disseminated gonococcal infection caused by *Neisseria gonorrhoeae*, characteristic skin lesions (called septic gonococcal dermatitis) may be observed. One or more crops of three or four macules or papules develop often over the extremities; these then become pustular or bullous. Occasionally, gonococci can be cultured from the skin lesions.

#### Tuberculosis

In tuberculosis, skin involvement may occur as the result of contiguous involvement of the skin from underlying lymph nodes, joints or bones, a condition called scrofuloderma.[4] A bluish-red nodule develops over the affected bone, joint (Fig. 12.1) or lymph node and multiple fistulae develop. Diagnosis must be confirmed by biopsy, which shows tuberculous granulation tissue. *Mycobacterium tuberculosis* can often be cultured from involved tissue.

Cutaneous involvement in tuberculosis may also occur secondary to hematogenous dissemination, so-called tuberculosis cutis miliaris disseminata.[5] In miliary tuberculosis, hematogenous dissemination of bacilli to the skin can produce profuse crops of bluish papules, which may become vesiculopustular and finally necrotic, leading to ulceration.

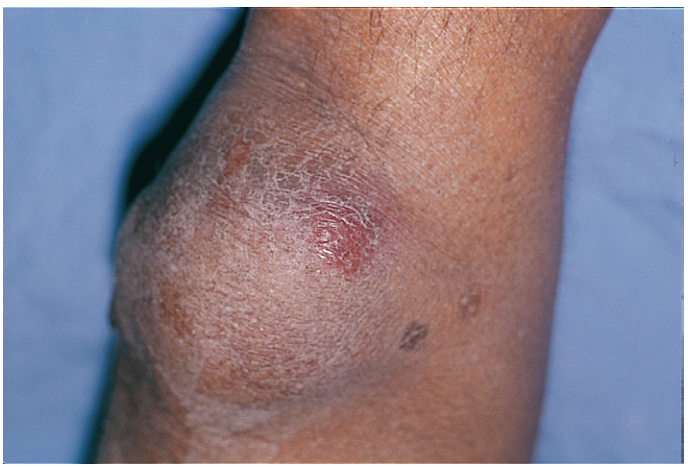

**Fig. 12.1** Scrofuloderma in a 60-year-old patient. A biopsy confirmed tuberculoid granulation tissue and the patient responded to antituberculous therapy.

Chronic hematogenous dissemination of tubercle bacilli in patients with moderate or high degrees of immunity may present as one of the tuberculides, which are regarded as localized hypersensitivity reactions to *Mycobacterium tuberculosis*:

- papulonecrotic tuberculid, in which there are symmetric crops of necrotic papules predominantly affecting the extremities;
- lichen scrofulosum, in which minute lichenoid papules appear predominantly on the trunk rather than on the limbs;
- erythema induratum (or Bazin's disease), in which persistent or recurrent nodular lesions appear in the calves of the legs and may lead to ulceration (Fig. 12.2); and
- nodular tuberculid, a more recently described form in which nonulcerating red or bluish nodules present on the lower limbs. This form is considered a hybrid between papulonecrotic tuberculid and erythema induratum with distinctive histologic features.[6]

The tuberculides respond rapidly to antituberculous therapy.

## Spirochetal infections

Disease caused by spirochetes tends to affect the skin as part of the primary manifestation, but it may also involve the skin during subsequent, disseminated disease.

### *Syphilis*

In syphilis, the primary lesion or chancre is cutaneous or mucosal, occurring at the site of inoculation. Secondary syphilis starts approximately 3 months after the primary infection and gives rise to nonirritating, coppery red symmetric lesions, which start as macules and become papular. Secondary syphilis is the 'great pretender'[7] and lesions of secondary syphilis can mimic acne, psoriasis and a number of other nonspecific dermatoses. Characteristically, the palms and soles are affected. When mucosal surfaces are involved, 'snail track' ulcers may develop. Later, condylomata may occur perianally and on the vulva or penis. Patchy hair loss is a characteristic sign of secondary syphilis, giving rise to a moth-eaten appearance of the scalp.

Late or tertiary syphilis occurs after a latent period of up to 20 years. Both skin and mucous membranes may be affected. Nodular syphilides present as nodular subcutaneous lesions appearing in groups and tending to develop a circinate arrangement. These are more common on the extensor surfaces of the arms, the back and the face (Fig. 12.3), but they may occur in the oral cavity. Gummas are masses of syphilitic granulomatous tissue; they may originate in the subcutis, underlying bone or muscle. These masses ulcerate to produce punched-out cutaneous defects.

