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240 Filarial and Related Infections

with nonspecific abdominal pain and watery diarrhea. If untreated, repeated rounds of autoinfection can lead to protein-losing enter opathy, severe malabsorption, and ultimately death from cachexia, cardiac failure, or superinfection. The diagnosis is made by identify ing characteristic peanut-shaped (20 × 40 µm) eggs on microscopic examination of stool. Severely ill patients require hospitalization and supportive therapy in addition to prolonged anthelmintic treatment with albendazole (400 mg twice daily for 10 days) or mebendazole (500 mg daily for 20 days; Chap. 229). ■ ■ABDOMINAL ANGIOSTRONGYLIASIS Abdominal angiostrongyliasis is primarily a disease of children living in Latin America. The zoonotic parasite Angiostrongylus costaricensis causes eosinophilic ileocolitis after the ingestion of contaminated vegetation. A. costaricensis normally parasitizes the cotton rat and other rodents, with slugs and snails serving as intermediate hosts. Humans become infected by accidentally ingesting infective larvae in mollusk slime deposited on fruits and vegetables; children are at highest risk. The larvae penetrate the gut wall and migrate to mesen teric arterioles, where they develop into adult worms. Eggs deposited in the gut wall provoke an intense eosinophilic granulomatous reac tion, and adult worms may cause mesenteric arteritis, thrombosis, or frank bowel infarction. Symptoms may mimic those of appendicitis, including abdominal pain and tenderness, fever, vomiting, and a pal pable mass in the right iliac fossa. Leukocytosis and eosinophilia are prominent. CT with contrast typically shows inflamed bowel, often with concomitant obstruction, but a definitive diagnosis is usually made histologically after partial bowel resection. Pathologic exami nation reveals a thickened bowel wall with eosinophilic granulomas surrounding the Angiostrongylus eggs. In nonsurgical cases, the diag nosis rests solely on clinical grounds because larvae and eggs cannot be detected in the stool and serologic tests are not available. Medical therapy for abdominal angiostrongyliasis is of uncertain efficacy. Careful observation and surgical resection for severe symptoms are the mainstays of treatment. Acknowledgment The authors wish to acknowledge and thank Peter F. Weller, MD, author of prior editions of this chapter. ■ ■FURTHER READING Costa IN et al: Diagnosis of human strongyloidiasis: Application in clinical practice. Acta Trop 223:106081, 2021. Else KJ et al: Whipworm and roundworm infections. Nat Rev Dis Primers 6:44, 2020. Holland C et al: Global prevalence of Ascaris infection in humans (2010–2021): A systematic review and meta-analysis. Infect Dis Pov erty 11:113, 2022. Krolewiecki A et al: Strongyloidiasis: A neglected tropical disease. Infect Dis Clin North Am 33:135, 2019. Loukas A et al: Hookworm infection. Nat Rev Dis Primers 2:16088, 2016. Montressor A et al: The global progress of soil-transmitted helmin thiases control in 2020 and World Health Organization targets for 2030. PLoS Negl Trop Dis 14:e0008505, 2020.

