CHAPTER 47

Filarial Infections

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Filarial worms are nematodes or roundworms that dwell in the subcutaneous tissues and the lymphatics. Although eight filarial species commonly infect humans, four are responsible for most of the pathology associated with these infections. These are (1) *Brugia malayi*, (2) *Wuchereria bancrofti*, (3) *Onchocerca volvulus*, and (4) *Loa loa*. The distribution and vectors of all the filarial parasites of humans are given in **Table 47.1**.

In general, each of the parasites is transmitted by biting arthropods. Each goes through a complex life cycle that includes an infective larval stage carried by the insects and an adult worm stage that resides in humans, either in the lymph nodes or adjacent lymphatics or in the subcutaneous tissue. The offspring of the adults, the *microfilariae* (200-250 μm long and 5-7 μm wide), either circulate in the blood or migrate through the skin. The microfilariae then can be ingested by the appropriate biting arthropod and develop over 1-2 weeks into infective larvae, which are capable of initiating the life cycle over again. A generalized schematic is shown in **Figure 47.1**.

Adult worms are long lived, whereas the lifespans of microfilariae range from 3 months to 3 years depending on the filarial species. Infection is generally not established unless exposure to infective larvae is intense and prolonged. Furthermore, clinical manifestations of these diseases develop rather slowly.

There are significant differences in the clinical manifestations of filariasis, or at least in the time course over which these infections are acquired, in patients native to the endemic areas and those who are travelers or recent arrivals in these same areas. Characteristically, the disease in previously unexposed individuals is more acute and intense than that found in natives of the endemic region; also, early removal of newly infected individuals tends to speed the end of clinical symptomatology or at least halt the progression of the disease.

LYMPHATIC FILARIASIS

There are three lymphatic-dwelling filarial parasites of humans: *B. malayi*, *Brugia timori*, and *W. bancrofti*. Adult worms usually reside in either the afferent lymphatic channels or the lymph nodes. These adult parasites may remain viable in the human host for decades.

Epidemiology

B. malayi *and* B. timori

The distribution of brugian filariasis is limited primarily to China, India, Indonesia, Korea, Japan, Malaysia, and the Philippines. In both brugian species, two forms of the parasite can be distinguished by the periodicity of their microfilariae. *Nocturnally periodic forms* have microfilariae present in the peripheral blood primarily at night, whereas the *sub-periodic forms* have microfilariae present in the blood at all times, but with maximal levels in the afternoon.

TABLE 47.1 Filarial Parasites of Humans

Species	Distribution	Vector	Primary Pathology
Brugia malayi	Southeast Asia	Mosquito	Lymphatic, pulmonary
Brugia timori	Indonesia	Mosquito	Lymphatic
Wuchereria bancrofti	Tropics	Mosquito	Lymphatic, pulmonary
Onchocerca volvulus	Africa and Central and South America	Blackfly	Dermal, ocular, lymphatic
Mansonella streptocerca	Africa	Midge	Dermal
Loa loa	Africa	Deerfly	Allergic
Mansonella perstans	Africa and South America	Midge	Probably allergic
Mansonella ozzardi	Central and South America	Midge	?

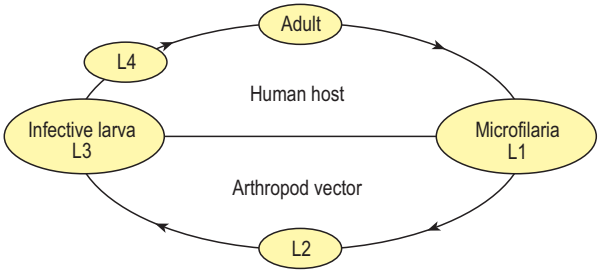

Fig. 47.1 General life cycle of the filarial parasites in humans. Microfilariae (*L1*) are produced by the adult worms. *L2* and *L3* are larval development stages in the arthropod vector. *L3* larval forms are infective for humans. *L4* develop from the newly arrived infective larval forms.

The nocturnal form of brugian filariasis is more common and is transmitted in areas of coastal rice fields (by *Mansonia* and *Anopheles* mosquitoes), whereas the subperiodic form is found in the swamp forests (*Mansonia* vector). Although humans are the common host, *B. malayi* can be a natural infection of cats. *B. timori* has been described only on two islands of the Indonesian archipelago (including East Timor).

