



Onchocerciasis—river blindness

Claes D. Enk, MD*

Department of Dermatology, The Hadassah-Hebrew University Medical Center, PO Box 12000, Jerusalem 91120, Israel

Abstract Onchocerciasis results from infestation by the nematode *Onchocerca volvulus* and is characterized by troublesome itching, skin lesions, and eye manifestations. Although partially controlled by international mass prevention programs, onchocerciasis remains a major health hazard and is endemic in Africa, Arabia, and the Americas. Onchocerciasis is spread by bites from infested black flies, which transmit larvae that subsequently develop into adult filariae. Skin symptoms are commonly nonspecific and include severe pruritus, acute and chronic dermatitis, vitiligo-like hypopigmentation, and atrophy. Onchocercal ocular disease covers a large spectrum of manifestations, which in severe cases, may lead to blindness. Diagnosis is usually made by direct visualization of the larvae emerging from superficial skin biopsies, “skin snips.” In some cases, the microfilariae can also be directly observed at the slit lamp when migrating into the anterior chamber of the eye. Ivermectin is, at present, the drug of choice for skin and ocular manifestations. Recent research using a chemotherapeutic approach that targets filarial *Wolbachia* symbionts in the treatment and control of onchocerciasis, however, suggests that 100 mg/d of doxycycline for 6 weeks might be effective in reducing the filarial load and preventing ocular symptoms.

© 2006 Elsevier Inc. All rights reserved.

The disease

Onchocerciasis or “river blindness” results from infestation by the nematode *Onchocerca volvulus* and is characterized by eye affections and skin lesions with severe troublesome itching. Onchocerciasis is a chronic and slowly progressive disease. The initial infestation often occurs in childhood, and many of the affected individuals remain asymptomatic for long periods. In recent years, the World Health Organization’s Onchocerciasis Control Program has successfully reduced the prevalence of onchocerciasis by interfering with the transmission of the parasite and by mass population treatment in the regions at risk. Despite

these laudable efforts, the socioeconomic burden resulting from the disabilities caused by onchocerciasis, however, remains enormous.¹

Epidemiology

Onchocerciasis occurs in 30 countries of the tropical sub-Saharan Africa, the African onchocercal belt extending from Senegal in the west to Ethiopia in the east. Onchocerciasis also occurs to a much lesser degree in Central and South America, in Yemen, and in Saudi Arabia. Among the 85 million people living in areas where onchocerciasis is endemic, an estimated 18 million are currently infested. Of these, 4 million patients have skin manifestations and 2 million are blind or severely visually impaired. Symptoms vary with geographic location; epidemiological studies

* Tel.: +972 26777111; fax: +972 26723468.

E-mail address: enk@md.huji.ac.il.

indicate that onchocerciasis manifests in two main forms, usually termed *savanna* and *forest*. Patients living in the western savanna woodland have a high prevalence of blindness, whereas cutaneous symptoms are more prevalent in the rainforest and in the East African highlands extending from Ethiopia to Malawi.^{2,3} Onchocercal depigmentation is less commonly seen in patients from East Africa; lymphadenopathy is more common in the rainforest; and severe skin atrophy is commonly encountered in the savanna, where the microfilarial load tends to be greater.⁴ These clinical differences may be due to variability in parasite strains and their pathogenicity, differences of vectors and their biting proclivities, altered host factors associated with genetic susceptibility or host immunity, and history of coinfection by other parasites. Travelers may acquire the disease during their stay in areas where onchocerciasis is endemic.⁵

The parasite

O. volvulus is spread by black flies belonging to the genus *Simulium*, which breed in fast-flowing rivers. When biting humans living near the rivers, the black flies ingest skin-dwelling microfilaria, which then go through two additional larval stages in the fly over the next week. When the black fly bites again a human being, the infective larvae escape through the wound and penetrate the tissues to develop into adult filariae that can be found in subcutaneous nodules scattered around the body. The nodules, which range from the size of a pea to that of a golf ball, typically contain two to four adult worms that can reach a length of 80 cm. The female filariae can live for as long as 15 years, during which time they produce many million living embryos of microfilariae (each about 0.3 mm long). Each day, one female worm releases 500 to 700 microfilariae. The incubation period is usually 1 to 2 years, but microfilariae can be detected as early as 3 months after exposure in an area where onchocerciasis is endemic.⁵ The microfilariae can survive 2 to 3 years.