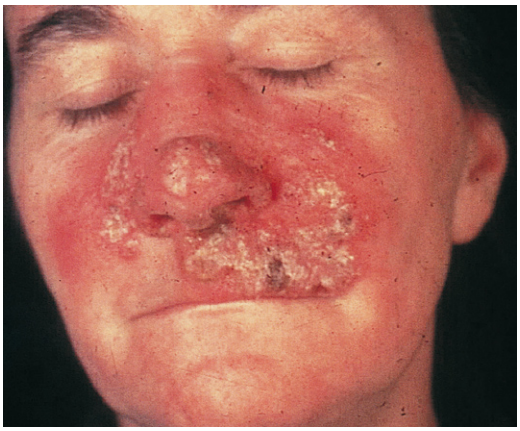

**Fig. 12.3** Tertiary syphilis on the face of a 56-year-old woman.

### *Yaws*

Yaws is caused by the spirochete *Treponema pertenue*. The primary lesion of yaws produces a cutaneous erythematous papule, which becomes papillomatous and resembles a raspberry, giving rise to its name, 'frambesia'. After 2–4 months the secondary eruption of yaws occurs, with multiple small papules developing into exudative papillomas (Fig. 12.4). Mucosal involvement does not occur in yaws. After 6 months to 3 years, tertiary yaws occurs; this is characterized by ulcerated nodular and tuberous cutaneous lesions and keratoderma of the palms and soles.

### *Pinta*

Pinta is caused by the spirochete *Treponema carateum*. The initial eruption starts in the skin as multiple erythematous papules and plaques. This is followed after months or years by generalized cutaneous lesions, where the skin becomes pale, pigmented or erythematosquamous. The late phase occurs 2–5 years after primary infection with irregular pigmentation, which can be grayish, steely or bluish in color. Areas of leukoderma, particularly around the elbows, knees, ankles and wrists, may develop. Hyperkeratosis occurs, particularly on the legs and arms, and is associated with areas of atrophy, particularly around the large joints.

## Lyme disease

In infections with *Borrelia burgdorferi*, the primary lesion occurs at the site of the Ixodes tick bite, with a characteristic eruption: erythema migrans.[8] The macular erythema starts up to 36 days after the bite and

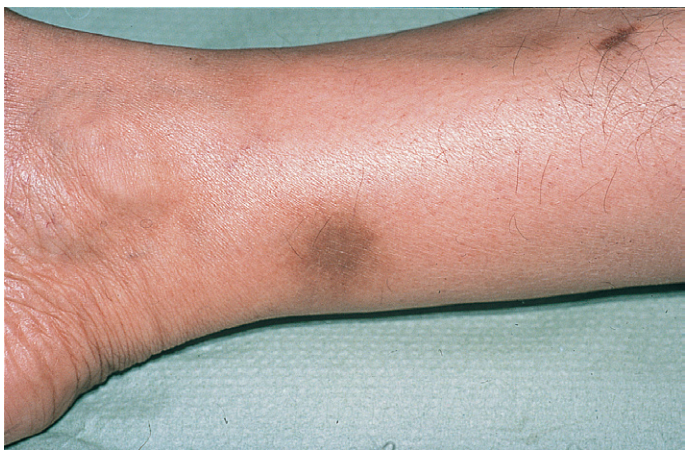

**Fig. 12.2** Erythema induratum on the back of the leg of a 45-year-old woman.

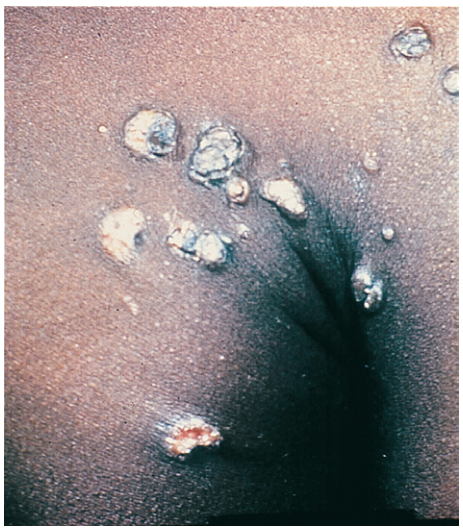

**Fig. 12.4** Secondary yaws showing papular and vegetative lesions on the anterior chest wall.

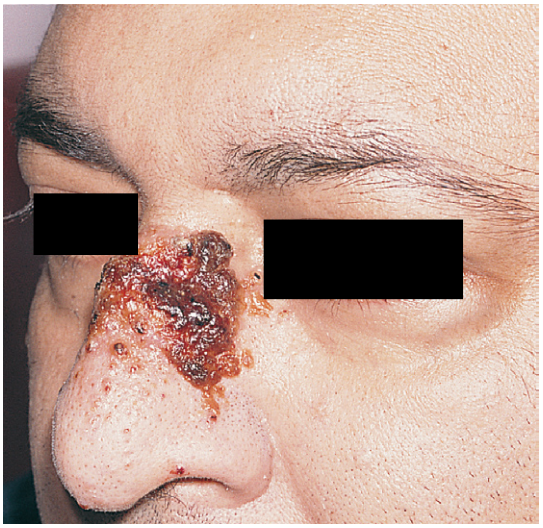

Fig. 12.5 Cutaneous cryptococcosis in a renal transplant patient. These lesions started as nodules that then rapidly ulcerated. CT scan of the patient's brain showed no abnormality but *Cryptococcus neoformans* was isolated from cerebrospinal fluid.

slowly increases in size by several centimeters each week. Subsequent dissemination in untreated patients leads to Lyme disease with involvement of the nervous system, heart and joints.[9]

