

# Study of Extrapulmonary Tuberculosis in a Tertiary Care Hospital

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## ABSTRACT

**Introduction:** India ranks fourth among the global Tuberculosis (TB) burden. Mycobacterium TB is the causative organism. The extrapulmonary involvement accounts for 10% to 42% of cases among them the pleura, lymph node and kidney are the most common organs affected. Other organs affected are quite rare.

**Aim:** To study clinical features, anatomical site and histological findings of the cases with extrapulmonary TB.

**Materials and Methods:** A prospective case series study was conducted in a tertiary care hospital for a duration of one year consisting of six cases of TB. Detailed History taking and clinical examination was done followed by blood investigations and radiological evaluation. Gross examination of the specimens followed by histopathological reporting was done. Ziehl-Neelsen (ZN) stain was also performed for the confirmation of the diagnosis.

**Results:** The present study describes six cases of TB each involving kidney, breast, endometrium, testis and two cases involving spleen. Affected patients mostly belonged to third and fourth decades of life with equal male and female distribution. All the patients underwent treatment, started on Anti-Tubercular Drugs (ATD) and were followed up as well.

**Conclusion:** TB presents with a varied spectrum of symptoms. In countries like India where TB is widely prevalent, it is always suggested to keep the rare possibility of extrapulmonary TB in mind when patients report. A detailed history, combined with thorough physical examination and vital investigations are necessary, particularly in identifying atypical forms of extrapulmonary TB. Histopathological examination is essential for confirmation. Management with ATD is effective.

**Keywords:** Breast, Endometrium, Kidney, Spleen, Testis

## INTRODUCTION

India accounts for one fourth of the global TB burden. Mycobacterium TB is the causative organism. TB affects various organs and consists of a wide range of clinical symptoms. A 10% to 42% cases include extrapulmonary involvement and the commonest organs involved are pleura, lymph node and kidney [1-4]. Other organs affected are relatively rare. The present study describes six cases of TB, highlighting the diagnostic dilemmas faced during the work up with an aim to expand on available literature and to emphasise on the need for careful scrutiny in the evaluation of these cases, both from a clinical and a pathological point of view.

## MATERIALS AND METHODS

A prospective case series study was conducted in a tertiary care hospital for duration of one year from April 2019 to April 2020 consisting of six cases of TB. Approval of the study was taken from Institutional Ethics Committee. Informed consent was taken. The patients presented with varied clinical features according to their site of infection. Proper history taking and clinical examination was done followed by blood investigations and radiological evaluation.

Specimens or biopsy specimens was sent for further processing. Gross examinations were done, sections were taken from the representative areas. Different sections were embedded in paraffin, and cut and stained by haematoxylin and eosin. The sections were reported using a light microscope. ZN stain was also performed for the confirmation of the diagnosis.

## STATISTICAL ANALYSIS

Demographic, clinical and laboratory data for each patient was recorded in statistical forms. Results were analysed using Microsoft excel 2016 and GraphPad InStat 3.

## RESULTS

Distribution of the cases are shown in [Table/Fig-1].

Site of lesion	Number of cases (N=6)	Age range (in years)	Sex (N=6)	
			Male	Female
Spleen	2	28-62 (45.0)	1	1
Breast	1	38	0	1
Kidney	1	35	1	0
Endometrium	1	45	0	1
Testis	1	50	1	0

[Table/Fig-1]: Showing the distribution of cases (N=6).

## TB of spleen

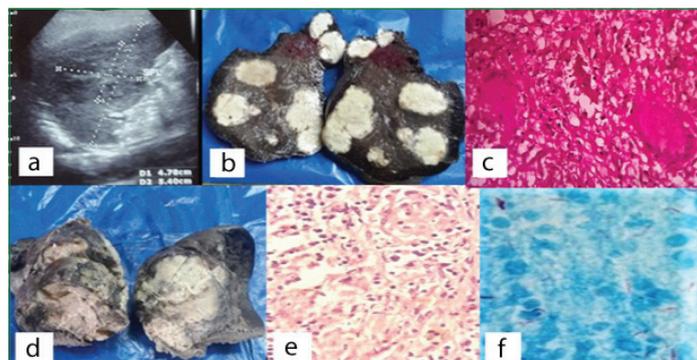
### Case 1:

