CUTANEOUS MANIFESTATIONS OF HIV/AIDS: PART I

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Human immunodeficiency virus (HIV) infection can lead to a variety of clinical cutaneous manifestations. These cutaneous disorders occur universally during the course of HIV infection. Cutaneous manifestations of HIV are very diverse. The course and clinical presentation of HIV in individuals who have access to highly active antiretroviral therapy (HAART) is completely different from that in those who do not. Many of the HIV cutaneous presentations seen in South Africa become chronic and progressive. There is a marked reduction in the incidence of opportunistic infections and neoplasms in North America, Western Europe and Australia, where there is access to HAART.

Approximately 90% of patients will develop one or more skin diseases during the course of their illness. It is therefore crucial that health professionals become familiar with and are able to recognise the various skin manifestations of HIV.

Thirty-seven per cent of patients present with skin lesions as a marker of HIV infection. As the CD4+ lymphocyte cell count decreases, the severity of the skin condition increases, multiple skin lesions are seen, and frequent relapses are encountered. There tends to be increased severity of infections with known pathogens and occurrence of infection with unusual and exotic pathogens.

Patients often present with florid clinical patterns which fail to respond to conventional therapy. Correlation between skin disorders with CD4+ lymphocyte count in patients with HIV/AIDS in an American study is illustrated in Fig. 1.

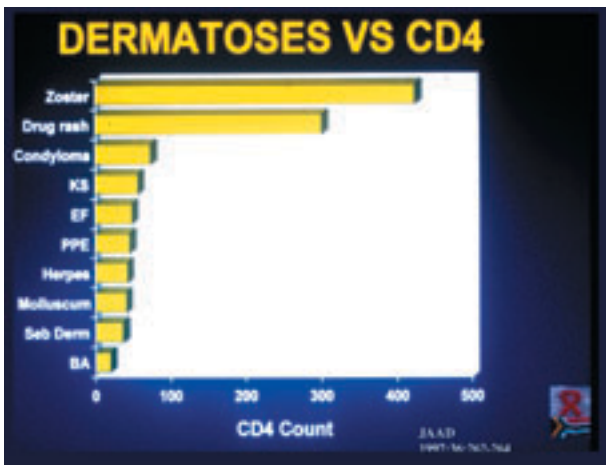

Fig. 1. Correlation between mean CD4 cell count and incidences of specific skin disorders in patients with HIV infection.

ACUTE SEROCONVERSION ILLNESS

The incubation period from the time of exposure to the development of an acute febrile syndrome is about 2 - 6 weeks. It is estimated that 50 - 70% of patients will have the acute syndrome after infection, however, of these only 25% have symptoms severe enough to warrant medical attention. Patients present with an infectious mono-nucleosis-like picture characterised by fever, sore throat,

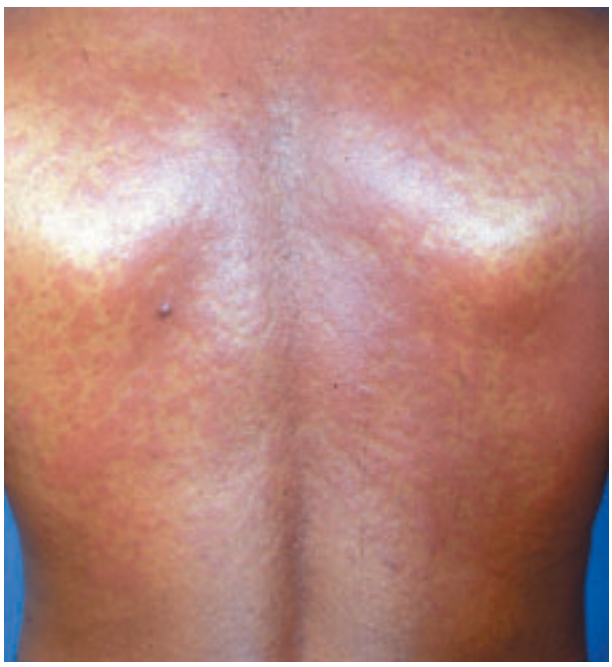

Fig. 2. Morbilliform rash of acute seroconversion illness.

myalgia, malaise, headache and enlarged cervical lymph nodes.