W. bancrofti

Bancroftian filariasis is found throughout the tropics and subtropics, including Asia and the Pacific islands, Africa, areas of South America, and the Caribbean basin. Humans are the only definitive host for this parasite and are therefore the natural reservoir for infection. Like brugian filariasis, there is both a periodic and a sub-periodic form of the parasite. Generally, the sub-periodic form is found only in the Pacific Islands (including Cook and Ellis Islands, Fiji, New Caledonia, the Marquesas, Samoa, and the Society Islands); elsewhere, *W. bancrofti* is nocturnally periodic. The natural vectors are *Culex fatigans* mosquitoes in urban settings and usually *Anopheles* or *Aedes* mosquitoes in rural areas.

Pathology

Most of the pathology associated with bancroftian and brugian filariasis is localized to the lymphatics. Damaged lymphatics first lead to reversible lymphedema and then to chronic

obstructive changes (in the limbs, breasts, or genitalia or to chyluria). The location of the lymphatic damage determines the type and site of the pathology.

Although the underlying mechanisms of pathology in this form of the disease are not yet known with certainty, it is thought that adult worms residing in the lymph nodes or neighboring lymphatics induce local inflammatory reactions and/or changes in lymphatic function. These reactions result in dilation of the lymphatics and hypertrophy of the vessel walls, although as long as the adult worm remains viable, the vessel is said to remain patent. Death of the worm, however, leads to local necrosis and a granulomatous reaction around the parasite. Fibrosis occurs and lymphatic obstruction develops. Although some recanalization and collateralization of the lymphatics takes place, lymphatic function remains compromised.

Clinical Manifestations in Those Native to the Endemic Region

The three most common presentations of the lymphatic filariases are asymptomatic (or subclinical) microfilaremia, adenolymphangitis (ADL), and lymphatic obstruction.

1. Patients with *asymptomatic microfilaremia* rarely come to the attention of medical personnel except through the incidental finding of microfilariae in the peripheral blood during surveys in endemic regions or when blood eosinophilia leads to a diagnostic evaluation for lymphatic filariasis. Such asymptomatic persons are clinically unaffected by the parasites, although lymphoscintigraphic evaluation of these individuals suggests that lymphatic dysfunction (and tortuosity) is common, as is scrotal lymphangiectasia (detectable by ultrasound) in men with *W. bancrofti* infection.
2. Acute *filarial* ADL is characterized by high fever (and shaking chills), lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde, extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. In brugian filariasis, a single local abscess may form along the involved lymphatic tract and subsequently rupture to the surface. The lymphadenitis and lymphangitis occur in both the upper and the lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. Genital involvement can be manifested by funiculitis, epididymitis, scrotal pain, and tenderness.
3. Chronic manifestations of lymphatic filariasis develop in only a small proportion of the filarial-infected population. If lymphatic damage progresses, transient lymphedema can develop into *lymphatic obstruction* and the permanent changes associated with elephantiasis. Brawny edema follows the early pitting edema, and thickening of the subcutaneous tissues and hyperkeratosis occur. Fissuring of the skin develops, as do hyperplastic changes. Superinfection of these poorly vascularized tissues becomes a problem. In bancroftian filariasis, when genital involvement is evident, scrotal lymphedema or hydrocele formation occurs. Furthermore, if there is obstruction of the retroperitoneal lymphatics, renal lymphatic pressure can increase to the point at which they rupture into the renal pelvis or tubules so that chyluria is seen. The chyluria is characteristically intermittent and is often prominent in the morning just after the patient arises.

Clinical Manifestations in New Arrivals to Endemic Areas

As mentioned previously, there are significant differences in the clinical manifestations of filarial infection, or at least in the time course over which they appear, between individuals who have recently entered the endemic areas (travelers or "transmigrants") and those who are native to these areas.

Given sufficient exposure to the vector (generally 3-6 months), patients often present with the signs and symptoms of acute lymphatic or scrotal inflammation. Urticaria and localized angioedema are common. Lymphadenitis of the epitrochlear, axillary, femoral, or inguinal nodes is often followed by lymphangitis, which is retrograde.

Acute attacks are short lived and, in contradistinction to filarial ADL, patients, are generally not accompanied by fever. If allowed to continue (by chronic exposure to infected mosquitoes), these attacks become increasingly severe and quickly (compared with the indigenous population) lead to permanent lymphatic inflammation and obstruction. Important to note, however, is that early removal of the patients from continued reexposure seems to hasten the end of the clinical syndrome.