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Filarial and Related

Infections Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filarial species infect humans (Table 240-1); of these, four—Wuchereria bancrofti, Brugia malayi, Onchocerca volvulus, and Loa loa—are responsible for most symptomatic filarial infec tions. Filarial parasites, which infect an estimated 170 million persons worldwide, are transmitted by specific species of mosquitoes or other arthropods and have a complex life cycle, including insect-borne infective larval stages and adult worms that reside in either lymphatic or subcutaneous tissues of humans. The offspring of adults are micro filariae, which, depending on their species, are 200–250 μm long and 5–7 μm wide, may or may not be enveloped in a loose sheath, and either circulate in the blood or migrate through the skin (Table 240-1). To complete the life cycle, microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae. Adult worms live for many years, whereas microfilariae survive for 3–36 months. The intracellular bacterial endosymbiont Wolbachia has been found in all stages of Brugia, Wuchereria, Mansonella, and Onchocerca species and has become a target for antifilarial chemotherapy. Usually, infection is established only with repeated, prolonged exposures to infective larvae. Since the clinical manifestations of filarial diseases develop relatively slowly, these infections should be considered chronic, with possible long-term debilitating effects. The nature, severity, and timing of clinical manifestations in patients with filarial infections who are native to endemic areas and have lifelong exposure may differ significantly from those who are travelers or who have recently moved to these areas. Characteristically, filarial disease is more acute and intense in newly exposed individuals than in natives of endemic areas. CHAPTER 240 Filarial and Related Infections LYMPHATIC FILARIASIS Lymphatic filariasis is caused by W. bancrofti, B. malayi, or Brugia timori. The threadlike adult parasites reside in afferent lymphatics or lymph nodes, where they may remain viable for more than two decades. ■ ■EPIDEMIOLOGY W. bancrofti, the most widely distributed filarial parasite of humans, affects an estimated 51 million people and 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 the parasite. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, W. bancrofti is noctur nally periodic. Nocturnally periodic forms of microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon. Natural vectors for W. bancrofti are Culex mosquitoes in urban settings and Anopheles or Aedes mosquitoes in rural areas. Brugian filariasis due to B. malayi occurs primarily in eastern India, Indonesia, Malaysia, and the Philippines. B. malayi also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. B. malayi naturally infects cats as well as humans. The distribution of B. timori is limited to the islands of southeastern Indonesia. ■ ■PATHOLOGY The principal pathologic changes of lymphatic filariasis

result from inflammatory damage to the lymphatics, which is typically caused by adult worms and not by microfilariae. Adult worms live in afferent lymphatics or sinuses of lymph nodes and cause lymphatic dilation and thickening of the vessel walls. The infiltration of plasma cells,

TABLE 240-1 Characteristics of the Filariae ORGANISM PERIODICITY DISTRIBUTION VECTOR LOCATION OF ADULT Wuchereria bancrofti Nocturnal Cosmopolitan areas worldwide, including South America, Africa, southern Asia, Papua New Guinea, China, Indonesia Subperiodic Eastern Pacific Aedes (mosquitoes) Lymphatic tissue Blood + Brugia malayi Nocturnal Southeast Asia, Indonesia, India Mansonia, Anopheles (mosquitoes) Lymphatic tissue Blood + Subperiodic Indonesia, Southeast Asia Coquillettidia, Mansonia (mosquitoes) Lymphatic tissue Blood + Brugia timori Nocturnal Indonesia Anopheles (mosquitoes) Lymphatic tissue Blood + Loa loa Diurnal West and Central Africa Chrysops (deerflies) Subcutaneous tissue Blood + Onchocerca volvulus None South and Central America, Africa Simulium (blackflies) Subcutaneous tissue Skin, eye – Mansonella ozzardi None South and Central America Culicoides (midges) Undetermined site Blood – None Caribbean Simulium (blackflies) Undetermined site Blood – Mansonella perstans None South and Central America, Africa Culicoides (midges) Body cavities, mesentery, perirenal tissue Mansonella streptocerca None West and Central Africa Culicoides (midges) Subcutaneous tissue Skin – eosinophils, and macrophages in and around the infected vessels, along with endothelial and connective tissue proliferation, leads to tortuosity of the lymphatics and damaged or incompetent lymph valves. Lymph edema and chronic stasis changes with hard or brawny edema develop in the overlying skin. These consequences of filarial infection are due both to the direct effects of the worms and to the host’s inflammatory response to the parasite. Inflammatory responses are believed to cause the granulomatous and proliferative processes that precede total lymphatic obstruction. It is thought that the lymphatic vessel remains patent as long as the worm remains viable, and that the death of the worm leads to enhanced granulomatous reactions and fibrosis. Lymphatic obstruction results, and despite collateralization, lymphatic function is compromised. PART 5 Infectious Diseases ■ ■CLINICAL FEATURES The most common presentations of the lymphatic filariases are asymp tomatic (or subclinical) microfilaremia, hydrocele (Fig. 240-1), acute adenolymphangitis (ADL), and chronic lymphatic disease. In areas FIGURE 240-1 Hydrocele associated with Wuchereria bancrofti infection.