The cutaneous manifestations may take the form of a diffuse morbilliform rash (Fig. 2), a papular exanthem or a maculopapular rash with central petechiae, with occasional involvement of the palms of the hands and soles of the feet.

In one-third of patients the picture may include an enanthem characterised by ulcerations, aphthous-like lesions and candidiasis.

The duration of the acute episode is about 1 - 2 weeks, and it may be complicated by hepatitis and neurological symptoms.

FUNGAL INFECTIONS

Cutaneous fungal infections are common in both HIV-infected and uninfected individuals. They are the commonest infectious manifestation of immunosuppression related to HIV, ranging from superficial mucocutaneous candidiasis to life-threatening disseminated infections like histoplasmosis. Fungal infections occur early in the course of HIV infection, when they manifest with oral candidiasis, and later on as AIDS-defining conditions like histoplasmosis and cryptococcosis. A thorough knowledge of the diagnosis and treatment of these conditions is therefore important to decrease the significant morbidity associated with cutaneous fungal infections in HIV/AIDS.

CANDIDIASIS

This is the commonest mucocutaneous manifestation, affecting 20 - 70% of individuals with HIV.[1] Asymptomatic colonisation of the oropharynx occurs in up to 60% of HIV-infected patients. The incidence of oral candidiasis increases as the CD4+ count declines, and it is a marker of rapid HIV progression. As oral candidiasis is common in infants under 6 months of age, other clinical markers of HIV should be sought in this age group. However, recurrent and severe oral candidiasis in the older child (over 6 months of age) is indicative of immunosuppression. The incidence has declined with the use of fluconazole prophylaxis for cryptococcal meningitis.

Candidiasis most often affects the tongue and buccal mucosa, causing thick, whitish plaques, but may also present as angular cheilitis. (Fig. 3). Less common manifestations are paronychia (Fig. 4), onychomycosis, recurrent vaginal and urethral involvement and cutaneous involvement, predominantly of the flexures. Children may present with candidiasis in the napkin area and other flexures (axillae and neck folds) and chronic paronychia with nail dystrophy. Severe oral involvement with dysphagia indicates oesophageal candidiasis. Disseminated candidiasis, although rare, is often fatal and should be considered in ill patients with fever and severe immunosuppression.

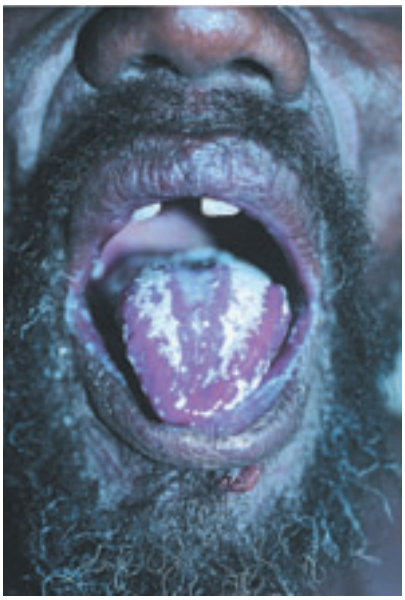

Fig. 3. Oral candidiasis.

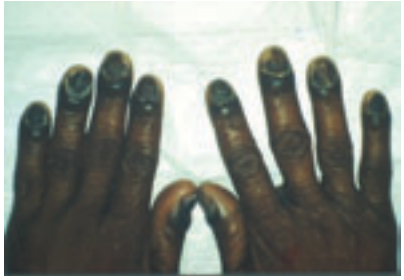

Fig. 4. Chronic paronychia.

