Onchocerciasis Presenting with Lower Extremity, Hypopigmented Macules

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GOAL

To outline the diagnosis and management of the parasitic infection, onchocerciasis, or "river blindness."

OBJECTIVES

1. To describe the life cycle and infestation with *Onchocerca volvulus*.
2. To discuss the diagnostic tests for onchocerciasis.
3. To describe the treatments and their complications for microfilariae.

CME Test on page 298

Onchocerciasis, or river blindness, is a parasitic infection caused by the filarial nematode, Onchocerca volvulus*. It infects 18 million people worldwide, but is rarely seen in the United States. It is one of the leading causes of blindness in the developing world. Although onchocerciasis is also known as river blindness, it is not just a disease of the eyes, but rather a chronic multisystem disease. Clinically, onchocerciasis takes three forms: 1) eye disease; 2) subcutaneous nodules; and 3) a pruritic hypopigmented or hyperpigmented papular dermatitis. We present an 18-year-old African female with a 5-year history of asymptomatic, hypopigmented, slightly atrophic macules on her anterior tibiae. Pathology revealed a scant perivascular inflammatory infiltrate with mononuclear cells, eosinophils, and rare microfilariae in the papillary dermis. Ivermectin is the treatment of choice for onchocerciasis and was initiated in this patient. We present this interesting patient with onchocerciasis to expand our differential of hypopigmented macules, especially in the African population. In addition, we discuss both the diagnosis and the treatment of onchocerciasis in expatriate patients living in nonendemic areas.*

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Onchocerciasis, or river blindness, is a parasitic infection of humans caused by the filarial nematode, *Onchocerca volvulus*. Eighteen million people are infected worldwide. The disease has been reported in over 34 countries throughout Africa, Latin America, and the Arabian Peninsula, with the majority of cases occurring in West Africa. Onochocerciasis is a chronic multisystem disease with skin manifestations, and is a leading cause of blindness. Microfilariae have been noted in blood, urine, cerebrospinal fluid, and internal organs. In heavily infected persons, 100 million or greater microfilariae may be present.[1]

O. volvulus is spread through the bite of blackflies from the genus *Simulium*, which breed in fast-flowing rivers of endemic regions. While the fly feeds on human blood, it also ingests skin-dwelling onchocercal

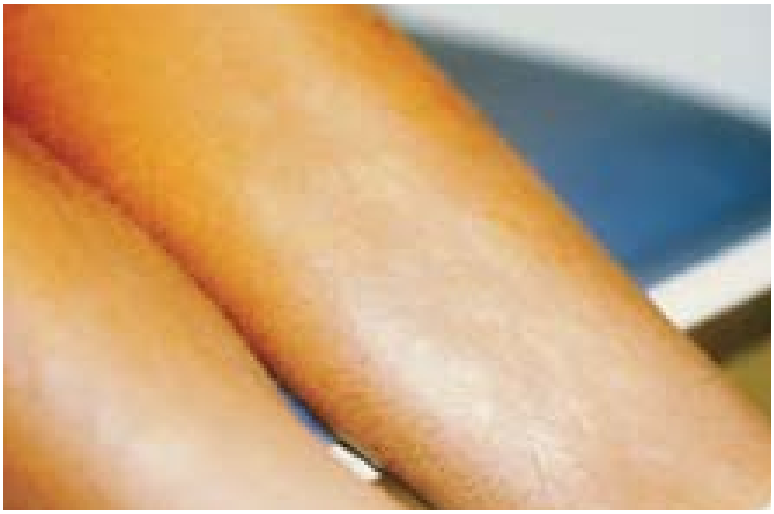

FIGURE 1. Multiple hypopigmented, slightly atrophic macules on the anterior tibia bilaterally.

microfilariae. The microfilariae develop into infective larvae in the proboscis of the fly over a period of 6 to 8 days. When the fly bites another human, the larvae are injected into the wound and develop into adult worms, living in the deep dermis and fascial planes. Scar tissue develops around the adult worms, forming thick, fibrous, subcutaneous nodules. Nodules contain one to two male and two to three female adults. Pregnant female adults can produce microfilariae within 10 to 12 months from the time of initial infection. The female worm may release 1300 to 1900 microfilariae a day for the reproductive life of the adult worm, which averages between 9 and 11 years.[1] However, the maximum rate of microfilarial production occurs during the first 5 years of the worm's reproductive life and declines linearly after that. The lifespan of microfilariae varies from 0.5 to 2 years.[2] The microfilariae can move easily through the skin and connective tissue, and have a predilection for the subepidermal lymphatics and the anterior chamber of the eye.