Fig. 1 Chronic papular onchodermatitis.



Fig. 2 Onchocercal atrophy.

Although not well characterized, the immunopathogenesis of onchocerciasis appears to correlate with the parasite load and with the clinical picture. The severe type of onchocercal dermatitis, known as *sowda*, occurs during the parasite-destroying phase of the infestation. It is associated with a delayed hypersensitivity immune response, usually observed in patients with small loads of microfilariae. In contrast, individuals with large microfilarial loads often lack an active immunologic response.⁶ Th2 class cytokines including IL-4 and IL-5 have been shown to play a role in the mediation of the antifilarial response.⁷

The recent demonstration of the *Wolbachia* bacteria in infected individuals has provided a breakthrough in our understanding of onchocerciasis pathogenesis with dramatic implications for treatment and prevention programs.⁸ *Wolbachia* bacteria are symbionts of the major pathogenic filarial nematodes of humans, including *O. volvulus*. They belong to the order of Recheetsiales and are abundant in all development stages of filarial nematodes, including the hypodermis and reproductive tissue of adult filarias. *Wolbachia* species seem to have evolved as symbionts essential for fertility of their nematode hosts, and depletion of *Wolbachia* results in disruption of embryogenesis in the female worm.⁹ Tetracyclines, rifampicin, and chloramphenicol have shown *in vivo* activity against *Wolbachia*.¹⁰

The skin

The skin manifestations of onchocerciasis are highly variable. A clinical classification of onchocercal dermatitis defining six different patterns was suggested by Murdoch et al¹¹: Acute papular onchodermatitis denotes a widespread eczematous rash with multiple small pruritic papules progressing to vesicles and pustules. Acute papular onchodermatitis often affects the face, the trunk, and the extremities. Chronic papular onchodermatitis is a severely itching maculopapular rash containing scattered flat-topped papules and hyperpigmented macules, typically affecting the shoulders, the buttocks, and the extremities (Fig. 1).

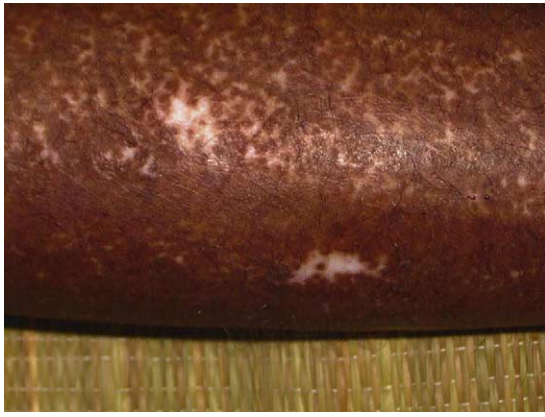


Fig. 3 Onchocercal depigmentation or leopard skin.

Lichenified onchodermatitis consists of hyperkeratotic and hyperpigmented confluent plaques most often affecting the lower extremities and associated with lymphadenopathy. Onchocercal atrophy consists of large atrophic plaques with finely wrinkled inelastic skin resembling cigarette paper, typically affecting the buttocks and the lower back (Fig. 2). Onchocercal depigmentation or “leopard skin” consists of vitiligo-like lesions with hypopigmented patches containing perifollicular spots of normally pigmented skin (Fig. 3). Onchocercal depigmentation often affects the shins in a symmetrical pattern and is rarely associated with itch and excoriations. Palpable onchocercal nodules are asymptomatic subcutaneous nodules of variable size located over bony prominence and containing the adult worms. Other classic clinical pictures include “lizard skin” with dry ichthyoses-like lesions with a mosaic pattern resembling the scales of a lizard (Fig. 4); “hanging groin” consists of folds of atrophic inelastic skin in the inguinal region associated with lymphadenopathy. In a population where onchodermatitis is endemic, the most common skin manifestation is chronic papular onchodermatitis followed by onchocercal depigmentation and onchocercal atrophy.¹² Different clinical patterns are not mutually exclusive because two or more



Fig. 4 Lizard skin with ichthyoses-like changes.

patterns may be present simultaneously and one pattern may evolve into another pattern.