One year or longer after the original infection, a late cutaneous manifestation may occur: acrodermatitis chronica atrophicans.[10] As the name suggests, this typically affects the hands and feet, but the elbows and knees may also be affected. Erythematous plaques develop, slowly enlarge and become atrophic. *B. burgdorferi* may be cultured from skin biopsies in this condition, though often with difficulty. Diagnosis therefore relies on clinical features supported by serologic testing and detection of *B. burgdorferi*-specific DNA in lesional skin biopsies by polymerase chain reaction.[8]

## Fungal infections

A number of deep fungal infections may have cutaneous involvement in the course of systemic disease. These include blastomycosis, coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, cryptococcosis and disseminated candidiasis.

Cutaneous manifestations tend to be nonspecific, with papules, nodules and ulcers developing on different parts of the skin. In disseminated blastomycosis cutaneous lesions start as papules or nodules, which then ulcerate and evolve into serpiginous lesions with raised warty borders. Disseminated coccidioidomycosis may result in cutaneous abscesses, granulomas and discharging sinuses, often on the face.

Disseminated cutaneous cryptococcosis is observed in immunocompromised patients, particularly those with AIDS. It presents as erythematous papules and nodules, which become exudative and eventually ulcerate (Fig. 12.5). Molluscum contagiosum-like lesions are a recognized feature of this disease in AIDS patients. These typically occur around the nose and mouth and punched-out ulcers with rolled edges may develop.

# SPECIFIC SKIN REACTIONS RESULTING FROM SYSTEMIC INFECTIONS

Systemic infections with viruses and bacteria can occasionally cause specific cutaneous reactions. These skin reactions can establish the diagnosis of the specific systemic infections and it is thus very important to recognize them.

## Viruses

### Roseola infantum and pityriasis rosea

Infection with human herpesvirus 6 (HHV-6) and HHV-7, usually in the first 3 years of life, gives rise to a specific dermatitis: roseola infantum (exanthem subitum).[11,12] After an incubation period of 10–15 days, fever starts abruptly and lasts for 3–5 days. Ulcers at the uvulopalatoglossal junction may be an early sign of roseola infantum.[13] As the fever subsides, a maculopapular eruption, which is characteristically rose pink in color, develops on the neck and trunk. This later spreads to the proximal extremities and face. The skin eruption subsides after 1–2 days, leaving no pigmentation or scaling of the skin. In common with other herpesviridae, latency is established. Reactivation in the immunocompromised host is linked to various diseases, including encephalitis.

A similar eruption, known as pityriasis rosea, is observed in adults. There is generally no prodromal syndrome but patients develop a single erythematous macular lesion, which may reach several centimeters in diameter, most commonly on the trunk, thigh or upper arm. The macule has a characteristic collarette of fine scale. This herald patch is followed after 5–15 days by a widespread eruption of small erythematous, scaly macules, which typically form a Christmas-tree pattern on the trunk and eventually spread down the limbs, usually resolving after 6 weeks. A viral etiology is suspected in this condition, although the roles of HHV-7 and to a lesser extent HHV-6 remain controversial.[14]

Cutaneous changes associated with HIV infection are discussed in Chapter 95.

## Bacterial infections

Specific bacterial infections may also cause a variety of cutaneous syndromes as a result of toxin production.

### Scarlet fever

Scarlet fever complicates acute infections by group A β-hemolytic streptococci that produce pyrogenic exotoxins. Production of the exotoxin depends on the presence of a temperate bacteriophage and is exclusive to group A streptococci. Three antigenically distinct exotoxins can be produced: types A, B and C. After an incubation period of 2–5 days, fever develops with localized signs at the portal of entry (e.g. tonsillitis and lymphadenopathy or tenderness at a wound site).

The eruption of scarlet fever occurs on the second day of infection. It begins on the upper trunk with punctuate erythema that becomes generalized over a few hours to 3–4 days. A characteristic sign, known as Pastia's lines, results from capillary damage and is characterized by transverse red streaks at the sites of skin folds. The face is erythematous but with a characteristic perioral pallor. After 7–10 days the eruption subsides with desquamation of the palms and soles.

### Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome is a blistering skin disorder caused by epidermolytic toxins produced by *Staphylococcus aureus*. Two major exfoliative toxin serotypes (ETA and ETB) have been identified.[15] Studies have shown that exfoliative toxins cleave desmoglein 1, resulting in loss of keratinocyte cell to cell adhesion within the epidermis.[16] Histologically, the epidermis is cleaved below the granular cell layer, resulting in the typical scalded skin appearance. The eruption usually starts suddenly with erythema and tenderness of the skin. Flaccid blistering occurs, which often rubs off, leaving raw exudative areas. This syndrome usually carries an excellent prognosis with resolution in 7–14 days following antibiotics.

The disease is one of infants and children. In the few reports of adults who have staphylococcal scaled skin syndrome there is generally an underlying medical problem, such as renal failure or immunosuppression, and it is thought that reduced clearance of the toxin by the kidneys in these patients may be important in the development of the disease.

