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Original Research Article

Serum adenosine deaminase levels and other laboratory parameters in the diagnosis of extrapulmonary tuberculosis: a clinicopathological study

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ABSTRACT

Background: Diagnosis of extra pulmonary tuberculosis (EPTB) is difficult due to its nonspecific signs and symptoms and paucibacillary nature. Early diagnosis and institution of appropriate therapy is essential to reduce the morbidity. The aim of the study was to study correlation between clinical findings, cytological/histological findings of EPTB with other laboratory parameters such as erythrocyte sedimentation rate (ESR), acid fast bacilli (AFB) status on Ziehl Neelson (ZN) stained sections /smears and serum adenosine de aminase (ADA) levels.
Methods: All histologically and cytologically diagnosed cases of EPTB were included in the study and were examined for AFB on ZN stained smears and correlated with clinical findings and laboratory parameters such as ESR and serum ADA levels.
Results: A total number of 230 cases of extrapulmonary tuberculosis were studied. Most common site of EPTB was lymph nodes. The most common age group affected was 3rd and 4th decade. Over half of the patients were females with male to female ratio 1:1.03. Majority had elevated ESR and caseating granuloma and only minority showed AFB positivity. Serum adenosine de aminase levels were raised in 83.3% (45 out of 54 cases). Majority of cases of EPTB with raised serum ADA levels had elevated ESR but negative for acid fast bacilli.
Conclusions: Both histopathology (including cytology smears) as well as Ziehl Neelsen smears for acid fast bacilli are an "independent" diagnostic parameter and still be considered as **"**gold standard**"** while serum ADA levels are most valuable surrogate parameter.

Keywords: Acid fast bacilli, Extrapulmonary tuberculosis, Serum adenosine de aminase

INTRODUCTION

Extra pulmonary tuberculosis (EPTB) is a relatively indolent disease and continues to be one of the major public health problem.[1] It can occur in isolation or along with a pulmonary focus. The cause of resurgence: co-existence of HIV infection, multidrug resistance, treatment compliance, underlying systemic disease and economic disruption.[2] The diagnosis is difficult due to nonspecific signs and symptoms and pauci bacillary nature. Culture is more accurate but takes longer time. A major limitation of nucleic acid amplification tests are their cost and feasibility. There are no pathognomonic imaging findings and hence diagnosis rests on histopathological and microbiological confirmation.[3,4]

Hence the present study is undertaken to evaluate the role of clinical and pathological correlation including other laboratory parameters such as AFB status in ZN stained smears and serum ADA levels in the diagnosis of EPTB.

The objective of this study was to study correlation between clinical findings, histological/ cytological findings and other laboratory parameters such as ESR, AFB status on ZN stained smears and serum ADA levels in the diagnosis of extra pulmonary tuberculosis.

METHODS

This study was done from November 2013 to April 2015. All Heamatoxylin and Eosin stained fine needle aspiration cytology smears as well as 10% formalin fixed routinely processed paraffin sections of excisional and incisional biopsies from patients presenting with swelling anywhere in the body with high clinical suspicion of tuberculosis which showed caseating granuloma or non-caseating granuloma or poorly formed granuloma were included in the study and were further examined for acid fast bacilli on Ziehl Neelsen stained smears and correlated with other laboratory parameters such as ESR and serum ADA levels.

Data regarding age, sex, presenting complaints, site of involvement, history of associated pulmonary tuberculosis, HIV status, results of relevant investigations including hemoglobin percentage, total leukocyte count, and platelet count were taken and correlated with histologic diagnosis.