Diagnosis

Diagnosis of filarial diseases can be problematic, because these infections most often require parasitologic techniques to demonstrate the offending organisms. In addition, satisfactory methods for the definitive diagnosis in amicrofilaremic states can be extremely difficult. The diagnostic procedures, however, should take advantage of the periodicity of each organism as well as its characteristic morphologic appearance. **Table 47.2** and **Figure 47.2** address

TABLE 47.2 Characteristics of Microfilariae in Humans

Species	Location	Periodicity	Presence of Sheath
Brugia malayi	Blood	Nocturnal, subperiodic	+
Brugia timori	Blood	Nocturnal	+
Wuchereria bancrofti	Blood, hydrocele fluid	Nocturnal, subperiodic	+
Onchocerca volvulus	Skin	None	–
Mansonella streptocerca	Skin	None	–
Loa loa	Blood	Diurnal	+
Mansonella perstans	Blood	None	–
Mansonella ozzardi	Blood	None	–

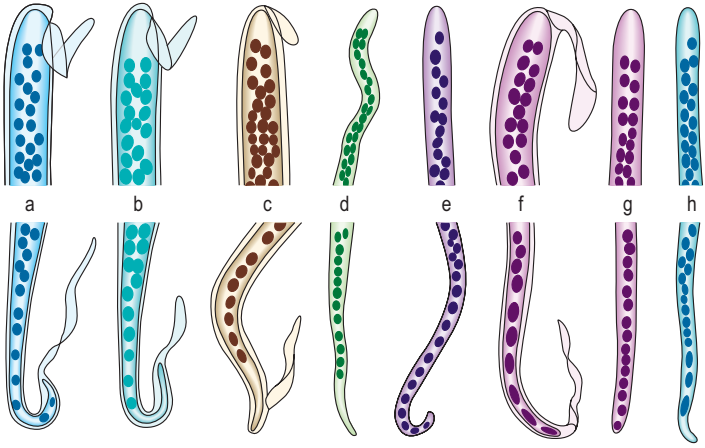

Fig. 47.2 Differential characterizations of the microfilariae. (a) *Brugia malayi*, (b) *Brugia timori*, (c) *Wuchereria bancrofti*, (d) *Onchocerca volvulus*, (e) *Mansonella streptocerca*, (f) *Loa loa*, (g) *Mansonella perstans*, (h) *Mansonella ozzardi*. (Adapted from Craig, C.F., Faust, E.C., 1964. Clinical Parasitology, seventh ed. Lea & Febiger, Philadelphia.)

these issues specifically. The following techniques may be used for examining blood or other fluids, such as chyle, urine, and hydrocele fluid.

Direct Examination

A small volume of fluid is spread on a clean slide. The slide is then air dried, stained with Giemsa stain, and examined microscopically.

Nuclepore™ filtration

A known volume of anticoagulated blood is passed through a polycarbonate (Nuclepore) filter with a 3-μm pore. A large volume (50 mL) of distilled (or filtered) water is passed through (the water will lyse or break open the red cells, leaving the microfilariae intact and more easily visible). The filter is then air dried, stained with Wright's or Giemsa stain, and examined by microscopy. For studies in the field, 1 mL of anticoagulated blood can be added to 9 mL of a solution of 2% formalin/10% Teepol and stored for up to 9 months before performing filtration.

Knott's concentration technique

In this technique, 1 mL of anticoagulated blood is placed in 9 mL of 2% formalin. The tube is centrifuged at 1500 rpm for 1 min. The sediment is spread on a slide and dried thoroughly. The slide is then stained with Wright's or Giemsa stain and examined microscopically.

Indirect Measures

Detection of circulating parasite antigen

Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. There are currently two commercially available tests, one in an enzyme-linked immunosorbent assay format (Trop-Ag *W. bancrofti*, manufactured by JCU Tropical Biotechnology, Townsville, Queensland, Australia), and the other a rapid-format card test (marketed by Allere, Scarborough, ME). Both assays have reported sensitivities that range from 96 to 100% and specificities that approach 100%. There are currently no tests for circulating antigens in brugian filariasis.

Serodiagnosis using parasite extract

Development of serodiagnostic assays of sufficient sensitivity and specificity for routine use has proven difficult, primarily because of their poor specificity. As is the case for serodiagnosis of most infectious diseases, it is difficult to differentiate previous infection or exposure to the parasite (aborted infection) from current active infection. Indeed, most residents of filariasis-endemic regions are antibody positive. Nevertheless, such serologic assays have a definite place in diagnosis, as a negative assay result effectively excludes past or present infection.

Molecular diagnostics

Polymerase chain reaction (PCR)-based assays for DNA of *W. bancrofti* and *B. malayi* in blood have also been developed. In a number of studies evaluating PCR-based diagnosis, the method is of equivalent or greater sensitivity compared with parasitologic methods, detecting patent infection in almost all infected subjects.

