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Case Report

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Neglected Tropical Diseases: Treatment of Dermatological Manifestation of Filariasis with Combination Regimen of Albendazole, Ivermectin, and Loratadine: A Case Report from a Suburban Community in Nigeria

Osede Ignis Iribhogbe*
Department of Pharmacology and Therapeutics, College of Medicine,
Ambrose Alli University Ekpoma, Edo State, Nigeria.

***Correspondence:** osedeignis@gmail.com

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Abstract
Threadlike filarial nematodes have been identified as the causative agent of filariasis. Cutaneous filariasis is caused primarily by *Loa loa, Onchocerca volvulus*, and *Mansonella streptocerca*. These parasites occupy the subcutaneous layer of the skin. However, other filarial parasites are usually associated with varying degrees of dermatological manifestations. In the present discourse, two cases of cutaneous filariasis were diagnosed in two female patients (21 and 40 years old, respectively) in Remitch Clinic and Maternity located in a nonriverine community in Ekpoma, Edo State, Nigeria. In this report, patients with body mass index (BMI) of 18.97 and 23.45 kg/m^2, respectively, presented on two different occasions at least 6 months apart with hyperpigmented skin lesions in the upper and lower limbs, respectively. There was associated intense pruritus with no evidence of lymphadenopathy and lymphoedema. Following laboratory confirmation of filariasis, the patients were placed on a single oral dose combination of albendazole (400 mg) + ivermectin (200 mcg/kg), while oral doses of loratadine 10 mg were administered daily for 5 days. Patients were carefully followed up for 6 weeks during which recession of the lesion and untoward reactions were monitored. It was observed that within 6 weeks of treatment, there was a dramatic recession of skin lesion. Adverse effect reported from use of the combination was mild. This case report revealed that cutaneous filariasis is not an uncommon presentation of filariasis infestation in Nigeria. The report also validates the safety and efficacy of the combination in the management of cutaneous manifestation of the disease.

Keywords: Filariasis; Efficacy; Safety.

1. INTRODUCTION

Millions of people living in tropical countries are often affected by pathogenic filarial parasites. Most of these infestations are associated with significant dermatological manifestations. Several parasites, such as *Wuchereria bancrofti, Brugia malayi, Brugia timori, Onchocerca volvulus, and Loa loa*, are known to be related to dermatological lesions in humans [1]. However, *Mansonella streptocerca* does not present a significant public health threat. Filarial worms of the genus *Dirofilaria* and zoonotic *Onchocerca* species, usually parasitic in animals, occasionally penetrate a human host and undergo incomplete growth, which may result in cutaneous or subcutaneous manifestation of the disease. Worldwide, up to 120 million people are infected, with 40 million inhabitants incapacitated by the disease [2, 3]. The affected population is distributed mainly in the tropics and subtropics. This includes areas that span across Southeast Asia, South America, Africa, and the Pacific islands. Research has shown that the parasitic disease is a significant cause of debilitating illness and is the second most common cause of long-term deformity globally [2].

Following the bite of an appropriate vector, filarial nematodes penetrate the human body in their third larval stage. Adult worms, which reside in body tissues, produce early larval forms called microfilaria, which are released into the bloodstream of the host. The circulating microfilaria get into the vector after being ingested during a blood meal (Figure 1). They then undergo development into infective larval forms that can be transmitted to a fresh host.

Infected individuals can be classified as being "microfilaraemic" or "amicrofilaraemic," based on the presence or absence of microfilaria in their peripheral blood. For individuals who are microfilaraemic, diagnosis of filariasis is made principally through the observation of microfilaria in peripheral blood smears. However, in amicrofilaraemic cases, a diagnosis is based on clinical observations and the presence of circulating blood antigens [4]. Most of the infestation caused by the parasite is usually associated with Rickettsial-like bacteria known as *Wolbachia* spp. [5-7]. This mainly initiates innate inflammation with attendant inflammatory reactions.

2. CASE REPORTS

2.1. Case Report 1

A 40-year-old woman (Table 1) resident in Esan Central Local Government Area of Edo State presented with a 2-month history of a hyperpigmented skin lesion in the right foot, which was associated with intense pruritus that was usually worse at night,

Figure 1: Life cycle of *Wuchereria bancrofti* (http://www.dpd.cdc.gov/dpdx).

