Onchocerciasis and Lymphatic Filariasis

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Infections with parasitic worms are widespread in tropical and sub-tropical areas of the world. In particular, infections with filarial nematodes occur in hot climate zones including *lymphatic filariasis*, *onchocerciasis* and *loiasis*; *Mansonella* species which occur in parts of Central Africa and Central and South America usually cause mild clinical symptoms. All filarial infections are transmitted by flying insects; humans are the only reservoir. Throughout the hot climate zones in Africa, approximately 130–150 million people are affected; the prevalence has clear association with poverty. Despite ongoing control programmes, lymphatic filariasis and onchocerciasis have been included in the list of *neglected tropical diseases (NTD)* by the WHO.

Today, filarial infections are occasionally seen in Europe in immigrants from the sub-Saharan countries [1]. Particularly, onchocerciasis may occur as an imported disease in the developed world; physicians should consider this tropical infection when caring for refugees, migrants and travellers with pruritus, skin lesions and eosinophilia [2]. Filariasis was one of the most frequent causes for eosinophilia and hyper-IgE among 362 immigrant children studied in Spain coming from sub-Saharan Africa [3]. Especially in patients with clinical pictures and findings suggestive of atopic dermatitis, onchocerciasis should be considered and excluded [4].

13.1 Onchocerciasis

Onchocerciasis is caused by the filarial nematode *Onchocerca (O.) volvulus* transmitted by *Simulium* black flies. According to recent estimates by the *African Programme for Onchocerciasis Control* (APOC), 21 million people are still infected, with main foci in Central Africa [5]. The adult worms may grow to a length up to 70 cm situated in subcutaneous nodules, whereas, the offspring *microfilariae* (MF) remain in the upper dermis and in the anterior chamber of the eye causing local damage. Accordingly, the main symptoms of onchocerciasis are related to skin lesions and eye inflammation.

13.1.1 Epidemiology

Transmission of *O. volvulus* occurs in tropical Africa, Latin and Central America and Yemen. More than 99% of the estimated 21–25 million infected individuals live in Africa, with 187 million people located in areas with potential risk for transmission [6]. Recent estimates calculate the overall burden of the disease by 1.1 million *disability-adjusted life years* (DALYs) in 2015. Exposure begins after birth; in adulthood, it is associated with physical work such as farming, where it is difficult to eliminate the vector despite the fact that the black flies need several minutes to sit on the victims before they start biting. *Simulium* is active during the day, does not enter houses, and mosquito nets are ineffective for prevention. Large-scale insecticide spraying programmes have been successful in West Africa, but vector control is difficult to implement in forested areas in the central part of the continent. *Mass drug administration* (MDA) with ivermectin has been the first successful drug donation programme for *neglected tropical diseases* (NTDs); it brought down the number of infected people by >50% and averted millions of DALYs and blindness.

13.1.2 Pathogenesis

Infection is caused by third-stage larvae (L3) transmitted by *Simulium* black flies during biting. They mature within 12 days from microfilariae (L1) taken up in a previous blood meal from an infected human host. The larvae moult

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twice during a few months, migrate through the body and settle in subcutaneous nodules (*onchocercomata*) which may contain several dozen adult female worms, thus increasing the size of the nodules to several cm. A fertile female releases up to several thousand MF up to 300 µm in length, which migrate into the papillary dermis; a load of several hundred MF per mg skin may result. Nevertheless, the skin often appears clinically not noticeably inflamed, due to active immunosuppression by adult female worms and also by the MF themselves. Immunosuppression is mediated by regulatory T cells leading to downregulation by macrophages, deactivation of eosinophils and neutrophils by TGF-β or IL10 and production of the immune regulatory subclass IgG4 [7]. A minority of infected people mount strong Th2-dependent immune responses with high eosinophilia, low or absent MF in their skin but strong dermal reaction.

Besides the skin, the eye is affected: MF in the anterior chamber induce chronic inflammation leading to sclerosing keratitis and blindness if untreated, giving the disease its popular name *river blindness*. Iridocyclitis with elliptical shape papillae, vasculitis and other damages of the retina and the optical nerve may occur.

13.1.3 Clinical Picture

The clinical picture of onchocerciasis is characterised by skin changes showing scattered pruritic papules, plaques and excoriations as a leading symptom, together with variable lymphadenopathy and inflammation of the eye, which is often absent in forest foci. In different geographic regions, varying types of onchodermatitis are seen, each type being graded for its severity, activity and distribution [8]. It is a cutaneous inflammatory response of the host to dying MF. The following types may occur, also depending on the stage of the infection:

(a) *Acute papular onchodermatitis,* highly pruritic, consisting of small papules mostly at the extremities, shoulder and trunk (Fig. 13.1). Progression of the lesions to hyalinised scar tissue is often seen, particularly after microfilaricidal treatment with ivermectin.
(b) *Chronic papular onchodermatitis*, mostly seen in hyperendemic areas, with flat hyperpigmented papules symmetrically located mainly on the buttocks, waist and shoulders, while the intensity of the pruritus decreases.
(c) *Lichenified onchodermatitis* with strongly pruritic papules and plaques (Fig. 13.2). In skin biopsies, MF can be detected in the upper dermis.
(d) *Skin atrophy* with loss of cutaneous elasticity due to chronic inflammation and release of elastase by eosinophils. Atrophic skin folds are seen, also called "hanging groins", containing groups of enlarged lymph nodes (Fig. 13.3).
(e) *Spotted depigmentation* called "leopard skin", particularly involving the interfollicular epidermis with the openings of the follicles still pigmented, mainly seen on the lower legs; the forearm and dorsum of the hand and the trunk may also be involved (Fig. 13.4).

Severe grade onchodermatitis may also occur localised, usually in one leg, often associated with considerable swelling of the regional lymph nodes [9], called *sowda* in Yemen (*sowda* = Arabic for black).

Most characteristic are *onchocercomata*, i.e. indolent cutaneous nodules, isolated or multiple, usually 0.5–3 cm in diameter, palpable in the subcutaneous tissue representing a marker for onchocerciasis. Preferred localisations are the iliac crest, the trochanter of the femoral bone, os sacrum, thorax, head and the median side of the knees (Figs. 13.5 and 13.6). Up to 50% of the nodules are less palpable, deeply located along the bones. Involvement of the eye initially shows punctate keratitis starting from the lower half of the cornea, progressing to sclerosing keratitis and leading to blindness. Inflammation of the posterior chamber includes changes of the retinal pigment with chorioretinitis, chorioretinal atrophy and atrophy of the optical nerve.

High eosinophilia (20–30%) is always present in patients with onchocerciasis, and eosinophilic cardiomyopathy is a cause of death if untreated.

13.1.4 Diagnosis

*S*erology shows cross reactivity to other filarial nematodes including *strongyloides*; it can only be applied in travellers who have not stayed long in endemic areas. Gold standard for diagnosis is to take from the suspected areas thin *skin snips* using a corneoscleral biopsy instrument (*Holth* punch), incubate the skin material taken in isotonic saline at room temperature for a minimum of 12 h, best done in a microtiter plate, and then examine the fluid at 40×. If present, motile MF can be seen and counted. If blood vessels were also opened, MF from other filarial infections such as *W. bancrofti*, *M. perstans* or *L. loa* can be present and misdiagnosed. The preferred site for the skin snips is the high end iliac crest. MF of *O. volvulus* should be differentiated from the smaller MF of *M. streptocerca* which have no sheath. If a patient has been recently infected, MF detection can be negative during prepatency for up to 2 years. If the procedure cannot be carried out in a local laboratory, it is also possible to preserve the biopsy for PCR.

