

# Clinicopathological Spectrum of Chronic Filarial Epididymo-Orchitis: Experience from a Tertiary Care Institute

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## ABSTRACT

**Background:** Filariasis is a vector-borne neglected tropical disease, most commonly caused by *Wuchereria bancrofti*. Chronic lymphatic filariasis in males usually presents as scrotal swelling with hydrocoele, although, a variety of other genital manifestations can also be seen. This study was undertaken to establish the clinicopathological spectrum of chronic filarial epididymo-orchitis (FEO) in a tertiary care institution in India.

**Methods:** Cross-sectional observational study spanning a retrospective period of 17 years from 2000-2017.

**Results:** Nineteen cases of chronic FEO were diagnosed, comprising 1.8% of all testicular and paratesticular biopsies (n=1055). Median age was 40 years. All patients presented with scrotal swelling. Examination revealed hydrocoele (12/19), lymph scrotum (5/19), epididymal nodules (4/19) or scrotal elephantiasis mimicking testicular tumour (3/19). Gross examination of orchidectomy specimens revealed cystic hydrocoele sacs with markedly thickened tunica, while four cases showed extensive parenchymal necrosis. Histopathology revealed adult filarial worms either within the epididymal/paratesticular tissues (9/19) or in the tunica vaginalis (7/19). Two cases, in addition, showed microfilarial larvae within the tissues. Six cases showed characteristic Meyers-Kouvenaar bodies surrounding adult worms.

**Conclusion:** This single institution study from India identifies chronic FEO as a rare but important cause of scrotal swelling. Since chronic FEO may be clinically mistaken for testicular tumour, awareness of the clinicopathological spectrum is essential. Biopsies with intense infiltrate of eosinophils and lymphangiectasia need high index of suspicion for filariasis and warrant careful search for adult filarial worm as well as microfilaria in tissue sections.

**Keywords:** Filariasis, epididymo-orchitis, *Wuchereria bancrofti*, hydrocoele, elephantiasis

## Introduction

Lymphatic filariasis (LF) is a neglected tropical disease and has a worldwide prevalence of 120 million.<sup>[1]</sup> India contributes to 40% of the global burden of filariasis, with an estimated 553.7 million people at risk for LF.<sup>[2]</sup> It is caused by three lymph-dwelling nematodes, *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, with various mosquito species acting as vectors.<sup>[3]</sup> In India 98% of infections are caused by *W. bancrofti* with the Culicine species being the most prevalent vector.<sup>[4,5]</sup> The highest burden of infection is seen in the states of Uttar Pradesh, Bihar, Andhra Pradesh, Tamil Nadu and Kerala.<sup>[6]</sup>

The complex life cycle begins with ingestion of microfilariae during the mosquito's blood meal. Infective third-stage larvae infect man during the mosquito bite, reach the lymphatic channels and develop into adult, sexually mature forms. Fertilization occurs and the gravid female adult worm gives birth to thousands of microfilariae (MF) that circulate in the peripheral blood for upto eight years.<sup>[7]</sup>

Common clinical findings in chronic LF include lymphoedema and hydrocoele. The latter is detectable in 40% of men in areas hyperendemic for filariasis.<sup>[8]</sup> Other genital manifestations in males include epididymal nodules, lymph scrotum with multiple discharging skin sinuses, or scrotal elephantiasis resembling testicular tumour.<sup>[3,9]</sup> Studies describing clinical and histopathological manifestations of chronic filarial epididymo-orchitis (FEO) are few. We undertook this study to describe our experience of chronic FEO in our hospital.

## Material and Methods

A retrospective cross-sectional observational study was carried out in the Department of Pathology of a Tertiary care Hospital over a retrospective period of 17 years from January 2000 to December 2017, on cases diagnosed as chronic FEO. The study protocol was approved by the Institutional Research Committee.

All biopsy specimens were received in 10% neutral buffered formalin and processed routinely for hematoxylin and eosin (H&E) staining. Special stains like Periodic

acid-Schiff and Ziehl-Neelsen were done where required. Histology slides were retrieved from records, reassessed and evaluated by two pathologists (PP and NC), and salient findings were noted as per protocol. Relevant details including clinical presentation, examination findings and indication for surgery were collected from the request form or hospital record file. Patients were grouped into the following categories: a) hydrocoele, b) epididymal nodules, c) lymph scrotum, and d) scrotal elephantiasis resembling testicular tumour.