The traditional method of diagnosis is by microscopically viewing skin-snips taken from infected areas, immersing them in saline, and directly observing microfilariae. Newer diagnostic modalities have been developed but are not in widespread use at this time. The treatment of choice is ivermectin, which is a microfilaricidal agent. Ivermectin has no effect on adult worms, so retreatment is usually required. There is currently much debate as to the proper frequency and length of treatment with ivermectin.

We present this interesting patient with onchocerciasis to expand our differential of hypopigmented macules, especially in the African population. In addition, we discuss both the diagnosis and the treatment of onchocerciasis in expatriate patients living in nonendemic areas.

Case Report

An 18-year-old African native female presented to our office complaining of asymptomatic hypopigmented macules on her anterior tibiae bilaterally (Figure 1). The lesions were present for 5 years and were of only a cosmetic concern to her. She had no other skin complaints and denied having symptoms of dermatitis, pruritus, nodules, or hyperpigmented macules. She was in her usual state of good health. On physical examination, both anterior tibia showed hypopigmented macules, which were slightly atrophic. There were no other skin lesions and no palpable lymphadenopathy. A 4-mm punch biopsy was performed during the office visit, which showed a scant perivascular inflammatory infiltrate with mononuclear cells, eosinophils, and rare microfilariae in the papillary dermis (Figure 2). She was started on ivermectin, 9 mg every 3 months for two doses, and then every 6 months for two doses. She had no complications and tolerated ivermectin well. The patient had an opthalmologic examination, which did not show any evidence of eye involvement. The patient did not return and was not available for follow-up.

Comments

The cutaneous manifestations and symptoms of onchocerciasis vary depending on the presence of adult worms or microfilariae and the age of the lesion. The adult worms live in coiled tangled masses or in nodules called onchocercomas within the deep dermis or subcutaneous tissue. Adult worms do not cause any harm. The onchocercomas are often few in number, firm, non-tender, and average about 0.5 to 3.0 cm in size. They are usually easily palpable and generally occur over a bony prominence. The adult worms are recognized by the immune system, with nodules typically surrounded by eosinophils and lymphocytes.

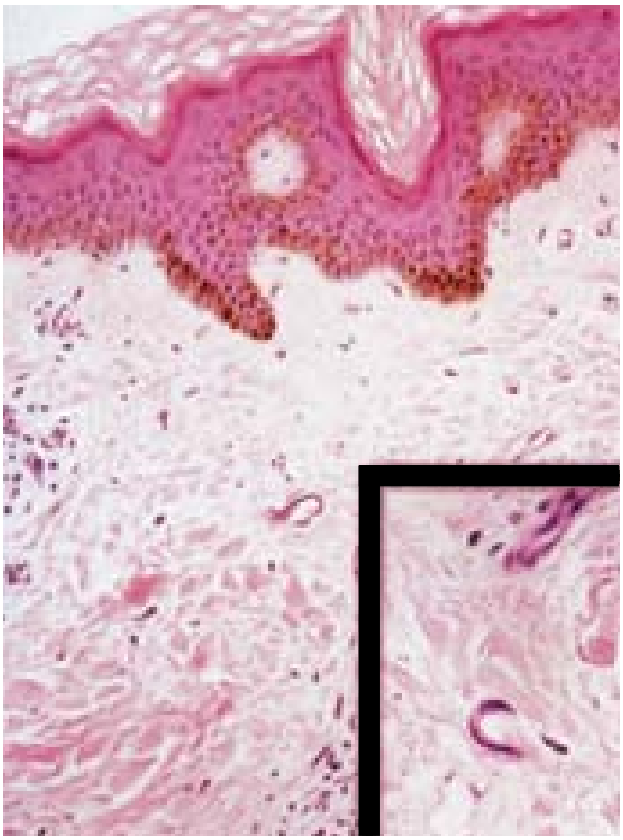

FIGURE 2. Scant perivascular inflammatory infiltrate and free-lying microfilaria in the papillary dermis. Inset, higher magnification of microfilaria with several anterior and terminal nuclei.