During and up to 6 months after oral intake of ivermectin, there are no MF detectable in the tissue, but the patient is still

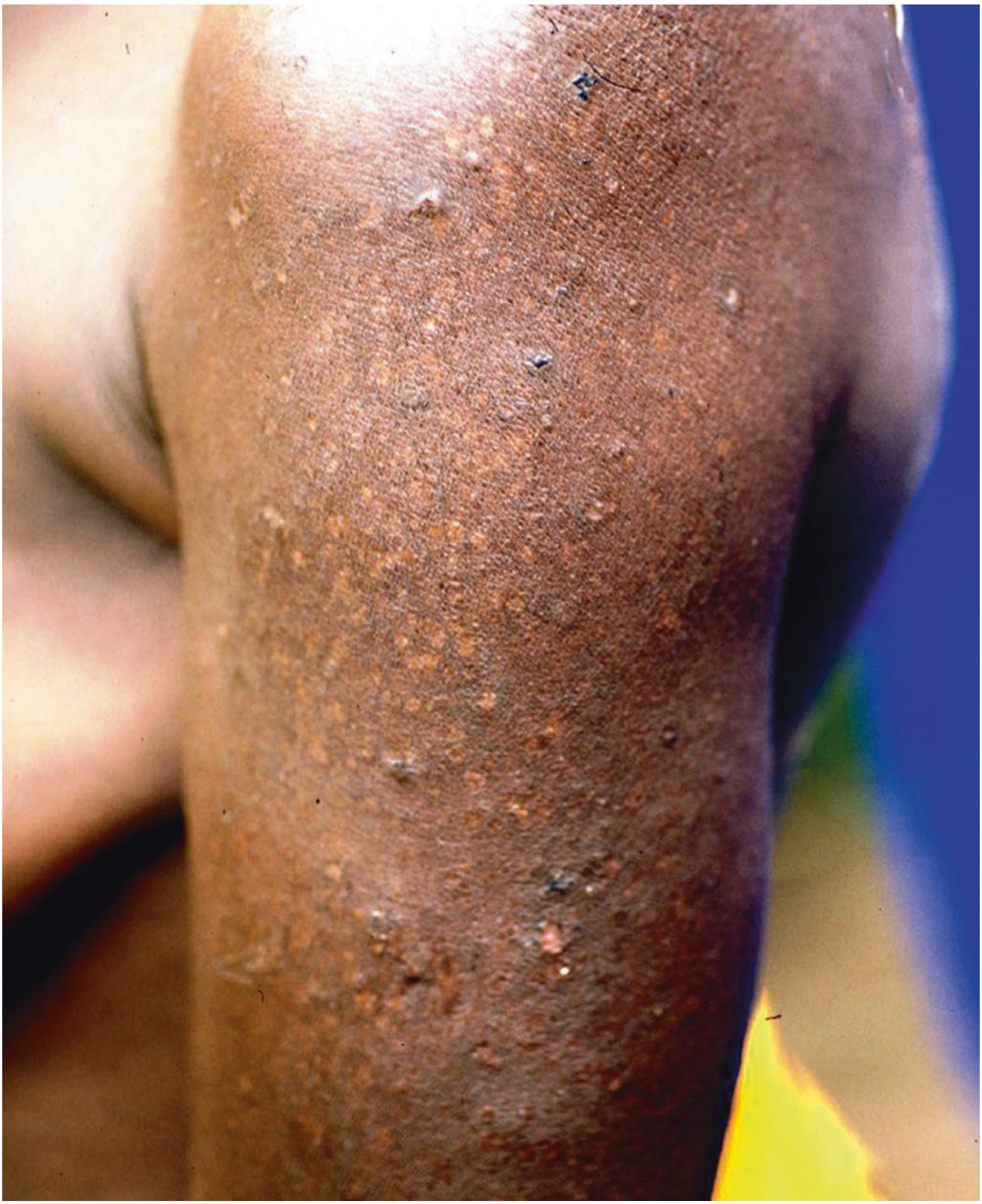

Fig. 13.1 Characteristic clinical presentation of *onchodermatitis* (acute type), associated with intense pruritus and scratching

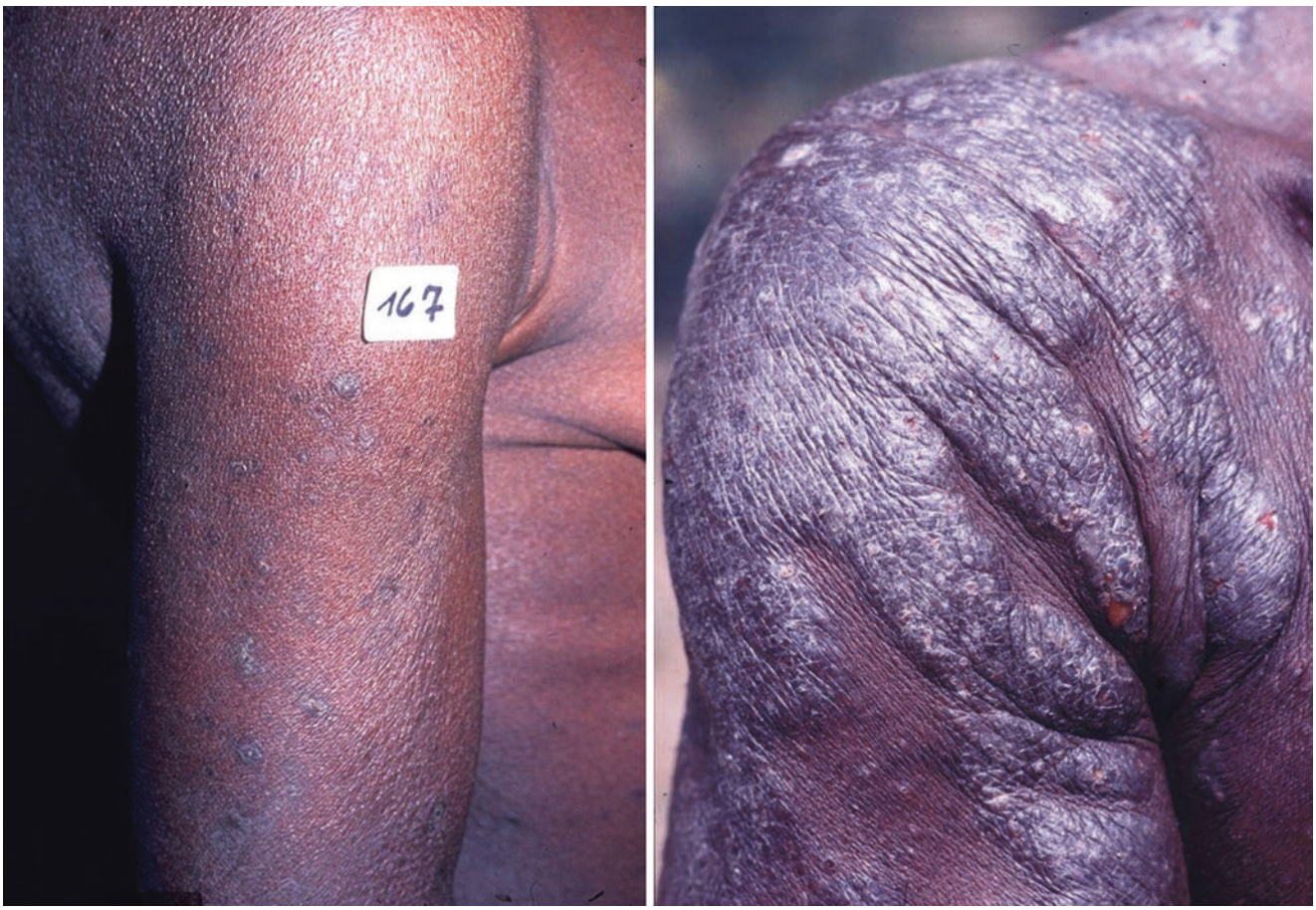

Fig. 13.2 *Chronic onchodermatitis*, with hyperpigmented pruritic papules (left); *Chronic onchodermatitis* with well-demarcated lichenified plaques, highly pruritic with excoriations (right)

infected. Since no markers to diagnose MF-negative onchocerciasis exist, one may pick up movements of the adult worms by using sonography of an onchocercoma. The *Mazzotti* patch test (topical application of diethylcarbamazine) is rarely used today, because the test is only positive if MF are present and also because the test cannot differentiate between *O. volvulus* and *M. streptocerca* infection, which clinically presents similar skin changes (Fig. 13.7).