Imaging studies

In cases of suspected lymphatic filariasis, examination of the scrotum or female breast using high-frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics. Worms may be visualized in the lymphatics of the spermatic cord in up to 80% of infected men with *W. bancrofti*. Live adult worms have a distinctive pattern of movement within the lymphatic vessels (termed the "filaria dance sign"). This technique may be useful to monitor the success of antifilarial chemotherapy, by observing for the disappearance of the dance sign.

Radionuclide lymphoscintigraphic imaging of the limbs reliably demonstrates widespread lymphatic abnormalities both in asymptomatic microfilaremic persons and in those with clinical manifestations of lymphatic pathology. While of potential utility in the delineation

of anatomic changes associated with infection, lymphoscintigraphy is unlikely to assume primacy in the diagnostic evaluation of individuals with suspected infection.

Differential Diagnosis

The diagnosis of filariasis often must be made clinically, because many patients with lymphatic filariasis are not microfilaremic. In acute episodes, the differential diagnosis includes thrombophlebitis, infection, and trauma. Edema and changes associated with chronic filariasis must be distinguished from the similar changes that are seen to occur with malignancy, post-surgical scarring, trauma, and congestive heart failure, along with the less common congenital or idiopathic lymphatic system abnormalities. The many disorders associated with eosinophil and serum immunoglobulin E elevations must be considered as well.

Treatment

With newer definitions of clinical syndromes in lymphatic filariasis and new tools to assess clinical status (e.g., ultrasound, lymphoscintigraphy, circulating filarial antigen assays), approaches to treatment based on infection status and pathogenesis have been proposed.

Microfilaria-Positive Individuals

A growing body of evidence indicates that although they may be asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of sub-clinical disease (hematuria, proteinuria, abnormalities on lymphoscintigraphy). Thus, early treatment of asymptomatic persons is recommended to prevent further lymphatic damage. Diethylcarbamazine (DEC), which has both macrofilaricidal and microfilaricidal properties, is the drug of choice.

Microfilaria-negative antigen-positive individuals

Because lymphatic disease is associated with the adult worm, treatment with DEC is recommended for microfilaria-negative adult worm carriers (i.e., persons who are microfilaria negative but filaria antigen or ultrasound positive).

Acute Manifestations of Lymphatic Filariasis

Filarial Adenolymphangitis (ADL)

Supportive treatment is recommended, including rest; postural drainage, particularly if the lower limb is affected; cold compresses at the site of inflammation; and antipyretics and analgesics for symptomatic relief. During the acute episode, treatment with antifilarial drugs is not recommended, because it may provoke additional adult worm death and exacerbate the inflammatory response. After the acute attack has resolved, if the patient remains microfilaria or antigen positive, DEC can be given to kill the remaining adult worms.

For patients with ADL secondary to bacterial or fungal infections, cold compresses, antipyretics, and analgesics are recommended. The patient should remain at rest, with the affected limb elevated. Antibiotic therapy must be initiated while awaiting results of cultures of blood or tissue aspirates. The bacteria isolated during these attacks are sensitive to most systemic antibiotics, including penicillin.

Chronic Manifestations of Lymphatic Filariasis

Chronic manifestations of lymphatic filariasis include lymphedema and urogenital disease. Although antifilarial drug therapy is rarely, if ever, the "definitive" treatment for these conditions, such treatment is indicated if the patient has evidence of active infection (e.g., detection of microfilaria or filarial antigen in the blood or of the "filaria dance sign" on ultrasound examination). Not infrequently, the inflammatory response secondary to treatment-induced death of the adult worm exacerbates manifestations of chronic disease.

Lymphedema

Careful attention must be paid to the management of lymphedema once it has occurred. Elevation of the affected limb, elastic stockings, and local foot care will ameliorate some of the symptoms associated with lymphedema. Data indicate that filarial elephantiasis and

lymphedema of the leg may be partially reversible with a treatment regimen that emphasizes hygiene, prevention of secondary bacterial infections, and physiotherapy. This regimen is similar to that now recommended for treatment of lymphedema of most nonfilarial causes where it is known by a variety of names, including complex decongestive physiotherapy and complex lymphedema therapy. A six week course of doxycycline has been shown to improve (but not reverse) filarial-associated lymphedema in a single study in Ghana. Surgical decompression using a nodovenous shunt may provide improvement in extreme cases. Hydroceles can be drained repeatedly or managed surgically.

Treatment Options and Dosage

The recommended course of DEC treatment (12 days; total dose 72 mg/kg) has remained standard for many years; however, data indicate that single-dose DEC treatment with 6 mg/kg may be equally efficacious. The 12-day course provides more rapid short-term microfilarial suppression.

