Journal of Pakistan Association of Dermatologists 2007; **17**: 32-45.

Review Article

Onchocerciasis: A review of a filarial disease of significant importance for dermatologists and ophthalmologists

Arfan ul Bari*, Simeen Ber Rahman**

* Department of Dermatology, CMH, Muzaffarabad, AJK, Pakistan.
** Department of Dermatology, Military Hospital, Rawalpindi.

Abstract Onchocerciasis is a common, chronic, multisystemic disease caused by the nematode *Onchocerca volvulus*. The disease characteristically includes dermatologic, lymphatic, ophthalmologic, and systemic manifestations. It is transmitted to humans by a bite from the intermediate host, the black fly (*Simulium damnosum*). It is endemic in Western and Central Africa and approximately 95% of all infected people live in these regions. Onchocerciasis has been associated with a high incidence of detrimental effects on socioeconomic development and public health in endemic areas. We, here in Asia, hardly see any case of this disease but due to globalization, frequent international traveling and deployment of military troops from Asian countries (as a part of UN forces) in endemic African countries. We should expect such diseases in our region also and should have a high index of suspicion. Here is a review of this troublesome filarial disease with emphasis of its clinical spectrum, so that dermatologists, ophthalmologists and physicians in our region would be able to keep this disease in mind as a differential diagnosis of some unusual case of dermatitis, blindness or arthritis etc. Patients described (figures) in this article are author's own collection during one year stay in Sierra Leone (an endemic country of West Africa for the disease).

Key words
Onchocerciasis, onchodermatitis, *Onchocerca volvulus,* black fly.

Historical background

In 1875, John O'Neill first observed *Onchocerca volvulus* microfilariae in a case of "craw-craw," as onchocerciasis is known in West Africa[1]. It was first described in Africa by Leukart and this full description was published by Manson in 1893.[2] Onchocerciasis was not reported in Latin America until 1917, when Robles[3] found ocular disease associated with scalp nodules in a boy. Almost 50 years later, Blacklock discovered the vector to be *Simulium* in Sierra Leone.[4]

Address for correspondence
Maj. Dr. Arfan ul Bari,
Consultant Dermatologist, Combined Military Hospital, Muzaffarabad, AJK, Pakistan
Ph # 00 92 58810 561 6155,
00 92 301 6547007
e-mail: albariul@yahoo.com,
albariul@gmail.com

Synonyms and some related clinical terms

Various synonyms of the disease have long been in use in African countries. These include; river blindness, African river blindness, blinding filariasis, Robles disease, craw-craw, onchocerciasis, and onchodermatitis. Following are some clinical terms used to describe various clinical presentations of the disease; onchodermatitis, onchocercal dermatitis, hanging groin, leopard skin, sowda, onchocercal dermatitis, acute papular onchodermatitis (APOD), chronic papular

onchodermatitis (CPOD), lichenified onchodermatitis (LOD).[5,6]

Causative agent [5-9]

Human onchocerciasis is caused by the filarial parasite *Onchocerca volvulus.* It is the main species of filarial parasite found in the skin and tissue. The microfilariae of *O. volvulus* are unsheathed with broad spatulate head and pointed tail free from nuclei (**Figure 1**). They measure between 221-287m long and migrate through the dermis (**Figure 2**) causing itching and skin texture changes and occasionally arrive in the eye where they cause blindness. These microfilariae are detected from skin snips or nodule biopsies. When high numbers of microfilariae are present, they can occasionally be found in the blood and urine. The whitish adult worm lies coiled within capsules in the fibrous tissue. The female can measure up to 50 cm while the males are shorter measuring up to 5 cm. The life cycle of *O. volvulus* occurs in two different hosts: black flies, and human (**Figure 3**). The infective larvae (stage L3) are normally transmitted by the bite of *Simulium* flies. Once in the human body, the larvae undergo moulting to stage L4, to reach the adult stage in about one year. Adult females are able to produce millions of microfilariae which they shed in the blood of their human host. When female black flies take a blood meal they ingest those microfilariae that undergo first transition in the fly host to L2 life stage. L2 larvae then moult to L3, the infective stage for human.[5-9]

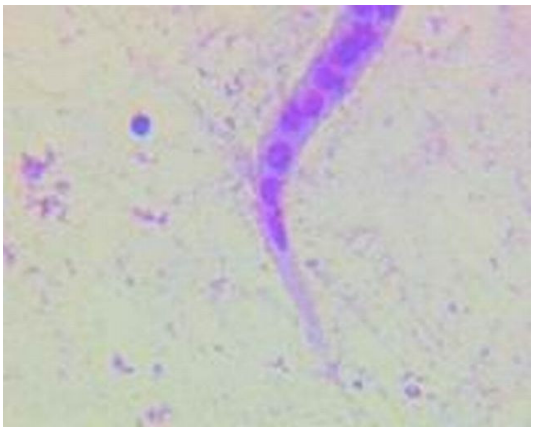

Figure 1 Sheathless microfilaria (*Onchocerca volvulus*) with sharply pointed, curved tails and measuring about 300 mm in length and 0.8 mm in diameter shed by female after mating in host tissue.

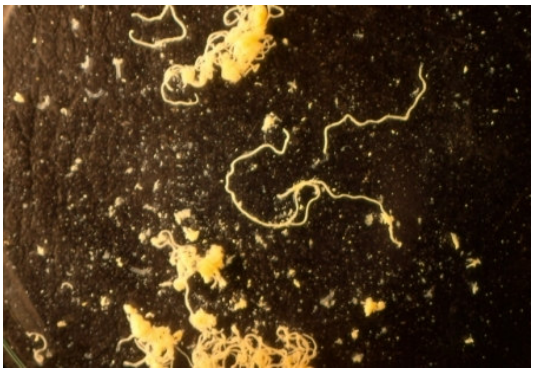

Figure 2 Adult worms in an explored subcutaneous nodule (onchocercoma).