## Toxic shock syndrome

The toxic shock syndrome is recognized as a complication of toxic shock syndrome toxin-1 (TSST-1) production by selected strains of *S. aureus*. Cases have been reported following tampon use, and postcontamination of surgical or traumatic skin wounds and burns. Involvement of the skin, oral mucosa and conjunctiva is common. Dermatologic manifestations include diffuse erythema, punctate lesions and petechiae with subsequent palmoplantar desquamation and occasional nail loss.

## Rheumatic fever

Rheumatic fever is caused by an abnormal immunologic reaction to previous infection with group A β-hemolytic streptococci. A specific (although now rare) cutaneous manifestation of rheumatic fever is erythema marginatum rheumaticum.[17] This consists of rings or arcs of pale, dull red erythema, which are either macular or slightly thickened. The rings make up a discrete or enlarged polycyclic pattern. These rings characteristically fade over a few hours or days and appear in recurrent crops, usually at different sites, over many weeks.

## Sepsis

Sepsis caused by a variety of bacteria can cause disseminated intravascular coagulation. This results in hemorrhagic skin lesions, particularly of dependent areas, followed by purpura and cutaneous necrosis. In acute meningococcal sepsis, so-called purpura fulminans predicts poor outcome and signifies rapidly progressive infection.[18] Septicemia and purpura fulminans may also uncommonly be caused by infection with *Capnocytophaga canimorsus* following a dog bite. This Gram-negative bacterium is part of the normal oral flora of dogs and septicemia in adults most often occurs in the setting of immunocompromise – usually because of previous splenectomy, alcoholism or glucocorticoid use[19] (Fig. 12.6).

## Henoch–Schönlein purpura

Henoch–Schönlein purpura (HSP) is an acute small vessel vasculitis, seen mainly in children and often following an upper respiratory tract infection. Although most cases are not directly linked to streptococcal infection, a substantial minority of patients with HSP have coexistent or previous streptococcal infection, as evidenced by positive throat culture (up to 30%) and raised anti-streptolysin O (up to 50%).[20] Henoch–Schönlein purpura has a characteristic appearance, with palpable purpuric papules developing on the lower legs and buttocks. This may be associated with arthritis, gastrointestinal syndromes and renal disease. Histologically, there is a leukocytoclastic vasculitis and characteristic deposition of IgA within the walls of affected blood vessels.

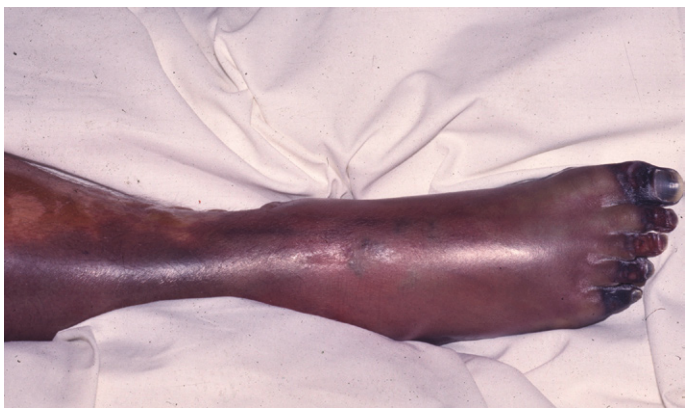

**Fig. 12.6** Purpura fulminans associated with *Capnocytophaga canimorsus* infection. Courtesy of Jos WM Van der Meer.

## Leprosy

*Mycobacterium leprae* affects the skin in all forms of leprosy. In tuberculoid leprosy (paucibacillary) the skin lesions tend to be few or solitary. They are often hypopigmented but they may have an indurated coppery color or a purple border. These patches tend to be hypoesthetic and dry with loss of hairs. In lepromatous leprosy (multibacillary) multiple small macules, papules and nodules develop in a symmetric manner in all sites apart from the hairy scalp, the axillae and the groin, where the temperature tends to be higher. Patients often develop leonine facies because of diffuse involvement of the facial skin (Fig. 12.7). Borderline types of leprosy have clinical features between these extremes of immunologic reaction to the causative agent.

Two types of immunologically mediated inflammatory reactions can occur during the course of leprosy. Type 1 leprae (reversal) reactions occur in borderline disease and are associated with upgrading of cell-mediated immunity. Existing skin lesions may become more inflamed, ulcerated and new lesions may appear. This is associated with acute or insidious pain and tenderness of affected nerves. Type 2 leprae reactions occur in patients who have lepromatous leprosy and borderline leprosy. Immune complexes form and a systemic inflammatory reaction ensues. The most common cutaneous manifestation is that of erythema nodosum leprosum, in which painful red nodules occur in the skin, most commonly on the face and extensor surfaces of the limbs.[21] Individual lesions may ultimately ulcerate. Erythema nodosum leprosum may be accompanied by uveitis, myositis, lymphadenitis, neuritis, dactylitis, arthritis and orchitis.

