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Lymphatic Filariasis of the Ovary and Mesosalpinx

Seema Sethi, Kiran Misra, Usha Rani Singh, and Dilip Kumar

Department of Pathology, University College of Medical Sciences, Guru Teg Bahadur Hospital, Delhi, India

Abstract

We report 2 cases of filariasis, one in the ovary and the other in the mesosalpinx. In the first case, the patient underwent panhystrectomy and in the second case, right ovarian cystectomy with right salpingectomy were performed under general anaesthesia. Histopathology showed adult filarial worms in the dilated lymphatics of the right ovary, in the first case and in the mesosalpinx, in the second case. Both patients presented with complaints related to gynecological problems and not filariasis. Reports of filariasis in the literature and possible treatments and prevention strategies are also discussed.

Key words: filariasis, ovary, mesosalpinx

Introduction

Of the many types of filarial nematodes 8 species infect humans and of those 3 species, *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* are primarily associated with acute and chronic inflammatory changes in the lymphatic system, and this group is known as lymphatic filariae. Infections by *Brugia timori* have not been reported in India.[1] The other types that infect humans are *Onchocerca volvulus*, *Loa loa*, *Mansonella ozzardi*, *M. perstans* and *M. streptocerca*, and these cause a range of distinct pathologies.

The distinctive pathology associated with lymphatic infection, particularly the gross enlargement of limbs known as elephantiasis (Sasa 1976,[2] Grove 1990,[3] and Nelson 1996[4]) has been recorded in the ancient medical literature of China, Egypt, India, Japan and Persia, and was referred to as elephantiasis arabicum by western physicians. The microfilarial stages were first discovered in the hydrocele of a patient from Cuba in 1863. Wucherer reported microfilariae in the urine of an infected patient in 1866 and Bancroft in Brisbane later found them in the abscess of a Chinese patient in 1876. Identification of other filariae was made much later. The name *Filaria bancrofti* was proposed by Cobbold in 1877 and the generic name *Wuchereria* given in 1878.

The major contributions to understanding the life cycle of *W. bancrofti* were made by Manson working in South China. In 1878, he identified mosquitoes as vectors of infection and in 1881, he reported the nocturnal periodicity of *W. bancrofti*. In 1899 Bancroft and in 1900, Low established the means of transmission of filaria by *Culex pipiens fatigans*, being identified as an important vector species.

Other than *Loa loa*, the location of adult worms in the body means that they are rarely seen intact, sometimes only in histological sections; however, it is difficult to identify the species in tissue sections. In contrast, the microfilariae, which appear in the blood, are easily seen and provide a good basis for identification.[5]

Filariasis commonly involves the male genital

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Reprint request to: Dr. Seema Sethi, 107 Old Gupta Colony, Delhi 110 009, India

system. Apart from lymph nodes and peripheral blood, adult filarial worm can be detected in subcutaneous nodules, epididymis, testes, breast, varices, uterus[6] and as incidental findings in gynecologic smears.[7] Only a few cases of filarial worms in the ovary[6] and related lesions of the ovary[8,9] have been reported. There has been only one report from India of the presence of filarial worm in a nodule over the fallopian tube,[10] and to our knowledge in the English literature there have been no reports of filariasis in the mesosalpinx. Thus, we report here 2 rare cases of filarial worm, one in the ovary and the other in the mesosalpinx.

Materials and Methods

Case 1

A 40-year-old female presented with a mass in the lower abdomen and a one-year history of irregular genital bleeding. Abdominal examination revealed a mass in the lower abdomen and vaginal examination showed the uterus to be irregular and bulky and of 14 weeks size. Bilateral adnexa were normal. Laboratory findings showed hemoglobin of 10.5 g%, a total leukocyte count of 10,700 per μl with normal differential count. Biochemical, urine, chest X-ray and ECG investigations were within normal limits. Panhystrectomy was performed and grossly, the uterus measured 14 cm × 12 cm × 10 cm with irregularly thickened myometrium showing small cystic spaces filled with blood. Right ovary showed a focal area of hemorrhage. Left ovary and both the fallopian tubes were unremarkable.

Case 2

A 26-year-old female presented with lower abdominal pain of one-week duration. Abdominal examination revealed a cystic, mildly tender and mobile mass. The same mass was palpable in the anterior fornix on vaginal examination. Left fornix was free and the uterus appeared normal. Laboratory findings showed hemoglobin of 11.2 g%, a total leukocyte count of 14,000 per μl with mild neutrophilia. Urine and biochemical investigations were within normal limits. Based on a clinical differential diagnosis of twisted ovarian cyst/dermoid, right cystectomy and right salpingectomy were performed. Grossly, an ovarian cyst with attached fallopian tube were observed. The cyst measured 10 cm × 10 cm × 8 cm, was uniloculated and contained clear fluid with a smooth inner wall. In the mesosalpinx a firm nodule measuring 1 cm in diameter was noted. The fallopian tube was unremarkable.