Vector [4, 8-11]

Black flies (buffalo gnats) are small (1.5-4 mm in length) and normally black with short hairless legs and antennae (**Figure 4**). They have large compound eyes and a characteristically hairy humped thorax (back) and can give a painful bite. The appearance has led to the colloquial name of buffalo gnats. Unlike a mosquito (which sucks up blood through a proboscis), black flies slash the skin and lap up the pooled blood. They usually bite in shaded or partially shaded areas and may fly as far as 15 miles from breeding areas. Their larvae

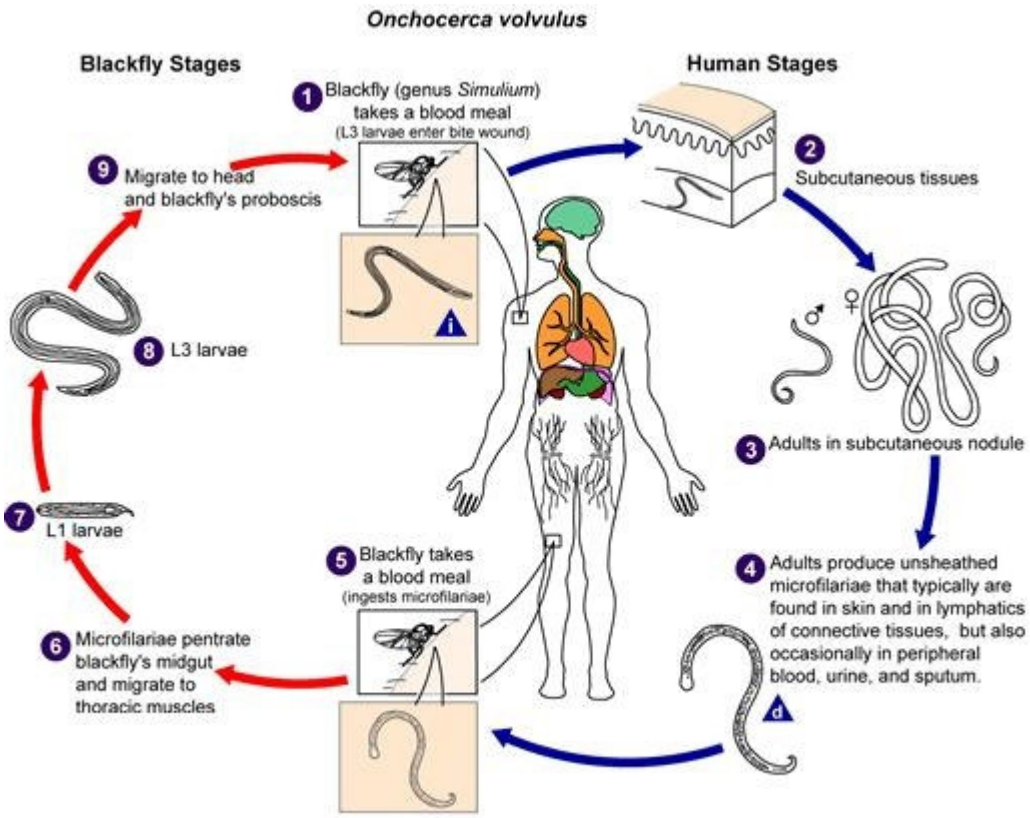

Figure 3 Life cycle showing different stages of *Onchocerca volvulus*.

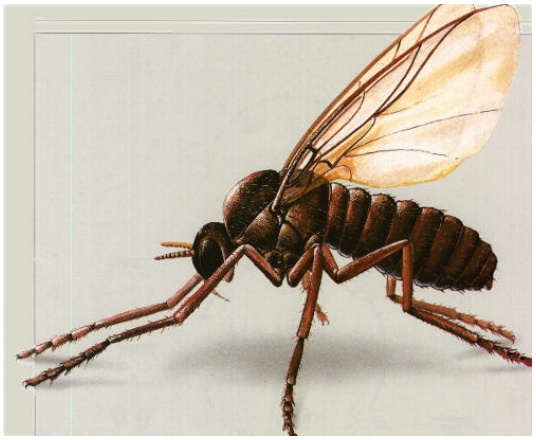

Figure 4 Adult black fly (*Simulium damnosum*).

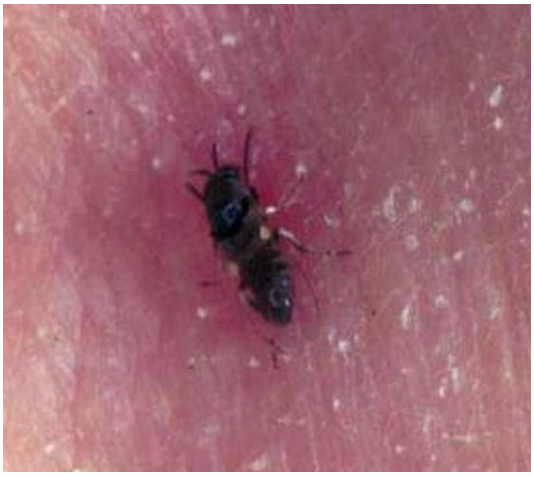

Figure 5 A black fly biting human skin.

and pupae usually attach themselves to rocks and vegetation in fast flowing streams and rivers. For this reason they can be very troublesome in mountainous areas. The saliva injected while feeding causes swelling and soreness that may persist for days

(**Figure 5**). They belong to the order *Diptera* (Flies), to the family *Simuliidae*. It is only the females that feed on blood with males being nectar feeders. The family contains approximately 1500 species and four genera.