MICROFILARIAL LOCATION SHEATH Culex, Anopheles (mosquitoes) Lymphatic tissue Blood + Blood – where W. bancrofti or B. malayi is endemic, most infected individuals have few overt clinical manifestations of filarial infection despite the presence of circulating microfilariae in the peripheral blood. Although they may be clinically asymptomatic, virtually all persons with

W. bancrofti or B. malayi microfilaremia have some degree of subclini cal disease that includes microscopic hematuria and/or proteinuria, dilated (and tortuous) lymphatics (visualized by imaging), and—in men with W. bancrofti infection—scrotal lymphangiectasia (detect able by ultrasound). Despite these findings, most individuals appear to remain clinically asymptomatic for years; in relatively few does the infection progress to either acute or chronic disease. ADL is characterized by high fever, lymphatic inflammation (lym phangitis and lymphadenitis), and transient local edema. The lym phangitis 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 sur face. The lymphadenitis and lymphangitis can involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with W. bancrofti infection. This genital involvement can be manifested by funiculitis, epididymitis, and scrotal pain and tenderness. In endemic areas, another type of acute disease—dermatolymphangioadenitis (DLA)—is recognized as a syndrome that includes high fever, chills, myalgias, and headache. Edematous inflammatory plaques clearly demarcated from normal skin are seen. Vesicles, ulcers, and hyperpig mentation also may be noted. There is often a history of trauma, burns, irradiation, insect bites, punctiform lesions, or chemical injury. Entry lesions, especially in the interdigital area, are common. DLA is often diagnosed as cellulitis. If lymphatic damage progresses, transient lymphedema can develop into lymphatic obstruction and the permanent changes associated with elephantiasis (Fig. 240-2). Brawny edema follows early pitting edema, the subcutaneous tissues thicken, and hyperkeratosis occurs. Fissur ing of the skin develops, as do hyperplastic changes. Superinfection of these poorly vascularized tissues becomes a problem. In bancroftian filariasis, in which genital involvement is common, hydroceles may develop (Fig. 240-1); in advanced stages, this condition may evolve into scrotal lymphedema and scrotal elephantiasis. Furthermore, if there is obstruction of the retroperitoneal lymphatics, increased renal lym phatic pressure leads to rupture of the renal lymphatics and the devel opment of chyluria, which is usually intermittent and most prominent in the morning.

FIGURE 240-2 Elephantiasis of the lower extremity associated with Wuchereria bancrofti infection. The clinical manifestations of filarial infections in travelers or trans migrants who have recently entered an endemic region are distinctive. Given a sufficient number of bites by infected vectors, usually over a 3- to 6-month period, recently exposed patients can develop acute lym phatic or scrotal inflammation with or without urticaria and localized angioedema. Lymphadenitis of epitrochlear, axillary, femoral, or ingui nal lymph nodes is often followed by evolving retrograde lymphangi tis. Acute attacks are short-lived and are not usually accompanied by fever. With prolonged exposure to infected mosquitoes, these attacks, if untreated, become more severe and lead to permanent lymphatic inflammation and obstruction. ■ ■DIAGNOSIS A definitive diagnosis can be made only by detection of the para sites and hence can be difficult. Adult worms localized in lymphatic vessels or nodes are largely inaccessible. Microfilariae can be found in blood, in hydrocele fluid, or (occasionally) in other body fluids. Such fluids can be examined microscopically, either directly or—for greater sensitivity—after concentration of the parasites by the pas sage of fluid through a polycarbonate cylindrical-pore filter (pore size, 3 μm) or by the centrifugation of fluid fixed in 2% formalin (Knott’s concentration technique). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved. Many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult. Assays for circulating antigens of W. bancrofti permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Two tests are commercially available: an enzyme-linked immunosorbent assay (ELISA) and a rapid-format lateral flow assay. Both assays have sen sitivities of 93–100% and specificities approaching 100%, although false positives can occur in individuals infected with Loa loa (see “Loiasis” below). There are currently no tests for circulating antigens in brugian filariasis. Polymerase chain reaction (PCR)–based assays for DNA of W. ban crofti and B. malayi in blood have been developed. A number of studies indicate that the sensitivity of this diagnostic method is equivalent to or greater than that of parasitologic methods.