Therapy is aimed at clearance and prevention of dissemination. Good oral hygiene is important, together with the use of topical azoles in the form of pastilles, troches or lozenges twice daily for 14 days. For refractory cases or where oesophageal involvement is suspected, oral azoles are indicated: itraconazole 200 mg daily for 5 days or fluconazole 100 mg daily for 5 days. The therapeutic dose in children is 3 - 6 mg/kg. Higher doses and longer duration of treatment may be necessary for recurrent episodes in severely immunosuppressed individuals. Cutaneous candidiasis may regress on HAART alone, in the absence of specific antifungal agents.

DERMATOPHYTOSIS

Dermatophytosis involving the skin, hair and nails is a common opportunistic infection in patients with HIV/AIDS. Although the frequency is not necessarily increased in these individuals, they are prone to more extensive and atypical forms which may be resistant to therapy. The commonest pathogen causing tinea infections is *Trichophyton rubrum*. Tinea corporis, pedis and capitis (Figs 5, 6 and 7) may present as typical 'ringworm' infection with active edges and central clearing, or present in atypical forms (extensive scaling, lack of an active edge, interdigital tinea pedis spreading to the dorsa of the feet, and 'two feet, one hand' syndrome with bilateral tinea manum and pedis). Folliculitis on hair-bearing areas may be complicated by Majocchi's granulomas and deep abscesses.

Certain types of onychomycosis (Fig. 8) are prevalent in HIV infection. Proximal white superficial onychomycosis and peri-ungual involvement are the commonest, and tend to spread to involve multiple fingers and toes as the CD4+ count declines.

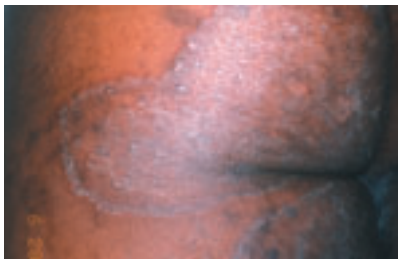

Fig. 5. Tinea corporis.

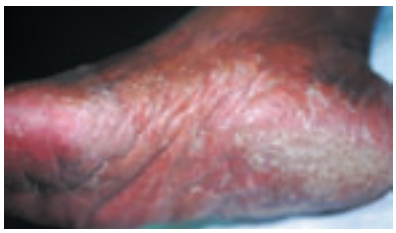

Fig. 6. Tinea pedis.

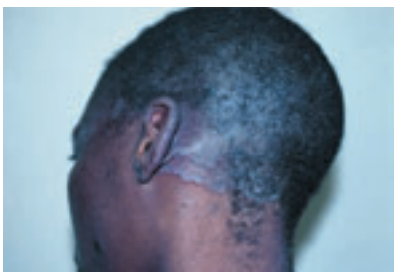

Fig. 7. Tinea capitis.

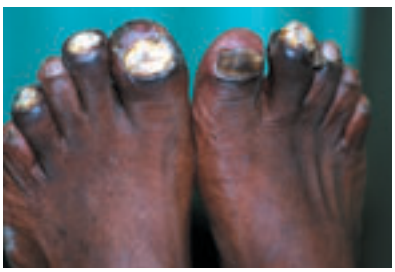

Fig. 8. Onychomycosis.

In children, HIV can present with painful tinea capitis, e.g. kerion, and may progress to scarring alopecia.

Since the diagnosis of superficial fungal infections may be difficult, confirmation with potassium hydroxide (KOH) microscopy is essential to exclude other pathologies. Therapy is important, as fungal infections are persistent and may act as a portal of entry for secondary staphylococcal and streptococcal infections.

Dermatophyte infections in HIV-infected adults and children are ideally treated with oral antifungals. The choice of antifungal agent depends on other concomitant therapies, as drug interactions are significant. Therapy may be required for longer than normal and HIV-infected patients are prone to relapse.