Black flies are important vectors of various pathogens, the most important of which is the filarial worm *O. volvulus* which causes river blindness in humans. The main vector in most of Africa is *Simulium damnosum;* in Ethiopia, Uganda, Tanzania, and the Democratic Republic of the Congo, *S. neavei* is common. In the Americas, the principal vectors are *S. metallicum, S. ochraceum,* and *S. exiguum*. Some vectors bite humans rather exclusively, whereas others are zoophilic to varying degrees. Animal reservoirs of *O volvulus* have not been found.[4, 8-11]

Pathophysiology [5,7-10]

When a black fly takes a blood meal from an infected human, it also ingests onchocercal microfilariae in the skin. Surviving microfilariae in the black fly burst through the peritrophic membrane formed by the blood meal, invade the midgut, and advance to the thoracic muscles. The differentiation of these microfilariae into L1 larva begins in muscle within 28 hours after the blood meal. The first molt produces L2 larva within 96 hours, followed by the second molt, which produces L3 larva by day 7. The infective L3 larva migrates to the insect's head and mouth for future deposition into human skin during the next blood meal. After L3 larva are transmitted to human skin, those that survive molt within 1 week to form L4 larva. Their development into male and female forms is completed by 1-3 months. The adult worms reside in the deep dermis and fascial planes. Thick, fibrous, subcutaneous nodules called onchocercomas are formed as the result of the development of scar tissue around the adult worms. They typically contain 2-3 female adults and 1-2 male adults and are surrounded by eosinophils and lymphocytes (**Figure 6**). Adult worms isolated in nodules are not directly harmful to the patient. Their progeny, which are released from the nodules, are responsible for most of the damage related to onchocerciasis. Within 10-12 months after the initial infection, adult female worms start producing microfilariae, which have an average lifespan of 6 months to 2 years. The reproductive life of the adult averages 9-11 years. During this time, female worms may release 1300-1900 microfilariae per day. The maximal production of offspring occurs during the first 5 years of the worm's reproductive life, after which this activity declines in a linear fashion. The microfilariae released from the nodules easily traverse the skin and connective tissue. The subepidermal lymphatics and the anterior chamber of the eye are the most common migration sites. The microfilariae can also be found in the blood, cerebrospinal fluid, urine, and internal organs. More than 100 million microfilariae may be present in severely affected individuals.[5,7-10]

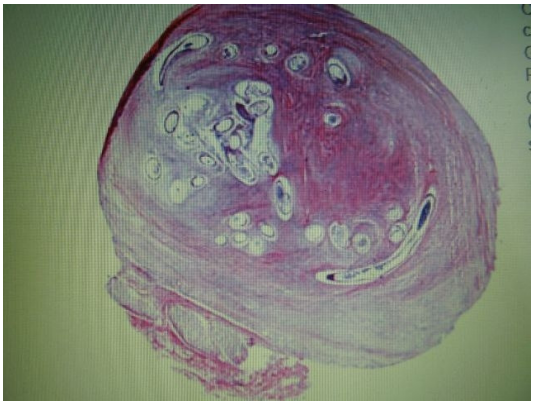

Figure 6 Cross section of a subcutaneous nodule showing numerous sections of adult worms.

Epidemiology

Human onchocerciasis is a major public health problem in many parts of the world and is found in both the Old and New World but about 96% of all cases are in Africa and mostly in Western Africa (**Figure 7**). Of the 36 countries where the disease is endemic, 30 are in sub-Sahara Africa (plus Yemen) and six are in the Americas. Indeed, important foci exist also in Mexico, Guatemala, Venezuela and Ecuador.[12] In 1995, an estimated 123 million people were at risk of contracting the disease according to the World Health Organization Expert Committee on Onchocerciasis. Another 17-18 million people were estimated to be infected. The disease is most severe along the major rivers in 30 countries across the northern, western and central areas of the African continent. Nigeria, Ethiopia, Cameroon, Uganda, Democratic Republic of the Congo, Ghana, Sierra Leone, Guinea, Senegal, Ivory Coast and Liberia have the largest number of infected people.[12,13] Onchocerciasis is uncommon in the United States. All reported cases result from the immigration of individuals from endemic areas. In Latin America, onchocerciasis can be found in Brazil, Venezuela, Colombia, Ecuador, and Guatemala, as well as in the southern mountainous states of Chiapas and Oaxaca in Mexico. In 1995, an estimated 270,000 people were blinded and another 500,000 had severe visual impairment as a result of the disease. A multicountry study showed that more than 30% of the population in endemic areas had onchocercal dermatitis. In a survey of skin disease in 7 endemic sites in 5 African countries, 40-50% of adults reported troublesome itching. Blindness is not

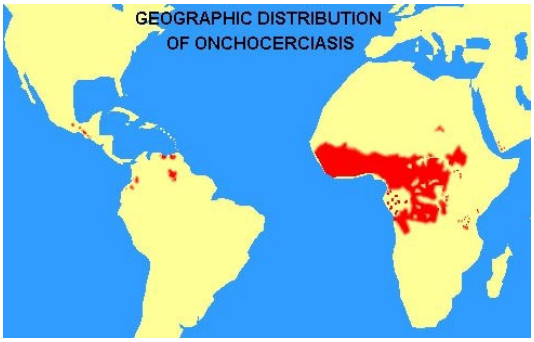

Figure 7 Geographical map showing Central and West Africa as worst affected regions in the world.

associated with excess mortality. However, increasing microfilarial load is associated with mortality in both males and females. The disease generally affects more men than women. This trend is partially attributed to increased exposures in men, which are related to the occupational risk in farmers, fishermen, and other workers. The prevalence of onchocerciasis is lowest in individuals aged 0-10 years. Afterward, the prevalence sharply increases, with a peak in individuals aged 20-30 years.[12-19]

Clinical spectrum

A large and variable spectrum of clinical disease can be seen but skin disease and eye lesions induced by inflammatory reactions to migrating larvae (microfilariae) are the major manifestations.

Systemic manifestations

Patients are asymptomatic in about 10% of cases. Localized inflammatory responses to dead or dying microfilariae are almost entirely responsible for the clinical manifestations of the disease. In a severely infected person, 100,000 or more microfilariae die each day. The earliest symptoms are fever, arthralgia, and transient

urticaria involving the trunk and face. Systemic manifestations of onchocerciasis may include weight loss, musculoskeletal pain, inguinal hernias, and systemic embolization of microfilariae. Many patients in endemic regions have associated the disease with secondary amenorrhea, lactation difficulties, spontaneous abortion, infertility, and sterility. However, these associations have never been proven.[13,14,18,19]

Dermatological presentations [5,20-28]

Onchocercal dermatitis is the most common symptom of the disease. Its initial manifestations, which can occur anywhere on the body, include itching, scratching, and alterations in skin pigmentation. Pruritus may be intermittent and mild, continuous and severe, or may be altogether absent. A maculopapular rash may appear anywhere on the body at any time. The papules may be small and densely packed or large and separated. The maculopapular rash is often associated with severe pruritus. Excess scratching may lead to bleeding, ulceration, and secondary infection (a condition West Africans call craw-craw). The following is a summary of the clinical classification system for onchocercal dermatitis, which Murdoch *et al*.6 developed to standardize and facilitate the collection of data worldwide:

Acute papular onchodermatitis (APOD) is characterized by a solid, scattered, pruritic papular rash (**Figure 8**). Vesicles or pustules at the apex may or may not be present. The obliteration of the skin creases due to edema also may or may not be present.

