

Clinicopathological spectrum of extrapulmonary tuberculosis in a tertiary care centre of Western Uttar Pradesh with review of literature and special emphasis on the rare sites involved

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Abstract

Background: Although extra pulmonary tuberculosis (EPTB) has existed as a disease entity for decades together, it has gained increased importance recently because of the increase in the number of cases. This increase has been observed after the emergence of HIV epidemic and also because of the diagnostic difficulty faced due to its obscure presentation.

Aims: The current study aims at analysing the various cases of EPTB diagnosed in our hospital in relation to their occurrence at various sites, age and sex predilection and modalities of diagnosis laying special emphasis on histopathology. We have attempted to study the spectrum, distribution and challenges in the diagnosis of EPTB especially when involving rare sites in the body.

Material and Methods: The present study is a retrospective one. The duration of study was two and a half years. We identified and segregated the cases of EPTB in our hospital which is a tertiary care centre of Western UP. A total of 103 cases were retrieved and analysed according to the age, sex, site specific distribution laying impetus on the rare sites involved.

Results: Out of the 103 cases, the maximum number of cases i.e.25 involved the skin(24.27%) followed second in line by lymph nodes(20.39%) in which 20 cases were reported. Rare sites like middle ear, eyelid, oral vestibule, thyroid, vulva and scrotum were also found to be involved. Maximum number of cases belonged to the age group of 21-30 years in both the sexes. The M:F ratio was 1:1.2.

Conclusion: EPTB is an important clinical problem in developing countries like India. The diagnosis is often missed due to the variable presentation as it can involve uncommon sites as well. Standard guidelines for its precise diagnosis and treatment are the need of the hour to lessen its burden on the existing health system.

Keywords: Tuberculosis, Extrapulmonary tuberculosis, Rare sites, Histopathology, Diagnosis.

Introduction

Tuberculosis has been a global health concern since ages especially in a developing country like ours. WHO claims that India has the highest incidence of tuberculosis in the World with 8.6 million new cases diagnosed every year.^[1]

Mycobacteria may spread to any organ of the body through lymphatic or haematogenous dissemination and lie dormant for years at a particular site before causing symptoms or disease. Manifestations may relate to the system involved, or there may be constitutional symptoms such as prolonged fever, anorexia, weight loss, malaise and fatigue. In these cases, diagnosis may be elusive and is usually delayed. Extrapulmonary tuberculosis(EPTB) is defined as patients with tuberculosis of organs other than lungs such as lymph nodes, abdomen, genitourinary system, musculoskeletal and meninges.^[2]

A retrospective study was carried out to identify the cases of extrapulmonary tuberculosis, and later on were analysed in accordance with various other parameters.

Material and Methods

The present study was a retrospective one. We obtained permission from the institutional ethical committee to study the cases of extrapulmonary tuberculosis that were diagnosed in the department of

Pathology in Rohilkhand Medical College and Hospital, a tertiary care institute. The period of study was two and a half years from May 2013 to November 2015. Inclusion and exclusion criteria were set. All the cases that were diagnosed as tuberculosis in organs other than lung by microscopic examination of the histopathological sections were included in the study. As per WHO guidelines, a patient with both pulmonary and extrapulmonary tuberculosis was labelled as having pulmonary tuberculosis and therefore excluded from the present study.^[3]

Biopsies received in the department were subjected to routine processing followed by H& E staining. Modified Ziehl Neelsen(ZN) staining for Acid Fast Bacilli was done in all the cases. Other investigations such as culture (Lowenstein Jenson media), serology, imaging studies including chest radiographs, sputum examination, PCR etc. were correlated with the histopathological diagnosis. These investigations were also used to rule out involvement of lung parenchyma there by reaching to the final diagnosis of EPTB.

Observations and Results

A total of 103 cases of extrapulmonary tuberculosis were included in the present study. A histopathological diagnosis based on gross, microscopic examination was made and correlated with other investigations also.

Table 1 demonstrates the distribution of EPTB cases in terms of the various sites involved.