The eye

Onchocercal ocular disease covers a wide spectrum, ranging from mild symptoms such as itching, redness, pain, photophobia, diffuse keratitis, and blurring of vision to more severe symptoms of corneal scarring, night blindness, intraocular inflammation, glaucoma, visual field loss, and, eventually, blindness.¹³ In untreated populations, the progressive nature of onchocercal ocular disease was responsible for the existence of entire villages in which the older population was blind and only the youngsters had functional vision. This phenomenon was first observed in villages in proximity of rivers, the breeding site of the *Simulium* black fly, hence, the name *river blindness*.

Ocular lesions are usually bilateral and can affect various structures of the anterior and posterior segments of the eye.¹⁴ Anterior segment disease is related to the presence of living or dead microfilariae in the eye. In the anterior chamber, the microfilariae can be seen with a slit lamp. Dead microfilariae may cause severe anterior uveitis with formation of synechiae, cataract, and glaucoma. Confluent opacities may obscure major portions of the cornea, ultimately leading to a sclerosing keratitis with fibrovascular pannus and marked reduction of the visual functions.

Posterior segment disease manifests as atrophy of the retinal-pigment epithelium and is associated with chorioretinal scarring and subretinal fibrosis.¹⁵ Optic neuritis followed by postneuritic optic atrophy may occur.¹⁶

Diagnosis

The diagnosis of onchocerciasis rests on the demonstration of living microfilaria in skin biopsies. Bloodless shave biopsies or “skin snips” are typically obtained by lifting the skin with the tip of a needle and excising a superficial disk

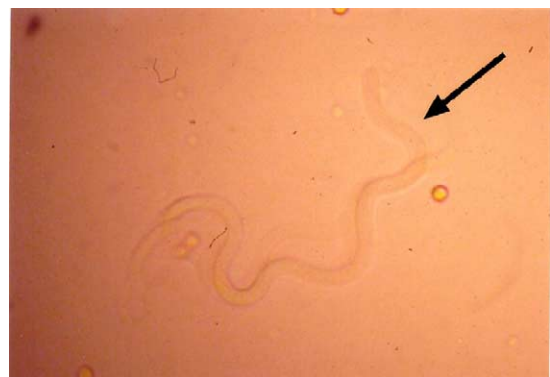


Fig. 5 Spirocete-like microfilaria emerging from the skin snip and observed microscopically with original magnification $\times 10$.

of skin with a razor blade, or by scraping the skin tangentially with a corneoscleral punch. Snips are obtained bilaterally from the shins, the buttocks, and the iliac crests. In Central and South America, where the clinical manifestations typically are more severe on the upper trunk, skin snips are obtained from the scapular areas. The snips are then placed in normal saline and inspected at intervals under the microscope for emerging spirocete-like microfilariae (Fig. 5). Microscopic demonstration of microfilariae is 100% specific for onchocerciasis; however, the technique is rather insensitive in latent or early disease with a small microfilarial load.

Immunodiagnosis has recently been made available by the development of various recombinant filarial antigens.¹⁷ This test, however, cannot reliably distinguish between past and present infection.¹⁸ A polymerase chain reaction-based assay was recently exploited to detect the repetitive DNA sequence known as O-150 (found only in *O. volvulus*) in skin snips.¹⁹ In spite of great promise in terms of high sensitivity, these newer techniques are not yet available under field conditions.