13.1.5 Treatment

For treatment of onchocerciasis, *ivermectin* is the drug of choice, administered in a single dose of 150 µg/kg body weight every 6–12 months. It inactivates the glutamate sensitive chloride channels present only in nematodes and leads to >90% reduction of MF within 3 months. However, since the drug does not sterilise or kill the female adult worms, MF and skin lesions reappear after 6 months. Adverse events of treatment due to MF killing are prominent in patients with heavy infestation (>20 mg/kg skin) including dermatitis, cutaneous oedema as well as orthostatic low blood pressure; the latter may require that the patient lay down the days during drug intake. Adverse reactions can be mitigated by premedication of cortisone. The drug is not administered to children below the age of 5, respectively, 15 kg body weight, as well as to pregnant and breast-feeding women. The beneficial effect of albendazole has been discussed; however, recent controlled trials were not supportive [10]. The comfortable administration 1–2× per year makes ivermectin the

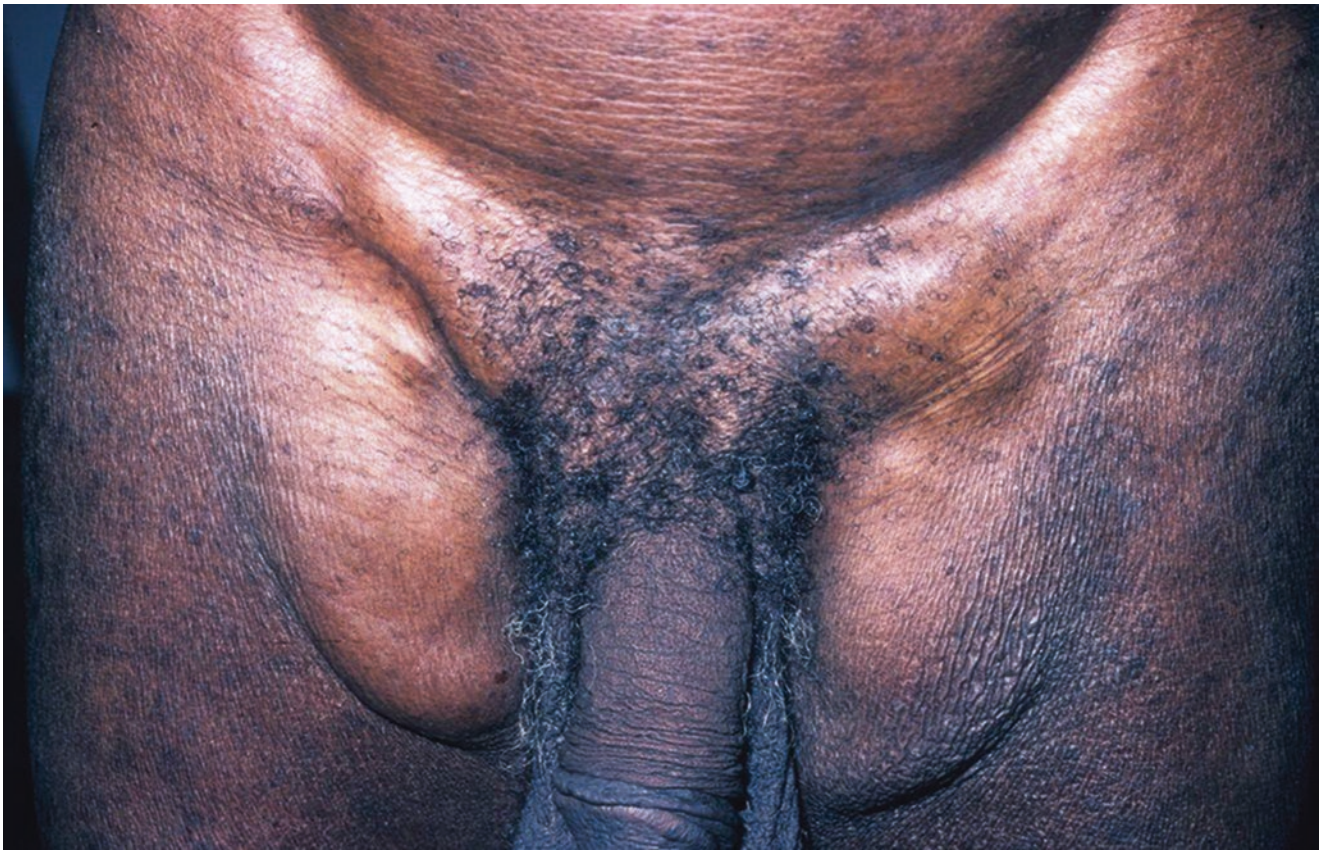

Fig. 13.3 *Hanging groins* in atrophic skin folds containing enlarged lymph nodes in onchocerciasis

drug of choice particularly for patients living in endemic areas under the risk of reinfection. MDA covering 80% of the eligible population living in endemic areas is the basis of WHO control programmes. Since ivermectin does not kill adult worms, MDA has to be repeated over many, in some areas >20 years until adult worms will have been eliminated in a given population.

Doxycycline was recently shown in randomised controlled trials to be a safe macrofilaricidal drug for onchocerciasis [11]; it targets *Wolbachia* endosymbiotic bacteria, necessary for reproduction and survival of the adult worms. The drug leads by depletion to worm sterility and death, administered at 100 mg/day for 5 weeks or 200 mg/day for 4 weeks. While doxycycline is indicated for all those who are not living in endemic areas and cures the individual patient, the long time required for treatment precludes its broad administration in MDA programmes. Contraindications for doxycycline are pregnancy or breast-feeding, and it is not administered to children below 9 years of age.

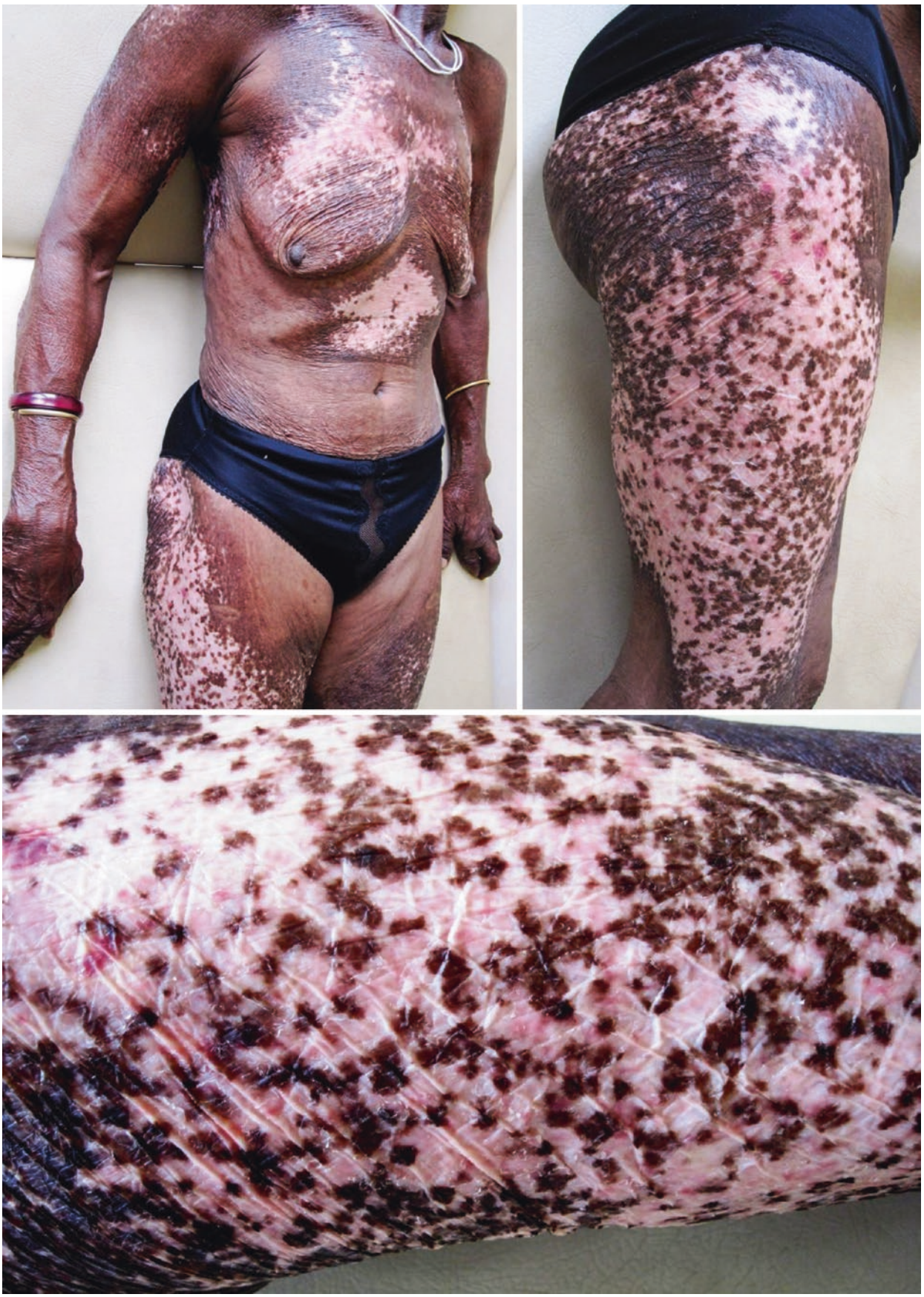

Fig. 13.4 Chronic onchocerciasis in an aged Maasai female with characteristic dyspigmentations, so-called *leopard skin.* Enlarged lymph nodes are seen in the inguinal area (left)