## Results

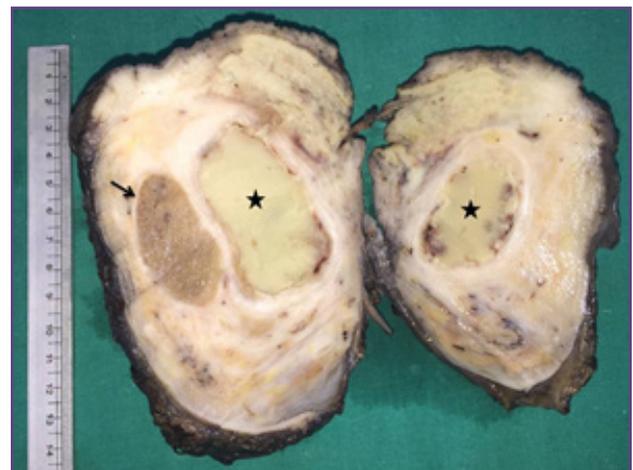
**Clinical Findings:** A total of 19 cases of chronic FEO were diagnosed over a period of 17 years, comprising 1.8% of all testicular and paratesticular biopsies (n=1055). The clinical profile of patients is depicted in Table 1. The median age of patients was 40 years (range 19-75 years). All patients presented with scrotal swelling, which was predominantly left sided (12 cases). Bilateral scrotal swelling was seen in two cases. Hydrocoele was present in 12 cases (63.1%), of which two patients had history of hydrocoele in the past. Other clinical features included scrotal pain (9/19), palpable epididymal nodules (4/19), fever (4/19) and Fournier's gangrene in one case. Five patients presented with multiple sinuses oozing chyle through scrotal skin (lymph scrotum). Median duration of illness was 12.1 months (range 7 days – 6 years). Inguinal lymphadenopathy was present in one patient. Details on patient follow up, MF demonstration in peripheral smear or antigen testing was not available as most were referral samples from peripheral hospitals. Orchidectomy was performed in 14/19 patients for clinical indication of chronic or tubercular epididymo-orchitis (9/17), suspected testicular tumour (4/17) or Fournier's gangrene with associated epididymo-orchitis (1/17). Epididymal grey-white nodules were biopsied in four patients, and testicular biopsy was taken in one case.

**Gross Findings:** Mean size of orchidectomy specimens was 8.8 cm (range 5 cm to 14.5 cm) and mean weight was 270 g. Gross examination revealed cystic hydrocoele sacs in eight cases (42.1%), which was either unilocular (6/19) or multiloculated (2/19). The hydrocoele cavities had thickened walls with roughened to nodular inner lining and were filled with mucoid, hemorrhagic or necrotic material (Fig 1). Orchidectomy specimens without hydrocoele showed marked thickening of tunica with grey-brown and necrotic areas. Four cases, in addition, showed extensive areas of necrosis within the testicular and paratesticular parenchyma. The spermatic cord, included in all orchidectomy specimens, was thickened and adherent to the tunica in three cases. Scrotal skin biopsies were also included in four cases which showed extensive induration,

ulceration and sinus formation. Table 2 gives the distribution of cases according to clinicopathological categories.

**Histopathological Findings:** Filarial parasites were recognized in 16 of 19 cases (Fig 2). The salient histopathological findings and location of parasite are depicted in Table 3. Three filarial parasites were identified within dilated lymphatic channels (tunica 2/19, epididymis 1/19), while parasites in the remaining 13 cases were localized within the soft tissues. A prominent inflammatory response with predominance of eosinophils was seen in the surrounding tissues, admixed with neutrophils, lymphocytes, plasma cells, and histiocytes. Cholesterol clefts and haemosiderin-laden macrophages were also seen in cases with long-standing hydrocoele. Characteristic Meyers-Kouvenaar bodies i.e., granulomata composed of epithelioid cells with Langhans and foreign body-type of multinucleated giant cells surrounding filarial parasite were also observed in six cases (31.5%) (Fig 2c). The granulomas also showed an admixture of eosinophils, neutrophils, lymphocytes and plasma cells.