Chronic papular onchodermatitis (CPOD) is a scattered, pruritic, hyperpigmented, and flat-topped papulomacular rash. The diameter of the papules is at least 3 mm, with or without excoriations (**Figure 9**).

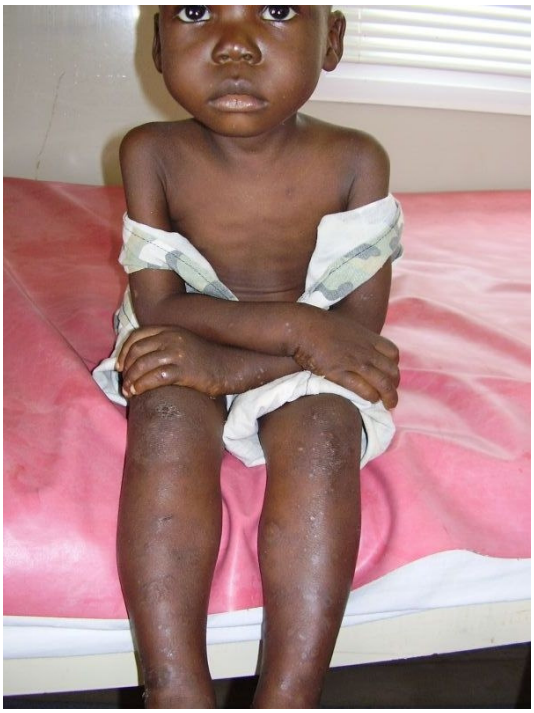

Figure 8 Acute papular onchodermatitis in a young child.

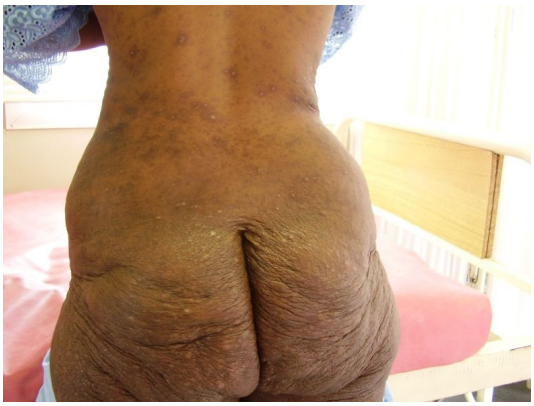

Figure 9 Chronic papular onchodermatitis in a young female.

Lichenified onchodermatitis (LOD) is characterized by raised, discrete, pruritic, and hyperpigmented papulonodular plaques associated with lymphadenopathy. The lesions may be confluent, with or without the presence of excoriations (**Figure 10**).

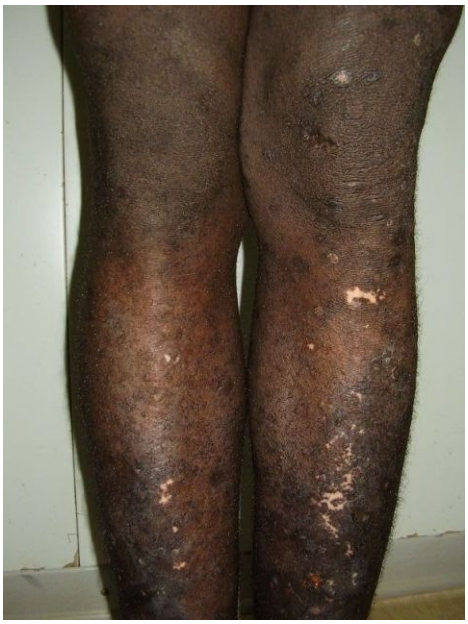

Figure 10 Lichenified onchodermatitis in a young male.

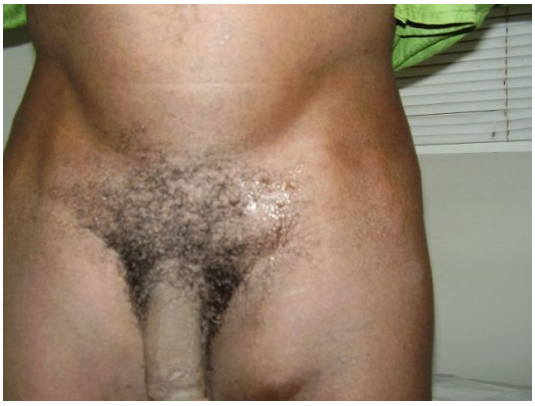

Figure 11 Lymphadenopathy in left inguinal region giving rise to hanging groin affect.

Atrophy (ATR) involves wrinkled and dry skin. Firmly pressing the edge of a finger along the skin reveals additional fine wrinkles. In patients younger than 50 years, atrophy is considered as a significant abnormality.

Depigmentation is characterized by areas of incomplete pigment loss, with associated islands or spots of normal pigment surrounding hair follicles. Leopard skin is similar, except that it is characterized by a complete loss of pigment, with islands or spots of normally pigmented skin around the follicles.

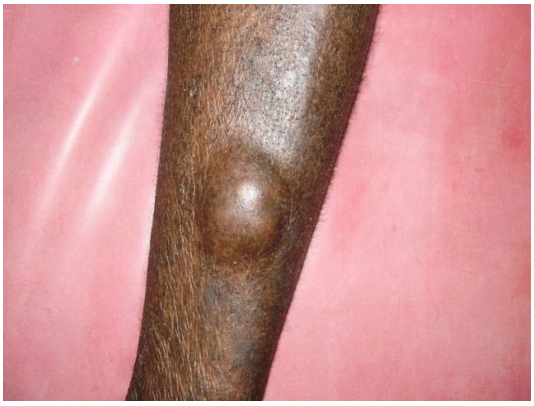

Figure 11 Onchocercoma; subcutaneous nodule over shin area.