The Mazzotti patch test is based on a contact hypersensitivity reaction induced by dead and dying microfilariae after topical application of diethylcarbamazine.²⁰ In spite of high sensitivity and specificity compared with the skin snip technique, the patch test is hampered by varying degrees of sensitivity in different geographic areas and by its inability to identify individuals with light infestation.²¹

Treatment

Ivermectin (Stromectol, Mectizan), the drug of choice for the treatment of onchocerciasis, is used in World Health Organization-sponsored multinational health programs. It is a synthetic derivative of a macrocyclic lactone produced by the actinomycete *Streptomyces avermitilis*, acting as an agonist of the parasite neurotransmitter, γ -aminobutyric acid,²² and by inducing an influx of Cl^- through channels not regulated by γ -aminobutyric acid.²³ Ivermectin has broad antiparasitic activity against nematodes. Ivermectin is an efficient microfilaricidal that does not kill the adult worm. Nonetheless, it probably impairs the release of microfilariae from the female adult worm already after the first dose.²⁴ Multiple doses of ivermectin have been shown to affect embryonic development of the worms and to cause gradual restitution of the cellular antifilarial immune response. Ivermectin has also been shown to reduce the incidence of onchodermatitis,²⁵ iridocyclitis, and sclerotic keratitis.¹⁴ There are conflicting data regarding the effectiveness of the drug in reducing onchocercal pruritus.^{26,27}

The optimal dose of ivermectin is 150 $\mu\text{g}/\text{kg}$, but the frequency of administration is still controversial, ranging from 150 $\mu\text{g}/\text{kg}$ once to three times yearly. The optimal duration of treatment has not been established. One third of patients treated with a single dose of ivermectin may be

cured. Though ivermectin, however, rapidly reduces the number of skin microfilariae, they reappear at levels of 20% of the pretreatment numbers within a year. Therefore, retreatment throughout the full length of life of the adult worm (12–15 years) has been suggested. Current recommendations call for several doses of ivermectin followed by regular clinical and microbiological monitoring. Ivermectin is well tolerated, causing mild adverse effects in approximately 10% of the patients. The adverse effects usually occur within the first 48 hours of treatment and appear to attenuate with repeated administrations. Adverse effects recorded include edema, fever, pruritus, arthralgias, lymphadenitis, and postural hypotension. Ivermectin should not be used in pregnant women during the first month of lactation, in children younger than 5 years, or in patients in poor health.

The symbiosis of filarial nematodes and intracellular *Wolbachia* bacteria has recently been exploited as a target for antibiotic therapy for onchocerciasis. Administration of 100 mg/d doxycycline for 6 weeks led to the depletion of *Wolbachia* followed by an interruption of embryogenesis in worms, which lasted for 18 months.²⁸ Furthermore, experiments in mice suggest that the onchocerciasis-related corneal inflammation is caused by *Wolbachia* endotoxins,²⁹ suggesting that clearance of *Wolbachia* with antibiotic treatment may also reduce and prevent onchocerciasis-related blindness. Though the results so far have been encouraging, the precise role of a chemotherapeutic approach that targets filarial *Wolbachia* in the treatment and control of onchocerciasis has not been determined and awaits future investigations.

References

1. Workneh W, Fletcher M, Olwit G. Onchocerciasis in field workers at Baya Farm, Teppi Coffee Plantation Project, southwestern Ethiopia: prevalence and impact on productivity. *Acta Trop* 1993;54:89–97.
2. Duke BO. Geographical aspects of onchocerciasis. *Ann Soc Belge Med Trop* 1981;61:179–86.
3. Woodruff AW, Anderson J, Pettitt LE, Tukur M, Woodruff AH. Some aspects of onchocerciasis in Sudan savanna and rain-forest. *J Trop Med Hyg* 1977;80:68–73.
4. Anderson J, Fuglsang H, Hamilton PJ, de Marshall TF. Studies on onchocerciasis in the United Cameroon Republic. II. Comparison of onchocerciasis in rain-forest and Sudan-savanna. *Trans R Soc Trop Med Hyg* 1974;68:209–22.
5. McCarthy JS, Ottesen EA, Nutman TB. Onchocerciasis in endemic and nonendemic populations: differences in clinical presentation and immunologic findings. *J Infect Dis* 1994;170:736–41.
6. Hay RJ, Mackenzie CD, Guderian R, et al. Onchodermatitis-correlation between skin disease and parasitic load in an endemic focus in Ecuador. *Br J Dermatol* 1989;121:187–98.
7. King CL, Nutman TB. Regulation of the immune response in lymphatic filariasis and onchocerciasis. *Immunol Today* 1991;12:A54–8.
8. Hoerauf A, Buttner DW, Adjei O, Pearlman E. Onchocerciasis. *BMJ* 2003;326:207–10.
9. Bandi C, Trees AJ, Brattig NW. *Wolbachia* in filarial nematodes: evolutionary aspects and implications for the pathogenesis and treatment of filarial diseases. *Vet Parasitol* 2001;98:215–38.