Three cases in which no parasite could be identified showed an intense inflammatory infiltrate rich in eosinophils in the testicular and epididymal parenchyma; however being referral samples from endemic areas with history of associated hydrocoele (two cases) and recurrent hydrocoele (one case) a suggestion of filariasis was rendered. The viable seminiferous tubules showed changes varying from normal spermatogenesis to diffuse germ cell aplasia, however interstitial Leydig cell population was unremarkable. The spermatic cord showed marked lymphangiectasia in all cases with granulomas in one case. Scrotal skin biopsies showed ulceration of the stratified squamous epithelium with granulation tissue formation and marked acute on chronic inflammatory infiltrates.



**Fig. 1:** Cut open orchidectomy specimen showing a cystic hydrocoele sac (star) with markedly thickened wall; normal testicular parenchyma is seen pushed to one side (arrow).

**Table 1: Salient clinical features of patients with chronic FEO. B/L: bilateral (add fullstop); R: right; L: left; Y: present.**

| Case number | Age (years) | Scrotal Swelling | Scrotal pain | Fever | Side affected | Scrotal sinuses | Hydrocoele | Clinical diagnosis & indication for biopsy    | Place                      |
|-------------|-------------|------------------|--------------|-------|---------------|-----------------|------------|---|----------------------------|
| 1           | 46          | Y                | Y            | -     | L             | -               | Y          | Chronic orchitis                              | Madhya Pradesh             |
| 2           | 30          | Y                | -            | -     | B/L           | -               | Y          | Epididymal nodule                             | ?Uttarakhand               |
| 3           | 23          | Y                | -            | -     | L             | -               | -          | Epididymal nodule                             | ?Punjab                    |
| 4           | 55          | Y                | -            | -     | R             | -               | -          | Chronic orchitis                              | ?Punjab                    |
| 5           | 75          | Y                | -            | -     | R             | -               | Y          | Tubercular epididymo-orchitis with hydrocoele | Madhya Pradesh             |
| 6           | 40          | Y                | Y            | -     | L             | -               | Y          | Chronic orchitis                              | Odisha                     |
| 7           | 21          | Y                | Y            | -     | L             | -               | Y          | Hydrocoele                                    | Odisha                     |
| 8           | 35          | Y                | -            | -     | L             | -               | Y          | Chronic orchitis with funiculitis ?Tubercular | Madhya Pradesh             |
| 9           | 30          | Y                | -            | Y     | B/L           | Y               | Y          | Bilateral testicular tumour                   | Odisha                     |
| 10          | 70          | Y                | Y            | -     | L             | Y               | Y          | Tubercular orchitis                           | Odisha                     |
| 11          | 19          | Y                | -            | -     | R             | -               | Y          | Testicular tumour                             | Odisha                     |
| 12          | 72          | Y                | Y            | -     | L             | Y               | Y          | Testicular tumour with scrotal sinuses        | Odisha                     |
| 13          | 45          | Y                | -            | Y     | L             | -               | -          | Recurrent orchitis                            | Odisha                     |
| 14          | 30          | Y                | Y            | -     | L             | -               | -          | Epididymal / cord mass                        | Odisha                     |
| 15          | 46          | Y                | Y            | Y     | L             | Y               | -          | Testicular abscess                            | Odisha                     |
| 16          | 24          | Y                | -            | -     | L             | -               | -          | Calcified epididymal mass                     | Odisha                     |
| 17          | 50          | Y                | Y            | -     | R             | Y               | Y          | Testicular tumour                             | Odisha                     |
| 18          | 55          | Y                | -            | -     | R             | -               | -          | Chronic orchitis                              | Odisha                     |
| 19          | 27          | Y                | Y            | Y     | L             | -               | Y          | Fournier's gangrene, epididymo-orchitis       | Punjab, Migrant from Bihar |