Histopathology

Histopathological examination of the first case showed adenomyosis of the uterus and chronic cervicitis. The right ovary had a focal area of hemorrhage, dilated lymphatics and filarial worms in the lymphatics. There was a chronic inflammatory reaction in the stroma with numerous eosinophils (Fig. 1). The ovary and both fallopian tubes were unremarkable.

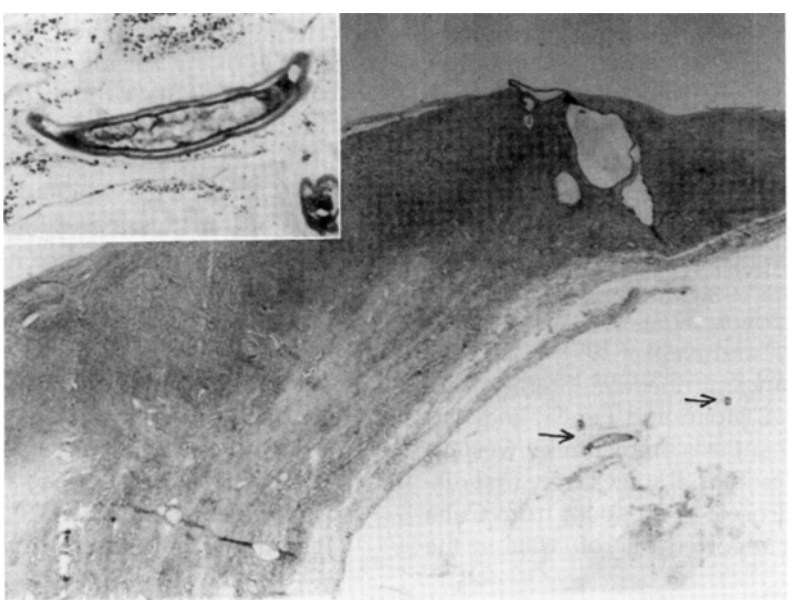

Fig. 1. Section from ovary showing adult filarial worms (arrows) in the dilated lymphatics (H& E × 16). Inset shows cross section of the adult filarial worms.

The second case showed simple serous cystadenoma of the ovary. The nodule in the mesosalpinx showed fibrosis, thickened and dilated lymphatics and filarial worms in the dilated lymphatics surrounded by inflammatory infiltrate of lymphocytes, plasma cells with a predominance of eosinophils (Fig. 2). The fallopian tubes showed normal histological findings.

Discussion

The clinical manifestations of lymphatic filariasis tends to vary according to the geographical locations.[11] The disease spectrum of bancroftian and brugian filariasis varies widely from an asymptomatic state to a severely debilitating chronic condition. Depending on the infection status of the individuals in endemic areas and the resulting clinical consequences, 5 main categories

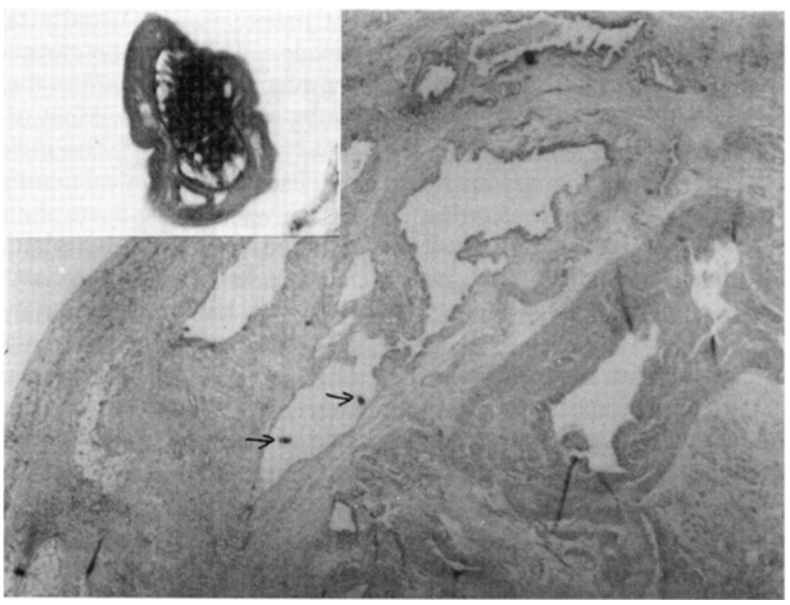

Fig. 2. Section from nodule in the mesosalpinx showing thickened and dilated lymphatic vessels with adult filarial worms (arrows) (H & E × 16). Inset shows cross section of the adult filarial worm.