10. Hoerauf A, Adjei O, Buttner DW. Antibiotics for the treatment of onchocerciasis and other filarial infections. *Curr Opin Investig Drugs* 2002;3:533-7.
11. Murdoch ME, Hay RJ, Mackenzie CD, et al. A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol* 1993;129:260-9.
12. Hagan M. Onchocercal dermatitis: clinical impact. *Ann Trop Med Parasitol* 1998;92(Suppl 1):S85-S96.
13. Enk CD, Anteby I, Abramson N, et al. Onchocerciasis among Ethiopian immigrants in Israel. *Isr Med Assoc J* 2003;5:485-8.
14. Abiose A. Onchocercal eye disease and the impact of Mectizan treatment. *Ann Trop Med Parasitol* 1998;92(Suppl 1):S11-S22.
15. Newland HS, White AT, Greene BM, Murphy RP, Taylor HR. Ocular manifestations of onchocerciasis in a rain forest area of West Africa. *Br J Ophthalmol* 1991;75:163-9.
16. Abiose A, Jones BR, Cousens SN, et al. Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993;341:130-4.
17. Ramachandran CP. Improved immunodiagnostic tests to monitor onchocerciasis control programmes—a multicenter effort. *Parasitol Today* 1993;9:77-9.
18. Nutman TB, Zimmerman PA, Kubofcik J, Kostyu DD. A universally applicable diagnostic approach to filarial and other infections. *Parasitol Today* 1994;10:239-43.
19. Zimmerman PA, Guderian RH, Aruajo E, et al. Polymerase chain reaction-based diagnosis of *Onchocerca volvulus* infection: improved detection of patients with onchocerciasis. *J Infect Dis* 1994; 169:686-9.
20. Stingl P, Ross M, Gibson DW, Ribas J, Connor DH. A diagnostic “patch test” for onchocerciasis using topical diethylcarbamazine. *Trans R Soc Trop Med Hyg* 1984;78:254-8.
21. Newland HS, Kaiser A, Taylor HR. The use of diethylcarbamazine cream in the diagnosis of onchocerciasis. *Trop Med Parasitol* 1987; 38:143-4.
22. Soboslay PT, Newland HS, White AT, et al. Ivermectin effect on microfilariae of *Onchocerca volvulus* after a single oral dose in humans. *Trop Med Parasitol* 1987;38:8-10.
23. Van Laethem Y, Lopes C. Treatment of onchocerciasis. *Drugs* 1996; 52:861-9.
24. Schulz-Key H, Soboslay PT, Hoffmann WH. Ivermectin-facilitated immunity. *Parasitol Today* 1992;8:152-3.
25. Pacque M, Elmetts C, Dukuly ZD, et al. Improvement in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991;90:590-4.
26. Ogbuagu KF, Eneanya CI. A multi-centre study of the effect of Mectizan treatment on onchocercal skin disease: clinical findings. *Ann Trop Med Parasitol* 1998;92(Suppl 1):S139-45.
27. Whitworth JA, Luty AJ, Maude GH, et al. Ivermectin does not reduce the burden of itching in an onchocerciasis endemic community. *Trans R Soc Trop Med Hyg* 1992;86:281-3.
28. Hoerauf A, Mand S, Adjei O, Fleischer B, Buttner DW. Depletion of *Wolbachia* endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001;357:1415-6.
29. Saint AA, Blackwell NM, Hall LR, et al. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. *Science* 2002;295:1892-5.