**Table 2: Clinicopathological categories of patients with chronic FEO.**

| Clinicopathological categories                     | Number of cases (%) n=19 |
|--|--------------------------|
| Hydrocoele   | 12 (63.1)                |
| Lymph scrotum*                                     | 5 (26.3)                 |
| Epididymal nodules                                 | 4 (21.1)                 |
| Scrotal elephantiasis resembling testicular tumour | 3 (15.7)                 |

\*Four patients with lymph scrotum had associated hydrocoele

**Table 3: Histopathological findings of cases with chronic FEO.**

| Histological features                              | Number of cases (%) |
|--|---------------------|
| <b>Morphology of Filarial parasite</b>             | <b>(n=16)*</b>      |
| Adult filarial worm                                | 15 (93.7)           |
| – Dead, fragmented                                 | 7 (43.7)            |
| – Viable gravid                                    | 6 (37.5)            |
| – Calcified “tomb-stone” appearance                | 2 (12.5)            |
| – With few microfilaria                            | 1 (6.25)            |
| Microfilaria only, without identifiable adult worm | 1 (6.25)            |
| <b>Location of parasite</b>                        | <b>(n=16)</b>       |
| Epididymis and paratesticular tissues              | 9 (56.3)            |
| Tunica vaginalis                                   | 7 (43.7)            |
| <b>Inflammatory response to parasites</b>          | <b>(n=19)</b>       |

| Histological features   | Number of cases (%) |
|---|---------------------|
| Eosinophil rich infiltrate  | 18 (94.7)           |
| Lymphangiectasia, thrombosed blood vessels, stromal fibroblastic reaction     | 19 (100)            |
| Meyers-Kouvenaar bodies   | 6 (31.5)            |
| Haemosiderin-laden macrophages cholesterol clefts                             | 3 (15.7)            |
| Epithelioid cell granulomas with caseation necrosis (associated tuberculosis) | 1 (5.2)             |
| <b>Changes in viable seminiferous tubules</b>                                 | <b>(n=14)</b>       |
| Partial atrophy   | 6 (42.8)            |
| Early maturation arrest   | 4 (28.5)            |
| Normal spermatogenesis  | 3 (21.4)            |
| Germ cell aplasia   | 1 (7.1)             |

\*In three cases, filarial parasite could not be identified (see text).