It can be concluded from Table 1 that the highest number of cases of EPTB i.e.25 were reported in the skin(24.27%) followed by 20 cases(19.42%) in the lymph nodes(Fig. 1a). The various subtypes of cutaneous tuberculosis that were observed in our study were lupus vulgaris(11 cases), tuberculosis cutis(8 cases), tuberculosis verrucosa cutis(5 cases), scrofuloderma(1 case). 17 cases of tuberculosis involving the musculoskeletal system(16.5%) at sites such as bones, joints, tendon were reported. Other sites where EPTB was diagnosed were intestine (Fig. 1b), omental tissue (15cases/14.56%) and female genital tract (10 cases/9.71%). Of all the cases reported in female genital tract, 8 cases were reported in the endometrium. A single case of fallopian tube involvement was seen. The case of EPTB in the fallopian tube was clinically interesting as it had a coexistent pathology of dermoid cyst, the wall of which showed tubercles(Fig. 3a). Another rare site to get involved was vulva. 4 cases(3.88%) were observed in the head and neck region with one case each reported in eye lid(Fig. 1c), middle ear, oral vestibule and thyroid.3 cases of EPTB were seen in breast biopsy specimens(2.91%) in which all the cases showed positivity for acid fast bacilli. 2 cases(1.94%) was reported in the male genital system in which one case involved the testis(Fig. 1d) and other involved the scrotum. 1 case(0.97%) of tuberculosis was reported in kidney. The distribution of the cases of EPTB according to the anatomical site has been illustrated in Fig. 2.



Fig. 1: Showing the gross and clinical pictures (a) gross specimen of matted tubercular nodes in cut section, (b) cut section of intestinal wall showing thickened grey white areas, (c) clinical picture of a patient with a pea sized eyelid swelling, (d) cut section of the testis is showing grey white areas involving the testicular tissue

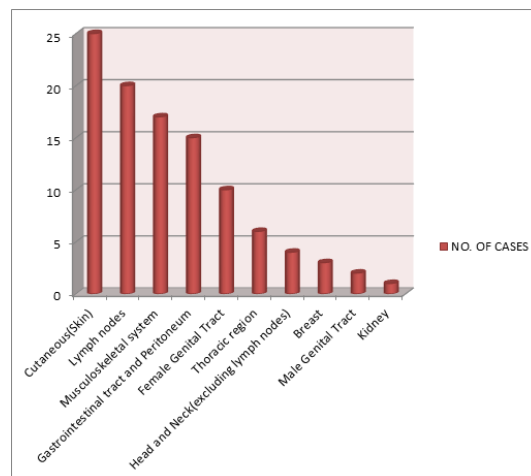


Fig. 2: Showing site specific distribution of the cases

Table 1: Showing the site specific distribution of EPTB

S. No.	Site	No. of cases	Percentage (%)
1	Cutaneous(Skin)	25	24.27
2	Lymph nodes	20	19.42
3	Musculoskeletal system	17	16.50
4	Gastrointestinal tract and Peritoneum	15	14.56
5	Female Genital Tract	10	9.71
6	Thoracic region	06	5.82
7	Head and Neck(excluding lymph nodes)	04	3.88
8	Breast	03	2.91
9	Male Genital Tract	02	1.94
10	Kidney	01	0.97
	Total		103

Here it is also important to highlight those cases where rare sites were involved and clinical signs and symptoms were obscure. In a 30 year old male, clinically diagnosed as intestinal obstruction, segment of intestine, including appendix were sent for histopathology. On grossing the appendix, the wall was thickened. Histopathology revealed well formed caseating epithelioid cell granulomas(Fig. 3b). In another case, a 50 year old female came with complaints of painful right wrist swelling since one year. In this case, tubercular pathology was suspected clinically and synovial biopsy was done. The biopsy was processed and it showed well formed epithelioid granulomas along with caseation and langhans giant cells(Fig. 3c). The patient was given the diagnosis of tubercular synovitis and given ATT. Lastly a 17 year old young female came with the complaints of midline swelling in neck that moved with deglutition. Ultrasound revealed a hypoechoic lesion in the thyroid. Biopsy was sent to our department which revealed well defined epithelioid cell granulomas with caseation necrosis. ZN staining for acid fast bacilli came positive.

A 32 year old Hindu female presented with two non-healing ulcers on the lateral aspect of vulva since 2 years. History of mild weight loss was elicited. Size of the lesion was 2X1X0.5 cms. She was provisionally diagnosed as having a STD, but when the patient did not respond to the treatment, punch biopsy was sent which showed well-formed granulomas, giant cells and caseation necrosis. ZN stain showed positivity for AFB. Patient promptly responded to ATT. In another instance, a 54 year old female housewife presented as an isolated right upper eyelid swelling measuring 5X8mm since 2 months. Stye and chalazion were excluded clinically and excisional biopsy was sent for histopathological examination which showed typical tubercles. Modified ZN stain showed occasional AFB. PCR for tuberculosis was positive in the biopsy specimen. In a very rare and interesting case presentation, a 45 year old male presented with a non-healing ulcer in the right side of oral vestibule. Examination showed a white patch. Histopathology of the excised tissue showed multiple epithelioid cell granulomas(Fig. 3d). AFB were demonstrated. No evidence of tubercular foci were found elsewhere in the body. A 2 year old male child presented with complaints of discharging sinus from scrotum along with swelling with no systemic symptoms. Exploration of right testis was done and tissue was sent for histopathology which showed features of tubercular pathology(Fig. 3e). No other site of spread could be found out. ZN stain for acid fast bacilli came positive(Fig. 3f).