In cases of suspected lymphatic filariasis, examination of the scro tum, the lymph nodes, or (in female patients) the breast by means of high-frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics (Video 240-1). Worms may be visualized in the lymphatics of the spermatic cord in up to 80% of men infected with W. bancrofti. Live adult worms have a distinctive pattern of movement within the lymphatic vessels (termed the filarial dance sign). Radionuclide lymphoscintigraphic imaging of the limbs reliably demonstrates wide spread lymphatic abnormalities in both subclinical microfilaremic persons and those with clinical manifestations of lymphatic pathology. Although 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; it is principally a research tool, although it has been used more widely for assessment of lymphedema of any cause. Eosinophilia and elevated serum concentrations of IgE and antifilarial antibody support the diagnosis of lymphatic filariasis. There is, however, exten sive cross-reactivity between filarial antigens and antigens of other helminths. Of note, W. bancrofti– and B. malayi–specific antigens have been identified and are now available for use in rapid diagnostic tests with specificities of >98%. However, seropositivity cannot be equated with active infection: residents of endemic areas can become sensitized to filarial antigens through exposure to infective mosquitoes without having patent filarial infections.

The ADL associated with lymphatic filariasis must be distinguished from thrombophlebitis, infection, and trauma. Retrograde evolution is a characteristic feature that helps distinguish filarial lymphangitis from ascending bacterial lymphangitis. Chronic filarial lymphedema must also be distinguished from the lymphedema of malignancy, post operative scarring, trauma, chronic edematous states, and congenital lymphatic system abnormalities. CHAPTER 240 Filarial and Related Infections TREATMENT Lymphatic Filariasis With newer definitions of clinical syndromes in lymphatic filariasis and new tools to assess clinical status (e.g., ultrasound, lymphos cintigraphy, circulating filarial antigen assays, PCR), approaches to treatment based on infection status can be considered. Orally administered diethylcarbamazine (DEC; 6 mg/kg daily for 12 days), which has both macro- and microfilaricidal properties, remains the drug of choice for the treatment of active lymphatic fila riasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound), although albendazole (400 mg twice daily by mouth for 21 days) also has demonstrated macrofilaricidal efficacy. A 4- to 6-week course of oral doxycycline (targeting the intracellular Wol bachia) also has significant macrofilaricidal activity, as does DEC/ albendazole used daily for 7 days. The addition of DEC to a 3-week course of doxycycline is also efficacious in lymphatic filariasis. Regimens that combine single doses of albendazole (400 mg) with either DEC (6 mg/kg) or ivermectin (200 µg/kg) all have a sustained microfilaricidal effect and are the mainstay of programs for the eradication of lymphatic filariasis in Africa (albendazole/ ivermectin) and elsewhere (albendazole/DEC) (see “Prevention and Control,” below). More recently, a regimen using single doses of the three major antifilarial drugs (albendazole/DEC/ivermectin)

has been shown to sustain microfilarial clearance out to at least 2 years. As already mentioned, 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 lympho scintigraphy). Thus, early treatment of asymptomatic persons who have microfilaremia is recommended to prevent further lymphatic damage. For ADL, supportive treatment (including the administra tion of antipyretics and analgesics) is

recommended, as is antibiotic therapy if secondary bacterial infection is likely. Similarly, because

lymphatic disease is associated with the presence of adult worms, treatment with DEC is recommended for microfilaria-negative car riers of adult worms.