However, the adults are not attacked within the fibrous nodules.[1]

Death of microfilariae causes the symptoms of onchocerciasis and leads to onchocercal dermatitis. While alive, microfilariae produce relatively little in the way of an inflammatory response. However, dead and dying microfilariae produce a strong, primarily humoral, immune response with a strong, cellular contribution from eosinophils. In a heavily affected person, 100,000 or more microfilariae die per day.[1] The immune response to microfilariae in the skin initially presents as pruritis, which can be severe, resulting in a secondary dermatitis. A localized acute papular dermatitis is typically seen, with 1- to 3-mm pruritic papules that can progress to vesicles and pustules. Excoriations often co-exist, as does edema, which stems from microfilariae and inflammatory cells filling lymphatic vessels. In mild cases, skin lesions may clear without treatment in several months. Chronic papular onchodermatitis presents with larger flat-topped lesions and post-inflammatory pigment changes. Patients may have chronic onchodermatitis coexisting with acute lesions. The chronic papular dermatitis may become hyperkeratotic or lichenified from scratching. Eventually the presence of microfilariae and a perivascular inflammatory reaction may lead to dermal fibrosis and overlying epidermal atrophy. Another late skin finding is known as onchocercal depigmentation or "leopard skin." It presents with patches of complete pigment loss, typically on the shins, which are flat or slightly depressed and are rarely pruritic.[3] Destruction of elastic fibers may also be seen in long-standing atrophic lesions. An extreme example of elastic fiber loss is exemplified by the "hanging groin," in which loose folds of skin hang dependently from the inguinal region.

Microfilariae may also be present in the anterior chamber of the eye and from here migrate into the cornea. The degenerative changes of the eye occur in the same manner as does skin disease in onchocerciasis. Corneal inflammation around dead microfilariae leads to a punctate keratitis, which clears after the inflammation settles. Sclerosing keratitis or iridocyclitis may develop after chronic inflammation, causing visual impairment and possibly blindness. Microfilariae can migrate to the retina, causing inflammation and optic neuritis and eventually optic atrophy.[1]

Other nonocular, noncutaneous manifestations of onchocerciasis include musculoskeletal complaints and weight loss, which can be extensive with malnutrition. The musculoskeletal complaints often present as a generalized body ache, backache, or joint pain. The mechanism is unclear, but it most likely represents the body's response to inflammation. A study in Malawi found that musculoskeletal complaints increased with the intensity of onchocercal infection and that average body weights were lower for patients with infection. The mechanism of weight loss is probably related to that of a chronic disease.[4] A study in Burundi found an increased incidence of onchocerciasis in epileptics.[5] A subset of patients with both epilepsy and onchocerciasis, who additionally presented with mental deficiencies and short stature, was also established. In the 1960s, the Nakalanga syndrome was first reported as the occurrence of growth arrest in patients, beginning at the ages of 6 to 10, from hyperendemic regions in Uganda. The syndrome has also been described in patients from Burundi and Ethiopia.[1] Finally, patients of endemic regions have associated the disease with infertility, sterility, spontaneous abortion, problems with lactation, and secondary amenorrhea, although there has been no definitive evidence proving this. In a study of a hyperendemic region in Ecuador, the rate of spontaneous abortions declined significantly several years after mass treatment with ivermectin.[6]

The diagnosis of onchocerciasis has traditionally been made following evaluation of a skin snip from an