The Lucio phenomenon is another type 2 leprae reaction. Here, a deep cutaneous necrotizing vasculitis leads to infarction of overlying skin. Irregular erythematous patches develop and these may necrose to leave deep painful ulcers.[22]

## Ecthyma gangrenosum

Ecthyma gangrenosum is an uncommon cutaneous manifestation of *Pseudomonas aeruginosa* septicemia, usually occurring in immunocompromised or debilitated patients. Erythematous or purple macules initially develop on extremities or the anogenital region. Lesions subsequently become bullous and hemorrhagic, and rupture to leave a

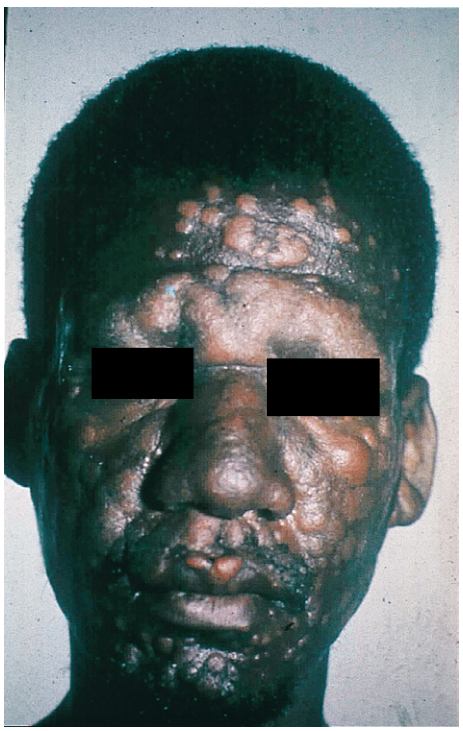

**Fig. 12.7** Lepromatous leprosy, with multiple symmetric lesions on the face, causing a leonine facies.

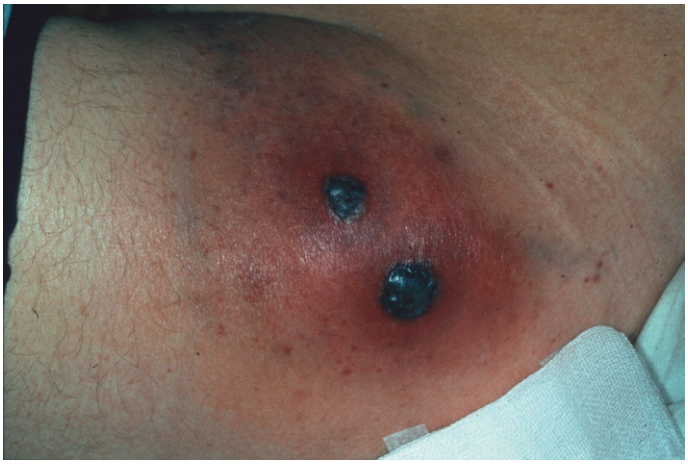

**Fig. 12.8** Ecthyma gangrenosum in the setting of *Pseudomonas aeruginosa* septicemia. Courtesy of WM van der Meer.

gangrenous ulcer with central black eschar (Fig. 12.8). The surrounding tissue is painful and inflamed. Histologically, a necrotizing hemorrhagic vasculitis is present and the Gram-negative organism may be seen within the walls of deeper vessels. When the diagnosis is suspected, culture and biopsy of skin lesions is essential, together with blood and urine cultures. Immediate treatment directed towards *P. aeruginosa* is indicated.

## NONSPECIFIC CUTANEOUS SIGNS OF SYSTEMIC INFECTIONS

### Erythema multiforme

Erythema multiforme (EM) may occur at any age although young adults are most commonly affected. The most common trigger for EM is herpes simplex infection but a variety of other infectious agents, including *Mycoplasma pneumoniae*, have also been implicated (Table 12.1).

The lesions are usually asymptomatic and start as dull red macules and papules that occur on acral sites (particularly the hands) and then spread more centrally. Typical target lesions occur; these have a central area of damaged skin (dusky-hued, blistering or eroded) and a raised edematous border (Fig. 12.9). Less commonly, the feet, elbows, knees, face, neck and trunk are affected. Oral lesions may be present and severe involvement of the lips may occasionally mimic the crusting seen in Stevens–Johnson syndrome, although these conditions are now considered distinct in adult patients.[23]

**Table 12.1** Infections and vaccines associated with erythema multiforme

| | |
|---|---|
| **Viral** | Herpes simplex virus<br>Human immunodeficiency virus<br>Hepatitis B and C viruses<br>Cytomegalovirus<br>Epstein–Barr virus<br>Coxsackie virus<br>Poxviruses – including orf, milker's nodules<br>Varicella-zoster virus<br>Adenovirus<br>Poliomyelitis virus |
| **Bacterial** | *Mycoplasma pneumoniae*<br>*Treponema pallidum*<br>*Legionella* spp.<br>*Mycobacterium tuberculosis*<br>*Rickettsia* spp. |
| **Fungal** | *Histoplasmosis capsulatum*<br>*Coccidioides immitis*<br>Dermatophytes |
| **Vaccines** | Diphtheria–tetanus–pertussis<br>Hepatitis B<br>Smallpox |