A 28-year-old female reported with complaint of fever, pain in abdomen and weight loss for six months. Her medical history was not so significant. An abdominal ultrasound showed multiple anechoic, crescentic cystic lesions (up to 23 mm) in the spleen [Table/Fig-2a]. A Mantoux test was also performed and showed an induration of 12x12 mm without any erythema, which was considered as a positive test. Chest X-ray did not reveal any lung parenchymal lesions. The patient underwent a splenectomy. The spleen showed multiple, small, greyish white nodular structures [Table/Fig-2b] which on histopathological examination showed extensive caseous necrosis with epithelioid granuloma formation and presence of Langhans giant cells suggestive of a tubercular granulomatous lesion [Table/Fig-2c]. ZN staining revealed presence of Acid Fast Bacilli (AFB), confirming the diagnosis. Following this, ATD therapy was initiated. The symptoms reduced in the post splenectomy period.

### Case 2:

A 62-year-old male presented with complaints of fever and pain in abdomen since three months. On ultrasonic imaging, abdomen, revealed an enlarged spleen showing a large, thick

walled hypoechoic Space Occupying Lesion (SOL) measuring 6.2x5.5 cm at the mid pole showing predominantly peripheral vascularity, suspicious of a splenic abscess. The patient underwent splenectomy for the splenic abscess. The specimen measured 8x8x3cm with a large whitish nodular area measuring 5x4cm was noted on cut-sections [Table/Fig-2d]. Microscopic examination revealed multiple granulomas comprising of epithelioid cells and multinucleate langhans giant cells, features were suggestive of Koch's lesion [Table/Fig-2e]. ZN stain showed presence of AFB which confirmed the diagnosis [Table/Fig-2f]. ATD therapy was started and complete recovery was reported on follow-up.



**[Table/Fig-2]:** Tuberculosis of spleen: (a) USG showing multiple anechoic, crescentic cystic lesions in the spleen; (b) Gross specimen; (c) Section showing epithelioid granuloma with multinucleate giant cells (x400, H&E); (d) Gross specimen; (e) Section showing epithelioid granuloma (x400, H&E); (f) ZN stain showing presence of AFB in the section (x100, oil immersion).

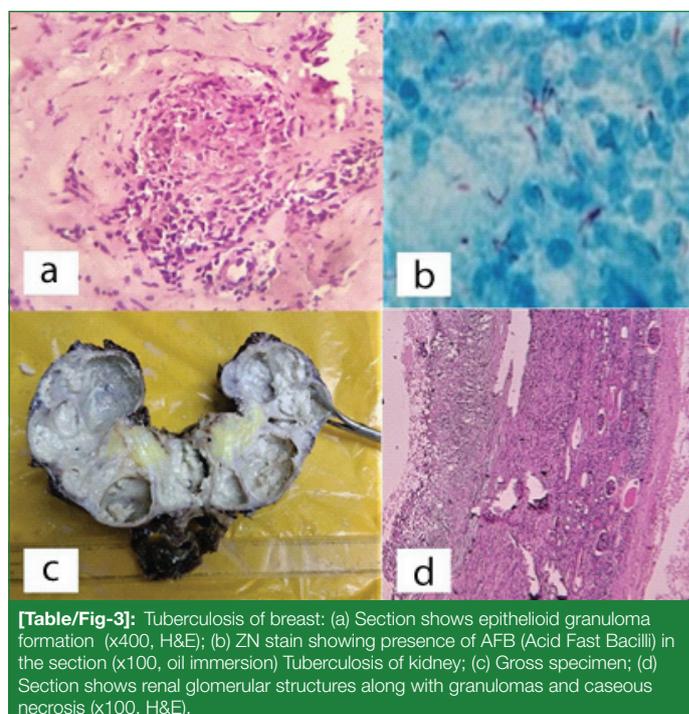
### Case 3: TB of breast:

A 38-year-old female presented with a tender breast lump for last four months. The patient was febrile and had no family history of breast carcinoma. On clinical examination, tender mass measuring 5x6 cm was noted in the lower outer quadrant of left breast. No nipple discharge or skin retraction was seen. Absence of axillary or cervical lymphadenopathy was noted. Examination of other systems was within normal limit. She had no past history of pulmonary TB. Breast Ultrasound Sonography Test (USG) showed a heterogenous thick walled cystic mass. Fine Needle Aspiration Cytology (FNAC) was performed, pus was aspirated and the smear showed granuloma formation. This was followed by tru-cut biopsy. Histological examination showed multiple granulomas comprising of epithelioid cells with caseous necrosis, features were suggestive of tubercular infection [Table/Fig-3a]. ZN staining revealed presence of AFB [Table/Fig-3b], confirming the diagnosis. Pus culture was also positive for AFB. Following this, the patient was started on ATD. The symptoms reduced on follow-up.

### Case 4: TB of kidney:

A 35-year-old male presented with intermittent pain in the area between upper abdomen and back and fever since last two months. Three months earlier, the patient had an episode of gross haematuria. The patient had no past history of pulmonary TB. Clinical examination revealed bimanually palpable ballotable swelling in the left hypochondrium. Blood investigations revealed a raised Erythrocyte Sedimentation Rate (ESR). Contrast Enhanced Computed Tomography (CECT) scan showed a heterogenous mass of lesion with areas of necrosis involving the left kidney. Aorticaval and paraaortic lymph nodes were enlarged.

The patient underwent left radical nephrectomy. Grossly, specimen measured 8x7 cm. On cut open, caseous material and areas of necrosis were noted [Table/Fig-3c]. Histology showed extensive caseous necrosis with epithelioid granuloma formation and langhans giant cells suggestive of a tubercular granulomatous lesion [Table/Fig-3d]. ZN staining revealed presence of AFB, confirming the diagnosis. The patient was then started on ATD and reported complete recovery on follow-up.



**[Table/Fig-3]:** Tuberculosis of breast: (a) Section shows epithelioid granuloma formation (x400, H&E); (b) ZN stain showing presence of AFB (Acid Fast Bacilli) in the section (x100, oil immersion) Tuberculosis of kidney; (c) Gross specimen; (d) Section shows renal glomerular structures along with granulomas and caseous necrosis (x100, H&E).

### Case 5: TB of endometrium:

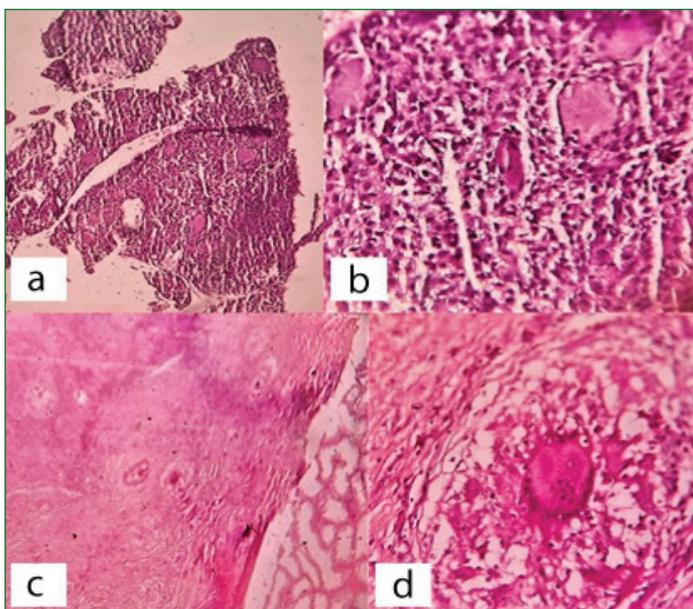
A 45-year-old female nullipara presented with menorrhagia for one year. This was also associated with history of intermenstrual bleeding. Clinically, pelvic and perineum showed no abnormality, uterus was not tender and enlarged. Cervix appeared normal on speculum examination, with no discharge from the external os. Examination of other systems showed no abnormality. Transvaginal pelvic ultrasound showed endometrial hyperplasia. Endometrial biopsy was performed by dilatation and curettage. Histology showed endometritis with presence of granuloma with caseous necrosis and langhans giant cells suggestive of TB [Table/Fig-4a,b]. ZN stain showed presence of AFB which confirmed the diagnosis. The patient was then started on ATD. On follow-up, normal menses was resumed.