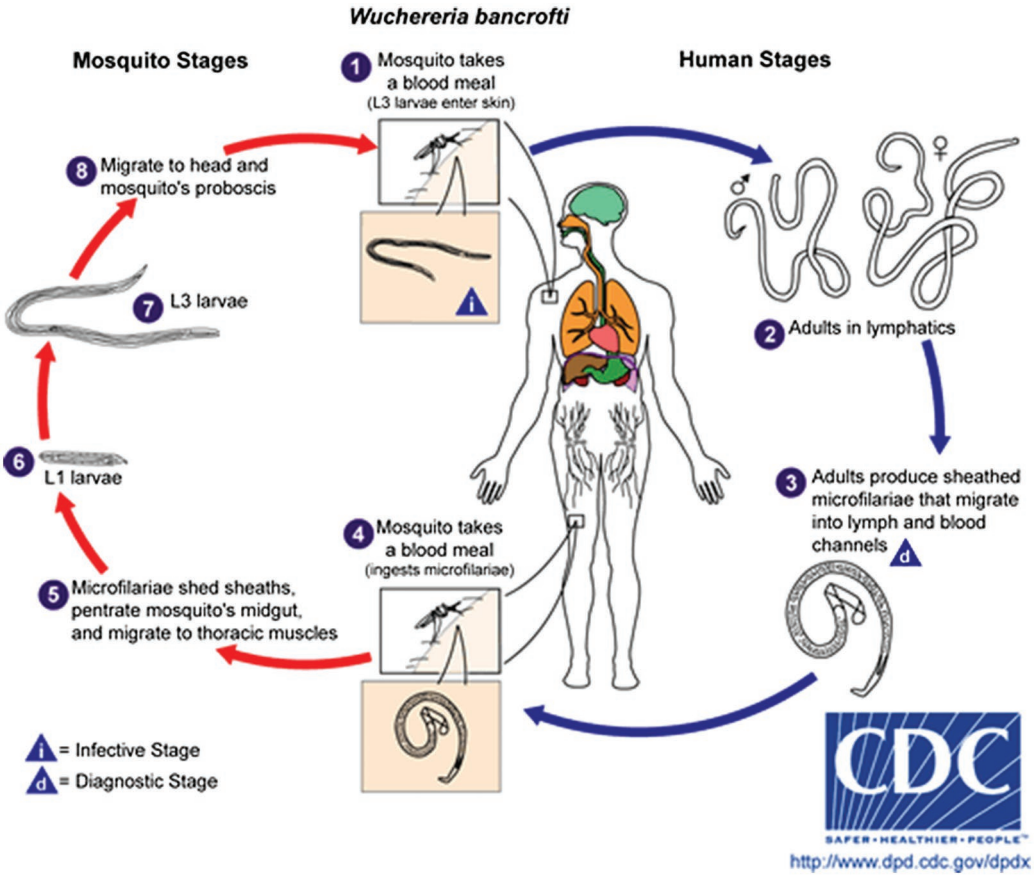


Table 1: Baseline characteristics/laboratory findings in patients (Cases 1 and 2).

Patients	Age (years)	BMI (kg/m²)	Giemsa-stained film		Wet mount (serum microfilaria)	Skin snip (microfilaria)
			Plasmodium falciparum	Microfilaria		
Case 1	21	18.97	+ (500/UL)	–	–	*O. volvulus*
Case 2	40	23.45	–	–	*W. bancrofti*	–

Table 2: Hematological findings in Cases 1 and 2.

Patients	PCV (%)	Hb (g/dl)	TWBC / mm³	Neutrophils (%)	Lymphocytes (%)	Eosinophil (%)	Monocyte (%)	Basophil (%)
Case 1	37	12.3	6,500	36	63	0	1	0
Case 2	30	10.3	4,800	38	60	1	1	0

PCV, packed cell volume; TWBC, total white blood cell count.

Table 3: Electrolyte/urea/creatinine, urine microscopy and liver function of the patients.

Patients	Urine		Electrolytes		Urea (10-55) mg/dl	Creatinine (0.7-1.4) mg/dl	Liver function test				
	Appearance	Wet mount microscopy	Na+ (135-140) mmol/l	K+ (3.5-5.3) mmol/l			TB (0.1-1.1) mg/dl	CB ≤0.5 mg/dl	AST ≤12 IU/l	ALT ≤12 IU/l	ALP (9-35) IU/l
Case 1	Amber	–	139	3.8	12	0.9	0.6	0.3	13	10	37
Case 2	Amber	–	135	3.6	13	0.7	0.4	0.4	15	9.1	28

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CB, conjugated bilirubin; TB, total bilirubin.