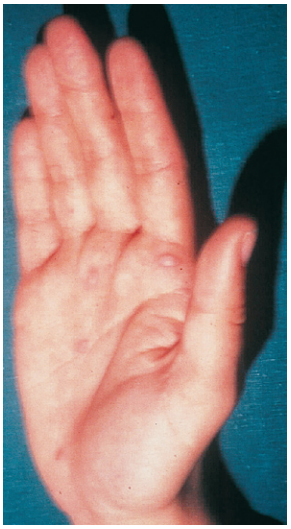

**Fig. 12.9** Erythema multiforme showing target lesions and bullous lesions on the palms of the hands.

### Erythema nodosum

Erythema nodosum is a type IV delayed hypersensitivity reaction to a number of different stimuli. The skin and subcutaneous fat are affected with a septal panniculitis. Clinically, there may be a short prodrome of mild fever, myalgia and malaise. Erythematous nodules develop on the shins and more rarely on the arms, face and neck; these may extend up to several centimeters in diameter (Fig. 12.10). The hallmark of erythema nodosum is pain and exquisite tenderness of the lesions. Initially, lesions are bright red but as they subside over the next 3 weeks or so, they undergo a bruise-like change, becoming dusky in color with mild scaling of the skin.

A number of infectious agents have been implicated in the etiology of erythema nodosum (Table 12.2).[24] These vary with the age of the patient and the country of residence. Streptococcal infections (particularly upper respiratory tract) are the commonest infectious cause in both adults and children, and tuberculosis is still a common cause in endemic areas. Infections with *Chlamydia psittaci* have been responsible for small outbreaks of erythema nodosum in adults in the UK, where contact with birds and poultry may be an important clue in

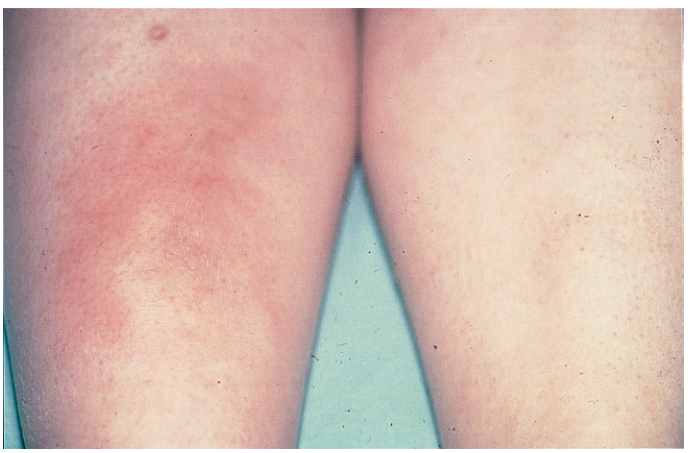

**Fig. 12.10** Erythema nodosum on the lower legs.

| Table 12.2 Infections associated with erythema nodosum | |
|---|---|
| **Bacterial** | Streptococci<br>*Mycobacterium tuberculosis*<br>*Yersinia* spp.<br>*Mycoplasma pneumoniae*<br>*Chlamydia* spp.<br>*Campylobacter* spp.<br>Rickettsiae<br>*Salmonella* spp.<br>*Bartonella* spp.<br>Treponema pallidum<br>*Leptospira* spp.<br>*Neisseria gonorrhoeae*<br>*Franciscella tularensis* |
| **Fungal** | *Histoplasma capsulatum*<br>*Coccidioides immitis*<br>Blastomycoses |
| **Viral** | Herpes simplex virus<br>Epstein–Barr virus<br>Hepatitis B and C viruses<br>Human immunodeficiency virus<br>Parvovirus B19 |
| **Parasitic** | *Entamoeba histolytica*<br>*Giardia lamblia* |

source identification. Infection with *Yersinia* spp. has been reported to cause erythema nodosum in France and Finland but is rare in other countries. Gonorrhea and varicella have been reported as rare causes of erythema nodosum in Singapore.[25]

Erythema nodosum may be related to inflammatory tinea capitis in children, particularly in association with kerion formation.[26] Deep fungal infection, particularly coccidioidomycosis, blastomycosis and histoplasmosis, has been associated with erythema nodosum. More rarely, erythema nodosum has been reported in association with tularemia, salmonellosis, *Campylobacter* spp. infection and leptospirosis.

## Cutaneous vasculitis

The clinical features of cutaneous vasculitis depend on the size of the blood vessels affected and on whether the vasculitis is acute or chronic. Acute leukocytoclastic vasculitis is caused primarily by immune complex deposition in cutaneous blood vessels with complement fixation and damage caused by neutrophil infiltration and activation. This vessel wall injury is highly regulated by adhesion molecules and selectins, which are upregulated at sites of vasculitis.[27] The targeted blood vessels tend to be small and superficial, and the clinical signs are of a purpuric macular or papular eruption on the lower legs and dependent areas; these eruptions may become bullous and ulcerate (Fig. 12.11).