In persons with chronic manifestations of lymphatic filariasis, treatment regimens that emphasize hygiene, prevention of sec ondary bacterial infections, and physiotherapy have gained wide acceptance for morbidity control. These regimens are similar to those recommended for lymphedema of most nonfilarial causes and are known by a variety of names, including complex deconges tive physiotherapy and complex lymphedema therapy. Hydroceles (Fig. 240-1) can be managed surgically. With chronic manifesta tions of lymphatic filariasis, drug treatment should be reserved for individuals who have evidence of active infection; however, in some settings, a 6-week course of doxycycline has been shown to provide improvement in filarial lymphedema irrespective of disease activity. Side effects of DEC treatment in infected individuals may include fever, chills, arthralgias, headaches, nausea, and vomit ing. Both the development and the severity of these reactions are directly related to the number of microfilariae circulating in the bloodstream. The adverse reactions may represent either an acute hypersensitivity reaction to the antigens being released by dead and dying parasites or an inflammatory reaction induced by the intracellular Wolbachia endosymbionts freed from their intracel lular niche. Ivermectin has a side effect profile similar to that of DEC when used in lymphatic filariasis. In patients infected with L. loa who have high levels of microfilaremia, DEC—like ivermectin (see “Loiasis,” below)—can elicit severe encephalopathic complications. When used in single-dose regimens for the treatment of lymphatic filariasis, albendazole is associated with relatively few side effects. PART 5 Infectious Diseases ■ ■PREVENTION AND CONTROL To protect themselves against filarial infection, individuals must avoid contact with infected mosquitoes by using personal protective measures, including bed nets, particularly those impregnated with insecticides such as permethrin. Mass drug administration (MDA) is the current approach to elimination of lymphatic filariasis as a public health problem. The underlying tenet of this approach is that mass annual distribution of antifilarial chemotherapy—albendazole with either DEC (for all areas except those where onchocerciasis is co-endemic; see section on onchocerciasis treatment, below) or iver mectin or with both ivermectin and DEC (triple-drug therapy)—will profoundly suppress microfilaremia. If the suppression is sustained, then transmission can be interrupted. Created by the World Health Organization in 1997, the Global Programme to Eliminate Lymphatic Filariasis is based on mass administration of single annual doses of DEC plus albendazole in nonAfrican regions and of albendazole plus ivermectin in Africa. Available information from late 2022 indicated that >935 million persons in 68 countries had thus far participated. Not only has lymphatic filariasis been eliminated in some defined areas, but collateral benefits—avoidance of disability and treatment of intestinal helminths and other condi tions (e.g., scabies and louse infestation)—also have been noted. The strategy of the global program is being refined, and attempts are being made to integrate this effort with other mass-treatment strategies (e.g., deworming programs, malaria control, and trachoma control) in an integrated control strategy. TROPICAL PULMONARY EOSINOPHILIA Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals infected with the lymphatic-dwelling filarial species. Most cases have been reported from India, Pakistan, Sri Lanka, Brazil, Guyana, and Southeast Asia; the decreasing inci dence of TPE in the past decade probably reflects global MDA efforts. ■ ■CLINICAL FEATURES The main features include a history of residence in filaria-endemic regions, paroxysmal cough and wheezing (usually nocturnal and

probably related to the nocturnal periodicity of microfilariae), weight loss, low-grade fever, lymphadenopathy, and pronounced blood eosin ophilia (>3000 eosinophils/µL). Chest x-rays or computed tomography (CT) scans may be normal but generally show increased bronchovascu lar markings. Diffuse miliary lesions or mottled opacities may be pres ent in the middle and lower lung fields. Tests of pulmonary function show restrictive abnormalities in most cases and obstructive defects in half. Characteristically, total serum IgE levels (4–40 KIU/mL) and antifilarial antibody levels are markedly elevated. ■ ■PATHOLOGY In TPE, microfilariae and parasite antigens are rapidly cleared from the bloodstream by the lungs. The clinical symptoms result from allergic and inflammatory reactions elicited by the cleared parasites. In some patients, trapping of microfilariae in other reticuloendothelial organs can cause hepatomegaly, splenomegaly, or lymphadenopathy. A prominent, eosinophil-enriched, intra-alveolar infiltrate is common, and with it comes the release of cytotoxic proinflammatory eosinophil granule proteins that may mediate some of the pathology seen in TPE. In the absence of successful treatment, interstitial fibrosis can lead to progressive pulmonary damage. ■ ■DIFFERENTIAL DIAGNOSIS TPE must be distinguished from asthma, Löffler’s syndrome, allergic bronchopulmonary aspergillosis, allergic granulomatosis with polyan giitis (eosinophilic granulomatosis with polyangiitis or Churg-Strauss syndrome), other systemic vasculitides (most notably, periarteritis nodosa), chronic eosinophilic pneumonia, and the hypereosinophilic syndromes (HESs). TREATMENT Tropical Pulmonary Eosinophilia DEC is used at a daily dosage of 4–6 mg/kg for 14 days. Symptoms usually resolve within 3–7 days after the initiation of therapy. Relapse, which occurs in ~12–25% of cases (sometimes after an interval of several years), requires re-treatment. ONCHOCERCIASIS ■ ■EPIDEMIOLOGY Onchocerciasis (“river blindness”) is caused by the filarial nematode O. volvulus, which infects an estimated 37 million individuals in 31 countries worldwide. The majority of individuals infected with O. volvulus live in the equatorial region of Africa extending from the Atlantic coast to the Red Sea. In the Americas, the only remaining countries with isolated foci are Venezuela and Brazil. The infection is also found in Yemen. ■ ■ETIOLOGY Infection in humans begins with the deposition of infective larvae on the skin by the bite of an infected blackfly. The larvae develop into adults, which are typically found in subcutaneous nodules. About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodule and throughout the tissues, concentrating in the dermis. Infection is transmitted to other persons when a female fly ingests microfilariae from the host’s skin and these microfilariae then develop into infective larvae. Adult O. volvulus females and males are ~40–60 cm and ~3–6 cm in length, respectively. The life span of adults can be as long as 18 years, with an average of ~9 years. Because the blackfly vector breeds along free-flowing rivers and streams (particu larly in rapids) and generally restricts its flight to an area within several kilometers of these breeding sites, both biting and disease transmission are most intense in these locations. ■ ■PATHOLOGY Onchocerciasis primarily affects the skin, eyes, and lymph nodes. In contrast to the pathology in lymphatic filariasis, the damage in