Figure 2: Localized erythematous macule in the early stage of infestation.

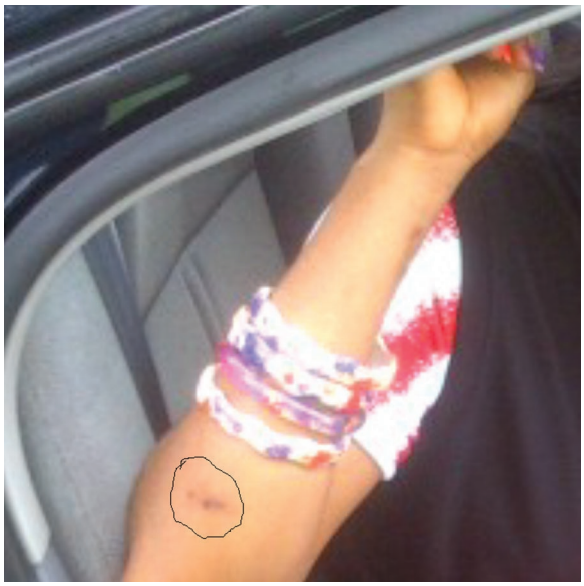


Figure 3: Extensive hyperpigmented skin lesion following disease progression.

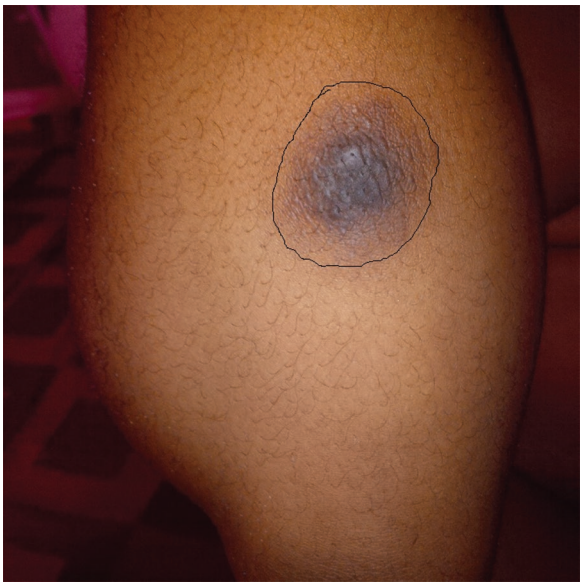
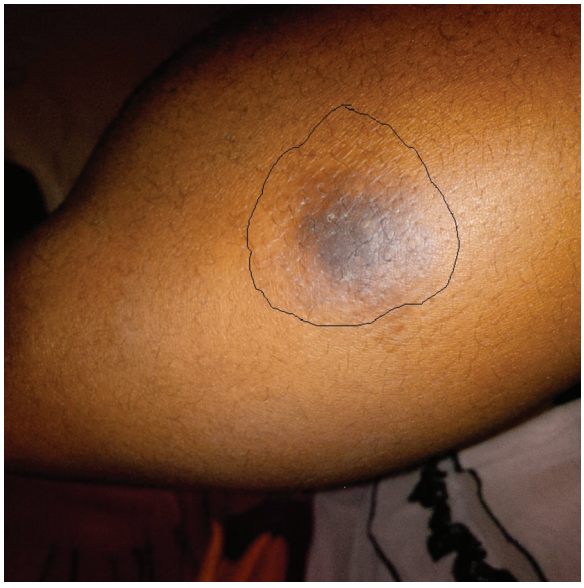


Figure 4: Progressive hyperpigmented macular lesion.