Tinea corporis is treated with either griseofulvin 500 mg - 1 g daily for 28 days, itraconazole 200 mg/day for 7 days or terbinafine 250 mg/d for 14 days.

Onychomycosis is more resistant to therapy and treatment needs to be of longer duration. Terbinafine 250 mg/d should be given for 3 months for fingernail infections and for 4 months for toenail infections, and itraconazole in a pulsed dosage of 400 mg/d for 1 week per month is necessary for 3 months for fingernail infections and for 4 months for toenail infections. Itraconazole should be taken with fatty food or an acidic drink to enhance absorption and also to combat the hypochlorhydria or achlorhydria to which HIV-infected individuals are susceptible. Itroconazole is a p450 enzyme inhibitor, so the prescribing physician needs to be aware of the danger of co-administration of other drugs metabolised by this enzyme system, e.g. protease inhibitors (PIs). In very ill patients with onychomycosis on multiple drugs it is best simply to keep the nails short and resort to topical therapy, e.g. amorolfine nail lacquer.

Primary and secondary prophylaxis is important to prevent relapse and re-infection. This may be achieved by benzoyl peroxide washes of the feet, drying carefully between the web spaces, and application of an antifungal cream or powder.

The first line of therapy for tinea capitis in children is micronised griseofulvin at 10 - 15 mg/kg for 6 - 8 weeks. Shorter duration of therapy can be achieved with itraconazole (5 mg/kg/d for 28 days) and terbinafine (250 mg > 40 kg, 125 mg 20 - 40 kg and 62.5 mg < 20 kg for 28 days). Compliance is best with shorter duration of therapy.

Patients on HAART will experience less frequent infections, which could clear without specific antifungal therapy. If treated with antifungals they will respond better to therapy and experience fewer relapses.

SYSTEMIC FUNGAL INFECTIONS

Disseminated cutaneous histoplasmosis and cryptococcosis are AIDS-defining conditions as they occur with profound immunodeficiency. Skin lesions signify dissemination via the bloodstream, the primary infection being in the lungs.

Cryptococcosis

This is a common systemic mycosis due to the yeast *Cryptococcus neoformans*. Skin involvement occurs in 10% of patients with systemic disease. The lesions are polymorphous and may present as papules, nodules, pustules or ulcers (Fig. 9).

The site most commonly affected is the head and neck, although lesions may be widespread. They may be confused with molluscum contagiosum, so biopsy is important to make a definitive diagnosis. Cryptococcosis is a life-threatening condition if untreated. Treatment involves intravenous injections of amphotericin B for 2 weeks followed by lifelong maintenance therapy with fluconazole

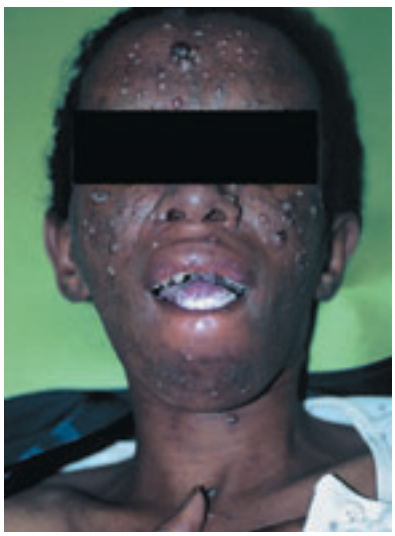

Fig. 9. Cryptococcus – umbilicated lesions resembling molluscum contagiosum.

200 mg daily. Patients on HAART may present with headache due to immune reconstitution of cryptococcal meningitis.

Histoplasmosis

Cutaneous histoplasmosis is associated with advanced immunosuppression, usually at a CD4+ lymphocyte count of < 75 cells/µl. Patients are usually ill, with fever, anaemia, respiratory symptoms, lymphadenopathy, hepatosplenomegaly and skin lesions. Histoplasmosis is therefore often misdiagnosed as tuberculosis, and patients are started on empiric anti-TB therapy, without response.

