Case Report

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Internal Medicine Section

A Case of Sepsis-induced MODS in Disseminated Filariasis: Cause or Co-incidence

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ABSTRACT

Filariasis, an affliction caused by thread-like filarial worms, poses a formidable health challenge in India, with diverse regional endemicities. It manifests in two distinct forms: lymphatic and extralymphatic. The former induces agonising limb swelling, while the latter, often overlooked due to its atypical presentation, can affect various organs. Here we, present a noteworthy case involving a 25-year-old woman who succumbed to septic shock, displaying Multiple Organ Dysfunction Syndrome (MODS). The patient exhibited bicytopaenia, leukocytosis, and progressively deteriorating liver and kidney functions, culminating in Acute Respiratory Distress Syndrome (ARDS). Postmortem examinations, conducted with proper consent, revealed sheathed microfilaria in liver and bone marrow tissues. This rare multisystem involvement in filariasis, leading to a fulminant course, raises questions about potential immunosuppression triggered by disseminated filarial dissemination. The hypothesis centres on the notion that the systemic spread of filaria might underlie the severe and rapid deterioration observed in this unique case, shedding light on the intricate dynamics of this parasitic disease and its implications for immune function.

Keywords: Extra lymphatic, Immunosuppression, Multiple organ dysfunction syndrome

CASE REPORT

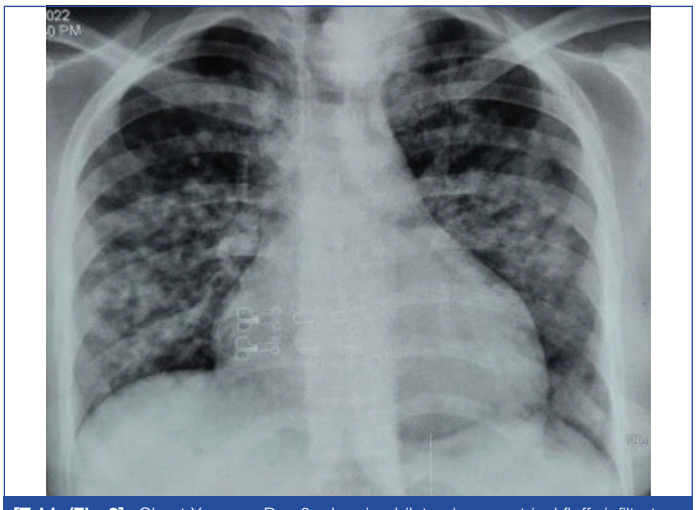
A 25-year-old female presented with complaints of high-grade fever with chills, documented up to 103°F, associated with a dry cough for 15 days, right upper quadrant pain for four days, which was dull aching in character, of moderate intensity, not radiating, and associated with non-projectile vomiting. She also experienced exertional shortness of breath, which was of a progressive nature. She noticed a decrease in her urine output for three days and developed irritable behaviour a day prior to presentation. There was no history of pedal oedema or facial puffiness. She had no history of co-morbidities such as diabetes or hypertension, and her family history was insignificant.

On examination, the patient was drowsy but arousable on presentation, visibly tachypneic (respiratory rate 34/min), had tachycardia and low BP (83/62 mmHg), and was febrile (102°F). She had oxygen saturation of 84% on room air, which improved to 97% with supplemental oxygen. She was pale and icteric but with no evidence or history of lymphoedema or lymphangitis. She also had no skin changes, genital swelling, or enlarged lymph nodes. Coarse crepitations were noted on auscultation, along with mild tenderness in the epigastric region on palpation but with no organomegaly. There was no focal neurological deficit, neck rigidity, or anisocoria on neurological examination.

The initial investigations were suggestive of bicytopaenia with leukocytosis (Hb 9.2 g/dL, WBC 30200/mm^3, and platelets 83000/mm^3) and deranged liver and kidney functions as provided in [Table/Fig-1]. Blood gas analysis revealed metabolic acidosis with respiratory acidosis with type 1 respiratory failure. The X-ray showed diffuse fluffy, inhomogeneous, airspace opacities in bilateral lung fields [Table/Fig-2]. Peripheral smear was suggestive of bicytopaenia with hypoochromic anaemia (MCV 57 fL) with the presence of eosinophilia (12%) and neutrophilia with left shift. The absolute eosinophil count came out to be 3800/mm^3 (range: 30-300/mm^3). Serum procalcitonin (14.9 ng/mL; range <0.5 ng/mL) and proBNP (635 pg/mL; range <125 pg/mL) were raised, as were the D-dimer values (3943 ng/mL; range <500 ng/mL). The echocardiography was normal. Urine routine revealed mild proteinuria, 10-15 pus cells with 20-30 normal RBCs.

Parameters	Patient's value	Normal range
Total bilirubin	8.6 mg/dL	0.2-1.3 mg/dL
Direct bilirubin	8.3 mg/dL	0.0-1.1 mg/dL
Alanine transaminase	91 U/L	5-30 U/L
Aspartate transaminase	168 U/L	5-30 U/L
Alkaline phosphatase	160 U/L	50-100 U/L
Blood urea nitrogen	210 mg/dL	8-21 mg/dl
Serum creatinine	11.8 mg/dL	0.6-1.2 mg/dL
D-dimer	3943 ng/mL	<500 ng/mL
Ferritin	3540 ng/mL	12-150 ng/mL

[Table/Fig-1]: Laboratory reports on Day 0.