RESULTS

A total number of 230 cases of extrapulmonary tuberculosis were diagnosed both histologically (54) and cytologically (176) during the study period from November 2013 to April 2015. Most common site of EPTB was lymph nodes (80%) and least was cutaneous involvement (0.87%) (Table 1). The most common age group affected by extra pulmonary tuberculosis was 3rd and 4th decades and least was observed in 7th decade (3.9%) (Figure 1). Over half of the patients were females (50.8%, 117 cases), with male to female ratio 1:1.03. Most common associated finding/ illness was anemia (69.56%) followed by HIV seropositivity, pulmonary tuberculosis, past history of EPTB, diabetes mellitus and least were chronic hepatitis and underlying cancer (0.86% each)(Table 2). Anemia was observed in 160 cases (69.56%) with mild, moderate, and severe degree in 55% (88 cases), 35.65% (57 cases) and 9.37% (15 cases) cases respectively. 77% of patients (177 cases) had normal leucocyte count while leucocytosis and leucopenia were seen in 15.6% (36 cases) and 7.4% (17 cases) respectively. 59.6% had normal differential leucocyte count whereas neutrophilia, lymphocytosis and eosinophilia were seen in 37.4%, 2.6% and 0.4% cases respectively (Table 3). Platelet count was normal in 98.69% (227 cases), while thrombocytosis and thrombocytopenia was seen in 0.4% (1 case) and 0.86% (2 cases) respectively. Erythrocyte sedimentation rate was elevated in 83% (190 cases) and was normal in 17% (40 cases) (Figure 2). The most common histological pattern was caseating granuloma (82.6%, 190 cases) followed by non-caseating granuloma (15.2%, 35 cases) and least was poorly formed granuloma (2.2%, 5 cases) (Figure 3 and 4). On ZN stained smears acid fast bacilli positivity was seen in 25.65% (59 cases). Serum adenosine de aminase levels were done for 54 cases of histologically diagnosed cases of EPTB and 83.3% (45 cases) of them were positive (levels >14 IU) (Figure 5).

Table 1: Distribution of extrapulmonary tuberculosis.

Site	Number	Percentage
Lymph node	184	80.00
Musculoskeletal	17	7.4
Abdominal	12	5.21
Female genital system	04	1.74
Male genital system	04	1.74
Mammary gland	04	1.74
Ear and Nose	03	1.30
Cutaneous	02	0.87
Total	230	100

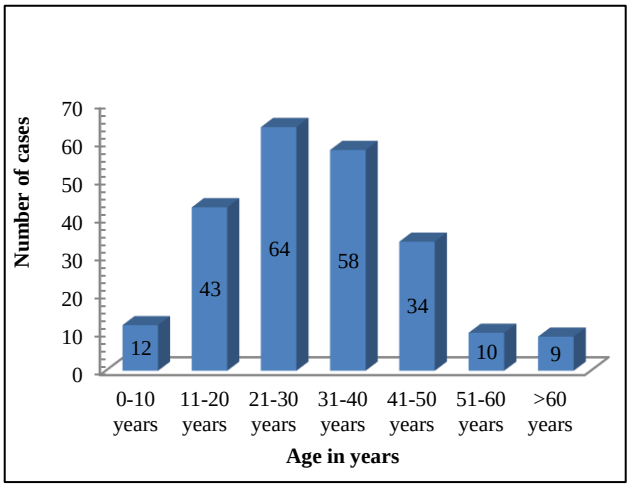

Figure 1: Age distribution of extra pulmonary tuberculosis.

Table 2: The incidence of other associated finding / illnesses.

Associated finding/ illness	Number of cases	%
Anemia	160	69.56
HIV seropositivity	60	26.1
Pulmonary tuberculosis	37 (primary-11, secondary-26)	16.1
Past history of extrapulmonary tuberculosis	23	10
Diabetes Mellites	04	1.73
Malignancy	02	0.86
Chronic Hepatitis	02	0.86