onchocerciasis is elicited by microfilariae and not by adult parasites. In the skin, there are mild but chronic inflammatory changes that can result in loss of elastic fibers, atrophy, and fibrosis. The subcutaneous nodules (onchocercomata) consist primarily of fibrous tissues sur rounding the adult worm, often with a peripheral ring of inflammatory cells surrounded by an endothelial layer (characterized as lymphatic in origin). In the eye, neovascularization and corneal scarring lead to cor neal opacities and blindness. Inflammation in the anterior and poste rior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy. Although punctate opacities are due to an inflammatory reaction surrounding dead or dying microfilariae, the pathogenesis of most

manifestations of onchocerciasis is still unclear. ■ ■CLINICAL FEATURES Skin Pruritus and rash are the most common manifestations of onchocerciasis. The pruritus can be incapacitating; the rash is typically a papular eruption (Fig. 240-3) that is generalized rather than localized to a particular region of the body. Long-term infection results in exag gerated and premature wrinkling of the skin, loss of elastic fibers, and epidermal atrophy that can lead to loose, redundant skin and hypo- or hyperpigmentation. Localized eczematoid dermatitis can cause hyper keratosis, scaling, and pigmentary changes. In an immunologically hyperreactive form of onchodermatitis (commonly termed sowdah or localized onchodermatitis), the affected skin darkens as a consequence of the profound inflammation that occurs as microfilariae in the skin are cleared. Onchocercomata These subcutaneous nodules, which can be pal pable and/or visible, contain the adult worm. They are most common over the coccyx and sacrum, the trochanter of the femur, the lateral anterior crest, and other bony prominences. Nodules vary in size and characteristically are firm and not tender. It has been estimated that, for every palpable nodule, there are four deeper nonpalpable ones. Ocular Tissue Visual impairment is the most serious complication of onchocerciasis and usually affects only those persons with moder ate or heavy infections. Lesions may develop in all parts of the eye. The most common early finding is conjunctivitis with photophobia. Punctate keratitis—acute inflammatory reactions surrounding dying microfilariae and manifested as “snowflake” opacities—is common among younger patients and resolves without apparent complications. Sclerosing keratitis occurs in 1–5% of infected persons and is the lead ing cause of onchocercal blindness. Anterior uveitis and iridocyclitis FIGURE 240-3 Papular eruption as a consequence of onchocerciasis.

develop in ~5% of infected persons. Characteristic chorioretinal lesions develop as a result of atrophy and hyperpigmentation of the retinal pigment epithelium. Constriction of the visual fields and overt optic atrophy may occur.