Regimens that utilize combinations of single doses of albendazole and either DEC or ivermectin have all been demonstrated to have a sustained microfilaricidal effect. Interestingly, 6 weeks of daily doxycycline (200 mg/day)—a regimen that targets the intracellular *Wolbachia* endosymbiont—or a 7-day course of DEC/albendazole has both significant macrofilaricidal activity and sustained microfilaricidal activity.

Side effects of DEC treatment include fever, chills, arthralgias, headaches, nausea, and vomiting. Both the development and severity of these reactions are directly related to the number of microfilariae circulating in the bloodstream and may represent an acute hypersensitivity reaction to the antigens being released by dead and dying parasites. To avoid these side effects, one can either initiate treatment with a very small dose of DEC and increase the dose to the full level over a few days or premedicate the patient with corticosteroids. Ivermectin has a side-effect profile similar to that of DEC when used in lymphatic filariasis. Albendazole (when used in single-dose regimens) has relatively few side effects associated with its use in lymphatic filariasis.

DEC is not commercially available in the United States and must be obtained from the Centers for Disease Control and Prevention. Albendazole, ivermectin, and doxycycline are all available commercially.

PREVENTION AND CONTROL

Avoidance of mosquito bites is usually not feasible for residents of endemic areas, but visitors should make use of insect repellent and mosquito nets. Impregnated bed nets have been shown to have a salutary effect. DEC can kill developing forms of filarial parasites and has been shown to be useful as a prophylactic agent in humans.

Mass drug administration is the current approach to elimination of lymphatic filariasis. The underlying tenet of this approach is that mass annual distribution of antimicrofilarial chemotherapy—albendazole with either DEC (for all areas except those where onchocerciasis is co-endemic) or ivermectin—will profoundly suppress microfilaremia. If the suppression is sustained, then transmission can be interrupted. As an added benefit, these combinations have secondary effects on gastrointestinal helminths. Community education and clinical care for persons already suffering from the chronic sequelae of lymphatic filariasis are important components of morbidity management that is currently part of the lymphatic filariasis elimination programs.

TROPICAL EOSINOPHILIA SYNDROME

Tropical eosinophilia syndrome, or tropical pulmonary eosinophilia (TPE), was recognized as being of filarial etiology only in the late 1950s or early 1960s, when it was noted that the antifilarial drug DEC was effective in this syndrome and that patients with TPE had extraordinarily high levels of antifilarial antibodies in their blood. Although circulating microfilariae were rarely found, lung and lymph node biopsies occasionally revealed trapped microfilariae.

Patients with this syndrome are primarily male (4:1 predominance). Characteristically, those with this form of the disease are in their third or fourth decade of life. A majority of cases have been reported from India, Pakistan, Sri Lanka, Southeast Asia, Guyana, and Brazil.

Clinical Features

The main features of this syndrome, besides a history of residence in a filarial-endemic region, include paroxysmal cough and wheezing (usually nocturnal), occasional weight loss, low-grade fever, adenopathy, and extreme peripheral blood eosinophilia (>3000/mm^3). Chest radiographs may be normal but generally show increased bronchovascular markings, diffuse miliary lesions, or mottled opacities primarily involving the mid and lower lung fields. Pulmonary function testing often shows restrictive abnormalities, which may be accompanied by obstructive defects.

This syndrome is associated with marked elevations of antifilarial antibodies, as well as extremely elevated levels of total serum IgE (10,000-100,000 ng/mL). Furthermore, in the absence of successful treatment, permanent pulmonary damage (interstitial fibrosis) can develop.

Pathology

Tropical eosinophilia is now considered to be a form of *occult filariasis* in which rapid clearance of the microfilariae occurs, presumably on the basis of host immunologic hyperresponsiveness to the parasite. This clearance takes place in the lung, and the clinical symptoms are probably the result of allergic and inflammatory reactions elicited by the cleared parasites. In some subjects, the microfilarial trapping occurs in other organs of the reticuloendothelial system (liver, spleen, lymph nodes), in which case hepatomegaly, splenomegaly, or lymphadenopathy occurs.

Differential Diagnosis

Tropical eosinophilia must be distinguished from Löffler syndrome, chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, some of the vasculitides, the idiopathic hypereosinophilic syndrome, drug allergies, and some other helminth infections. Although there is no single clinical or laboratory criterion that aids in distinguishing tropical eosinophilia from these diseases, residence in the tropics, the presence of high levels of antifilarial antibodies, and a rapid clinical response to DEC favor the diagnosis of tropical eosinophilia.