Skin involvement occurs in 5 - 10% of patients (Figs 10 and 11), and mucosal involvement is characteristic with gingival ulcers, plaques, nodules and abscesses. Owing to the polymorphous presentation, a high index of suspicion is required and biopsy and culture of lesions is mandatory. In the absence of skin lesions, blood and bone marrow culture are sensitive methodologies. Therapy in the acute stage is amphotericin B 15 mg/kg by intravenous injection or itraconazole 400 mg daily for 8 weeks. Lifelong maintenance therapy should be given, with itraconazole 200 mg/d or fluconazole 200 mg/d.

Sporotrichosis

Sporotrichosis is caused by the organism *Sporothrix schenckii* and can be classified as lymphocutaneous, fixed cutaneous, disseminated cutaneous or systemic. In HIV/AIDS, skin lesions may consist of widespread ulcers, papules, nodules and plaques, often with systemic involvement (Fig. 12). Local cutaneous infection is more likely to disseminate. Biopsy and culture is important to make a diagnosis, and therapy with itraconazole is effective.

Other systemic mycoses that may occur but are rare in South Africa are

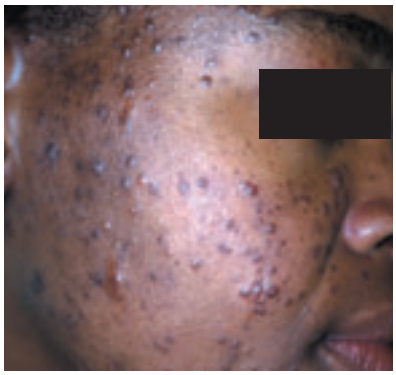

Fig. 10. Disseminated histoplasmosis – facial lesions.

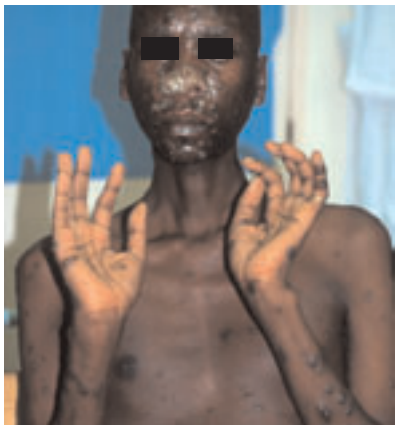

Fig. 11. Disseminated histoplasmosis.

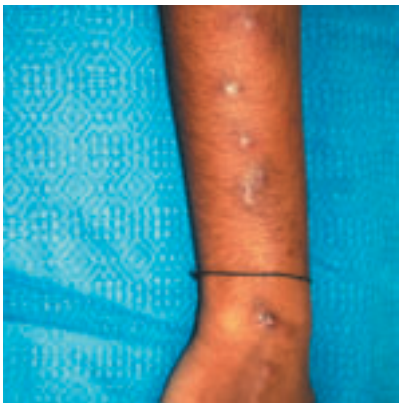

Fig. 12. Linear sporotrichosis.

blastomycosis, penicilliosis and coccidioidomycosis. Accurate diagnosis can only be made utilising pathological and mycological investigations. As more patients are being treated with HAART, the incidence of systemic fungal infections will decline.

BACTERIAL INFECTIONS

The most common bacterial infections in HIV-infected patients are due to *Staphylococcus aureus* and *Staphylococcus epidermidis*. These are common in the general population, but in HIV-infected individuals may be more widespread, recurrent and resistant to therapy. *S. aureus* is the most common cutaneous and systemic bacterial pathogen in adults. HIV-infected patients have increased *Staphylococcus* carriage in their nares. Infection presents with folliculitis, impetigo, ecthyma and cellulitis. In addition to *S. aureus*, Gram-negative infections such as ecthyma gangrenosum caused by *Pseudomonas* occur.