Lymph Nodes Mild to moderate lymphadenopathy is common, particularly in the inguinal and femoral areas, where the enlarged nodes may hang down in response to gravity (“hanging groin”), some times predisposing to inguinal and femoral hernias. Other Manifestations Some heavily infected individuals develop cachexia with loss of adipose tissue and muscle mass. A form of dwarf ism, Nakalanga dwarfism, has been attributed to pituitary involvement in this infection. An association between onchocerciasis and epilepsy (including an epidemic form termed nodding syndrome) has gained attention recently. Among adults who become blind, there is a three- to fourfold increase in mortality rate. ■ ■DIAGNOSIS Definitive diagnosis depends on the detection of an adult worm in an excised nodule or, more commonly, of microfilariae in a skin snip. Skin snips are obtained with a corneal-scleral punch or by lifting of the skin with the tip of a needle and excision of a small (1- to 3-mm) piece with a sterile scalpel blade. Both methods collect a blood-free skin biopsy sample extending to just below the epidermis. The biopsy tissue can be incubated in tissue culture medium or in saline on a glass slide or flat-bottomed microtiter plate. After incubation for 2–4 h (or occasionally overnight in light infections), microfilariae emer gent from the skin can be seen by low-power microscopy or can be detected by PCR. CHAPTER 240 Eosinophilia and elevated serum IgE levels are common, but, because these features are seen in many parasitic infections, are not diagnostic in themselves. Immunoassays to detect antibodies to Onchocercaspecific antigens are being used both in specialized laboratories and at the point of contact in rapid-diagnostic formats. Filarial and Related Infections TREATMENT Onchocerciasis The main goals of therapy are to prevent the development of irre versible lesions and to alleviate

symptoms. Chemotherapy is the mainstay of management. Ivermectin, a semisynthetic macrocyclic lactone active against microfilariae, is the first-line agent for the treatment of onchocerciasis. It is given orally in a single dose of 150 µg/kg, either yearly or semiannually. More frequent ivermectin administration (every 3 months) has been suggested to ameliorate pruritus and skin disease. After treatment, most individuals have few or no reactions. Pruri tus, cutaneous edema, and/or maculopapular rash occur in ~1–10% of treated individuals. In areas of Africa co-endemic for O. volvulus and L. loa, however, ivermectin is contraindicated (as it is for preg nant or breast-feeding women) because of severe posttreatment encephalopathy, especially in patients who are heavily microfilaremic for L. loa (>30,000 microfilariae/mL). Although ivermectin treatment results in a marked drop in microfilarial density, its effect can be short-lived (<3 months in some cases). Thus, it is occasionally nec essary to give ivermectin more frequently for persistent symptoms. Another macrocyclic lactone, moxidectin, has a more prolonged microfilaricidal effect but is not yet commercially available. A 6-week course of doxycycline is macrofilaristatic, rendering female adult worms sterile for long periods. ■ ■PREVENTION Vector control has been beneficial in highly endemic areas in which breeding sites are vulnerable to insecticide spraying, but most areas endemic for onchocerciasis are not suited to this type of control. Community-based administration of ivermectin every 6–12 months is being used to interrupt transmission in endemic areas. This measure, in conjunction with vector control, has already helped eliminate the

FIGURE 240-4 Adult Loa loa worm being surgically removed after its subconjunctival migration. infection in most of Latin America and has reduced the prevalence of disease in many endemic foci in Africa. No drug has proved useful for prophylaxis of O. volvulus infection. LOIASIS ■ ■ETIOLOGY AND EPIDEMIOLOGY Loiasis is caused by L. loa (the African eye worm), which is present in the rainforests of West and Central Africa. Adult parasites (females, 50–70 mm long and 0.5 mm wide; males, 25–35 mm long and 0.25 mm wide) live in subcutaneous tissues. Microfilariae circulate in the blood with a diurnal periodicity that peaks between 10:00 a.m. and 2:00 p.m. PART 5 Infectious Diseases ■ ■CLINICAL FEATURES Manifestations of loiasis in natives of endemic areas may differ from those in temporary residents or visitors. Among the indigenous popu lation, loiasis is often an asymptomatic infection with microfilaremia. Infection may be recognized only after subconjunctival migration of an adult worm (Fig. 240-4) or may be manifested by episodic Calabar swellings—evanescent localized areas of angioedema and erythema developing on the extremities and less frequently at other sites. Nephropathy, encephalopathy, and cardiomyopathy can occur but are infrequently diagnosed. Although historically considered relatively benign in endemic populations, recent studies show loiasis is associated with chronic morbidity and increased mortality in endemic populations. In patients who are not residents of endemic areas, aller gic symptoms predominate, episodes of Calabar swelling tend to be more frequent, microfilaremia is less common, and eosinophilia and increased levels of antifilarial antibodies are characteristic. ■ ■PATHOLOGY The pathogenesis of the manifestations of loiasis is poorly understood. Calabar swellings are thought to result from a hypersensitivity reaction to adult worm antigens. ■ ■DIAGNOSIS Definitive diagnosis of loiasis requires the detection of microfilariae in the peripheral blood or the isolation of the adult worm from the eye (Fig. 240-4) or from a subcutaneous biopsy specimen collected from a site of swelling developing after treatment. PCR-based assays for the detection of L. loa DNA in blood are available in specialized laboratories and are highly sensitive and specific, as are some newer recombinant antigen–based serologic techniques. In practice, the diagnosis must often be based on a characteristic history and clinical presentation, blood eosinophilia, and elevated levels of antifilarial antibodies, particu larly in travelers to an endemic