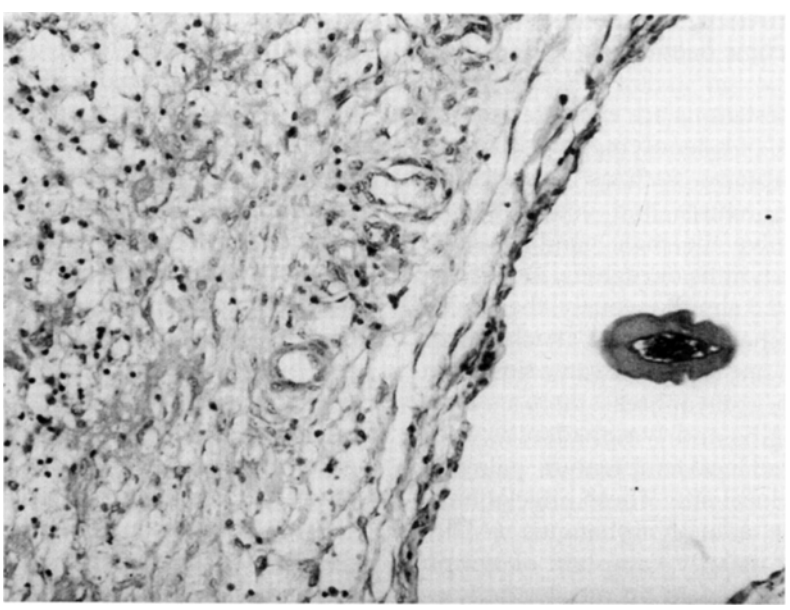

Fig. 3. Another area from the nodule in the mesosalpinx showing a cross section of adult filarial worm with inflammatory infiltrate in the surrounding stroma (H & E × 16).

of the filarial clinical spectrum have been recognized[12]: 1. asymptomatic amicrofilaremia, 2. asymptomatic microfilaremia, 3. acute manifestations, 4. chronic manifestations, and 5. allergic manifestations. In addition, there are reports of manifestations similar to glomerulonephritis and monoarthritis in patients with bancroftian filariasis.[13–16]

A proportion of individuals in endemic areas with asymptomatic amicrofilaremia do not show microfilaria in the blood and do not exhibit any clinical signs and symptoms, as noted in both our cases. This group may be comprised of persons who have not been sufficiently exposed to become infected or persons who have been sufficiently exposed but, do not show any detectable infection by current diagnostic techniques.[12] Such subjects may have already successfully cleared the infection or are harboring developing worms of one sex or unfertilized female adult worms. This group may have subclinical infection as evidenced by detectable antigenaemia.[17–20]

Some individuals who develop microfilaremia do not manifest any clinical disease. Among these some may remain asymptomatic for years, even for life, while others manifest clinical disease with/without losing the microfilaremic status.[12] In addition, this group of individuals show lowered parasite specific IgE response but generate large amounts of specific antibodies of the IgG_4 class, which is considered to be a blocking antibody.[19,21] These patients have lymphatic abnormalities as detected by lymphangioscintigraphy[22] and also renal[23] abnormalities as evidenced by microscopic haematuria and/or proteinuria.

The acute manifestations are characterized by an episodic attack of adenolymphangitis with constitutional symptoms such as fever, chills, malaise, headache, nausea and vomiting.[12,24,25] These attacks involve the male genitals, acute funiculitis or epididymitis or orchitis, most commonly involving all 3 simultaneously, the female breast and rarely other sites. Acute attacks never occur at more than one site at the same time.[24] In the case of the limb, groin or breast there are local signs of lymphangitis and lymphadenitis; redness, swelling, raised local temperature, pain and tenderness at the local site. These attacks have been described as adenolymphangitis (ADL), since the patients usually complain of lymph node involvement followed by retrograde lymphangitis.[24,26] These attacks usually last for about 3 to 5 days but rarely last longer than a fortnight.[25,27–29] The attacks can also occur in asymptomatic subjects, many of whom present with lymphoedema with the first attack itself. Most often, repeated attacks of ADL precede the development of chronic lymphatic pathology of filariasis and these often continue for many years[20,29] Lymphoedema is frequently present during each episode but usually subsides after the acute stage. Over time, the resolution of lymphoedema becomes less complete after each attack and the characteristic chronic changes develop.[30]