Treatment

DEC is the drug of choice for treatment of TPE, the dose typically being 6 mg/kg per day for 14 days. Symptoms usually resolve between days 4 and 7 of therapy. Characteristically, respiratory symptoms rapidly resolve after treatment with DEC. Despite dramatic initial improvement after conventional treatment with DEC, symptoms recur in approximately 20% of patients 12-24 months after treatment, and a majority of patients continue to have subtle clinical, radiographic, and functional abnormalities. Repeat treatment may be necessary to prevent pulmonary fibrosis, a serious sequela of TPE if left untreated.

ONCHOCERCIASIS

Epidemiology

Onchocerciasis, sometimes called river blindness, is caused by infection with *Onchocerca volvulus*, a subcutaneous-dwelling filarial worm. Approximately 18 million people are infected, mostly in equatorial Africa, the Sahara, and Yemen, with only a few remaining foci in Central and South America (Venezuela and Brazil). The infection is transmitted to humans through the bites of black flies of the genus *Simulium*, which breed along fast-flowing rivers in the previously mentioned tropical areas.

Pathology

The pathology of onchocerciasis is limited primarily to the skin, lymphatic system, and eyes.

Onchocerciasis is a *cumulative* infection. Intense infections, which lead to the disease's severest complications, are believed to reflect repeated inoculation of infective larvae.

Skin

In the skin, granulomatous and fibrous reactions tend to occur in response to the adult worm. Similarly, dead microfilariae in the skin tend to produce small granulomata with eosinophilic infiltrates. Over a period of years, adult worms are encased by host tissue, thereby forming the characteristic subcutaneous nodules (onchocercomata).

Lymph Nodes

The pathology of the lymph nodes consists of scarring of the lymphoid areas (*O. volvulus* infection in Africa) or follicular hyperplasia (*O. volvulus* infection in Yemen). Histologically the lymph nodes draining areas of onchodermatitis show capsular fibrosis, atrophic follicles, and dilation of the subcapsular sinusoids and lymphatics.

Eyes

The pathologic processes that occur in the ocular tissues are not yet well elucidated. The conjunctiva can show an infiltrate with plasma cells, eosinophils, and mast cells. Punctate keratitis occurs and is believed to reflect inflammation around degenerating microfilariae. Anterior uveitis and chorioretinitis may occur and are thought to be a result of a low-grade inflammation, although autoimmune reactions may play a role.

Clinical Features

The major disease manifestations of onchocerciasis are localized to the skin, lymph nodes and lymphatics, and eyes.

Skin

Pruritus is the most frequent manifestation of onchocercal dermatitis. This pruritus may be accompanied by the appearance of localized areas of edema and erythema that is characteristically evanescent. If the infection is prolonged, lichenification and pigment changes (either hypopigmentation or hyperpigmentation) can occur; these often lead to atrophy, "lizard skin," and mottling of the skin. The skin can also become superinfected, particularly in the presence of excoriation or trauma. An immunologically hyperreactive form of dermatitis (commonly termed "sowda," or localized onchodermatitis) can occur with the affected skin becoming darker as a consequence of the profound inflammation that occurs as microfilariae in the skin are being cleared.

The subcutaneous nodules contain the adult worm. In Africa, the onchocercomata tend to be found over bony prominences, such as the coccyx, femoral trochanter, iliac crests, lateral aspects of the knee and elbow, and head. Interestingly, it is thought that for every palpable nodule, there are probably at least five deeper nodules.

Lymph Nodes

Lymphadenopathy is frequently found, particularly in the inguinal and femoral areas. As the glands enlarge, they can come to lie within areas of loose skin (so-called hanging groin), which predisposes the affected patients to hernias. Scarring in lymph nodes may lead to regional lymphedema.

Eyes

Onchocercal eye disease can take many forms, and most can lead to severe visual loss or blindness. Usually seen in persons with moderate or heavy infections, the ocular disease spares no part of the eye. Conjunctivitis, anterior uveitis, iridocyclitis leading to secondary glaucoma, sclerosing keratitis, optic atrophy, and chorioretinal lesions can be found.

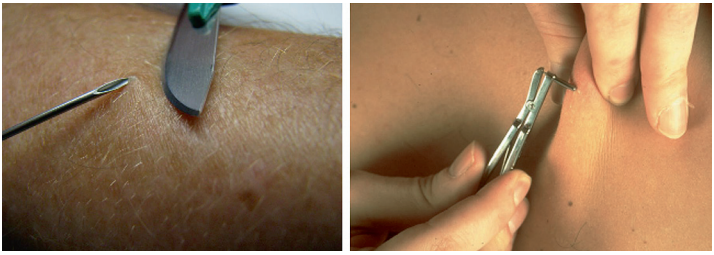

Fig. 47.3 ***Left panel*: Skin snips being removed with needle and scalpel. Note the small tent of skin that is lifted up the needle. *Right panel*: Skin snip being performed using a corneoscleral punch.**

Diagnosis

Definitive diagnosis depends on finding an adult worm in an excised nodule or, more commonly, microfilariae in a skin snip.