region, who are often amicrofilaremic.

TREATMENT Loiasis DEC (8–10 mg/kg per day administered orally for 21 days) is effec tive against both the adult and the microfilarial forms of L. loa, but multiple courses are frequently necessary before loiasis resolves completely. In cases of heavy microfilaremia, allergic or other inflammatory reactions can take place during treatment, including central nervous system involvement with coma and encephalitis. Heavy infections can be treated initially with apheresis to remove the microfilariae and with glucocorticoids (40–60 mg of predni sone per day) followed by low doses of DEC (0.5 mg/kg per day). If antifilarial treatment has no adverse effects, the prednisone dose can be tapered rapidly and the dose of DEC gradually increased to 8–10 mg/kg per day. Albendazole or ivermectin is effective in reducing microfilarial loads, although neither is approved for this purpose by the U.S. Food and Drug Administration. Moreover, ivermectin is contra indicated in patients with >30,000 microfilariae/mL because this drug has been associated with severe adverse events (including encephalopathy and death) in heavily infected patients with loiasis in West and Central Africa. DEC (300 mg weekly) is an effective prophylactic regimen for loiasis. STREPTOCERCIASIS Mansonella streptocerca, found mainly in the tropical forest belt of Africa from Ghana to the Democratic Republic of the Congo, is trans mitted by biting midges. The major clinical manifestations involve the skin and include pruritus, papular rashes, and pigmentation changes. Many infected individuals have inguinal adenopathy, although most are asymptomatic. The diagnosis is made by detection of the charac teristic microfilariae in skin snips. Ivermectin at a single dose of 150 µg/kg leads to sustained suppression of microfilariae in the skin and is probably the treatment of choice for streptocerciasis. MANSONELLA PERSTANS INFECTION M. perstans, distributed across the center of Africa and in northeastern South America, is transmitted by midges. Adult worms reside in serous cavities—pericardial, pleural, and peritoneal—as well as in the mesentery and the perirenal and retroperitoneal tissues. Microfilariae circulate in the blood without periodicity. The clinical and pathologic features of the infection are poorly defined. Most patients appear to be asymptomatic, but manifestations may include transient angioedema and pruritus of the arms, face, or other parts of the body (analogous to the Calabar swellings of loiasis); fever; headache; arthralgias; and right-upper-quadrant pain. Occasionally, pericarditis and hepatitis occur. The diagnosis is based on the demonstration of microfilariae in blood or serosal effusions. Perstans filariasis is often associated with peripheral-blood eosinophilia and antifilarial antibody elevations. With the identification of a Wolbachia endosymbiont in M. perstans, doxycycline (200 mg twice a day) for 6 weeks has been established as the first effective treatment for this infection. MANSONELLA OZZARDI INFECTION The distribution of M. ozzardi is restricted to Central and South America and certain Caribbean islands. Adult worms are rarely recovered from humans. Microfilariae circulate in the blood without periodicity. Although this organism has often been considered nonpathogenic, headache, articular pain, fever, pulmonary symptoms, adenopathy, hepatomegaly, pruritus, and eosinophilia have been ascribed to M. ozzardi infection. The diagnosis is made by detection of microfilariae in peripheral blood. Ivermectin is effective in treating this infection. ZOONOTIC FILARIAL INFECTIONS Dirofilariae that affect primarily dogs, cats, and raccoons occasionally infect humans incidentally, as do Brugia and Onchocerca parasites that affect small mammals. Because humans are an abnormal host, the

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