affected area. The snips, weighing up to 5 mg, are placed in saline and the microfilariae are allowed to emerge by waiting 30 to 60 minutes or longer. The live microfilariae can then be viewed microscopically. The presence of microfilariae is diagnostic; thus, this method is extremely specific. It also allows for a quantification of the intensity of infection by counting the number of microfilariae. However, it is not overly sensitive to early infections or lesions with a paucity of microfilariae. Finally, it is also an invasive test. Another method of diagnosis, which is now seldom used, is the Mazzotti test. It involves the administration of 6 mg of diethylcarbamazine, a drug that inhibits nematode neurotransmission and promotes cellular cytotoxicity. A positive test produces itching and sometimes intense inflammation within 2 hours at sites where dying microfilariae are present. Newer tests have been developed and include polymerase chain reaction (PCR) amplification of parasite DNA and recombinant antigen immunoassays. By taking skin-snippings from infected regions, a PCR amplification of DNA sequences found only in *O. volvulus* can be made. This method improves sensitivity for patients with low-intensity infections over traditional skin snips. It also can detect the return of microfilariae to the skin after drug treatment before a traditional skin-snipping would. The disadvantages of PCR are its high cost and that it is an invasive test. Immunoassays are also extremely sensitive and specific. An enzyme-linked immunosorbent assay study is used to detect antibodies that recognize specific microfilariae antigens. This test is more sensitive than traditional skin-snipping and also is less invasive, requiring only a finger stick. Immunoassays cannot distinguish past infections from current ones, an especially important problem in endemic areas. Finally, diethylcarbamazine applied topically to infected areas producing inflammation has been found to be very specific and noninvasive, but less sensitive than skin-snipping.[7] Despite the benefits of the newer diagnostic modalities, traditional skin snipping is the first line for detection of onchocerciasis in nonendemic areas. If the results of this test are negative, and the clinical suspicion is still high, the other methods may be employed. Visualization of microfilariae in the anterior chamber of the eye or the cornea with a slit-lamp is also diagnostic.[8]

A reasonable differential diagnosis for hypopigmented atrophic macules on the tibiae would include lichen sclerosus et atrophicus, atrophic scars secondary to trauma or neurodermatitis, malignant atrophic papulosis, guttate lesions of morphea, and possibly hypopigmented mycosis fungoides or sarcoidosis, but in these latter two conditions atrophy is not expected. In addition, leprosy and treponemal infection may be considered.[9] In subtle cases like the one presented in this paper, especially in expatriates presenting in nonendemic areas, the diagnosis of onchocerciasis might not be in the practitioner's differential. In this scenario, it would be unlikely that the above diagnostic modalities would be tried, and a punch biopsy of affected areas would probably be undertaken.

Histopathologic study of punch biopsy specimens may show diagnostic findings. *O. volvulus* may be seen in tissue sections in the cutaneous lymphatic vessels, as well as lying freely in the dermis, especially the papillary dermis. There may be an associated perivascular lymphohistocytic infiltrate of variable intensity, with or without eosinophils, as well as interstitial edema. The free microfilariae in the dermis are unsheathed and measure approximately 220 to 360 µm in length and 5 to 9 µm in width. There are several nuclei within the organism. The anterior two or three nuclei are side by side, and the terminal nuclei are elongated.[10] Histologically, on skin biopsy specimens the microfilariae may be mistaken for reactive fibroblasts in the papillary dermis, but closer examination will reveal the presence of multiple nuclei.

The treatment of choice is ivermectin, which not only can prevent eye disease but also can improve and eliminate skin manifestations.[11] It is a broad-spectrum antiparasitic agent with activity against most nematodes. Its mechanism is through impairing neuromuscular function leading to nematode paralysis.[8] Ivermectin was developed in 1987 and its mass distribution through Africa and Latin America during the 1990s has limited infection and reduced transmission. In a trial in Ghana, ivermectin given annually for 5 years reduced microfilariae loads to 7% of pretreatment levels. A single dose of ivermectin clears microfilariae from the skin and eyes for several months. In addition to being microfilaricidal, it also appears to impair the release of microfilariae from pregnant female adults.[1] Unfortunately, it has no effect on adult worms. Thus, new microfilariae may be produced when the effects of ivermectin wane. The optimal dose is 150 µg/kg. The tablets should be taken fasting, and the patient should remain fasting for 2 hours for maximal absorption.[8] There is significant debate as to both the ideal frequency and the length of treatment with ivermectin. Researchers in Malawi found annual ivermectin treatments to be inadequate and stated that infections with skin manifestations may require treatment three to four times a year.[11] A group in Burundi found that biannual treatments led to a greater reduction in parasitologic parameters, severity of pruritus, and frequency of side effects over annual treatments. However, they believed that the improvements with biannual over annual treatments were modest and that annual treatments were adequate to reduce morbidity, especially when cost constraints and patient compliance were

factors.[12] For patients in nonendemic areas, a reasonable approach is an initial single dose of ivermectin, which can then be repeated every 3 to 6 months as needed, depending on the patient's skin symptoms. After several doses, strict clinical follow-up is recommended to determine the need for retreatment. The necessity of treatment throughout the 12- to 15-year life cycle of the adult has never been proven. In fact, up to one-third of patients in nonendemic areas were cured by a single dose of ivermectin. The development of a macrofilaricidal drug that is safe would decrease the treatment length required for ivermectin.[8]