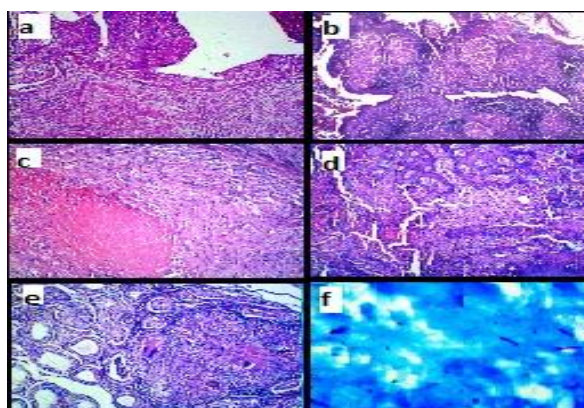


Fig. 3: Microscopic pictures: (a) wall of dermoid cyst in ovary with well-formed epithelioid cell granulomas(H&E 100X); (b) transverse section of appendix with lymphoid tissue and epithelioid cell granulomas(H&E 100X); (c) sections from wrist tissue showing abundant caseation necrosis and epithelioid cells(H&E 400X); (d) sections from oral vestibule showing epithelioid cell granulomas(H&E 100X); (e) testicular tissue showing epithelioid cell granulomas with langhans giant cells(H&E 100X); (f) Ziehl Neelsen staining showing positivity for AFB(1000X)

Table 2: Showing age and sex distribution of the cases

S. No.	Age Group	Male	Female	Total
1	1-10	5	0	5
2	11-20	10	8	18
3	21-30	18	22	40
4	31-40	7	8	15
5	41-50	4	6	10
6	51-60	4	6	10
7	Above 60	2	3	5
Grand Total		50	53	103

The data was also analysed regarding the age and sex distribution and it was observed that in both the sexes, maximum number of cases i.e. 40(38.8%) belonged to the age group of 21 to 30years followed by 11-20 years age group with 16 cases falling in that group. The minimum number of cases(5) belonged to the extremes of age group i.e. of less than 10 years and more than 60 years in both the sexes. In terms of sex distribution, there were almost equal cases in both the sexes with a slight preponderance of females. The ratio of M:F ratio being 1:1.06. The data has been illustrated in Fig. 4.

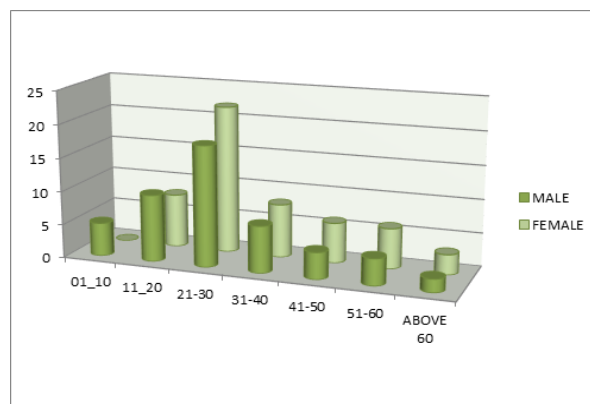


Fig. 4: Showing age and sex distribution of the cases

Diagnosis of tubercular pathology of the various sites on histopathology was followed by correlation with other investigations of the patient. Pulmonary involvement was ruled out and follow up was done to term the patient as a case of EPTB.

Fig. 5 illustrates the other diagnostic techniques besides histopathology that were also carried out during the work up for extrapulmonary tuberculosis. Modified ZN staining was employed in all the biopsies. It came out positive in 40 cases. While radiological methods like X ray, ultrasound, CT scan were done in 48 cases only. Other diagnostic techniques used were biochemistry, culture on LJ media and PCR.