### Case 6: TB of testis:

A 50-year-old male presented with right-sided testicular swelling for last three months. Clinical examination showed testicular swelling of 3x2 cm which was gradually increasing without any discharging sinus or scrotal ulceration. Systemic examination was unremarkable. USG revealed heterogenous mass lesion of 4x3 cm arising from right testis. Left testis was normal. Then, the patient underwent Magnetic Resonance Imaging (MRI) examination of the right testicle which revealed 4x3 cm space occupying formation on the right scrotum. The case was mistaken as testicular tumour and orchidectomy was performed. Histopathological examination showed extensive caseous necrosis with epithelioid granuloma formation and langhans giant cells suggestive of a tubercular granulomatous lesion [Table/Fig-4c,d]. ZN staining revealed presence of AFB, confirming the diagnosis. The patient was commenced on ATD and was under follow-up.

## DISCUSSION

The global TB report published by the World Health Organization (WHO) in the year 2017 has enlisted India in the top 20 in terms of incidence of TB and Multidrug Resistant TB [5]. The annual TB report published by the Government of India estimated the incidence of TB at 28,00,000 cases [6]. The rampant nature of this disease makes it essential to discuss the spectrum of clinical presentations observed in this infection. Apart from the lungs, TB can affect lymph nodes, the genitourinary tract, bones, meninges, gastrointestinal tract, skin as well as serosal surfaces [7].



**[Table/Fig-4]:** Tuberculosis (TB) of endometrium: (a) Section shows caseous necrosis, epithelioid granulomas, multinucleate giant cells (x100, H&E); (b) Section showing epithelioid granuloma with caseous necrosis (x400, H&E) Tuberculosis (TB) of testis; (c) Section shows seminiferous tubules along with epithelioid granuloma (x100, H&E); (d) Section shows Langhans type of giant cell (x400, H&E).

About 11% of cases of extra pulmonary TB affect abdominal organs, usually the GIT or liver [8]. Immunosuppression, preceding pyogenic infections, trauma, sickle cell disease or other haemoglobinopathies and primary infection by TB in a different organ are all considered to be risk factors associated with acquiring TB in the spleen [4]. The common form of infection is when it occurs as part of miliary TB, observed in immunocompromised individuals and usually affecting the liver and lungs. Primary infection of the spleen is considered less common [8]. A differential diagnosis of cysts (tubercular or hydatid), haematoma, fungal infection, abscesses, infarcts, vascular tumours, lymphomas or metastatic tumours should be considered. Two patients presented with complaints of fever and abdominal pain with radiological findings of a splenic pathology without prior history of TB. Neither FNAC nor Core Needle Biopsy (CNB) was performed in the either cases, due to the suspicion of hydatid cysts and splenic abscess. Both cases were clinically deceptive and were diagnosed by histopathology. Ultimately, both patients underwent splenectomy and were started on anti-tubercular therapy based on the histopathological report. On follow-up, both patients showed recovery to normal health.

In 1829, Sir Astley Cooper first described mammary TB [9]. It is an exceptionally rare condition with an incidence of 0.1% of all breast lesions in Western countries and 4% of all breast lesions in TB endemic countries [10]. It is categorised as primary and secondary, of which primary is rather infrequent [11]. In the present case of breast TB, as there were neither foci of additional TB on physical or radiological inspection nor any prior history of TB, breast was the primary focus. On the basis of clinical, radiological, pathological, breast TB is classified into three forms: nodular, disseminated and sclerosing [12,13]. Nodular form is most common and diagnostically mimics fibroadenoma or carcinoma [14]. Histological study of the tissue sample, aspirate culture and Polymerase Chain Reaction

(PCR) for mycobacterium are the most dependable and definitive investigations. Of all TB cases, urogenital TB is diagnosed in 1.1-1.5% cases and 5-6% among extrapulmonary TB [15]. It mostly affects male aged between 30 and 50 years old. Miliary TB generally affects the renal cortex because of its high oxygen tension. Clinically and radiologically, it mimics renal cell carcinoma, lymphoma, metastasis and abscess. Accordingly, the patient undergoes surgery for the affected kidney, whose histopathological study surprisingly establishes the diagnosis of TB [16,17].

