



“TUBERCULOSIS – A COMMON GRANULOMATOUS DISEASE AT UNCOMMON SITES: A COMPREHENSIVE HISTOCYTOLOGICAL STUDY IN A TERTIARY CARE HOSPITAL OF CENTRAL INDIA”

Pathology

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ABSTRACT

Background: Tuberculosis (TB) is a common granulomatous disease caused by *Mycobacterium tuberculosis*, which primarily affects lungs in about 80 % of cases. Extrapulmonary tuberculosis (EPTB) is defined according to WHO classification criteria as an infection by *M. tuberculosis* which affects tissues and organs outside the pulmonary parenchyma. Among EPTB the most common location is cervical lymphadenopathy (63-77%). Involvement of other organs or location is extremely rare, even in countries in which tuberculosis is endemic.

Aim: To study the common granulomatous lesion, tuberculosis at uncommon sites on histological and cytological preparations.

Materials and methods: A retrospective study of 76 cases (presented during two years), of extrapulmonary tuberculosis excluding lung, pleura and cervical lymph nodes was undertaken. Cases were selected according to the inclusion and exclusion criteria. After morphological diagnosis, cases were subjected to modified ZN staining. This was correlated with ultrasonography and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) wherever available.

Results: Majority of cases (63.2%) were females. Most of the cases (28/60) belonged to the age group between 21 and 30 years. Most common of the uncommon sites were axilla followed by breast and submandibular region.

Conclusions: Extrapulmonary tuberculosis is quite common and keeping a high index of suspicion helps in early diagnosis and hence early treatment of this disease.

KEYWORDS

Extrapulmonary tuberculosis, tuberculosis, uncommon sites.

INTRODUCTION

Tuberculosis (TB) is a common granulomatous disease caused by *Mycobacterium tuberculosis*. It is a small, aerobic, non-motile bacillus.

Roughly one-quarter of the world's population has been infected with *M. tuberculosis*¹, with new infections occurring in about 1% of the population each year². According to WHO Global Tuberculosis report 2020; globally, an estimated 10.0 million people fell ill with TB in 2019³. A total of 1.4 million people died from TB in 2019 (including 208000 people with HIV). Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS)⁴. In 2019, the 30 high TB burden countries accounted for 87% of new TB cases. Eight countries account for two thirds of the total, with India leading the count, followed by Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa⁵.

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis)⁶ in about 80 % of cases⁶. Extra Pulmonary Tuberculosis (EPTB) is defined according to WHO classification criteria as an infection by *M. tuberculosis* which affects tissues and organs outside the pulmonary parenchyma. It represents between 20 and 25% of all TB cases⁷. TB lymphadenitis is the commonest form of EPTB and mainly affects cervical lymph nodes^{8,9}. Involvement of other organ or location is extremely rare, even in countries in which tuberculosis is endemic. The sign and symptoms of EPTB vary, depending on the organs involved¹⁰.

This study aims to study a wide range of uncommon sites of tuberculosis diagnosed by Fine Needle Aspiration Cytology (FNAC) or Biopsy including salivary gland, wrist, elbow, breast, axilla, toe, elbow and many more.

MATERIAL AND METHODS

This retrospective study was conducted in Cytology and Histopathology sections of Department of Pathology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh. Study duration was 2 years i.e. from January 2019 to December 2020. The study protocol was approved by the Institutional Ethical Committee (IEC) and Scientific Research Review Committee (SRRC).

INCLUSION CRITERIA -

Patients with all age groups and either of the sex diagnosed with tuberculosis at uncommon location by FNAC or Biopsy were included in this study

EXCLUSION CRITERIA -

Patients diagnosed with tuberculosis at common sites like lung, pleura and cervical lymph nodes were excluded in this study.

FNACs were performed in Cytology section of the department. The area of skin overlying the palpable lump was cleaned and disinfected using spirit swabs. After fixing of the lump, FNAC was done using 22 G needle with 10 ml disposable syringe. The aspirated material was then transferred to the glass slides and then smears were prepared. Smears were stained with Haematoxylin & Eosin (H&E) and Papanicolaou stain. Few slides were kept aside for modified Ziehl Neelsen (ZN) stain for Acid Fast Bacilli (AFB).

Biopsies were received in sterile container in 10% formalin for the histopathological examination in Histopathology section of the department. They were then processed following the standard operating procedures of tissue processing, followed by H&E staining and ZN staining, wherever required.

The smears/sections were examined under the microscope and diagnosis of tuberculosis was made on the basis of presence of epithelioid cell granuloma, caseous necrosis and Langhans type giant cells. The diagnosis was confirmed by AFB positivity in modified ZN stained smear/section. Cases in which AFB were negative, the diagnosis of TB was confirmed by clinico-radiological correlation and CBNAAT.