Adverse effects of ivermectin are no different from the usual response of the body to dying microfilariae, except for an increase in intensity and pace. Effects include edema, fever, pruritus, body pains, lymphadenitis, and postural hypotension. They generally appear after the first dose and become milder with subsequent treatments. Since reactions usually occur within 48 hours after treatment, some recommend that the first dose be given under medical supervision. Although ivermectin is microfilaricidal, it does not cause severe reactions in either the eyes or the skin, as is seen with the Mazzotti test reaction and diethylcarbamazine. Ivermectin should not be used during pregnancy, during lactation, in children less then 5 years old, and in those with significantly poor health.[8]

The World Health Organization no longer recommends the use of diethlycarbamazine for the treatment of onchocerciasis. Its adverse effects are similar to those of ivermectin, but with increased intensity and it may accelerate optic impairment.[8]

Presently, the only drug that has macrofilaricidal activity is suramin. It damages the intestinal tract of adults and microfilariae, and must be given intravenously. Suramin has a very narrow therapeutic index and is associated with severe adverse effects. Idiosyncratic reactions with neurologic and gastrointestinal manifestations are seen in addition to exfoliative dermatitis and renal impairment. It also may exacerbate eye disease. The World Health Organization recommends its use only in nonendemic areas when ivermectin could not adequately control the disease.[8]

We present this patient with a probable longstanding infection of onchocerciasis, which was clinically unsuspected. It reminds us to consider nationality and travel history when formulating a differential diagnosis, as well as always to consider an expanded differential diagnosis when assessing patients. Although our patient did not have any severe manifestations of the disease, a misdiagnosis or delayed diagnosis could have had severe ramifications. Prolonged infection with *Onchocerca* can lead to blindness, disfiguring skin changes, infertility, severe weight loss, and possibly growth arrest and epilepsy.

REFERENCES

1. Burnham G: Onchocerciasis. *Lancet* 351: 1341-1346, 1998.
2. Plaisier AP: The reproductive lifespan of *Onchocerca volvulus* in West African Savanna. *Acta Tropica* 48: 271-284, 1991.
3. Murdoch ME: A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol* 129: 260-269, 1993.
4. Burnham G: Onchocerciasis in Malawi.2. Subjective complaints and decreased weight in persons infected with *Onchocerca volvulus* in the Thyolo highlands. *Trans R Soc Trop Med Hyg* 85: 497-500, 1991.
5. Newell ED: Epilepsy, retarded growth and Onchocerciasis, in two areas of different endemicity of Onchocerciasis in Burundi. *Trans R Soc Trop Med Hyg* 91: 525-527, 1997.
6. Gurderian RH: Onchocerciasis and reproductive health in Ecuador. *Trans R Soc Trop Med Hyg* 91: 315-317, 1997.
7. Boatin BA: Diagnostics in Onchocerciasis: future challenges. *Ann Trop Med Parasitol* 92: S41-S45, 1998.
8. Laethem YV, Lopes C: Treatment of Onchocerciasis. *Drugs* 52: 861-869, 1996.
9. Guderian RH: Onchocerciasis in Ecuador: dermal depigmentation, "leopard skin" and comparison with treponemal infection. *Trans R Soc Trop Med Hyg* 85: 639, 1991.
10. Connor DH, Neafie RC: Onchocerciasis. *Pathology of Tropical and Extraordinary Disease* 3: 360-372.
11. Burnham G: Ivermectin treatment of Onchocercial skin lesions: observations from a placebo-controlled, double blind trail in Malawi. *Am J Trop Med Hyg* 52: 270-275, 1995.
12. Vyungimana F, Newell E: Treatment of onchocerciasis with ivermectin (Province of Burari, Burundi): parasitologic and clinical evaluation of different periodicities of treatment. *Am J Trop Med Hyg* 59: 828-831, 1998.

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Drs. Vernick, Turner, Burov and Telang report no conflict of interest.