FOLLICULITIS

This common bacterial infection presents with acneiform papules and pustules, which may be excoriated. The common causative organisms are *S. aureus, S. epidermidis* and *P. aeruginosa*.

IMPETIGO

These lesions begin as macules that progress to vesicles and pustules, which then rupture leaving honey-coloured crusts. They are particular common in the perioral and perinasal areas. The causative organism is *S. aureus*, which is a common cause of cutaneous infection in the general population. In HIV infections, however, lesions may be seen more commonly in the intertriginous areas.

SOFT-TISSUE INFECTION

This presents as a warm, red and tender swelling which may progress to necrotising fasciitis.

Therapy for a first episode is the empiric use of antibiotics that will treat staphylococcal and streptococcal infections, and taking a specimen for a Gram stain. Deeper and recurrent infection warrants samples for microscopy and culture. If the patient is severely ill, admission for intravenous antibiotic therapy should be considered and longer duration of therapy may be required. If the infection is recurrent, therapy of staphylococcal carriage with mupirocin may be effective.

BACILLARY ANGIOMATOSIS

This rare condition caused by the spirocheate *Rochalimea henselae* presents with angiomatous papules, nodules and abscesses (Fig. 13). It occurs in patients with severe immunosuppression and may be clinically confused with Kaposi's sarcoma. Systemic involvement may occur with pulmonary, hepatic, bone and central nervous system symptoms. Histology is important as it is a fastidious organism and hence difficult to culture. Patients respond well to erythromycin 500 mg 6-hourly or doxycycline 100 mg twice a day until the lesion resolves. If the condition is recurrent, secondary prophylaxis is necessary. Alternative drugs are the cephalosporins and quinolones.

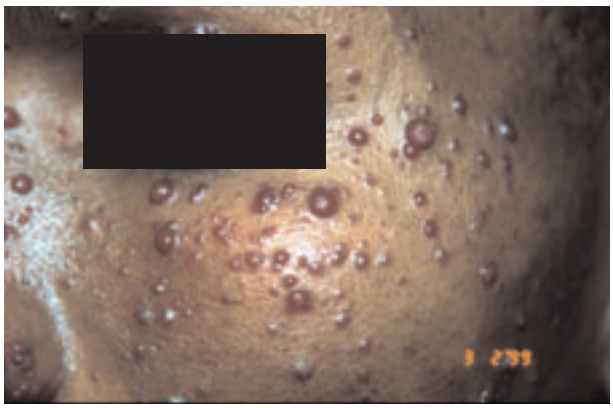

Fig. 13. Bacillary angiomatosis.

SYPHILIS

In HIV disease, syphilis progresses more rapidly through all of the stages. Syphilis may present atypically or be refractory to therapy, and laboratory investigations may be difficult to interpret owing to unusual serological responses. The primary chancre may consist of multiple lesions and may be extensive. Secondary syphilis presents as in the immunocompetent patient, with scaly plaques on the trunk, muzzle area of the face, palms and soles (Figs 14 and 15). However, it may mimic any other cutaneous disease and hence a high index of suspicion is required for diagnosis. Progression to neurosyphilis occurs more rapidly even if the patient has had optimal treatment. Lues maligna, an unusual form of secondary syphilis with ulcers, has been described. False-positive VDRL and RPR tests and delayed titre responses occur more commonly in HIV-infected patients. Treatment for primary, secondary and early latent syphilis is one dose of 2.4 million units of benzathine penicillin G, and for late latent syphilis or syphilis of unknown duration 2.4 million units of penicillin G weekly for 3 weeks.