Cutaneous vasculitis is associated with underlying infection in approximately 15–20% of cases.[28] A variety of infectious agents including bacteria, viruses, fungi, protozoa and helminths have been associated with vasculitis (Table 12.3). Hepatitis B and C viruses may cause both cutaneous leukocytoclastic vasculitis and specific systemic vasculitis syndromes; hepatitis B virus is associated with polyarteritis nodosa and hepatitis C with cryglobulinemic vasculitis.[29]

## Gianotti–Crosti syndrome

Gianotti–Crosti syndrome (GCS) is a self-limited cutaneous dermatosis, characteristically seen in children aged between 6 months and 12 years. It was first described in Europe associated with hepatitis B virus (HBV) infection; however, Epstein–Barr virus now appears to be the commonest cause.[30] This may relate to the increased use of anti-HBV immunizations worldwide. Many other viruses have been linked to GCS including cytomegalovirus, coxsackieviruses A16, B4 and B5, human herpesvirus 6, echovirus, rotavirus, respiratory syncytial virus, hepatitis A or C viruses and parainfluenza virus. There are rare reports of bacteria triggering GCS.

The eruption presents acutely with dull red papules of 5–10 mm diameter. These develop symmetrically over 3–4 days, starting on the buttocks and thighs and spreading to the arms and face. The papules may become vesicular or purpuric and are often mildly itchy. Axillary and inguinal lymphadenopathy is often present and may persist for several months after the eruption has settled, which generally occurs within 2–8 weeks to leave mild scaling but no scarring.

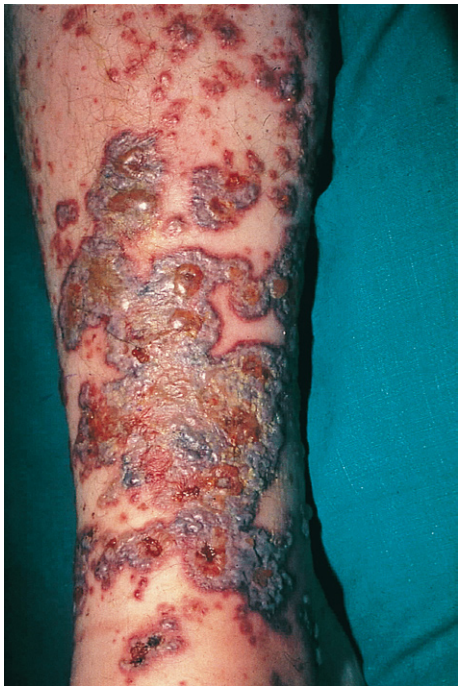

**Fig. 12.11** Acute leukocytoclastic vasculitis showing bullous lesions on the lower leg. This patient was found to have a high antistreptolysin titer.

| Table 12.3 Infections associated with cutaneous vasculitis | |
|---|---|
| **Viral** | Hepatitis virus A, B and C<br>Human immunodeficiency virus<br>Herpes simplex virus<br>Varicella-zoster virus<br>Hantavirus<br>Cytomegalovirus<br>Human T-cell lymphotrophic virus (HTLV-1) |
| **Bacterial** | Streptococci<br>Staphylococci<br>*Chlamydia* spp.<br>*Mycobacterium* spp.<br>*Treponema pallidum*<br>*Neisseria* spp.<br>*Rickettsia rickettsii*<br>*Brucella* spp.<br>Salmonellae |
| **Fungal** | *Candida* spp.<br>*Cryptococcus neoformans* |
| **Protozoal** | *Acanthamoeba*<br>*Plasmodia* |

## Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis affecting medium-sized vessels, including the coronary arteries. Generally, children between 6 months and 4 years are affected. Although the etiology remains unknown, there is epidemiologic evidence that KD may be triggered by a response to an infectious agent.[31] Proposed but unproven causes of KD include adenovirus, herpesvirus, Epstein–Barr virus, streptococci, staphylococci and *Rickettsia* spp., a newly described human coronavirus [32] and human bocavirus.[33] In most cases no agent is identified. The incidence is highest in Japan although it has been reported worldwide.

The disease is acute in onset with fever lasting more than 5 days. The conjunctivae become injected and the lips and tongue are red. At the onset of fever, a generalized polymorphic eruption develops on the trunk and proximal limbs; this is associated with redness and induration of the palms and soles. Cervical lymphadenopathy develops in about three-quarters of children. As the fever subsides, the skin scales and the patient may develop arthralgia and arthropathy. Coronary artery aneurysms develop in up to 30% of untreated patients and myocardial infarction occurs in approximately 2% of those with coronary lesions.[31]

# INFLAMMATORY DERMATOSES MIMICKING INFECTION

## Acute febrile neutrophilic dermatosis (Sweet's syndrome)

Acute febrile neutrophilic dermatosis was first described by Sweet in 1964.[34] It is characterized by an explosive cutaneous eruption of raised violaceous plaques in association with constitutional symptoms and fever. Sweet's syndrome (SS) is now classified in three groups: classic (or idiopathic), malignancy associated and drug induced. Malignancy is present in approximately 20% of all patients with SS. Both hematologic malignancy and solid tumors occur but acute myelogenous leukemia is most commonly associated. Drug-induced SS is well described following administration of granulocyte-colony stimulating factor, as well as a number of other agents.[35] Uncommon or rare associations include streptococcal, *Salmonella* and nontuberculous mycobacterial infections, vaccination,[36] inflammatory bowel disease and pregnancy.