RESULT

Table 1: Distribution of cases according to gender

Gender	Number of cases	Percentage (%)
Males	28	36.8
Females	48	63.2

Table 2: Distribution of cases according to age

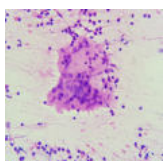
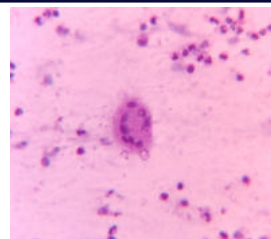
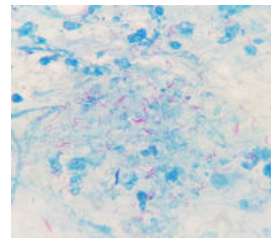
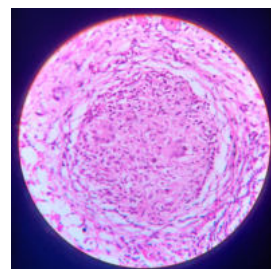
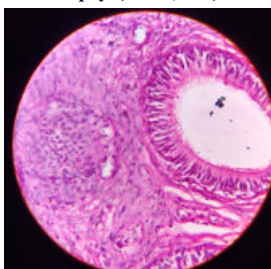
Age range (in years)	Number of cases	Percentage (%)
0 – 10	07	9.2
11 – 20	10	13.2
21 – 30	28	36.8
31 – 40	12	15.8
41 – 50	12	15.8
51 – 60	03	3.9
61 – 70	04	5.3

Table 3: Distribution of cases according to site

Site	Number of cases	Percentage (%)
Axilla	12	15.8
Breast	11	14.5
Submandibular	10	13.2
Parotid	05	6.7
Elbow/forearm	05	6.7
Submental	04	5.3
Sternal/chest wall	04	5.3
Abdomen	03	3.9
Infra-auricular	02	2.6
Foot	02	2.6
Midline neck/suprasternal	02	2.6
Perianal	02	2.6
Intestine	02	2.6
Mesenteric Lymph Node	02	2.6
Ischial region	02	2.6
Wrist	01	1.3
Eyelid	01	1.3
Inguinal	01	1.3
Posterior auricular	01	1.3
Testes	01	1.3
Ovary	01	1.3
Endometrium	01	1.3
Mastoid Region	01	1.3

A total of 76 cases of TB at uncommon sites were included, out of which 56 cases were diagnosed by FNAC and 20 by histopathological examination. Among study population 28 (36.8%) people were males and 48 (63.2%) were females (Table 1); male to female ratio was 1:1.71. Table 2 shows the distribution of cases according to age. Maximum numbers of cases were seen in the age range 21-30 years i.e. 28 cases (36.8%).

Tuberculosis at common sites like lung, pleura and cervical lymph nodes were excluded. Among other sites which are rare, most frequent site of involvement was Axilla 12 cases (15.8%) followed by Breast 11 cases (14.5%) and Submandibular region 10 cases (13.2%). Parotid region 5 cases, Forearm near elbow 5 cases, Submental region 4 cases, Sternal region 4 cases and Abdomen 3 cases were found. 2 cases each were diagnosed at Infra-auricular region, foot, midline neck, Perianal region, Intestine, Mesenteric lymph node and Ischial region. Only one case each were found in other very rare sites including Wrist, Inguinal region, Posterior auricular, Testes, Ovary, Endometrium and Mastoid region.

**Figure 1 – Right upper eye lid swelling of a 60 year old female patient.****Figure 2 – Cytological picture of Granuloma comprising of epithelioid cells, lymphocytes and macrophages. (H&E, 40x)****Figure 3 – Multinucleated giant cell (Langhans type) (H&E, 40x)****Figure 4 – ZN for AFB positive for tubercular bacilli (ZN, 40x)****Figure 5 – Histological picture of granuloma comprising of epithelioid cells, lymphocytes, macrophages and Langhans type giant cells in intestinal biopsy. (H&E, 40x)****Figure 6 – Histological picture of granuloma adjacent to seminiferous tubule in testicular biopsy (H&E, 40x)**

We found one case of TB at Upper eyelid swelling in a 60 years old female patient. The lesion was a globular swelling of size 2x1.5 cm which was soft in consistency and was non tender. After FNAC blood mixed purulent material was aspirated (Figure 1). Smears were stained with H&E stain and Modified ZN stain. H&E stained smears were richly cellular. They showed well-formed granulomas composed of epithelioid cells, lymphocytes and macrophages along with multinucleated Langhans type giant cells. RBCs were seen in the background (Figure 2 & 3). Modified ZN stained smear was positive for AFB (Figure 4).