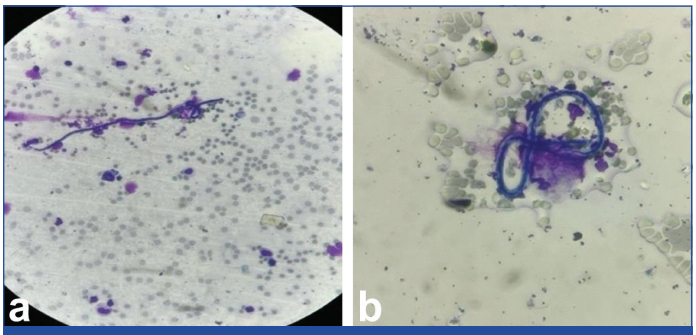
[Table/Fig-2]: Chest X-ray on Day 0- showing bilateral symmetrical fluffy infiltrates.

The viral markers (HIV, hepatitis A, B, C, and E) were negative. Malarial antigen, dengue antigen, and IgM antibody were negative. Autoimmune screening revealed insignificant titres for Antinuclear Antibodies (ANA), perinuclear Antineutrophilic Cytoplasmic Antibody (pANCA), and cytoplasmic Antineutrophilic Cytoplasmic Antibody (cANCA). C3 and C4 levels were normal, and the Antistreptolysin O (ASO) titre was negative. The serology for leptospira, rickettsia,

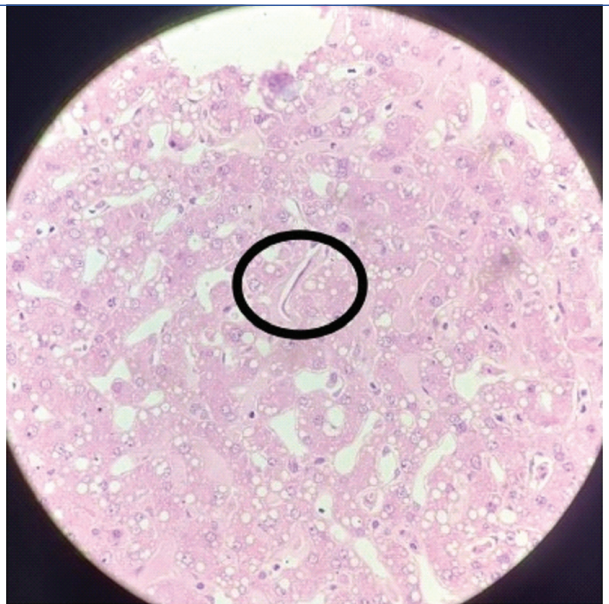
and scrub typhus were also negative, as were the Parvovirus and Cytomegalovirus (CMV). Her abdominal ultrasound revealed neither organomegaly nor any foci of infection. The blood and urine cultures showed no growth.

She was managed with broad-spectrum antibiotics (meropenem 1 gram 8 hourly, teicoplanin 400 mg 12 hourly, and doxycycline 100 mg 12 hourly), fluids, and inotropes. Due to progressively worsening kidney function, persistent metabolic acidosis, and oliguria, she underwent haemodialysis. However, there was no improvement in her condition, and she developed severe respiratory distress (PaO_2/FiO_2<100), requiring invasive ventilation. Despite the efforts, she succumbed to her illness on Day 3 of admission.

Postmortem biopsies were performed after obtaining written informed consent from the patient's relative. The marrow biopsy [Table/Fig-3a,b] showed the presence of sheathed microfilaria, while the liver biopsy [Table/Fig-4] revealed sinusoidal dilatation with microfilarial larvae. The kidney biopsy was suggestive of acute tubular necrosis but showed no evidence of any microfilariae.



[Table/Fig-3]: a,b) Bone marrow aspirates showing cellular reactive marrow with presence of Sheathed Microfilaria.



[Table/Fig-4]: Liver biopsy showing hepatocytes with diffuse steatosis and moderate intrahepatic cholestasis, but no fibrosis. It also showed dilated sinusoids with presence of larva of microfilaria (encircled).

DISCUSSION

Filariasis is an illness caused by slender, thread-like nematode parasites, specifically *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, which reside in the tissues beneath the skin and the lymphatic system. Filariasis poses a significant public health risk and is endemic in the Indian population. *Wuchereria bancrofti* can be distinguished by certain identifying characteristics, including the presence of a hyaline sheath, elongated terminal nuclei, a cephalic space ranging from 5 to 15 µm in length, and a pointed posterior end, which may or may not have terminal or subterminal swelling. Common lymphatic manifestations of filariasis include asymptomatic microfilariaemia, elephantiasis, acute adenolymphangitis, hydrocoele, and chronic lymphatic disease, none of which were present in our patient on presentation, nor was there any history of such complaints [1]. Additionally, microfilariae have been found in locations outside the lymphatic system, such as subcutaneous swellings, breast tissue, the thyroid gland, lymph nodes, body cavity effusions, and bronchial washings [2]. The precise mechanism by which microfilariae traverse from the vascular system into extravascular tissue spaces is not fully understood. One plausible hypothesis suggests that microfilariae may cross blood vessel walls through their capacity to penetrate tissues, effectively reaching the tissue spaces [3].