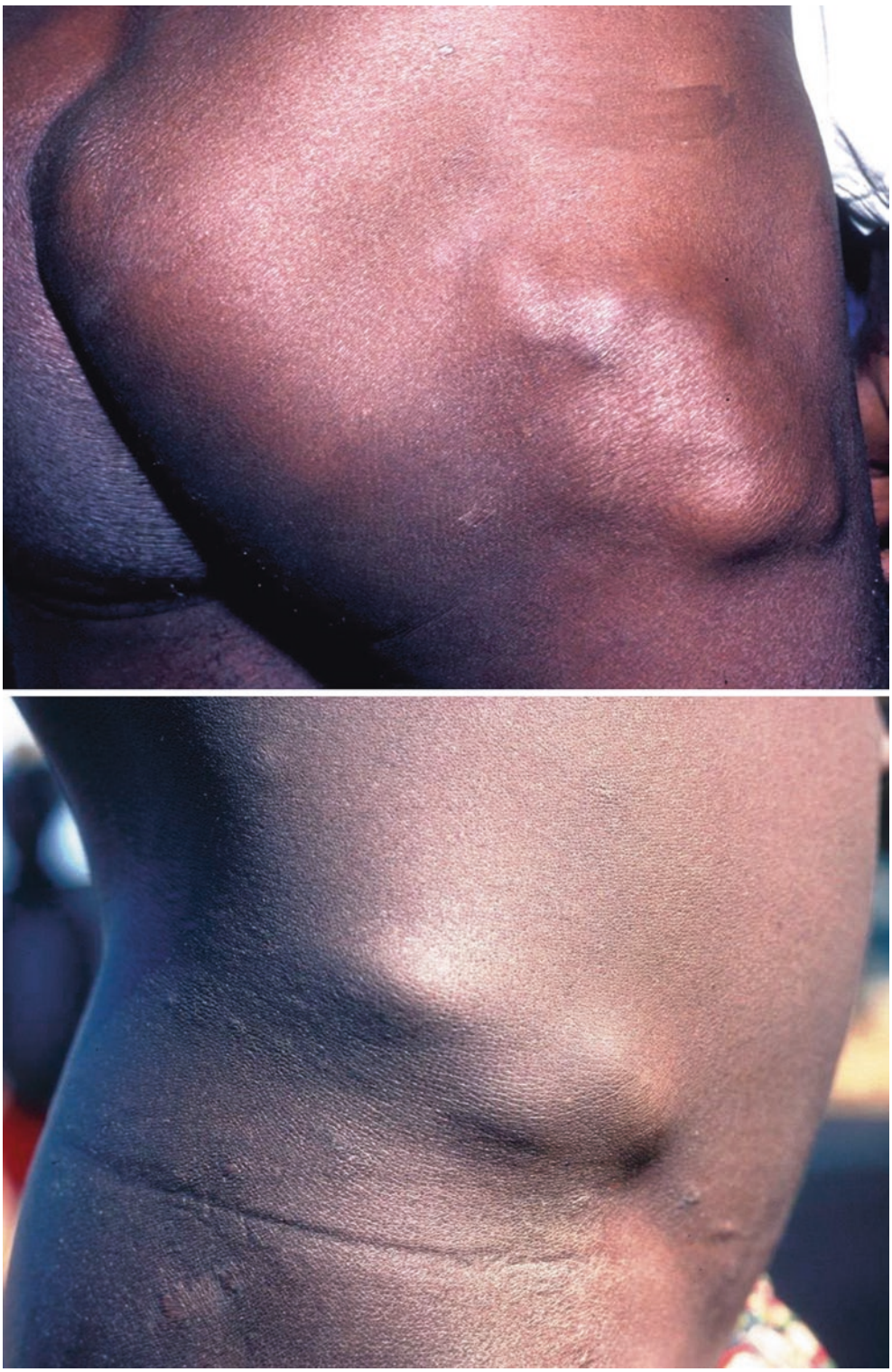

Fig. 13.5 *Onchocercomata* in typical localisation

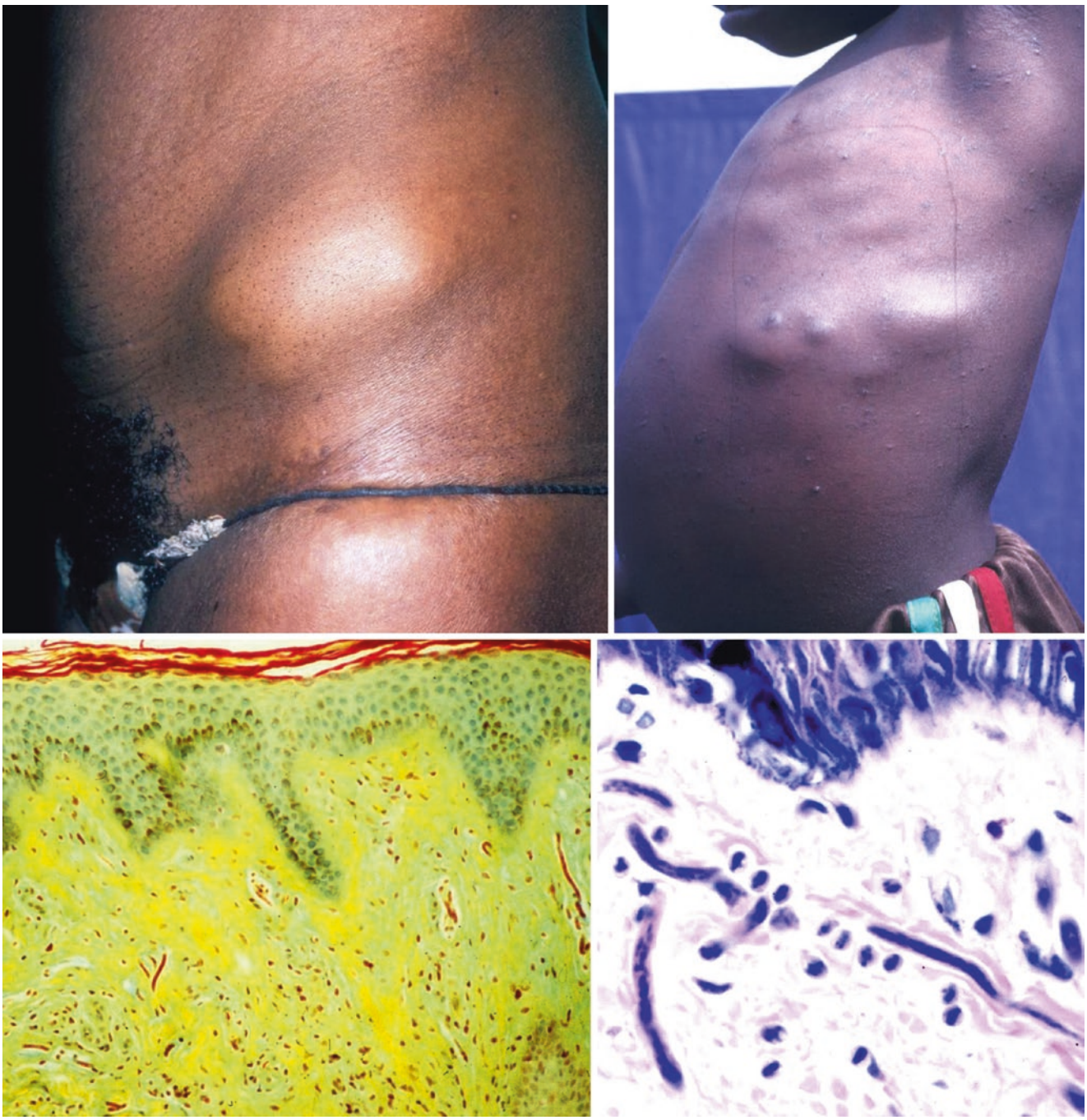

Fig. 13.6 Large conglomerates of *onchocercomata.* In skin biopsies, numerous MF of *O. volvulus* are seen in the upper papillary dermis