Skin Snip

A small piece of skin is elevated by the tip of a needle or skin hook held parallel to the surface, and a razor or scalpel blade is used to shave off the skin area stretched across the top surface of the needle (**Fig. 47.3**). Alternatively, a sclerocorneal punch can be used to obtain a blood-free circular skin specimen.

Skin snips are generally obtained from an area of affected skin or from the scapular, gluteal, and calf areas. Once obtained, the skin snips are incubated in a physiologic solution (such as normal saline); the emergent microfilariae can be seen under a microscope after 2-4 hours. Occasionally, in light infections, overnight incubation is necessary.

Serodiagnosis

A variety of serodiagnostic and antigenic skin tests have been described. Recently, recombinant onchocercal-specific antigens have been produced, one of which has been developed into a rapid format card test.

Molecular Diagnosis

Highly specific and sensitive PCR-based assays have been developed for the detection of *O. volvulus* DNA in skin snips that are microscopically negative. This has proved useful in the detection of very low infection levels but requires expensive equipment and reagents, as well as rigorous training and quality control.

Differential Diagnosis

Onchocerciasis must be differentiated from scabies, contact dermatitis, and, rarely, streptocerciasis (see the following section).

Treatment

The major goals of therapy are to prevent irreversible lesions and to alleviate bothersome symptoms. Surgical excision of nodules is recommended when the nodules are located on the head because of the proximity of the microfilaria-producing adult worms to the eye, but chemotherapy is the mainstay of treatment.

Ivermectin, a semisynthetic macrocyclic lactone, is considered first-line therapy for onchocerciasis. It is given orally in a single dose of 150 μg/kg. It is characteristically given yearly or semiannually. With treatment, most patients have a mild or no reaction. Pruritus, cutaneous edema, and/or a maculopapular rash occur in approximately 1–10% of treated individuals. Significant ocular complications are extremely rare, as is hypotension (1 in

10,000). Contraindications to treatment include pregnancy, breastfeeding, age <5 years, and central nervous system (CNS) disorders that might increase the penetration of ivermectin into the CNS (e.g., meningitis).

Although treatment with ivermectin results in a marked drop in microfilarial density, its effect can be short lived (much less than 6 months in some cases). Thus, it is occasionally necessary to give ivermectin more frequently for persistent symptoms.

STREPTOCERCIASIS

Mansonella streptocerca (formerly *Dipetalonema streptocerca*, *Tetrapetalonema streptocerca*) is largely found in the tropical forest belt of Africa from Ghana to Zaire. It is transmitted to the human host by biting midges (*Culicoides* spp.).

The pathology of streptocerciasis is both dermal and lymphatic. In the skin, there are hypopigmented macules (and occasionally papular rashes) that are thought to be secondary to inflammatory reactions around microfilariae. The distribution of the parasite in the skin of the human host tends to be across the shoulders and upper torso. Lymph nodes of affected individuals may show chronic lymphadenitis with scarring.

The major clinical manifestations are related to the skin: pruritus, papular rashes, and pigmentation changes. Most infected individuals also show inguinal lymphadenopathy; however, many patients are completely asymptomatic.

The diagnosis is made after finding the characteristic microfilariae on skin-snip examination. Leprosy and granuloma multiforme are the two other diseases that must be distinguished from streptocerciasis.

DEC is particularly effective in treating infection by both the microfilarial and the adult form of the parasite. The recommended dosage is 6 mg/kg per day in divided doses for 21 days. After treatment, as in onchocerciasis, one can often see urticaria, arthralgias, myalgias, headaches, and abdominal discomfort. Ivermectin at a dose of 150 μg/kg appears to have a salutary microfilaricidal effect that can be sustained at least a year following therapy.

LOIASIS

The distribution of *Loa loa* is limited to the rain forests of West and Central Africa. Tabanid flies (deer flies) of the genus *Chrysops* are the intermediate hosts. The adult parasite lives in the subcutaneous tissues in humans; then microfilariae circulate in the bloodstream with a diurnal periodicity.

Pathology

The pathology associated with loiasis includes: (1) the classic "Calabar swelling" (localized areas of transient angioedema), found predominantly on the extremities; (2) peripheral (entrapment) neuropathy; (3) nephropathy presumed to be immune complex mediated; (4) encephalopathy thought to be secondary to either an acute cerebral edema or a chronic, subacute encephalitis; and (5) cardiomyopathy presumably related to the marked hypereosinophilia that these patients may have.