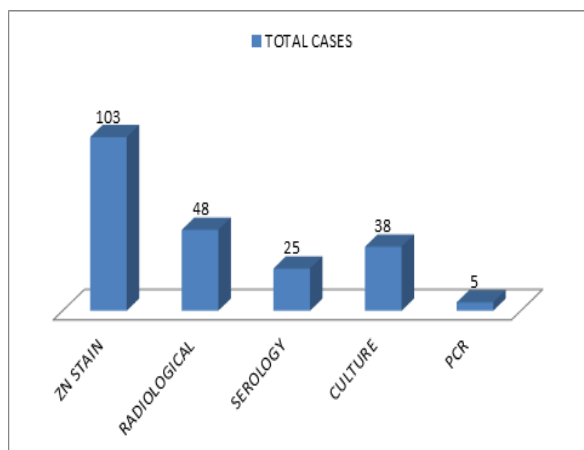


Fig. 5: Showing other diagnostic tests performed besides histopathology

Discussion

Tuberculosis is caused by *Mycobacterium tuberculosis*. Inhalation is the most common route of infection and pulmonary tuberculosis is the predominant clinical form. Resurgence in Tuberculosis cases has been recorded all over the world with more than 8 million people estimated of being infected with the disease.^[4] Tuberculosis remains an endemic disease and is the seventh leading cause of death globally.^[2,3] Extrapulmonary Tuberculosis (EPTB) is defined as the isolated occurrence of tuberculosis in any part of the body other than lungs. Before the advent of HIV pandemic, majority of tuberculosis cases(85%) were pulmonary, and only 15% were extra pulmonary.^[5,6] In HIV positive cases, EPTB accounts for more than 50% of all cases of tuberculosis.^[7] Diagnosis of EPTB is important because it can involve a variety of sites and thus at times may mimic various disease processes. Types of EPTB that have been reported all over the world are lymphatic, pleural, skeletal, central nervous system, pleural, ocular, and pancreatic. The other cases of extra pulmonary tuberculosis include genitourinary and cerebral tuberculosis.^[8]

Extrapulmonary tuberculosis usually presents with a more difficult diagnostic problem. It is less encountered in clinical practice and therefore less familiar to many clinicians. Patients with EPTB may manifest with constitutional symptoms which are not organ specific, such as fever(37-80% cases), anorexia, weight loss, weakness, night sweats, malaise and fatigue.^[9] Sometimes pyrexia of unknown origin(PUO), can be the sole presenting feature especially when the disease is located at an obscure or occult site.

Diagnosis of EPTB is challenging at times. No single test can lead to a correct diagnosis. A variety of direct and indirect methods have to be employed. The bacilli and its products are demonstrated in the direct methods which include Ziehl Neelsen staining, fluorescent microscopy, Lowenstein Jensen culture,

BACTEC culture system, Polymerase chain reaction, Antigen based serology, molecular methods, immunohistochemistry and immunocytochemistry. Whereas the indirect methods include histopathology which offers an advantage of differential diagnosis, cytology, antibody based serology, skin tests, interferon release assay, adenosine deaminase assay.^[10] Among the indirect methods, histopathology of tissue along with ZN staining and culture for *Mycobacterium Tuberculosis* is considered the method of choice for the diagnosis of EPTB. Precise localisation of the lesion and adequate biopsy has been further made easier with the advent of computerised tomographic scan, magnetic resonance imaging, laparoscopy, endoscopy.^[11]

In our study, age and sex distribution data showed that EPTB was almost equal in both the sexes with a slight predilection for females (male to female ratio 1:1.05). It was also observed that the majority patients affected were in the younger age group (21-30 years followed by 11-20 years). This correlates with other similar study conducted by Sreeramareddy et al^[12] where the ratio for sex distribution was 1.07:1 and younger age group was more affected with 40.9% of the total cases occurring in <25 years age group. Chandir et al^[13] reported maximum number of EPTB cases in 15-29 years age group in Pakistan. These results are comparable with our study. On the other hand, in the same study, the female to male ratio was 3:1, much greater than the present study. It can be attributed to the fact that Pakistani women suffer from Vitamin D deficiency which has been documented as one of the risk factors for tuberculosis.^[14] Studies have been carried out regarding the role of socio economic as well as cultural factors determining gender differentials in tuberculosis. Various determinants including, nutrition, educational status, compliance with treatment, fear and stigma associated with tuberculosis have been found to play an important role.^[15]

Amongst the distribution of sites involved by EPTB, cutaneous tuberculosis(24.27%) was the most frequent site affected, followed by lymph nodes(19.42%) and skeletal system(16.50%). In the present case series, it was also observed cases of extrapulmonary tuberculosis with unusual presentations especially when EPTB presented at rare sites. Such cases were clinically interesting as EPTB was not suspected clinically in any of these cases. We reported cases in sites such as vulva, eyelid, oral vestibule, wrist and scrotum.