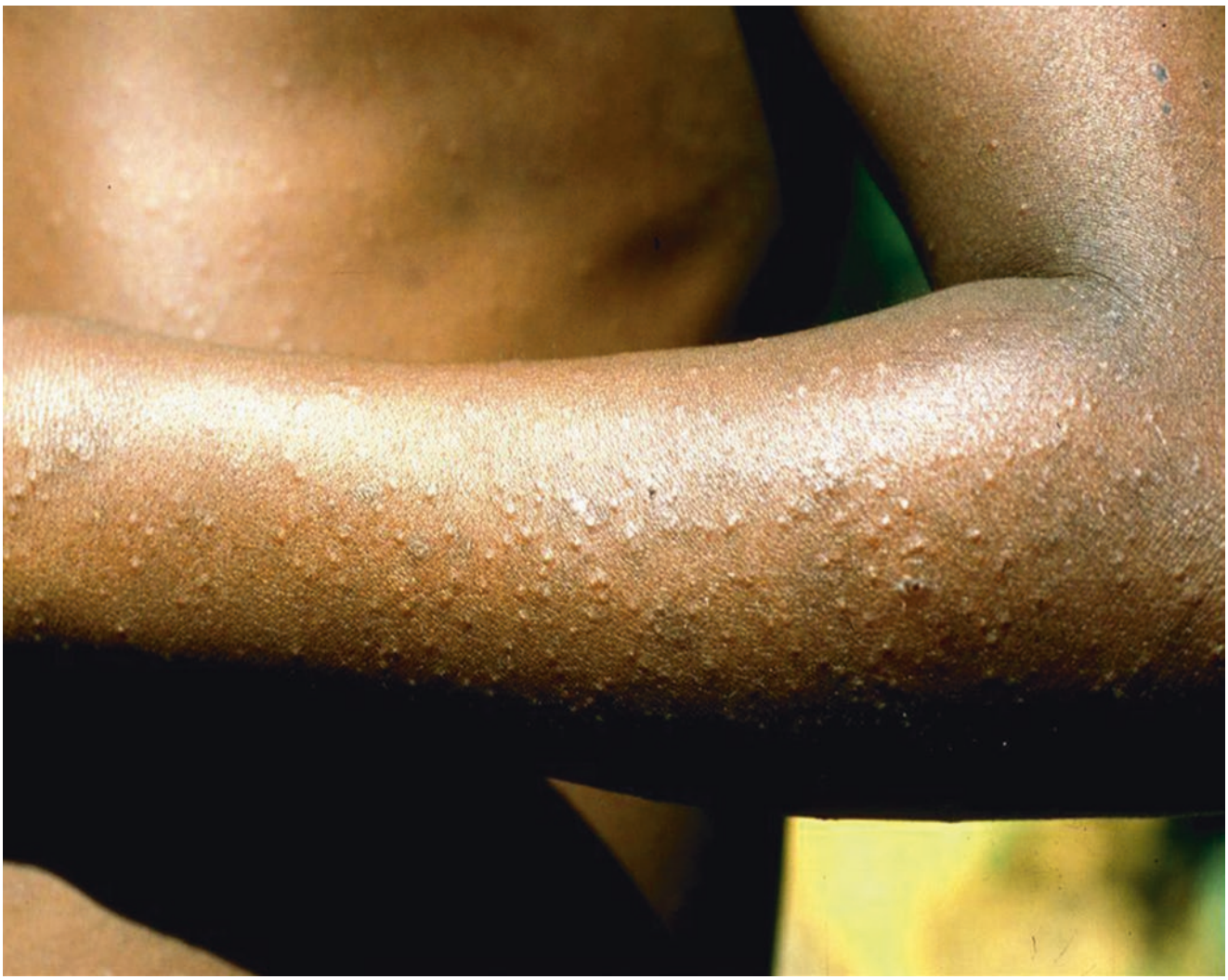

Fig. 13.7 Pruritic dermatitis due to infection with *Mansonella streptocerca*, seen in West and Central Africa, to be considered in differential diagnosis. Lymph nodes may be enlarged

13.2 Lymphatic Filariasis

Lymphatic filariasis (LF) is prevalent in all tropical regions except in Australia. The disease is commonly caused by *Wuchereria (W.) bancrofti*; the species *Brugia malayi* and *Brugia timori* are only found in Southeast Asia and will not be further considered here. *W. bancrofti* infective third-stage (L3) larvae are transmitted by bites of several infected mosquito species, including *Anopheles* in Africa, *Culex* mainly in Asia and *Aedes* in the Pacific islands. The adult worms live in the human lymphatic system, vessels and lymph nodes, grow to a length of 10–20 cm and cause inflammatory and mechanical aberrations to the vessels leading to lymphoedema (*lymphatic elephantiasis*) and hydrocele. Their offspring MF can be detected in the peripheral blood. Therapeutic modalities should not only prevent the transmission of MF but also be directed against the adult worms to prevent clinical damage.

13.2.1 Epidemiology

Updated figures on LF prevalence are yearly presented in epidemiological WHO reports. Successful implementation of MDA in endemic areas has greatly reduced the prevalence of LF from formerly 120 million down to 68 million cases and an estimated 36 million MF carriers. Not all infected individuals suffer from disease symptoms; around 66% of the infected individuals remain clinically symptomless. There are 19 million with lymphoedema and another 16 with hydrocele; however, the

relative proportion of disabled people increases as infection is controlled, since the clinical damage is largely irreversible.

The prevalence of LF varies considerably in endemic areas with 30% in a given village and <1% in another, without noticeable differences in the mosquito environment; only in Papua New Guinea >70% can be observed. This is an obstacle for control programmes and measurements of prevalence. In addition, only 50% of the individuals affected present MF in their peripheral blood, the rest merely shows positivity for circulating filarial antigen measured by an antigen detection card test applicable in the field. The measurements correlate well with the detection of moving adult worms by ultrasound in the scrotal area of adult men.

LF has been assigned as one of NTDs amenable to preventive chemotherapy and control by the WHO. A Global Alliance for Elimination of Lymphatic Filariasis (GAELF) unites WHO and private NGOs as well as governments with the goal to eliminate LF in many areas of the world by 2020, and from all countries by 2025. This ambitious goal is aimed by implementing MDA with *diethylcarbamazine* (DEC; "mass deworming") at 6 mg/kg combined with a single dose of *albendazole* 400 mg outside Africa and of *ivermectin* 200 µg/kg plus albendazole 400 mg in Africa. DEC is not distributed in African countries because of the eye damage it causes in patients suffering from concomitant onchocerciasis.

13.2.2 Pathogenesis

The transmission cycle of *W. bancrofti* is similar to that of *O. volvulus*: L3 larvae mature from MF in the insect vector within 12–14 days and develop into adult worms within lymphatic tissue in a few months. Adult worms live in lymphatic tissue, in lymph vessels and lymph nodes. They are most stable in the scrotal tissue of men after puberty and can be detected by ultrasound over time periods of years. Chronic filarial inflammation induced by the worms leads to *elephantiasis* via lymph vessel dilation and lymph angiogenesis, visualised in its initial stages by sonography or lymphoscintigraphy. However, MDA against LF does not roll back the progression of lymphoedema once it is established, it may continue after eliminating filarial infection clustered in families with genetic predisposition. Individuals with lymphoedema have a much stronger immune reaction of Th1 and Th17 cell types, as opposed to patients with high worm load and microfilaremia who often present no clinical symptoms showing strong immunosuppression mediated by regulatory T-cell responses and high IL10 [12].

Hydrocele is a second most important feature seen in *W. bancrofti* infections due to inflammatory changes of the lymph vessels by draining the fluid secreted between the two layers of the *tunica vaginalis*. As secretion continues, lymph efflux is impaired and fluid accumulates. Lymphoedema and/or chyluria in the genital area in men and women are all consequences of the impaired lymph efflux.

13.2.3 Clinical Picture

The clinical manifestations of LF comprise lymphangitis and lymphadenitis, lymphedema/elephantiasis and hydrocele. Acute manifestations of the disease impose as *acute filarial lymphangitis* (AFL) or *acute filarial dermatolymphangioadenitis* (ADLA). Lymph vessel dilation impairs lymph transport, leading to extravasation of fluid particularly in the lower limbs and feet. Fissures and open wounds may then result and bacterial super infection perpetuate the inflammatory process. Genital manifestations in women, e.g. oedema of the labia majora, are much less frequent than those in men. Chyluria and tropical pulmonary eosinophilia are relatively rare.