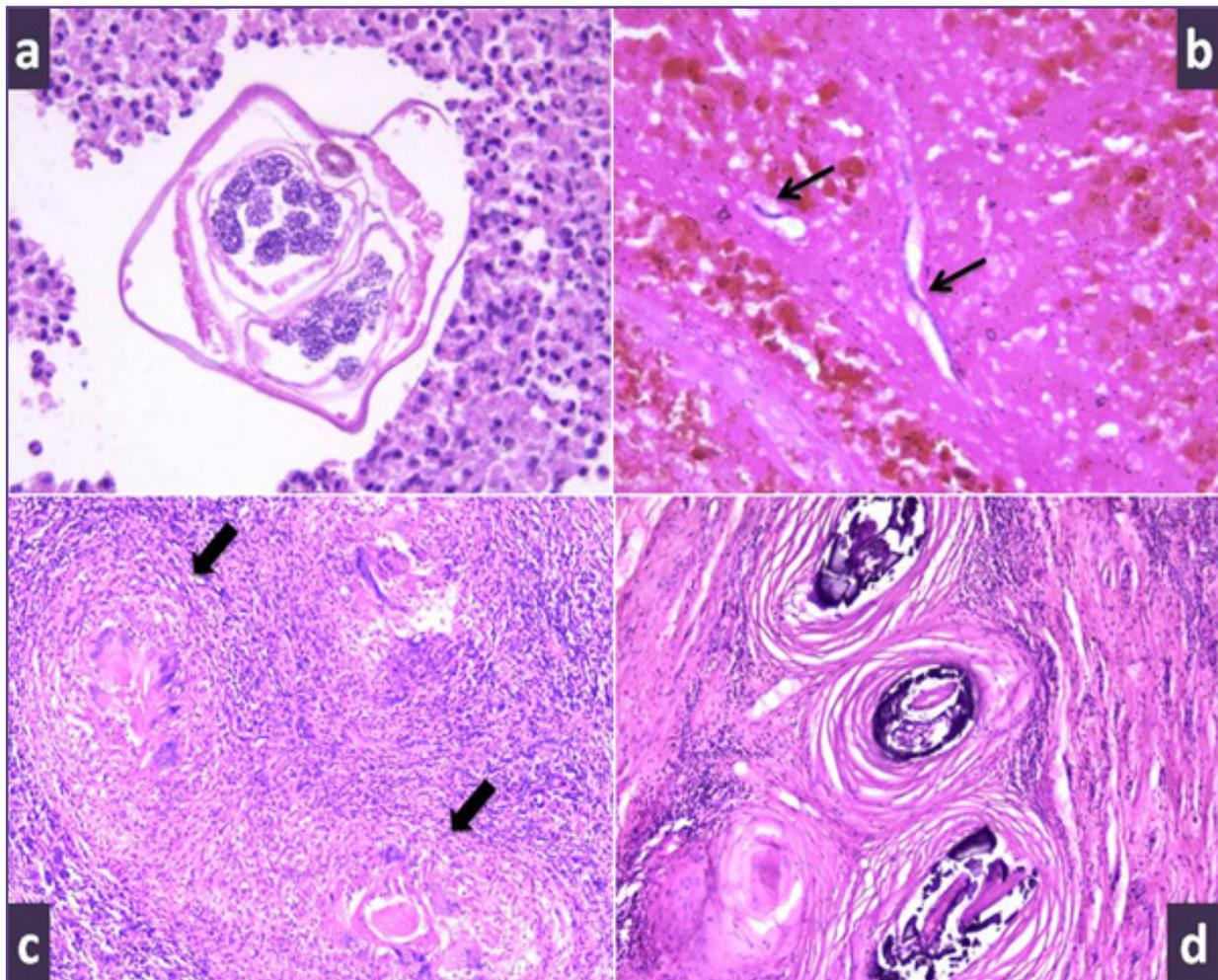


Fig. 2: (a) Filarial epididymo-orchitis with viable gravid adult filarial parasite; (b) microfilariae in tissue section (arrow); (c) Meyers-Kouvenaar bodies surrounding remnants of filarial parasite (block arrows); (d) reaction around dead and degenerating parasite - "parasite onion" appearance. H&E.

## Discussion

Chronic LF continues to prevail as a major public health problem in India. The incidence of chronic FEO among testicular and paratesticular biopsies was found to be 1.8% in our series, which is higher than the incidence of 0.8% reported in other parts of India.<sup>[10]</sup> In an autopsy study in Puerto-Rico, the incidence of male genital filariasis was found to be 3.9%.<sup>[11]</sup>

In our study, majority of patients were from the states of Odisha and Madhya Pradesh. Among the four cases diagnosed in the non-endemic states of Punjab and Uttrakhand, one patient was a migrant labourer from Bihar, while in the other cases history of travel to endemic areas or ethnicity could not be ascertained. The endemic areas for LF include Bihar, Kerala, Andhra Pradesh, Odisha, West Bengal, Madhya Pradesh, Tamil Nadu, Gujarat, and Uttar Pradesh, which add upto 95% of the total national burden of filariasis.<sup>[12,13]</sup> Rare cases of filariasis have been reported from non-endemic regions of Uttrakhand and Punjab, which are due to migration from endemic areas.<sup>[14,15,16]</sup>

In the present series, the commonest mode of presentation was hydrocoele (63.1%), with few having symptoms of acute filariasis like scrotal pain, fever, and inguinal lymphadenopathy. Hydrocoele accounts for upto 90% of genital bancroftian filariasis in males, but is rare with *B. malayi*.<sup>[17]</sup> Individuals with chronic LF are prone to repeated acute attacks presenting as scrotal pain, fever and inguinal lymphadenopathy.<sup>[8,18]</sup> LF has a wide clinical spectrum ranging from microfilaremia with down-regulated immune responses, to lymphoedema or hydrocoele, with few parasites but vigorous specific immune responses.<sup>[7]</sup>