Clinical presentation is an acute eruption of dull red elevated inflammatory nodules and plaques, which may pustulate in later stages or clear centrally to give an annular appearance. The majority of patients have a persistent fever and neutrophilia with an elevated erythrocyte sedimentation rate. Diagnosis may be confirmed by cutaneous biopsy, which reveals a florid dermal polymorphonuclear cell infiltrate. Cases respond rapidly to systemic corticosteroid therapy, which is usually required for several weeks.

## Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a serious drug-induced skin disorder, which clinically may be difficult to distinguish from staphylococcal scalded skin syndrome (SSSS). Both conditions are characterized by an acute, widespread cutaneous erythema with sloughing of the epidermis in sheets. As described, SSSS occurs mainly in childhood and is caused by staphylococcal toxin-mediated superficial cleavage of the epidermis below the granular layer. It has an excellent prognosis if appropriately treated. In comparison, TEN is usually a drug-induced phenomenon causing full-thickness necrosis of the epidermis, with subsequent impairment of cutaneous barrier function and a high mortality (30%).[37]

Stevens–Johnson syndrome (SJS) and TEN are now recognized as variants of a single entity, with TEN being of greater severity.[23] The precise pathogenesis is poorly understood, although increased circulating levels of fasL, a ligand for the fas keratinocyte death receptor, have been identified in patients with TEN. Perforin and granzyme, proteins contained within lytic granules of cytotoxic T cells, have also been shown to induce keratinocyte apoptosis in TEN.[37]

The most commonly implicated drugs in TEN are antibiotics, particularly sulfonamides, and anticonvulsants, allopurinol and non-steroidal anti-inflammatory drugs. Nevirapine and lamotrigine have also recently been shown to be strongly associated with TEN.[38] TEN may be distinguished from SSSS by histologic examination of biopsied skin, allowing assessment of the level of epidermal splitting and identification of the presence or absence of micro-organisms. Treatment outcome is improved by intensive nursing in a specialist burns unit and by prompt withdrawal of all potential precipitants. No specific treatment has been unequivocally proven to be effective; however, intravenous immunoglobulins and plasmapheresis have been used.

## Oral ulceration

Oral ulceration is a frequent clinical funding, with a wide differential diagnosis including infectious disease.

Primary herpes simplex gingivostomatitis usually occurs in early childhood. Fever is followed by development of painful vesicles on the lips, buccal mucosa, tongue and palate, with tender regional lymphadenopathy. Later in life, recurrences are usually less severe and lesions fewer in number.

Aphthous ulceration is common, painful and often occurs in crops. Minor aphthous ulcers are 2–4 mm in diameter with a gray–white surface and red margin. Commonest on the lips, buccal mucosa or floor of the mouth, they rarely occur on the gingiva, palate or dorsal tongue. Major aphthous ulcers may exceed 1 cm in diameter and occur anywhere in the mouth. They are more painful and protracted and often heal with scarring. Herpetiform aphthous ulceration produces painful vesicles and multiple tiny ulcers less than 2 mm in diameter. These coalesce to produce larger lesions and tend to recur frequently. This syndrome resembles herpetic gingivostomatitis, although there is no evidence of viral etiology.

Behçet's syndrome is characterized by the presence of recurrent oral and genital ulcers, and ocular disease. Other features which may be present include central nervous system disease, arthropathy, skin lesions (e.g. pustules, pathergy, erythema nodosum) and vascular disease.[39] Oral lesions in Behçet's syndrome start as small erythematous papules or pustules, which erode to form ulcers. Pain is variable. Recurrent ulceration may predate the syndrome by months or years.

Pemphigus vulgaris affects the oral mucosa in almost all patients and is the presenting feature in 50–70%. Bullae are fragile and therefore rarely seen. Ruptured bullae form painful large irregular erosions on any part of the oral mucosa. Most patients will also go on to develop flaccid cutaneous bullae which rupture easily.[40]

## Eosinophilic cellulitis (Wells' syndrome)

Eosinophilic cellulitis is a rare syndrome which may closely mimic bacterial cellulitis or bullous erysipelas.[41] The etiology is unknown. It is characterized by development of indurated areas of erythema, usually on a distal limb, which may be single or multiple. Systemic illness is unusual, although associated fever has been reported and peripheral eosinophilia is common. Early lesions are often pruritic, infiltrated and may blister but then resolve without scarring within a few weeks. Diagnosis is suggested on skin pathology by the demonstration of marked dermal eosinophilia with areas of granulomatous change surrounding aggregates of eosinophilic material, known as 'flame figures'. The condition responds to oral corticosteroid therapy.

# REFERENCES

References for this chapter can be found online at http://www.expertconsult.com