DISCUSSION

Pulmonary localization is the most common site of TB and the most contagious form. EPTB with the rarest and most unexpected localizations represents a significant proportion of all cases of tuberculosis and remains an important public health problem¹¹. The annual global incidence of extra pulmonary TB has been increasing in the last decade due to changing TB control practices, spread of HIV and population growth. The diagnosis of EPTB poses particular challenge for clinicians because of atypical presentations and lacking health facilities¹².

In our study axilla was the most common site involved by TB among uncommon sites. 12 out of 76 cases were found in axillary lymph nodes. Similar findings were observed by Fujii T et al and Nwagbara

VI et al in which they found that axillary nodes were affected in 3.8-20.3% cases of tuberculous lymphadenitis^{13,14}. Isolated axillary tuberculous lymphadenitis is rare and described in patients without previous or active pulmonary TB and no evidence of the origin of TB detected elsewhere^{15,16}. Tuberculous lymphadenitis presents as a painless, slowly progressive swelling of a single group of nodes and in 85% of cases involvement is unilateral¹⁷. It may resemble breast carcinoma or both may exist at the same time resulting in diagnostic and therapeutic challenges^{13,18}.

According to **Tewari M and Shukla HS**, breast TB is an uncommon disease, with an incidence of less than 0.1% of all breast lesions in Western countries and 4% of all breast lesions in TB endemic countries¹⁹. The diagnosis of TB mastitis is difficult since the disease has multiple patterns of clinical presentation. The most common form is a slow-growing, solitary, painless mass that mammographically mimics carcinoma²⁰. In our study breast was the 2nd most frequent site of involvement among the uncommon sites, involving 11 out of 76 cases.

The salivary gland TB is a very rare entity. **Bruzgielewicz A. et al.** observed that most of the TB salivary gland involved the parotid gland followed by the submandibular gland²¹. In our study parotid gland involvement was present in 5 cases. 2 out of 10 cases involving submandibular region were present in submandibular salivary gland and rest 8 were cases TB lymphadenitis involving submandibular lymph nodes.

Chopra D et al opine that Cutaneous Tuberculosis (CTB) is an uncommon small subset of extrapulmonary tuberculosis, comprising 1-1.5% of all extrapulmonary tuberculosis manifestations²¹. In the present study, we reported 4 cases of cutaneous tuberculosis at 4 different sites. 1st case was 36 years male with painful, crusty, papulonodular lesions at perianal region. 2nd case was 14 year male with large fibrous scar along with small papules and nodules on forearm. 3rd case was 63 year female who had extensive irregular serpiginous plaque and a small nodule over foot. 4th case was 48 year male with multiple small nodules with discharging sinus on chest wall, near sternum.

There are only a few studies done on unusual sites of tuberculosis. **Najmi A et al**²² in their study found tuberculosis with unusual presentation at neck swelling, epiglottitis and pre auricular region. They concluded that extra pulmonary TB is rare compared to the pulmonary counterpart. However, the presentation is not unusual that can mimic other entities. Hence, it is very important to have a high index of suspicion to rule out TB, as this disease is a curable disease. **Kulkarni DR et al**²³ presented TB at unusual sites: A case series from a tertiary care center in North Karnataka and included 5 cases. 1st a 25 year lady with caesarian section wound; 2nd a 35 year old lady with painful left breast mass; 3rd a 45 year old male with a mass over bulbar conjunctiva; 4th a 46 year old male with multiple nodules over lung, liver, spleen and kidney; and 5th a 27 year old with testicular torsion. **Hernandez ATS et al**²⁴ presented three cases of TB affecting unusual sites including face, endometrium and palm; among patients with different rheumatologic conditions. They concluded that the gold standard of diagnosing EPTB remains to be TB culture, and although no uniform test among these three cases was used, AFB smears or compatible biopsy findings are acceptable.

CONCLUSION

- 1) TB is endemic in a country like India.
- 2) Extrapulmonary TB is also common.
- 3) Thus on a cytological preparation or a histopathological slide, caseous necrosis with epithelioid cell granulomas even in the absence of AFB should alert one in the diagnosis of TB.
- 4) It can be seen at any uncommon sites, thus one should always have a high index of suspicion.
- 5) The treatment of TB is curative if it is diagnosed early, hence lies the importance of early diagnosis.
- 6) TB is curable and preventable. About 85% of people who develop TB disease can be successfully treated with a 6-month drug regimen.
- 7) Treatment has the additional benefit of curtailing onward transmission of infection.

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