Chronic disease usually takes 10–15 years to develop. The common chronic manifestations of lymphatic filariasis affect the male genitals and limbs of both sexes. Most of these patients are amicrofilaremic.[31–34] The incidence and severity of these chronic clinical manifestations tend to increase with age and are the result of structural damage following lymphatic obstruction and fibrosis. In brugian filariasis, genitals are rarely involved. Hydrocele is the most common manifestation of chronic bancroftian filariasis, although it is rare in brugian filariasis, and sometimes microfilaria can be detected in the hydrocele fluid.[12,35] Other genital manifestations include chronic epididymitis, funiculitis, lymphscrotum. Lymphoedema affects the lower limbs, genitals in both sexes and female breast and rarely the upper limbs. Elephantiasis supervenes following persistent fibrotic changes in the skin and the subcutaneous tissue and can also affect the genitals, lymphscrotum or penis in males and vulva in females and female breast.[12,31] Chyluria is another manifestation and is an excretion of chyle in urine. A few patients develop gross haematuria due to the blockade of the retroperitonial lymph nodes below the cisterna chyli, with consequent reflux and flow of the intestinal lymph directly into the renal lymphatics, which may rupture and permit the flow of chyle into the urinary tract. Microfilaremia may or may not be present in these patients. The urinary sediment may contain microfilaria and red cells but seldom contain leukocytes. Chyluria is often symptomless but some patients complain of fatigue and weight loss due to fat and protein[12,31,36] loss.

Tropical pulmonary eosinophilia is a form of occult filariasis that occurs in a small proportion of individuals in areas endemic of filariasis. It is considered to be an allergic manifestation of the disease with extremely high titers of antifilarial antibodies.[12] The majority of these antibodies are of IgE class and are directed against microfilaria. Hypereosinophilia is the common feature with

absolute eosinophil counts ranging from 3,000–50,000 per mm^3 of blood. Classical clinical manifestations are not present but, the commonest presentation is nocturnal paroxysmal cough with radiological evidence of diffuse milliary lesions or an increase in broncho-vascular markings, low grade fever, weight loss, splenomegaly and elevated ESR.[12] Circulating microfilaria is absent in the blood but present in tissue particularly the lung and there is an impaired lung tunction in most cases with a reduction in the vital capacity and residual volume.[37] Males are affected twice as often as females and the disease is rarely reported in children. The therapeutic response to diethylcarbamazine (DEC) is generally good. If untreated (even in some treated cases) tropical pulmonary eosinophilia may progress to chronic pulmonary fibrosis.[37]

Other manifestations of occult filariasis include the Meyers-Kouwenaar syndrome, found particularly in areas of the Pacific and the east Indies. In this syndrome, microfilaria are not present in peripheral circulation, but benign lymphadenitis is noted with enlargement of the lymph nodes and spleen with many tissue eosinophils and granulomas often surrounding dead microfilariae. Both these conditions resolve rapidly after treatment with DEC and this is diagnostic.

The appearance of microfilaria in the peripheral blood shows marked periodicity and this phenomenon was demonstrated by Manson in *W. bancrofti*: microfilaria appeared for about 1–2 hours before and after midnight and then disappeared almost completely for the rest of the 24 hrs period through much of its geographical range. However, there are non-periodic forms in Pacific areas where microfilaria are present in the peripheral blood almost constantly through much of the 24 hrs period and in south east Asia there are sub-periodic forms in which, although microfilaria are present throughout the 24 hrs period, their numbers in the blood are elevated at night. The biological rationale of periodicity is always explained in terms of accessibility of the parasite to vectors, the appearance of the microfilaria coinciding with the periods of feeding activity in the arthropod and adaptation that clearly has evolutionary and survival advantages for the worm. Physiological explanations for periodicity were explored in great detail by Hawking (1967).[38] In their simplest terms they pinpointed differential respiratory gas tensions (O_2 and CO_2) in pulmonary vessels as a decisive factor in triggering behavioral responses in the microfilaria. In mammals that are active during the day the difference in gas tensions between the blood in pulmonary veins and arteries is greatest during the day and reduced at night. Microfilariae that show nocturnal periodicity accumulate in the lungs during the day, actively swimming against the blood flow to maintain their position. When the difference in gas tension is decreased at night the microfilariae pass through the lungs and circulate in the peripheral blood. Other hypotheses have been reported and several other host factors, including body temperature have been implicated.