Lymphadenopathy is characterized by lymph nodes 1 cm or larger in diameter. They may or may not be tender (**Figure 10)**.

Hanging groin (HG) involves the folds of inelastic, atrophic skin in the inguinal areas. The condition may be unilateral or bilateral, and it may involve enlarged lymph nodes.

Lymphedema (LYM) is characterized by edema of a limb or external genitalia.

Onchocercomas are fibrous, subcutaneous nodules containing adult worms. These nodules are generally located over bony prominences, and they are easily palpable (**Figure 11**). The number of palpable nodules is not correlated with the microfilarial load or the severity of disease. In Africa, the nodules are often observed along the iliac crests, ribs, greater trochanters, and ischial tuberosities. Juxta-articular areas, such as the knees, elbows, patella, and scalp, may also have nodules. In the American forms, nodules are fewer and have a greater tendency to be located on the

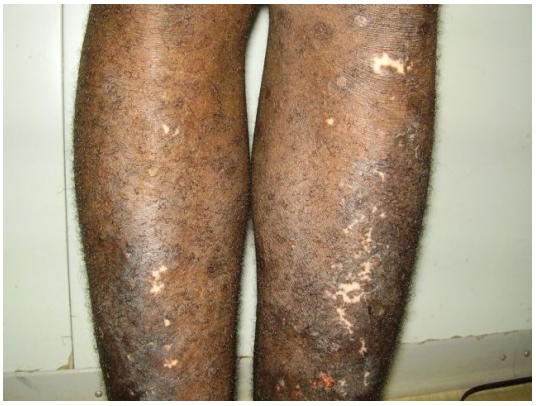

Figure 12 Chronic onchodermatitis with Leopard spotting over lower legs.

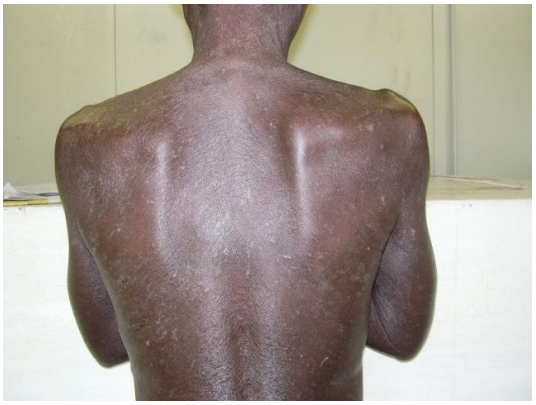

Figure 13 Chronic onchodermatitis producing a Lizard skin appearance in a young patient.

scalp. In patients with scalp nodules, the risk of ocular complications is generally higher than that of patients without scalp nodules. Onchocercomas are less common in the Yemen form of the disease than in other forms.

Sowda, a severe form of dermatitis first described in Yemen, is associated with an active delayed hypersensitivity response. Many patients are travelers or temporary workers in nonendemic areas. These patients have dark, thickened, intensely pruritic skin with papules. The regional lymph nodes are soft, nontender, and enlarged. Sowda is usually localized to a single lower extremity. A less common, more generalized form can involve both lower extremities or other parts of the body. Patients have either focal swelling or a more diffuse LYM. Skin-snips do not usually contain microfilariae. Sowda may also be found in patients in West Africa, Ethiopia, Sudan, Cameroon, Venezuela, and Ecuador.

Leopard skin is a characteristic finding in older patients. It involves depigmentation of the pretibial areas of the lower extremities (**Figure 12**). This pattern is initially seen as discrete depigmented macules, with sparing of the hair follicles. Later, the macules may become confluent, involving a large area of the anterior portion below the knee. This pattern can sometimes be seen in the groin or lower abdomen as well.

Lizard skin is the name given to the generalized hyperpigmented and ashy appearance of the skin resulting from chronic onchodermatitis (**Figure 13**).

Adenolymphocele is a severe degenerative condition in older individuals. The inguinal and femoral lymph nodes become progressively enlarged and fibrotic, leading to lymphatic obstruction. Concomitantly, progressive destruction of elastic fibers leaves the skin thinned and wrinkled. The atrophied skin tends to hang in apron-like folds under the weight of the accumulating lymphedematous tissue. This condition is more common in men than in women.

Ocular manifestations [18-20]

Ocular manifestations of onchocerciasis are late, serious reactions that occur in about 5% of affected persons. Infection of the cornea produces punctate keratitis in the areas around dead microfilariae. This condition eventually clears when the inflammation

settles. Severe and prolonged infection over a number of years is likely to produce sclerosing keratitis, iridocyclitis, and uveitis. Permanent visual impairment, secondary glaucoma, or blindness (**Figure 14**) is often the result. Posterior segment changes may coexist with anterior segment lesions. The changes are caused by inflammation around microfilariae that invade the retina via the posterior ciliary vessels. Choroidoretinal lesions are common around the optic disk or on the outer portion of the macula. Active optic neuritis is a major cause of blindness in areas with endemic disease.[18-20]

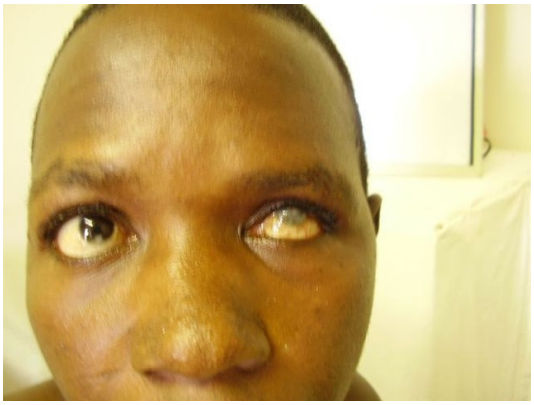

Figure 14 River blindness produced by microfilariae infiltrating cornea and other eye segments and ultimately producing blindness.