Clinical Manifestations

Loa loa infection may be present as asymptomatic microfilaremia, with the infection being recognized only after subconjunctival migration of an adult worm (the so-called eye worm). Other patients have episodic Calabar swellings. If the associated inflammation extends to the nearby joints or peripheral nerves, corresponding symptoms (such as entrapment neuropathy or arthritis) can develop. Nephropathy, encephalopathy, and cardiomyopathy can occur, but rarely.

There appears to be a difference between the presentation of loiasis in those native to the endemic area and those who are visitors. The latter tend to have a greater predominance of allergic symptomatology. The episodes of Calabar swellings tend to be more frequent and debilitating, and such patients rarely have microfilaremia. In addition, those who are

not native to the endemic area have extreme elevation of eosinophils in the blood, as well as marked increases in antifilarial antibody titers.

Diagnosis

Definitive diagnosis is made through parasitologic examination, either by finding microfilariae in the peripheral blood or by isolating the adult worm from the eye or in subcutaneous biopsy material following treatment. Molecular diagnostics (PCR) can be used for definitive diagnosis as well. However, the diagnosis must often be made on clinical grounds, particularly in travelers (usually amicrofilaremic) to the endemic region.

Treatment

DEC, 8-10 mg/kg per day for 21 days, is the recommended treatment. The drug is effective against both the adult and microfilarial forms of the parasite, but multiple courses of therapy are necessary before there is complete resolution of the disease. In cases of heavy microfilaremia, allergic or other inflammatory reactions can occur; in the most severe cases, there may be CNS involvement, with coma and encephalitis. Heavy infections can be managed initially with low doses of DEC (0.5-1.0 mg/kg per day) and the simultaneous administration of corticosteroids.

Albendazole or ivermectin (although neither is approved for this use by the US Food and Drug Administration) has been shown to be effective in reducing microfilarial loads, although ivermectin has been implicated in serious (and life-threatening) adverse events in heavily loa-microfilaremic individuals. DEC (300 mg weekly) is an effective prophylactic regimen for loiasis.

PERSTANS FILARIASIS

Mansonella perstans is distributed across the center of Africa and in northeastern South America. The infection is transmitted to humans through the bites of midges (*Culicoides* spp.). The adult worms reside in the body cavities (pericardial, pleural, peritoneal) as well as in the mesentery and the perirenal and retroperitoneal tissues. The microfilariae circulate in the blood without periodicity. As with *Mansonella ozzardi* (see the following discussion), the pathology relating to this infection is ill-defined.

Although most patients appear to be asymptomatic, clinical manifestations of this infection include transient angioedematous swellings of the arms, face, or other body parts (not unlike the Calabar swellings of *Loa loa* infection); pruritus; fever; headache; arthralgias; neurologic or psychologic symptoms; and right upper quadrant pain. Occasionally, pericarditis and hepatitis occur.

The diagnosis is made through parasitologic evaluation by finding the microfilariae in the blood or in other body fluids (serosal effusions). Perstans filariasis is often associated with peripheral blood eosinophilia and antifilarial antibody elevations. Although DEC, ivermectin, and albendazole have all been tried in this infection, none has proven to be of significant benefit. With the discovery of a *Wolbachia* endosymbiont specific to *M. perstans*, targeted therapy with doxycycline (200 mg daily for 6 weeks) has been shown to be effective.

MANSONELLA OZZARDI INFECTION

The distribution of *Mansonella ozzardi* is restricted to Central and South America, as well as certain Caribbean islands. The parasite is transmitted to the human host by biting midges (*Culicoides furens*) and black flies (*Simulium amazonicum*). Although adult worms have only twice been recovered from humans, studies on the microfilariae show that they circulate in the bloodstream with little periodicity. The pathology of *M. ozzardi* infection is poorly characterized. Furthermore, many consider this organism to be nonpathogenic. However, headache, articular pain, fever, pulmonary symptoms, adenopathy, hepatomegaly, and pruritus have been ascribed to infection with this organism. Eosinophilia accompanies *M. ozzardi* infection as well. Diagnosis is made by demonstrating the characteristic microfilariae in the peripheral blood. DEC has little or no effect on this infection, but ivermectin has

been shown to be effective in reducing symptoms and circulating microfilariae. Like *M. perstans*, *M. ozzardi* also has a *Wolbachia* endosymbiont, suggesting that a 6-week course of doxycycline should be effective.

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