An interesting presentation involved a rare site i.e. vulva.^[16] Genital tuberculosis is reported in only 0.2 to 2% of all gynaecological cases out of which only 1-2% involve the external genitalia.^[17,18] Most commonly fallopian tubes and endometrium get involved in genital tuberculosis. External genitalia may be involved due to blood spread, direct spread or sexual contact with a person harbouring epididymal or renal tuberculosis. So, vulvovaginal ulcers should investigated for tubercular etiology especially in a developing country like ours.

Eyelid tuberculosis was also reported in our case series. Although cases of eye lid tuberculosis following blepharoplasty have been reported earlier.^[19,20] But, primary tuberculosis of the eye lid, presenting as an isolated painless swelling is extremely unusual.^[21] Without histopathology or direct demonstration of mycobacteria, diagnosis of tuberculosis can be missed at this obscure site.

A rare case was reported in oral vestibule in a 45 year old male. Commonest site to be involved in oral tuberculosis are the tongue and the gingiva, followed by that of tooth sockets, soft palate, floor of mouth, lips and buccal mucosa. Involvement of oral vestibule has been reported in only few case reports.^[22] Therefore, in oral lesions, without any systemic involvement, diagnosis of extrapulmonary tuberculosis can be challenging.

In the present study EPTB was also diagnosed in a 2 year old child. Genitourinary tuberculosis accounts for 20-73% of all cases of extrapulmonary tuberculosis and is extremely uncommon in pediatric population, even in the endemic regions.^[23] In such cases histopathology plays a pivotal role in reaching at a definite diagnosis.

Another rare site to be involved was wrist in a 55 year old female. Skeletal tuberculosis is quite common in developing countries. In our study it constituted 16.7% of all the cases of extrapulmonary tuberculosis. Vertebral site involvement is the most common.^[24] The site involvement in decreasing order of frequency are spine, hip, knee, foot, elbow, hand, shoulder and bursal sheaths. In addition, tuberculosis of the wrist is extremely rare with handful of cases being reported in the literature.^[25] Often diagnosis is missed at this site due to the various differential diagnosis possible. Biopsy and histopathology is frequently the saviour in such cases.

Lastly, we reported a case of tuberculosis in thyroid of a 25 year old female. Tuberculosis of the thyroid gland is rare and primary involvement is extremely uncommon possibly because of its rich vascular, lymphatic supply and thick capsule.^[26] Its frequency of occurrence is 0.1-0.4%. Till date only limited number case reports have been reported in literature.^[27] Most often, it presents with an isolated thyroid swelling without any symptoms. So tuberculosis should always be kept in the differential diagnosis of thyroid swellings especially in a country like ours with high prevalence of tuberculosis.

In all the cases of EPTB, patients responded well to the anti-tubercular therapy. The above mentioned findings are of great importance because the diagnosis of EPTB in such cases poses a difficult diagnostic challenge and thorough clinical, serological, radiological and histopathological correlation has to be made for coming to a definitive diagnosis. Histopathology plays a pivotal role in such cases.

While comparing the present study with the previous studies, it is observed that, sites of localization of EPTB can be variable from place to place. In a study conducted by Noertjojo et al,^[28] the genitourinary system and the skin were the common sites affected, whereas in

a USA based study carried out by Yang et al^[29], bones and/or joints were the most common sites. While in the study conducted by Chandir et al^[13] the frequency of EPTB cases by site was highest in lymph nodes (35.6%), followed by spine (26.3%). Similarly, in a study conducted by Sreeramareddy et al,^[12] the most common site of EPTB was the lymph nodes (42.6%) followed by the peritoneum and/or intestines (14.8%), then bones and/or joints (12.4%).

Conclusion

To conclude, EPTB is increasingly becoming an entity that poses a diagnostic dilemma for the clinicians. The clinicians must be aware of the various sites that can be affected including the rarely affected sites. In a developing country like India extrapulmonary tuberculosis should be kept in the differential diagnosis. Definitive diagnosis of tuberculosis involves demonstration of M.tuberculosis by histopathological, microbiological, cytopathological and molecular methods. Histopathology, in particular assumes great importance when EPTB involves obscure occult sites. It is one of best method to diagnose EPTB especially when clubbed with tissue culture and ZN staining. Molecular diagnostic techniques are also used for rapid and accurate detection of tuberculosis.

It came out in our study that females and younger age group population(21-30 years followed by 11-20 years) may be independent on modifiable risk factors for EPTB. Specific programs can be formulated by the health care givers targeted at reducing its incidence in females and youngsters. In a developing country like India with a high burden of pulmonary as well as extrapulmonary tuberculosis, it is important that more researches be carried out on this topic. This would ultimately result in overall decreased morbidity and mortality of EPTB.

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