AFL is a skin reaction of the carrier against dying worms in lymph vessels or lymph nodes (natural or drug-induced) which can ulcerate releasing a serous fluid and heals with scarring. It is frequently seen in femoral lymph nodes in endemic areas. The process tends to heal without chronic lymph vessel dilation, but after several episodes of chronic lymphangiectasia with subcutaneous oedema may occur, leading to the development of interdigital fissures and bacterial super infection even in the absence of filarial worms. In ADLA, different to AFL, there is always cutaneous oedema with a few enlarged and painful lymph nodes. ADLA episodes heal and the skin peels off after 1 week. Such episodes occur repeatedly, thus enlarging the size of lymphedema.

In the lower extremities, chronic lymphoedema with thickening of the skin and the underlying tissues occurs, usually starting at the ankles, but can also involve the arms, breasts, scrotum, vulva and penis. Based on the staging by *Dreyer* early stages are more easily reversible, whereas late stages usually progress towards elephantiasis (Figs. 13.8 and 13.9). The extensive chronic lymphoedema often present additional findings, such as other bacterial co-infections and ulcers; lymphoedema due to Kaposi's sarcoma or podoconiosis may complicate and/or mimic lymphatic filariasis (Figs. 13.10 and 13.11).

Hydrocele is most frequently found in men (after puberty) and silently progresses accompanied by attacks of funiculitis and epididymitis. In the majority of cases, the tunica vaginalis thickens and the efflux obliterates (Fig. 13.12). Hydroceles due to LF can reach the size of a basketball due to continuous secretion of fluid. Small hydroceles can disappear spontaneously, occasionally triggered by worm-killing drugs such as DEC.

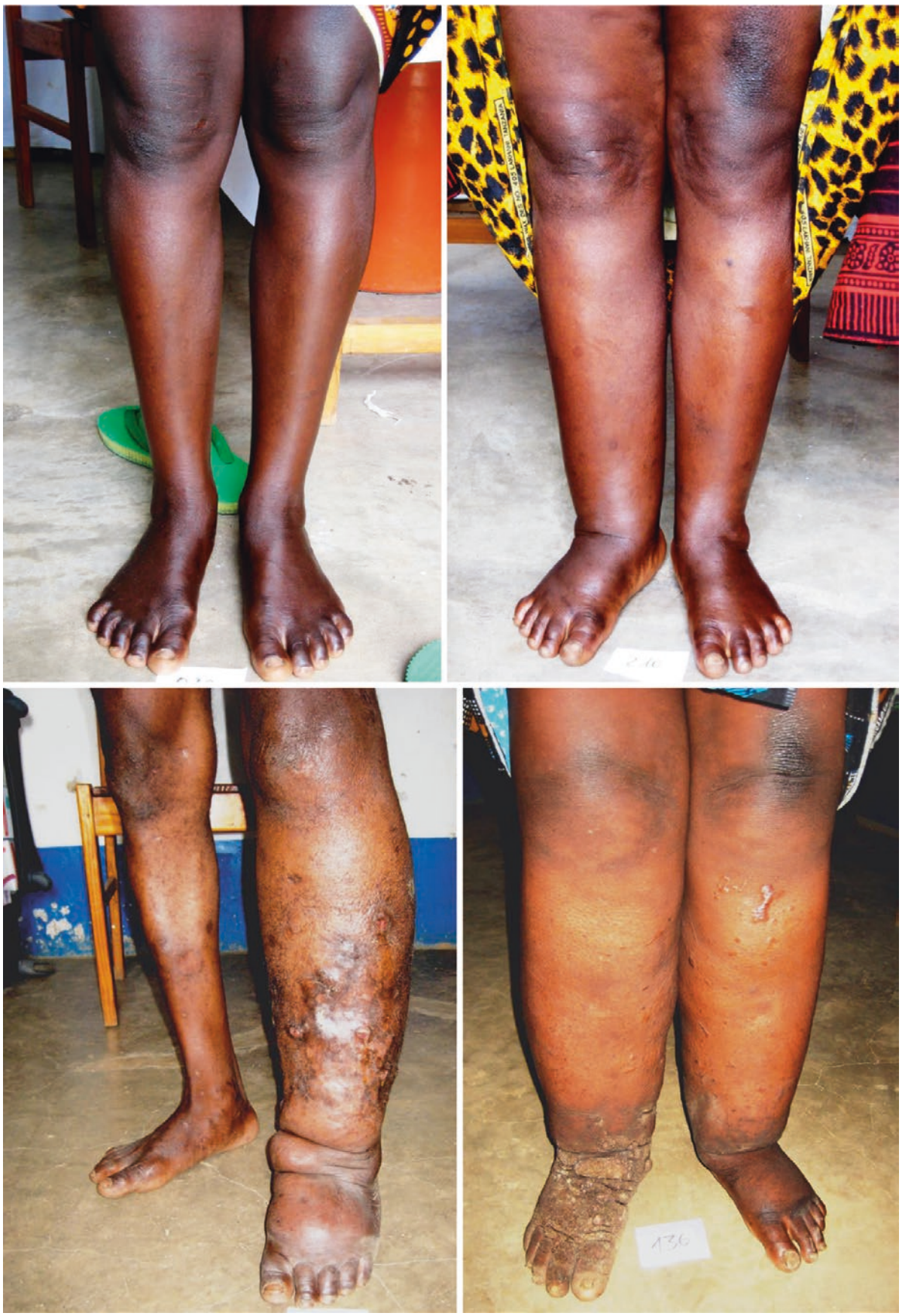

Fig. 13.8 *Lymphatic filariasis* presenting elephantiasis in different stages: *Dreyer* stages 1 and 2 (up); stages 4 and 6–7 (down)