Parasitic infections induce eosinophilia, with differentials encompassing inflammatory, allergic, and neoplastic causes. Eosinophil counts exceeding 1500/mm^3 warrant evaluation for hypereosinophilic syndromes [1]. Tropical Pulmonary Eosinophilia (TPE), a manifestation of lymphatic filariasis, arises from an immune hyper-responsiveness to lung-trapped microfilariae. The diagnosis of TPE involves eosinophilia >3000/mm^3, IgE levels >1000 U/mL, and elevated filarial antibody titers. In such cases, acute eosinophilic pneumonia should be considered, featuring neutrophilic leukocytosis, elevated CRP, and chest radiograph infiltrates. Confirmatory analysis of bronchoalveolar lavage fluid (>25% eosinophilia) was impeded in this case due to clinical deterioration [2].

The detection of microfilariae in bone marrow aspirate is a rare occurrence. The earliest recorded instance of microfilariae in bone marrow aspirate in the literature dates back to 1976, attributed to Pradhan S et al., [4]. Notably, none of the documented cases featuring microfilariae in bone marrow aspirate displayed the typical clinical presentation of lymphatic filariasis [2,5,6]. The reports also suggest that the presence of microfilariae may lead to the release of potentially toxic metabolites, resulting in bone marrow suppression characterised by pancytopenia [7]. The bicytopaenia in our patient can be attributed to filarial infestation.

Limited case reports have described the incidental discovery of filaria in the liver, even in individuals displaying no signs or symptoms of filariasis [8]. This anomalous migration to such locations is likely influenced by factors such as lymphatic obstruction due to scarring or tumours, as well as vessel wall damage caused by inflammation, trauma, or stagnant blood flow. A plausible explanation could be that larvae are present in the vasculature, and the act of aspiration leads to vessel rupture, resulting in haemorrhage and the release of microfilariae [9]. The isolation of microfilariae from the liver in the case confirmed the disseminated nature of the disease.

About half of untreated microfilaremic patients exhibit kidney abnormalities, characterised by microscopic haematuria (35%) and proteinuria (20%) [10,11]. Renal issues can be due to physical damage to the glomeruli or the deposition of immune complexes (more common). In a study conducted by Rath RN et al., nine out of 14 filariasis patients displayed histopathological changes, with mesangial cell hyperplasia being the most consistent finding [12]. Furthermore, research by Langhammer J et al., has shown that microfilariae can lead to tubular damage in the kidneys, potentially resulting in renal failure. This can also be the cause of worsening renal function in our case, in addition to sepsis [13].

Filarial parasites intricately modulate host immune responses through antigen-specific and generalised immunomodulation mechanisms, inducing profound immunoregulatory effects. Prominent features include immunosuppression and the induction of immunological tolerance, involving cytokine-induced immune response suppression and the induction of immune tolerance in effector T cells [14]. Notably, a modified Th2 response manifests with antibody isotype switching to non-inflammatory IgG4 and the induction of alternatively activated macrophages. Patients with lymphatic filariasis exhibit diminished responses to parasite antigens and non-specific inhibition of bystander antigen responses. The secretion of immunomodulatory products, such as ES-62 containing Phosphorylcholine (PC), demonstrates

diverse properties and is key to immune evasion. Regulatory T cells, especially those associated with IL-10 and TGFβ, play pivotal roles in filarial immunoevasion, influencing host immune function [15].

The presence of microfilariae in both the liver and bone marrow provides a plausible explanation for the patient's bicytopaenia. Furthermore, the patient experienced acute tubular necrosis in the kidneys, potentially influenced by the combined impact of sepsis and filarial infection, although the biopsy did not reveal the presence of the organism. The probable hypothesis is that disseminated filaria resulted in immunosuppression, making the patient vulnerable to a secondary infection, leading to a severe septic condition with MODS. However, it is impossible to completely rule out the possibility of a coincidental association of disseminated filariasis. Nevertheless, despite an exhaustive review of the literature, we were unable to uncover any case reports detailing the concurrent presence of filarial infestation across multiple sites within a single patient, although there are case reports of isolated extralymphatic filariasis in the liver, kidney, and bone marrow as mentioned above [6-8,10].

CONCLUSION(S)

The present case highlighted the rare but significant occurrence of extralymphatic filariasis in various tissues and the associated tubular injury to the kidneys. Disseminated filariasis led to an immunosuppressive state, which can predispose to life-threatening serious infections. Clinicians in endemic areas should maintain a high index of suspicion and actively screen for filarial parasites in various tissues to facilitate timely intervention, thus preventing severe complications. Early diagnosis of filariasis can be crucial, as it is a treatable condition.

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