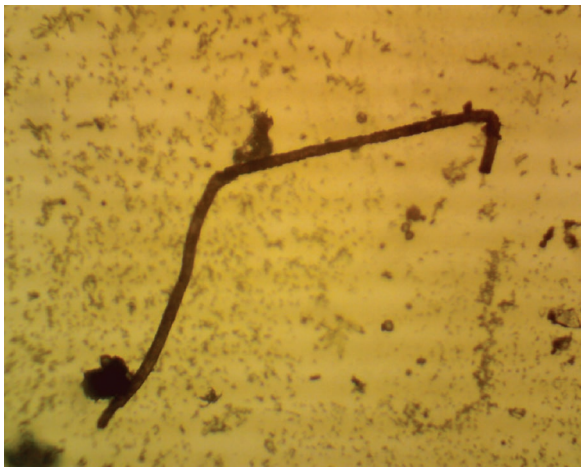


particularly after bathing. The lesion was noticed to have progressively involved the lower limbs. There was also a history of fetching water from a stream close to her residence. On examination, there was no evidence of swelling of the affected limbs and no signs of peripheral lymph node enlargement. Urine and venous blood samples (Micrograph 2a-2c) were collected for microscopy. Liver function test, electrolyte/urea/creatinine, white blood cell, and a differential count were also evaluated (Table 2 and 3).

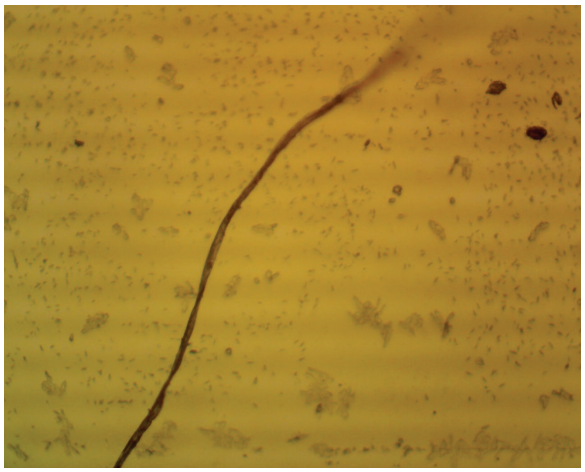
2.2. Case Report 2

A 21-year-old female student resident in Benin City Nigeria presented with a 3-month history of hyperpigmented skin lesion over the right elbow. The lesion started as an erythematous macule (circumscribed area in Figure 2), which progressively spread and became hyperpigmented with associated intense pruritus (Figures 2-4), which was usually worse at night. There was also a history of occasional visits to Warri Beach in Delta State, Nigeria. Further evaluation revealed that there was no swelling of the affected limb and no peripheral lymph node enlargement. Venous blood, as well as a skin snip (Micrograph 1), was obtained for microscopic evaluation.

Micrograph 1: Wet mount microscopy of skin snip showing *O. volvulus* 40× magnification.



Micrograph 2a: Wet mount microscopy of serum showing *W. bancrofti* 40× magnification.



Micrograph 2b: Wet mount microscopy of serum showing the anterior and posterior end of *W. bancrofti* 40× magnification.

Micrograph 2c: Wet mount microscopy of serum showing a protrusion in the middle half of the body of *W. bancrofti* 40× magnification.

3. DISCUSSION

Wuchereria bancrofti is prevalent in many parts of the tropics and subtropics. It is rarely fatal, but it is one of the leading causes of long-term physical deformities worldwide [8]. Reports by World Health Organization show that filariasis is one of the six "potentially eradicable" infectious diseases in the world and thus instituted a 20-year campaign program to eradicate the disease [2, 3]. Lymphatic filariasis being the most common form of the illness is attributed to the presence of adult worms in the lymphatic vessels adjacent to lymph nodes. The worms cause structural distortion of the vessels in addition to the local inflammatory process involved in the etiopathogenesis of the disease.

In advance stages of the disease, the worms can obstruct the vessels, causing the surrounding tissues to become enlarged. In Bancroftian filariasis, the legs and genitals are most commonly involved, while the Malayan variety affects mainly the legs. Repeated episodes of inflammation lead to obstruction in the lymphatic system, especially the genitals and legs. This result in gross enlargement of the affected area with associated thickening and coarsening of the skin, leading to a condition referred to as elephantiasis.

In another condition referred to as conjunctival filariasis, the microfilaria of *O. volvulus* migrates to the eye and may be seen moving beneath the skin or beneath the conjunctiva. In patients with conjunctival filariasis, the disease may progress to a condition known as onchocerciasis, which results in blindness.

Symptoms usually depend on the type of parasitic worm involved. Most infestation begins with febrile episodes of chills, headache, and fever. The onset of symptoms ranges from 3 months to 1 year after the bite of the vector. In the early stages of the infestation, there may be swelling, erythema, and pain in the affected area (arms, legs, or scrotum). Abscesses may develop from dying worms or secondary bacterial infection.