The principal pathology is associated with the presence of adult worm in the lymph nodes and lymphatic vessels. The nodes become hyperplastic and microscopically show the presence of many lymphocytes, plasma cells and polymorphs particularly eosinophils and there may be foci of necrosis. The lymph vessels show proliferation, dilatation and edema formation due to the presence of living adults and obstructive, obliterative reactions in the lymphatics around dead parasites.

Microfilarial infection can elicit strong immunity and this can be seen in the control of microfilaremia, killing of adult worm or resistance to reinfection that operates against the filariform infective third stage larva. Recent work has emphasized the importance of the balance between T helper-I and T helper-2 mediated events in determining the outcome of infection.[39–41] Filarial infections, like many helminth infections, are characterised by eosinophilia and elevated serum IgE, i.e. responses that are T helper-2 mediated. This particular combination of cells and antibody could play an important role in antibody dependent cellular cytotoxic mechanisms that help to protect against incoming filariform infective third stage larva, but might also contribute to immunopathological responses such as tropical pulmonary eosinophilia. Individuals who are microfilaremic but lack major pathological changes, tend to have high levels of parasite-specific IgG_4 antibody in contrast those who are amicrofilaremic and those who have pathological lesions have higher levels of IgE and IgG_3.

The etiology behind the altered immune responsiveness seen in categories of individuals in endemic regions remains unclear and we speculate that genetically different individuals vary in their responses to given levels and frequency of infection. Diagnosis depends on findings of microfilaria in peripheral blood, which in turn requires the blood sample to be collected at the appropriate time. In cases of symptomatic lym-

phatic filariasis, 10 ml of sequestrated blood in a hypodermic syringe can be passed through a polycarbonate filter, which can be stained and examined, on a microscopic slide.[42] Blood can also be preserved in 2% formalin with 10% teepol for later examination.

Clinical diagnosis is made based on symptoms and signs of lymphangitis, lymphadenitis or manifestations of lymph stasis in a patient in an endemic area, often with eosinophilia and in chronic cases, calcified lymph nodes are often evident on radiography.

Immunodiagnosis is by detection of circulating filarial antigen in a drop of blood with the use of monoclonal antibodies using a dot ELISA technique.[43] This test is very sensitive but, may not be very specific; thus, results should be treated with caution in regions where other filaria may be present.

The mainstay in the treatment of filariasis is DEC at a dose of 6 mg per kg body weight daily for 12 days. This treatment kills the microfilaria and also has some action against the adult worms. However, it sometime has to be repeated after several months and must be used with great care in areas of Africa where, *O. volvulus* and *L. loa* infections may be present in the same individual. Treatment is also unlikely to be effective in the chronic stages of the disease. It has also been reported that a single annual dose of 6 mg/kg body weight of DEC reduced microfilarial density of Wuchereria and Brugia by 80–90%.[12] Clinical trials of ivermectin, a macrocyclic lactone with very few side effects, in a single annual dose of 400 μg per kg body weight completely cleared blood microfilaria for long periods and the 2 drugs can be used in combination.[12,44] Additional trials indicate that treatment with albendazole has some microfilaricidal action and can markedly reduce the recurrence of lymphangitis.[45] These findings have greatly improved the prospects for worldwide mass chemotherapy campaigns and the use of this treatment has already been successful in the past in countries where there has been a high level of compliance such as Japan, Taiwan and South Korea.

Integrated control campaigns are likely to be the most successful and these will involve control of the vectors. *Culex quinquefasciatus* is the most important vector species of the *C. pipiens* complex for *W. bancrofti* transmission. Environment control of this mosquito can best be achieved by adequate maintenance of open drains, septic tanks, soakage pits and flooded pit latrines. In rural areas, the Anopheles vector of *W. bancrofti* and periodic *B. malayi* breed in bodies of fairly clean water such as ponds, roadside pits and flood or irrigation water and these can be filled in. Larva insecticides are also widely used although resistance to organochlorines and increasingly organophosphates is widespread.[46] Control of the Aedes vector of the sub-periodic bancroftian filariasis in the South Pacific is more problematic since they breed in so many scattered and inaccessible sites and the adults are not found inside houses. However, efforts are being made to involve local population in removing man-made breeding sides such as old car tyres, tin cans and coconut shells.

The 2 cases reported in this study belonged to the first category of asymptomatic amicrofilaremia, since the patients presented with symptoms related to the genital tract pathology. The first patient had an adenomyosis uterus and presented with a mass in the abdomen, and the second patient presented with a cystic lesion of the ovary and abdominal pain. The identification of filarial worm on histology, should be conveyed to the treating physician, since treatment is required to prevent the development of later complications.

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