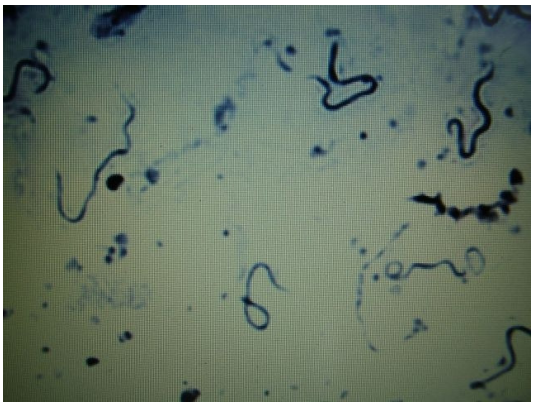

Figure 15 Impression smear of skin snip showing heavy infection with *Onchocerca volvulus* (Giemsa stain).

Diagnosis [29-35]

Skin snips

The traditional standard diagnosis of onchocerciasis is based on the acquisition of 3- to 5-mg skin snips from an affected area. These snips are immediately immersed in sodium chloride solution and placed under a microscope. The emerging microfilariae are then counted (**Figure 15**). This method is specific, and it has been most accurate. However, the use of skin snips is not sensitive for detecting early or mild infections, and this method is becoming increasingly unacceptable to people in endemic communities because of its invasiveness.

Mazzotti test

Now seldom used, this test involves the administration of 6 mg of diethylcarbamazine (DEC). DEC inhibits neuromuscular transmission in nematodes. Within 2 hours, a positive result produces pruritus and, sometimes, intense inflammation in the areas of dying microfilariae. Other possible effects such as vomiting, conjunctivitis, albuminuria, hypotension, and sudden death (rare) limit its usefulness. Oral DEC was formerly used in treatment of the disease.

DEC patch test *(Mazzotti patch test)*

It involves a topical application of DEC, which produces a local reaction to dying microfilariae at the patch site. This noninvasive test is specific, but it is less sensitive than the skin-snip test. In future, this test may be more valuable in detecting the recrudescence of infection in onchocerciasis-free zones than in diagnosing the disease.

Enzyme-linked immunosorbent assay (ELISA)

It requires only a finger-stick sample, is more sensitive and less invasive than skin-snip tests. This test is used to recognize specific microfilarial antigens. However, ELISA results cannot be used to distinguish past and current infections, a considerable problem in endemic areas.

Polymerase chain reaction (PCR)

PCR amplifies repetitive parasite DNA sequences in skin-snip specimens. Compared with skin-snip tests, this method has greater sensitivity in patients with low-level infections. The major disadvantage of PCR is its high cost.

Rapid-format antibody card tests are being developed to diagnose onchocerciasis. In these tests, serum samples can be used to detect antibodies, such as immunoglobulin G4 (IgG4) antibodies to recombinant *O volvulus* antigen Ov16. Tests for additional antibodies are currently under development. Initial studies show good sensitivity and specificity in small numbers of samples and controls using various methods. Recently, an oncho-C27 antigen detection dipstick assay using urine and tears has been developed. The test can be completed in as short as 3 hours, and the strips maintain reactivity when kept at room temperature for up to 8 months. Sensitivity and specificity were good in an initial study.

Microfilariae can often be directly observed by means of **slit lamp examination** of the cornea and anterior chamber of the eye.

Histology [11,25]

In early untreated cases, tissue biopsy samples may show a mild chronic inflammatory infiltration; eosinophils, lymphocytes, and histiocytes may surround the microfilariae. Microfilariae are often present without a surrounding cellular reaction. Later cases show hyperkeratosis, parakeratosis, tortuous dermal vessels, dilated lymphatics, and pigment incontinence. An increased number of dermal fibroblasts leads to perivascular fibrosis. In more advanced cases, hyalinized scar tissue replaces the collagen and elastic fibers in the dermis.

The microfilariae have pointed tails, elongated posterior nuclei, paired anterior nuclei, and large spaces between the tip or tail and the first nuclei. They lack sheaths. *Onchocercomas* are made up of an outer vascular fibrous stroma embedded with groups of perivascular leukocytes. The inner layer is composed of hyaline connective tissue intermingled with coiled adult worms. A dense cellular infiltrate composed of eosinophils, lymphocytes, macrophages, and giant cells surrounds the worm. The coiled appearance of the worm, the presence of microfilaria in gravid females, and the presence of a gut help in identifying the worm.

Treatment [36-46]

Biochemical pathways in parasites are sufficiently different from those in the human host to allow selective interference by using chemotherapeutic agents in relatively small doses. The treatment of onchocerciasis was revolutionized with the introduction of ivermectin in 1987. *Ivermectin* is now the drug of choice in the treatment of onchocerciasis. *Suramin* may

be indicated for use only if ivermectin cannot adequately control the disease. *Amocarzine* has not been shown to be effective in treating onchocerciasis. Both suramin and amocarzine are capable of destroying adult worms. DEC (diethylcarbamazine) therapy is no longer recommended.

Ivermectin therapy does not have the adverse reactions of DEC, and it eliminates the need for 6 weekly injections of suramin. The treatment is suitable for both clinical use and mass distribution in endemic areas. Ivermectin is a compound derived from the bacterium *Streptomyces avermitilis*. The drug causes nematode paralysis by impairing neuromuscular function. Ivermectin not only prevents ocular disease but also improves and eliminates the skin disease. A single dose of 150 µg/kg clears the microfilariae from the skin for several months. It temporarily decreases the release of microfilariae, but it does not kill adult worms. Adverse reactions are similar to the responses of the body to dying microfilariae, but the intensity and rate of development are increased. These include fever, edema, pruritus, lymphadenitis, and body pains. The frequency and duration of ivermectin therapy still is being debated. As many as 33% of patients in nonendemic areas are cured with only 1 dose of ivermectin, but most patients require additional therapy. *In endemic areas*, the drug is given from every 3 months to every year, depending on the degree of symptoms, cost constraints, and patient compliance. *In nonendemic areas*, a reasonable approach is the administration of a single dose of ivermectin. Depending on the patient's skin symptoms, the dose can be repeated every 3-6 months as needed.