In gynaecology, female pelvic TB is one of the most under diagnosed conditions. In young women, an increase in extrapulmonary TB is being reported worldwide. In India, of all gynaecological admissions, incidence of genital TB is 0.75 to 1% [18]. Majority of female genitourinary TB are asymptomatic, so they are difficult to diagnose (11%) [19]. When TB affects endometrium, it causes either acute or chronic endometritis so as in this case. Histopathological examination is the basis for final diagnosis.

Testicular TB is extremely rare, comprising of only 3% of genital TB [20]. Testicular TB occurs commonly in a disseminated form, isolated testicular TB is extremely rare. The commonest site of genital TB in men is epididymis followed by seminal vesicles, prostate, testis and the vas deferens [21]. Testicular involvement is caused by local spread or retrograde seeding from the epididymis [22,23]. So, testicular TB without epididymal involvement is exceptionally rare, so as seen in one of the cases. In elderly age group, testicular TB mimics testicular malignancy.

All the patients were considered immunocompetent, in view of the negative HIV serology and also a negative history of recurrent infections or ulceration. The presence of granulomas points towards a competent immune system. These cases appear to have affected the organs in isolation, as noted by radiological investigations. This misled the search for TB in these patients. Microbiological investigations are essential in establishing the diagnosis and range from simple tests like culture to higher end techniques as the Cartridge Based Nuclear Acid Amplification Test (CBNAAT) PCR. High costs and requirement of sophisticated laboratory infrastructure makes it of limited use in developing countries. Regarding management, combined pharmacotherapy with rifampicin, isoniazid, pyrazinamide and ethambutol is the suggested protocol for both pulmonary and extrapulmonary TB [24]. Evidence suggests that anti tubercular therapy can prove beneficial in eradicating the infection in most cases. Details of few cases of extrapulmonary TB reported earlier in literature from world along with comparison with present case series is shown in [Table/Fig-5] [8,13,24-31].

## CONCLUSION(S)

TB presents with a varied spectrum of symptoms. In countries like India where TB is widely prevalent, it is always suggested to keep the rare possibility of extrapulmonary TB in mind when patients present. A detailed history, combined with thorough physical examination and vital investigations are necessary, particularly in identifying atypical forms of extrapulmonary TB. Culture is also an essential step in diagnosis. Sophisticated techniques like PCR may not be available in a setup with limited resources. Histopathological examination is essential for confirmation. Management with ATD is effective.

Author's name and year and type of study	Site	Diagnostic modalities	Radiographic features	Type of specimen	Microscopic features	Outcome
Wangai F et al., 2017 [24] (Case report)	Spleen	CBC, CRP, ESR, ZN stain, USG, CT scan	USG: Hypoechoic mass was present in spleen. CT scan: Enlarged spleen with multiple hypodense non-enhancing nodules.	Core needle biopsy	Extensive granulomas, mainly necrotising with multinucleate histiocytes, eosinophils and areas of fibrosis.	No adverse events were reported. Patient did well and had completed the anti-TB therapy.
Ray S et al., 2012 [8] (Case report)	Spleen	CBC CXR, ESR, Mantoux test, USG, CT scan, ZN stain	USG: Enlarged spleen with multiple hypoechoic areas. CT scan: Multiple well-defined hypodense lesions in spleen.	CT-guided FNAB (Fine needle aspiration and biopsy)	Granulomas with areas of caseation in the centre surrounded by langhans giant cells and epithelioid cells.	Regimen of anti-TB therapy was given. No signs of recurrence till date.