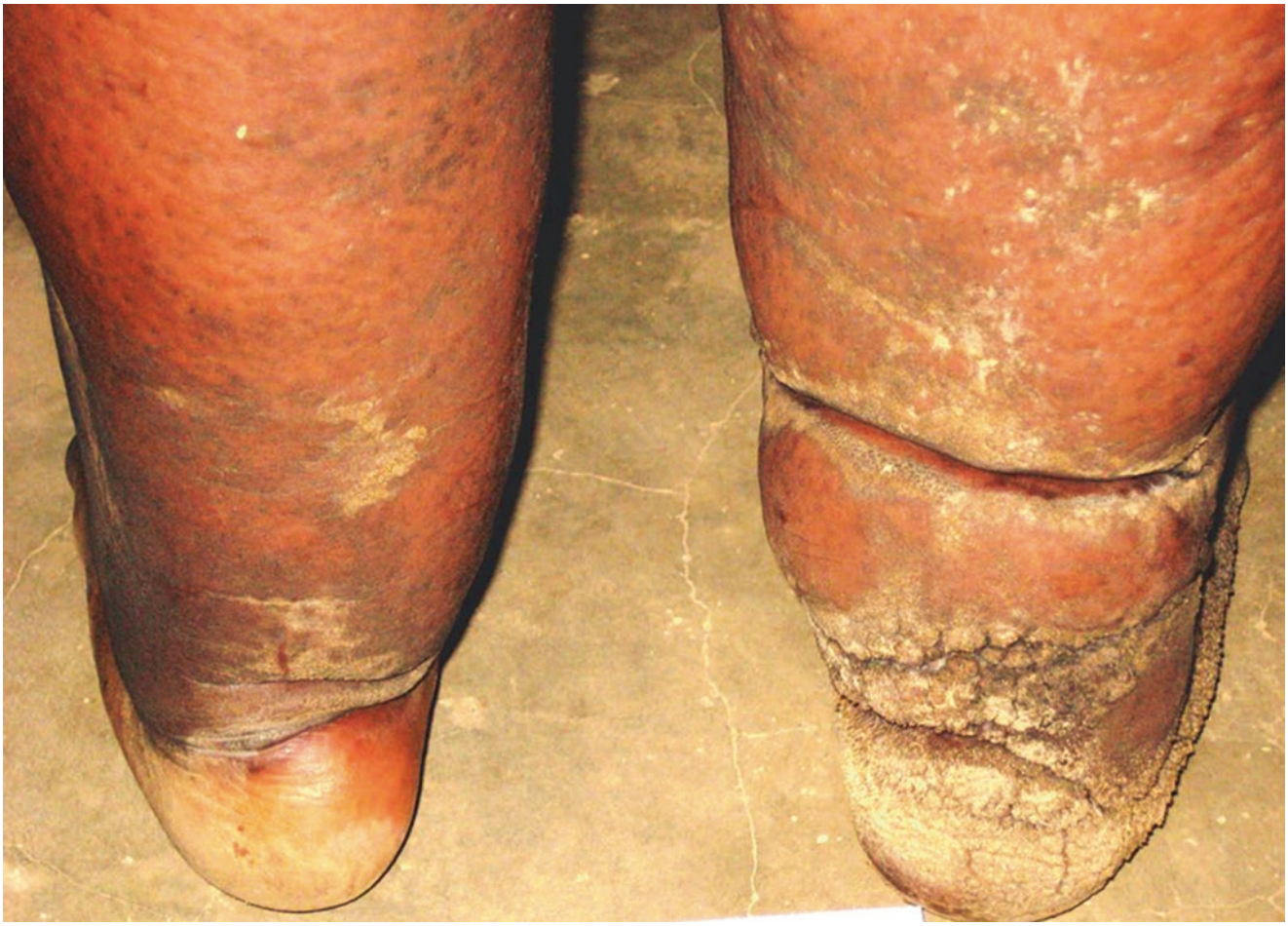

Fig. 13.9 Lymphatic elephantiasis *Dreyer* stage 7

13.2.4 Diagnosis

The diagnosis of LF is confirmed by the detection of MF in the peripheral blood, to be differentiated from other species of nematodes such as *L. loa* and *M. perstans* by their size, presence of a sheath and characteristic nuclei in their tail. Depending on the biting habits of the vectors, MF are found in the peripheral blood either at night (*Anopheles, Culex, Mansonia*) or during the day (*Aedes*). EDTA blood (10–20 µL) will allow detecting higher numbers of MF, approximately 500 MF/mL; since MF are 20–50× larger in size than erythrocytes, low magnifications are sufficient for microscopic examination with a light microscope. In patients with low MF load, the blood has to be enriched in a thick smear (such as with malaria) or lysis of 3 mL anticoagulated blood with 6 mL formalin solution 2% followed by centrifugation. Another possibility is to pass the blood through a polycarbonate filter allowing the passage of blood cells but not of the MF (nucleopore 3 µm). MF can also be amplified and the species classified by PCR.

A more recent diagnostic technique is to determine the circulating filarial antigen (CFA) by a rapid immunochromatographic card test that can be used in the field. Positivity does not vary between day and night so that examination can be made at all times. By using the *CFA test* in endemic areas, twice as many individuals were found positive than the number of those showing presence of MF in their blood, indicating an equal number of occult infections. There is also the possibility to detect moving filariae in scrotal areas of men or, less easily, in lymph node areas in men and women [13].

13.2.5 Treatment

Mass drug administration programmes for treatment of LF are organised in endemic areas by governmental health services in collaboration with the WHO and NGOs. In areas where onchocerciasis is not endemic or present, a single-dose albendazole 400 mg plus DEC 6 mg/kg was given and albendazole 400 mg plus 200 µg/kg ivermectin in African

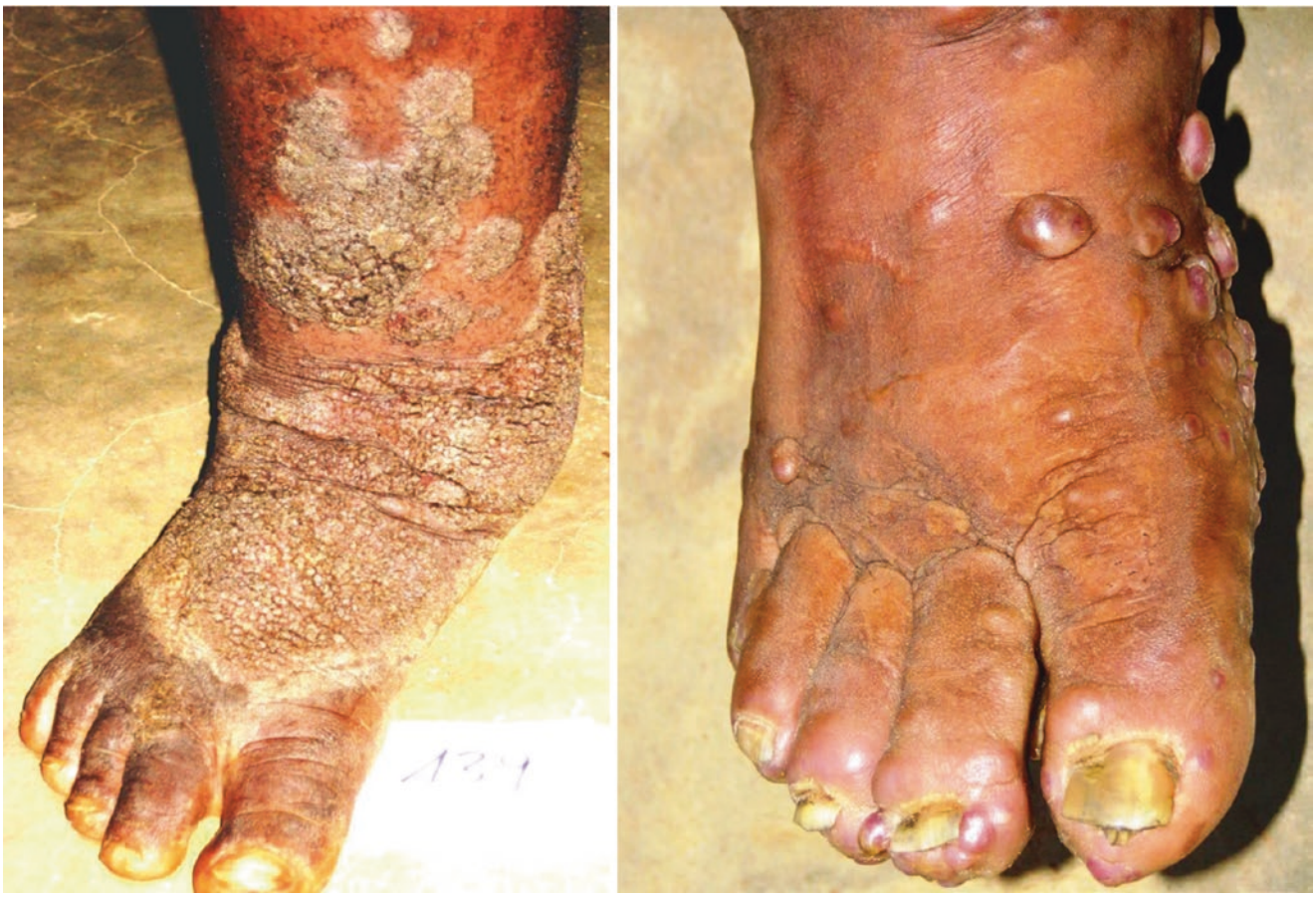

Fig. 13.10 *Podoconiosis* (left) and possible co-infection with *bacillary angiomatosis* (right)

countries with coexistence of onchocerciasis. These drug combinations deplete MF in infected patients over a period of >6 months, also having an additional but epidemiologically not relevant macrofilaricidal activity. A biannual MAD with albendazole on LF diagnosed with the CFA test in Congo has been recently reported successful [15].

Treatment with doxycycline 200 mg for 4–6 weeks has been shown effective against adult worms [14, 16], in recent studies also in a lower dose, 100 mg for 4–5 weeks; efficacy up to 90% has been observed after 12–18 months (Klarmann-Schulz et al.; in preparation). The mode of action is the same as in onchocerciasis targeting *Wolbachia* endobacteria. Doxycycline also reverts early stages of lymphoedema (Dreyer 1–3), recommended to be administered in 6-week courses every 1–2 years [16, 17].

Triple combinations of single doses of DEC, ivermectin and albendazole showed strong macrofilaricidal activity in pilot studies [18]; if confirmed, this may introduce a change in the recommendations for individual therapies, as well for MDA. As an alternative to doxycycline, rifampicin has been recently reported to be effective and safe in preclinical models [19].

Since lymphoedema progresses even without the initial trigger, management of LF is not limited to antifilarial treatment. The effect of doxycycline may be due to impairment of lymph angiogenesis rather than to infection control [17]. In addition, it is essential to instruct the patients that hygiene is a key to impede the entry of opportunistic bacteria through skin lesions with proper footwear and daily washings with local antiseptics. WHO issues a series of instructions (http://www.who.int/lymphatic_filariasis/resources/training/en/) for patients and physicians. Surgical intervention is necessary in large hydroceles in order to prevent relapses.