Nodulectomy has been a traditional form of surgical therapy in Mexico and Guatemala. Healthcare workers, moving from village to village, remove nodules from patients especially nodules in the head. This surgical approach may reduce the number of microfilariae that enter the eye, but no strong evidence supports its effectiveness in preventing blindness. The removal of nodules may be a valuable adjunct in patients treated with ivermectin. Recently[46] a treatment regimen of doxycycline for 4 weeks, accompanied by two doses of ivermectin has been found effective (based on bacterial endosymbionts of *O. volvulus).* Onchocerciasis patients are in a delicate immunological balance with their parasites, and host responses are clearly integral to the clinical outcome. Treatment with filariacides disturbs this balance. It must be emphasized that it is the rule rather than the exception for a treated individual infected with onchocerciasis to experience some form of clinical discomfort or systemic change after treatment with antifilarial drugs. Remarkably few serious reactions are reported with the use of ivermectin. These include nausea, headache, minor fever and dermatological responses associated with the presence of dying microfilaria in the skin; pruritic injection of the conjunctiva has also been reported. These Mazzotti-type reactions are similar in many respects to those seen with other microfilariacidal agents, such as DEC, although lesser in extent and intensity than with the latter drug.[45-47]

Prevention

The Onchocerciasis Control Programme (OCP) began in 7 West African countries in

1974. The major strategy for interrupting transmission of onchocerciasis was vector control. Hand spraying of black fly breeding sites along rivers, combined with the aerial distribution of larvicide, has been successful in this region. To prevent reinvasion by black flies, parts of 4 other countries were also included in 1986. Onchocerciasis is no longer a public health problem in those 11 countries. The introduction of ivermectin in 1987 allowed assistance to be extended to other areas. Merck & Co decided to provide the drug, at no cost, in whatever quantities were needed, for as long as it was needed. Community-based distribution programs were established in endemic areas to administer the drug 1-2 times per year, even to remote villages. Encouraged by successes with the OCP and ivermectin, the World Bank launched the African Programme for Onchocerciasis (APOC) in the remaining areas of Africa in 1995. The goal of the program is to eliminate the disease as a public health issue in these areas by 2007. Unlike the OCP, the APOC uses the community-based distribution of ivermectin as its primary control strategy. The Onchocerciasis Elimination Program for the Americas (OEPA), a similar program, also aims to eliminate onchocerciasis by 2007 in the Americas. These programs face many challenges in the future. Whether or not successful control of the disease can be accomplished without the use of vector control has yet to be determined. The organization, effectiveness of community control programs, and their funding, may need to be addressed.[47-52]

Prognosis

The prognosis for onchocerciasis is good in patients who receive proper therapy before irreversible eye lesions develop. Ivermectin is effective in reducing the skin manifestations of the disease; it thereby reduces morbidity and improves the patient's quality of life.[12,13,16,53]

References

1. Manson P. Filaria Volvuloxus. In Hygiene and Diseases of Warm Climates. (Davidson AH.). Y.J. Pentland, London.p.1016.1893.
2. O'Neill J. On the presence of filarial in "Craw Craw". *Lancet* 1875; **1**: 265-6.
3. Robles R. Enfermidad nueva en Guatemala. *Juventad Med* 1917; 17: 97-115.
4. Blacklock DB. The insect transmission of Onchocerca volvulus (Leukart 1893.) The cause of worm nodule in man in Africa. *BMJ* 1927; **1**: 129-33.
5. Maso MJ, Kapila R, Schwartz RA *et al.* Cutaneous onchocerciasis. *Int J Dermatol* 1987; **26**: 593-6.
6. 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.
7. Duke BO. The population dynamics of *Onchocerca volvulus* in the human host. *Trop Med Parasitol* 1993; **44**: 61-8.
8. Buttner DW, von Laer G, Mannweiler E, Buttner M. Clinical, parasitological and serological studies on onchocerciasis in the Yemen Arab Republic. *Tropenmed Parasitol* 1982; **33**: 201-12.
9. Dozie IN, Onwuliri CO, Nwoke BE, Onwuliri VA. Clinical and parasitological aspects of onchocercal skin diseases in Nigeria. *Trop Doct* 2005; **35**: 142-4.
10. Trpis M. Consequences of vector behavior in epidemiology of onchocerciasis on the firestone rubber plantation in Liberia. *Am J Trop Med Hyg* 2006; **74**: 833-40.