MYCOBACTERIAL DISEASE

Tuberculosis

HIV-infected adults are susceptible to tuberculosis and

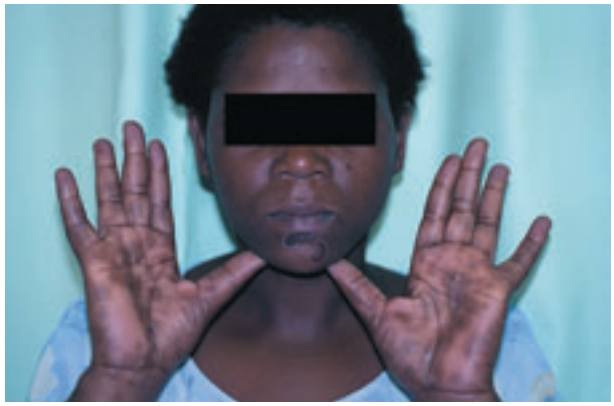

Fig. 14. Secondary syphilis, face and palms.

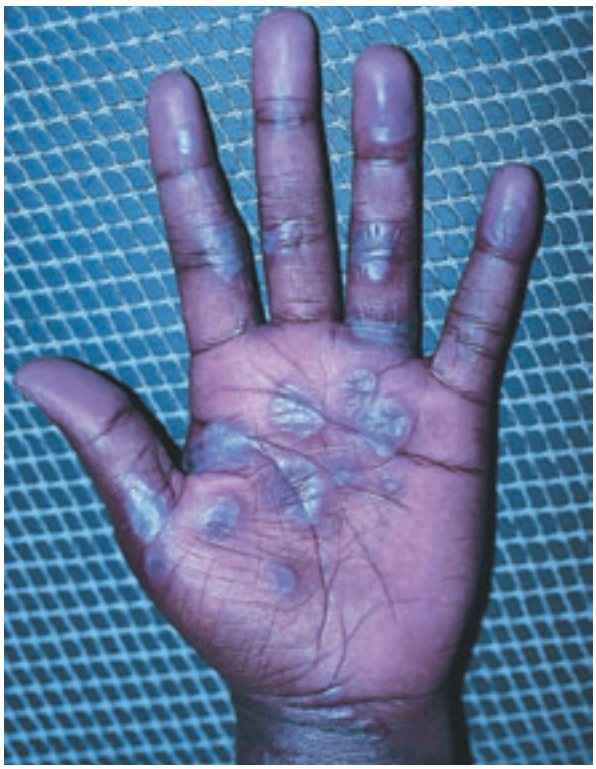

Fig. 15. Secondary syphilis with typical palmar lesions.

therefore at increased risk of presenting with cutaneous hypersensitivity reactions.

Papulonecrotic tuberculid can present with papules and pustules which ulcerate, usually involving the acral sites (earlobes, elbows, knees, extensors and buttocks) (Figs 16 and 17).

Lichen scrofulosorum presents as grouped papules on the trunk (Fig. 18) in patients with underlying lymphadeno-pathic and bone tuberculosis.

Erythema induratum/nodosum causes ulcers and painful nodules on the lower limbs, with a bluish edge (Fig.19).

Diagnosis of any of the above hypersensitivity reactions to tuberculosis is supported by a strongly positive Mantoux test, histology and investigation for underlying tuberculosis. Treatment with standard antituberculosis therapy for 6 months is effective.

Atypical mycobacteria

Mycobacterium avium, *haemophilum* and *bovis* may cause skin lesions with systemic mycobacterial disease in 10% of HIV-positive individuals. These infections are associated with advanced immunosuppression and are uncommon, partly because of the widespread use of antituberculosis therapy. Cutaneous lesions can present as papules, pustules, abscesses and ulcers. Lesions may present as nodules involving ascending lymph nodes of a limb. Biopsy and culture is essential for an accurate diagnosis, and therapy with clarithromycin and rifampicin is effective.