Singal R et al., 2013 [25] (Case report)	Breast	CBC, ESR, CXR, ZN stain	--	FNAC	Granulomas, epithelioid cells, and mixed inflammatory cells and necrotic material in background	Regimen of anti-TB therapy was given. No signs of recurrence till date
Gupta R et al., 2012 [13] (Case report)	Breast	CBC, ESR, CXR, USG, ZN stain	USG: Hypochoic lesion with multiple internal echoes in right breast	FNAB	Caseating granuloma with epithelioid cells	Patient recovered well after anti-TB medication.
Chaker K et al., 2019 [26] (Case report)	Kidney	CBC, ESR, CT scan, ZN stain	CT scan: Large heterogeneously enhancing mass in the right kidney	Radical nephrectomy	Numerous confluent caseating granulomas	Treatment with anti-TB drugs was started.
Kumar S et al., 2014 [27] (Case report)	Kidney	CBC, ESR, CXR, CECT, ZN stain	CT scan: Heterogeneously enhancing lesion with areas of necrosis, involving the right kidney.	Radical nephrectomy	Multiple granulomas with caseating necrosis	Patient completed her antitubercular therapy and after one year of follow-up was free of TB.
Esa NYM et al., 2017 [28] (Case report)	Endometrium	CBC, CXR, USG, Mantoux test, ZN stain	USG: No abnormality detected	Endometrial sampling	Caseating granulomatous inflammation	Patient resumed normal menses completed the regime of anti-TB treatment.
Shirazi M et al., 2015 [29] (Case report)	Endometrium	CBC, CXR, USG, ZN stain	USG: Heterogenic hypochoic solid mass lying posteriorly on the uterus suspicious of degenerated leiomyoma.	Hysterectomy	Epithelioid cells and langhans type giant cells lymphocytes, plasma cells, surround a central area of necrosis	The patient underwent anti-TB therapy. During a two-year follow-up, no relapse was detected.
Hamrouni IE et al., 2017 [30] (Case report)	Testis	CBC, CRP, color doppler USG, ZN stain	USG: Enlargement of the left epididymis and multiple hypochoic avascular micronodules scattered throughout the left testis.	Orchidectomy	Multiple necrotising granulomas with multinucleated giant cells.	Patient recovered well after anti-TB medication.
Das A et al., 2016 [31] (Case report)	Testis	CBC, FBS, Mantoux test, CXR, USG, ZN stain	USG: Left testis was enlarged with heterochoic space occupying lesion with hypochoic components and small cystic areas	USG guided FNAC	Epithelioid cell granulomas in a background of large amount necrosis and mixed inflammatory cells	Complete resolution of left testicular swelling at the end of anti-TB treatment.
Present study (Case series)	Spleen	CBC, Mantoux test, CXR, USG, ZN stain	USG: Multiple anechoic, crescentic cystic lesions in spleen	Splenectomy	Caseous necrosis with epithelioid granuloma formation and presence of langhans giant cells	ATD therapy was initiated. The symptoms reduced in the post splenectomy period.
	Spleen	CBC, USG, ZN stain	USG: Enlarged spleen showing a large, thick walled hypochoic SOL, suspicious of a splenic abscess	Splenectomy	Multiple granulomas comprising of epithelioid cells and langhans giant cells	ATD therapy was started and complete recovery was reported on follow-up
	Breast	CBC, CXR, USG, FNAC, ZN stain,	USG: Heterogenous thick walled cystic mass.	Tru-cut biopsy	Multiple granulomas comprising of epithelioid cells with caseous necrosis	Patient was given ATD. The symptoms reduced on follow-up.
	Kidney	CBC, ESR, CECT scan, ZN stain	CECT scan: Heterogenous mass of lesion with areas of necrosis involving the left kidney. Aortocaval and paraaortic lymph nodes were enlarged.	Radical nephrectomy	Extensive caseous necrosis with epithelioid granuloma formation and langhans giant cells	Patient was on ATD and reported complete recovery on follow-up
	Endometrium	CBC, USG, ZN stain	USG: Endometrial hyperplasia	Endometrial biopsy	Endometritis with presence of granuloma with caseous necrosis and langhans giant cells	Started on ATD. On follow-up she resumed her normal menses
	Testis	CBC, USG, MRI, ZN stain	USG: Heterogenous mass lesion in right testis MRI: space occupying lesion on right testicle	Orchidectomy	Extensive caseous necrosis with epithelioid granuloma formation and langhans giant cells	He was commenced on ATD and was under follow-up.

**[Table/Fig-5]:** Review of cases of extrapulmonary Tuberculosis (TB) reported earlier in literature worldwide [8,13,24-31].

ZN: Ziehl-neelsen; FNAC: Fine needle aspiration cytology; FBS: Fasting blood sugar test; CRP: C-reactive protein; CT: Computerized tomography; FNAB: Fine needle aspiration biopsy; ATD: Anti-tubercular drugs

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