11. Krueger A. Guide to blackflies of the Simulium damnosum complex in eastern and southern Africa. *Med Vet Entomol* 2006; **20**:60-75.
12. Levine R and the What Work Working group. Millions Saved, Proven Safe in Global Health, 6 case, Controlling Onchocerciasis in Sub-Saharan Africa. Washington DC: Centre for Global Development; 2004. p. 57-64.
13. Richards FO, Miri E, Meredith S, *et al*. Onchocerciasis. *Bull World Health Organ* 1998; **76** (Suppl 2): 147-9.
14. Burnham G: Onchocerciasis. *Lancet* 1998; **351**: 1341-6.
15. Hailu A, Balcha F, Birrie H *et al*. Prevalence of onchocercal skin disease and infection among workers of coffee plantation farms in Teppi, Southwestern Ethiopia. *Ethiop Med J* 2002; **40**: 259-69.
16. Brooker S, Clements AC, Bundy DA. Global epidemiology, ecology and control of soil-transmitted helminth infections. *Adv Parasitol* 2006; **62**: 221-61.
17. Michael E, Bundy DAP, Grenfell BT. Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology* 1996, **112**: 409-28.
18. Murdoch ME, Asuzu MC, Hagan M *et al*. Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. *Ann Trop Med Parasitol* 2002; **96**: 283-96.
19. Kale OO. Onchocerciasis: the burden of disease. *Ann Trop Med Parasitol* 1998; **92**: S101-15.
20. Stingl P. Onchocerciasis: clinical presentation and host parasite interactions in patients of Southern Sudan. *Int J Dermatol* 1997; **36**: 23-8.
21. Connor DH, Williams PH, Helwig EB, Winslow DJ. Dermal changes in onchocerciasis. *Arch Pathol* 1969; **87**: 193-200.
22. Hagan M. Onchocercal dermatitis: clinical impact. *Ann Trop Med Parasitol* 1998; **92**: S85-96.
23. Lazarov A, Amihai B, Sion-Vardy N. Pruritus and chronic papular dermatitis in an Ethiopian man. Onchocerciasis (chronic papular onchodermatitis). *Arch Dermatol* 1997; **133**: 382-3, 385-6.
24. Meyers WM, Neafie RC, Connor DH. Onchocerciasis: invasion of deep organs by Onchocerca volvulus. *Am J Trop Med Hyg* 1977; **26**: 650-7.
25. Vernick W, Turner SE, Burov E, Telang GH. Onchocerciasis presenting with lower extremity, hypopigmented macules. *Cutis* 2000; **65**: 293-7.
26. Kipp W, Bamhuhiiga J. Onchodermal skin disease in a hyperendemic onchocerciasis focus in western Uganda. *Am J Trop Med Hyg* 2002; **67**: 475-9.
27. Mahe E, Torchet MF, Chretiennot C *et al.* Papular filariasis. *Arch Pediatr* 2001; **8**: 604-7.
28. Richard-Lenoble D, al Qubati Y, Toe L *et al.* Human onchocerciasis and "sowda" in the Republic of Yemen. *Bull Acad Natl Med* 2001; **185**: 1447-59; discussion 1459-61.
29. Boatin BA, Toe L, Alley ES *et al*. Diagnostics in onchocerciasis: future challenges. *Ann Trop Med Parasitol* 1998; **92**: S41-5.
30. Ayong LS, Tume CB, Wembe FE *et al*. Development and evaluation of an antigen detection dipstick assay for the diagnosis of human onchocerciasis. *Trop Med Int Health* 2005; **10**: 228-33.
31. Rodríguez-Pérez MA, Domínguez-Vázquez A, Méndez-Galván J *et al*. Antibody detection tests for *Onchocerca volvulus*: comparison of the sensitivity of a cocktail of recombinant antigens used in the indirect enzyme-linked immunosorbent assay with a rapid-format antibody card test. *Trans R Soc Trop Med Hyg* 2003; **97**: 539-41.
32. Stingl P, Ross M, Gibson DW *et al.* A diagnostic "patch test" for onchocerciasis using topical diethylcarbamazine. *Trans R Soc Trop Med Hyg* 1984; **78**: 254-8.
33. Toe L, Adjami AG, Boatin BA, Back C, Alley ES, Dembele N, et al. Topical application of diethylcarbamazine to detect onchocerciasis recrudescence in west Africa. *Trans R Soc Trop Med Hyg* 2000; **94**: 519-25.
34. Toe L, Boatin BA, Adjami A *et al. Onchocerca volvulus* infection by O-150 polymerase chain reaction analysis of skin scratches. *J Infect Dis* 1998; **178**: 282-5.
35. Weil GJ, Steel C, Liftis F *et al.* A rapid-format antibody card test for

diagnosis of onchocerciasis. *J Infect Dis* 2000; **182**: 1796-9.
36. Baraka OZ, Mahmoud BM, Ali MM *et al.* Ivermectin treatment in severe asymmetric reactive onchodermatitis (sowda) in Sudan. *Trans R Soc Trop Med Hyg* 1995; **89**: 312-5.
37. Burnham G. Ivermectin treatment of onchocercal skin lesions: observations from a placebo-controlled, double-blind trial in Malawi. *Am J Trop Med Hyg* 1995; **52**: 270-6.
38. Awadzi K, Opoku NO, Attah SK *et al.* The safety and efficacy of amocarzine in African onchocerciasis and the influence of ivermectin on the clinical and parasitological response to treatment. *Ann Trop Med Parasitol* 1997; **91**: 281-96.
39. 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.
40. Pacque M, Elmets C, Dukuly ZD *et al.* Improvement in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991; **90**: 590-4.
41. Mackenzie CD, Geary TG, Gerlach JA. Possible pathogenic pathways in the adverse clinical events seen following ivermectin administration to onchocerciasis patients. *Filaria J* 2003; **2**: S1-S5.
42. Ogbuagu KF, Eneanya CI. A multicentre study of the treatment on onchocercal skin clinical findings effect of Mectizan disease: *Ann Trop Med Parasitol* 1998; **92**: 139-45.
43. Awadzi K, Edwards G, Duke BO *et al.* The co-administration of ivermectin and albendazole-safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol* 2003, **97**: 165-78.
44. Keiser PB, Reynolds SM, Awadzi K *et al.* Bacterial endosymbionts of *Onchocerca volvulus* in the pathogenesis of posttreatment reactions. *J Infect Dis* 2002, **185**: 805-11.
45. Ali MM, Baraka OZ, AbdelRahman SI *et al.* Immune responses directed against microfilariae correlate with severity of clinical onchodermatitis and treatment history. *J Infect Dis* 2003; **187**: 714-7.
46. Debrah AY, Mand S, Marfo-Debrekyei Y *et al.* Assessment of microfilarial loads in the skin of onchocerciasis patients after treatment with different regimens of doxycycline plus ivermectin. *Filaria J* 2006; **5**: 1-9.
47. Richards F, Hopkins D, Cupp E. Programmatic goals and approaches to onchocerciasis. *Lancet* 2000; **355**: 1663-4.
48. Evans BD, Gelband H, Vlassoff C. Social and economical factors and the control of lymphatic filariasis a review. *Acta Trop* 1993, **53**: 1-26.
49. Ottesen EA, Duke BOL, Karam M, Behbehani K. Strategies and tools for the control/elimination of lymphatic filariasis. *Bull World Health Organ* 1997, **75**: 491-503.
50. Hoerauf A. Control of filarial infections: not the beginning of the end, but more research is needed. *Curr Opin Infect Dis* 2003, **16**: 1-8.
51. Dadzie Y, Neira M, Hopkins D. Final report of the Conference on the eradicability of onchocerciasis. *Filaria J* 2003, **2**: 2-10.
52. Abiose A, Homeida M, Liese B *et al.* Onchocerciasis control strategies. *Lancet* 2000, **356**: 1523-4.
53. Little MP, Breitling LP, Basáñez MG *et al.* Association between microfilarial load and excess mortality in onchocerciasis: an epidemiological study. *Lancet* 2004; **363**: 1514-21.