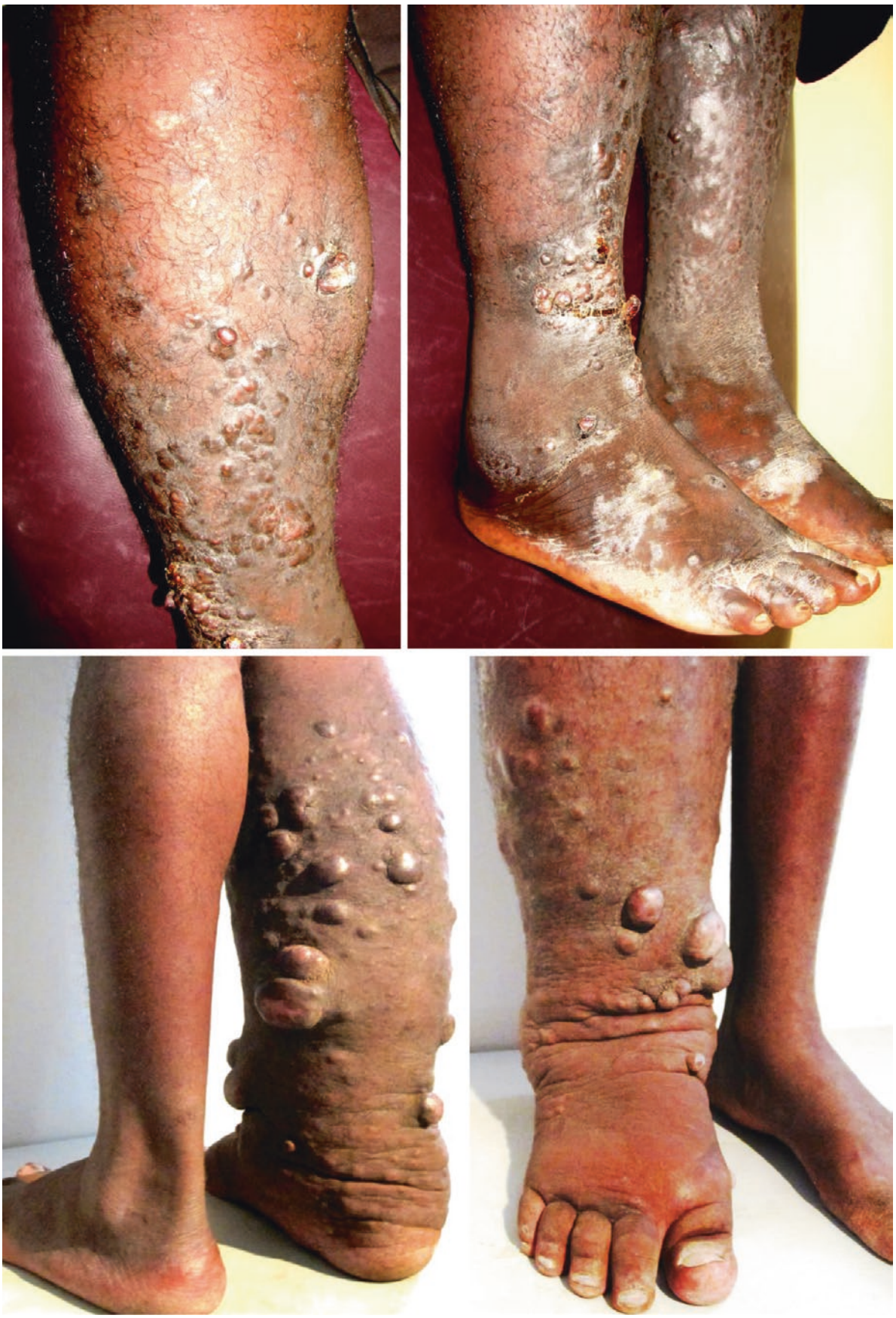

Fig. 13.11 Comorbidities: Bacterial super infections (up) and nodular type of *African Kaposi's sarcoma* (down)

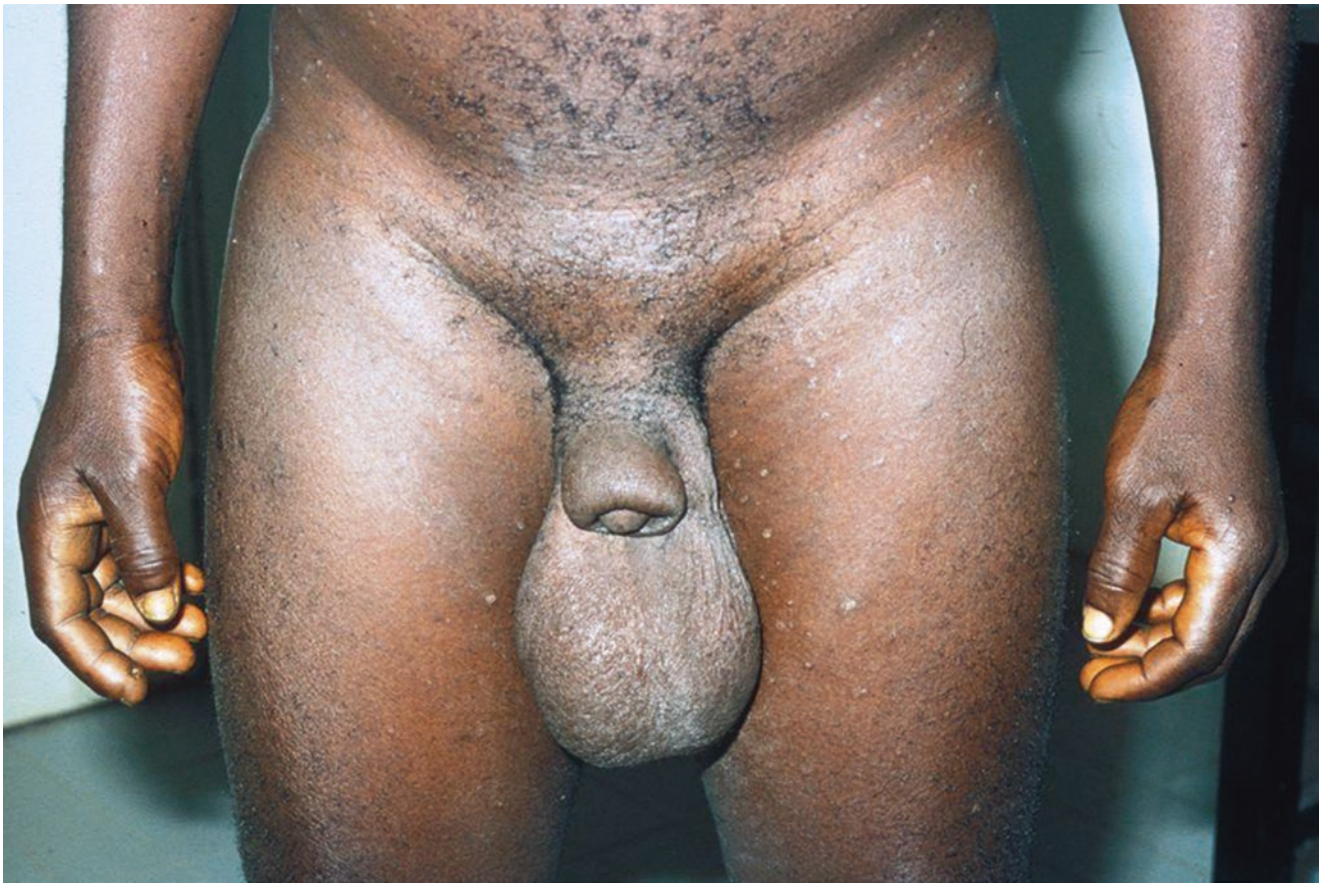

Fig. 13.12 Scrotal *hydrocele* due to lymphatic filariasis

Conclusions

Onchocerciasis and lymphatic filariasis are major infections with widespread parasitic worms transmitted by insect bites in hot climate zones. They are associated with local environmental conditions and poverty and represent a major public health issue of the populations in endemic areas. Several mass drug administration programmes have been introduced by governmental agencies and the WHO which reduced the prevalence of these infestations; however, filariases are still a challenge. In recent years, cases were imported to developed countries by immigrants and refugees or by international travellers not following hygienic rules and prevention. Recognition of these tropical infestations and treatment with antifilarial drugs such as ivermectin, diethylcarbamazine and albendazole are required. Physicians should be aware of their clinical picture, diagnosis and management, since these entities are not included in medical curricula and routine medical education in the Western world.

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