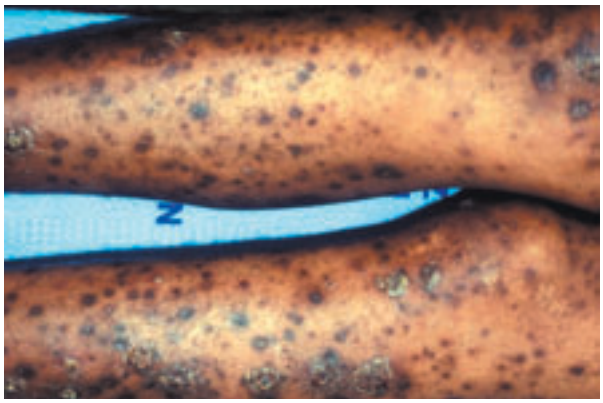

Fig. 16. Papulonecrotic tuberculid.

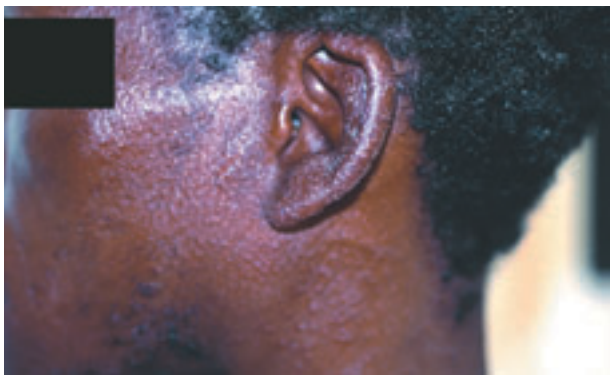

Fig. 17. Papulonecrotic tuberculid with classic earlobe lesions.

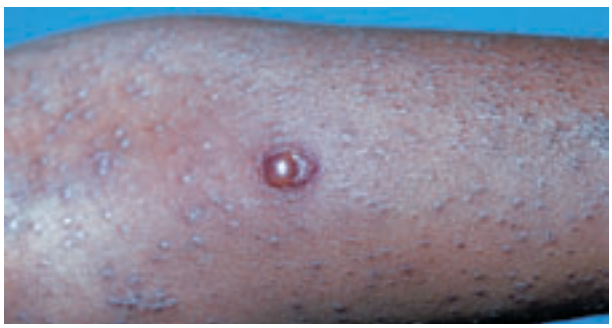

Fig. 18. Lichen scrofulosorum with blistering mantoux.

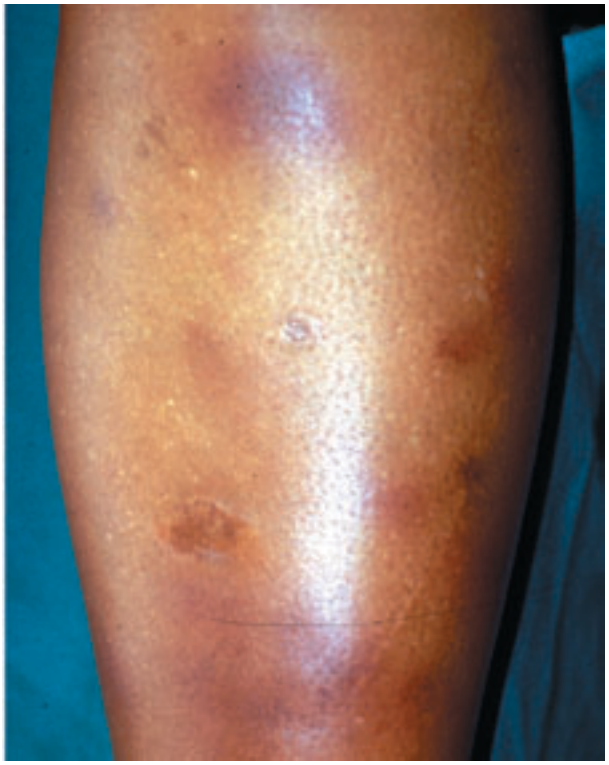

Fig. 19. Erythema nodosum, lower limbs.

READING

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