Ivermectin, albendazole, or diethylcarbamazine is used to treat filariasis. They act by eliminating the larvae and impairing the ability of adult worms to reproduce [9, 10]. Additionally, they kill adult filarial worms. Much of the tissue damaged during this process may not be reversible. The medication is usually started at low doses to prevent reactions caused by scores of dying parasites [10, 11].

Though effective, the drugs contribute significantly to severe adverse effects in up to 70% of patients [11, 12]. This may be attributed to the action of the drug or the ensuing death of parasites after the administration of the drug. However, the administration of diethylcarbamazine has been linked to severe allergic reactions and abscess formation.

These side effects are usually controlled with antihistamines and anti-inflammatory drugs such as corticosteroids. Treatment with diethylcarbamazine in individuals with very high levels of the filarial worm may lead to a fatal inflammation of the brain called encephalitis. In encephalitis, the fever is followed by a headache, confusion, stupor, and coma, which results from the death of a high number of larvae and parasites in the blood. Other observed drug reactions include dizziness, weakness, and nausea.

Other symptoms attributed to parasite mortality include fever, headache, muscle pain, abdominal pain, nausea, vomiting, weakness, dizziness, lethargy, and asthma. Additionally, adverse reactions usually begin within 2 days of starting the treatment and may last from 2 to 4 days.

In the present case study, there was no derangement in hematological and biochemical parameters assessed for both patients. Although the affected patients were microfilaremic based on laboratory assessment, there was no evidence of systemic involvement apart from the localized skin lesion. The combination of albendazole, ivermectin, and loratadine was effective in causing recession of the lesion and preventing the progression of the disease.

Eosinophilic degradation is strongly associated with the mazzotti reaction, which is usually more severe in heavily infested individuals [13, 14]. Ivermectin causes a dose-dependent sequestration, activation, and degranulation of eosinophils and destroys microfilaria within the female worms and the human tissues [14]. The drug blocks neurotransmission across neurons that use glutamate-gated anion channels or gamma amino butyric acid (GABA) gated chloride channels. This selective paralysis occurs only in invertebrates. The destruction of the microfilaria within the female worm prevents further microfilaria production [1, 9]. The available report shows that adverse reaction occurs in up to 30% of patients receiving the first dose of ivermectin. However, their use in large-scale treatment of filariasis is safe [12]. Adverse reactions involve anorexia, asthenia, headache, arthralgia, myalgia, fever, and eosinophilia. Mazzotti reaction can also occur from the release of degradation products of the parasite. The drug is usually administered at a dose of 150-200 mcg/kg, which translates to 6 mg tablets bid for adults.

Studies by Fox *et al*. [15] suggest that there is an elevation of histamine, which is induced by invasive tissue helminthes, that may aid the survival of helminths by decreasing eosinophilic response. Use of H1 receptor antagonist was found to reduce worm burden from increased eosinophilic clearance significantly, which suggests that the use of H1 antihistamines, such as loratadine, may enhance the efficacy of treatment for filaria and other tissue invasive helminthic infestation.

Common side effects associated with albendazole use includes nausea, abdominal pains, and headache [16-19]. In the present report, the patients who received treatment with the combination of these agents (albendazole + ivermectin + loratadine) complained only of weakness and abdominal discomfort. These side effects were well tolerated by the patients. Other potentially serious side effects associated with albendazole use are bone marrow suppression and liver toxicity. Patients with underlying liver disease are at increased risk of toxicity. Albendazole acts by causing a degenerative alteration in intestinal cells of the worm; this occurs following its binding to the colchicine-sensitive site of tubulin resulting in the inhibition of polymerization or assembly of cytoplasmic microtubules. There is also a depletion of glycogen stores and reduced uptake of glucose by the developmental and adult stages of susceptible parasites. A degenerative change in the endoplasmic reticulum and the mitochondria also occur with the eventual release of lysosomal constituents.

4. CONCLUSION

Filariasis remains a neglected disease in the tropics, and early-stage cutaneous lesions are most of the time misdiagnosed. It is my opinion that ivermectin should not be used routinely as monotherapy in individual and mass treatment of filariasis; rather it

should be available as coformulations with albendazole and antihistamines to improve its efficacy and reduce the adverse drug reactions commonly associated with its antifilaria activity.

Source of Funding
None.

Conflict of Interest
None.

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