Lymph scrotum presents as multiple sinuses oozing chyle through markedly deformed scrotal skin and results from superficial scrotal lymphangiomas.<sup>[8]</sup> Thickening of the scrotal sac and its contents as a result of long-standing lymph accumulation and low grade inflammation leads to scrotal elephantiasis. Elephantiasis may be the end result of scrotal involvement and may clinically present as a solid, tumour-like mass.<sup>[19]</sup> In our study, the pre-operative diagnosis in majority was either inflammatory orchitis or testicular tumour. Since the clinical picture of chronic genital LF greatly mimics other diseases like pyocoele, hematoceole, tuberculosis and malignancy, it often results in unilateral orchidectomy.<sup>[20]</sup>

In 21.1% of cases palpable epididymal nodules were found. Epididymal nodules correspond to the inflammatory reaction around dead adult worm in tissues. The adult worms coil tightly as they die and thus, in spite of the

length of parasite, the diameters of nodules are less than 2-3 cm in size.<sup>[21]</sup>

Histopathological findings of filariasis consists of distinct morphological features related to the presence of live or dead parasites associated with blockage and destruction of the lymphatic system.<sup>[22, 23]</sup> A large proportion (56.3%) of filarial worms in this study were found within epididymal and/or paratesticular soft tissues or lymphatics, while the remaining were identified within the tunica vaginalis. Histological tissue reaction is minimal around live filariae, and almost all are found completely free within the lumen of a lymphatic vessel.<sup>[22]</sup> A prominent inflammatory response in tissues results from either spontaneous or drug-induced death of worms.<sup>[24]</sup> Lethally injured adult worms may rupture their external membranes and eosinophils can be seen surrounding or attached to the adult worm cuticle.<sup>[23]</sup> A brightly eosinophilic Splendore-Hoeppli phenomenon may also be seen surrounding MF or adult worms.<sup>[24]</sup>

In this study we also identified MF larvae within the tunica, surrounded by a dense fibrinopurulent inflammatory reaction. Rare account of dead and degenerating MF adherent to the walls of lymphatic vessels and within paratesticular tissues has been reported.<sup>[25]</sup> In the later stages, the parasite may become calcified and surrounded by a thick fibrotic capsule called “parasite onion”, representing dead filarial “tombstone”.<sup>[4]</sup> Thickening and dilatation of the spermatic cord lymphatics may lead to funicular lymphangiomas. The lymphatic channels may also show endolymphangitis with thrombus formation.<sup>[19]</sup>

Meyers-Kouvenaar bodies comprised of macrophages, giant cells, eosinophils, lymphocytes and plasma cells are formed around dead worms.<sup>[7,20]</sup> Multiple patterns of immune response can be seen in the same patient – eosinophil rich granulation tissue, neutrophilic abscesses and multinucleate giant cells – implying induction of more than one type of immune response.<sup>[25]</sup> In the present series, one case was diagnosed with concomitant tubercular epididymo-orchitis due to extensive areas of caseation necrosis. Literature search revealed rare case report of tubercular orchitis with coexistent filarial infestation of the spermatic cord.<sup>[26]</sup>

Adult filarial worms elicit a  $T_H2$  helper T cell response resulting in peripheral blood and tissue eosinophilia.<sup>[27]</sup> Eosinophil degranulation disrupt filarial worms via eosinophil peroxidase, major basic protein and eosinophil cationic protein.<sup>[24]</sup> A  $T_H1$ -mediated immune response causes formation of granulomas around parasites.<sup>[27]</sup>

Diethylcarbamazine (DEC) is considered the drug of choice as it is effective against both MF and adult worms. The Global Programme to Eliminate Lymphatic Filariasis plans to eradicate LF by 2020 via mass drug administration with preventive chemotherapy to populations at risk to prevent morbidity of disease.<sup>[28]</sup>

**Conclusion:** This study from Punjab identifies chronic FEO as an important cause of scrotal swelling in non-endemic states like Punjab and Uttarakhand. Since Punjab has significant migrant population, filariasis may become rampant in Punjab if steps are not taken to control it. Clinically FEO may be mistaken for a testicular tumour, hence awareness of the clinicopathological spectrum is essential. For the pathologist, testicular and paratesticular biopsies with intense infiltration by eosinophils and lymphangiectasia need high index of suspicion for filariasis and warrant careful search for adult filarial worm as well as microfilaria in tissue sections.

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