Over half of the patients with tubercular lymphadenopathy were females (51.1%, 94 cases) with

male to female ratio 1:1.04. Most common lymph node group involved was cervical group (81.53%, 150 cases), followed by axillary group (13%, 24 cases) and least was inguinal group (5.47%, 10 cases). Most common presentation of tubercular lymphadenopathy on local examination was multiple, discrete involvement of lymph nodes (36.41%, 67 cases), followed by solitary lymph node involvement (35.33%, 65 cases), multiple matted (19.03%, 35 cases) and least presentation was cold abscess with discharging sinus (9.23%, 17 cases). The most common finding in Tubercular lymphadenopathy was Elevated ESR (85.32%), followed by fever, weight loss, loss of appetite, AFB positivity, associated HIV seropositivity and the least was underlying pulmonary tuberculosis (Table 4). Serum ADA levels were done in 11 cases and all of them showed elevated levels. Majority of the cases of tubercular lymphadenopathy had well-formed caseating epithelioid cell granulomas (82.06%, 151 cases) followed by non-caseating epithelioid cell granulomas (15.21%, 28 cases), least was poorly formed granuloma (2.1%, 4 cases).

Table 3: Showing differential leucocyte count in extrapulmonary tuberculosis.

DLC	Number of cases	Percentage
Normal DLC	137	59.6
Neutrophilia	86	37.4
Lymphocytosis	6	2.6
Eosinophilia	1	0.4

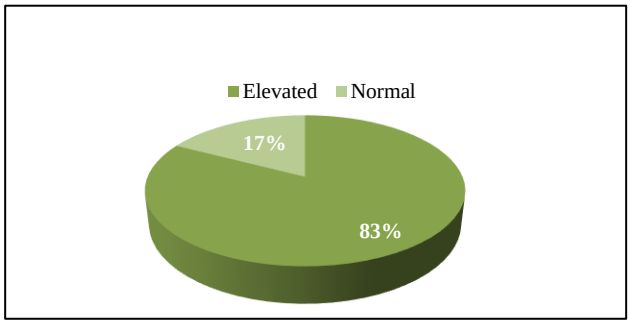

Figure 2: Erythrocyte seddimentation rate in EPTB.

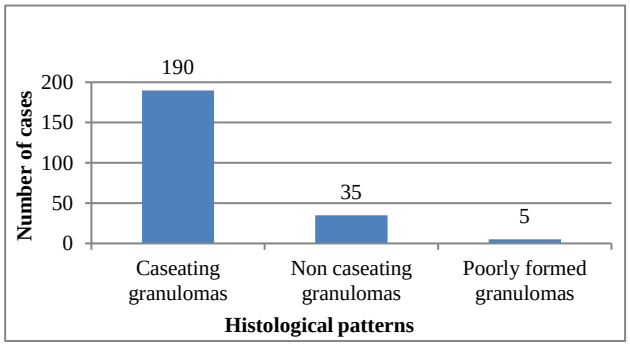

Figure 3: Histologic pattern in extrapulmonary tuberculosis.

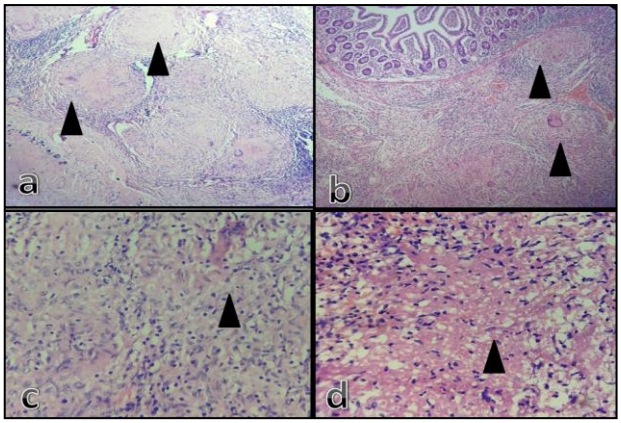

Figure 4: Caseating granuloma (A) (arrow heads) (H and E, x 10), non-caseating granulomas (B) (arrow heads) (H and E, x 10), poorly formed granulomas (C) (arrow heads)(H and E, x 40), and scattered epithelioid cells with mixed inflammatory cells infiltration (D) (arrow heads) (H and E, x 40).

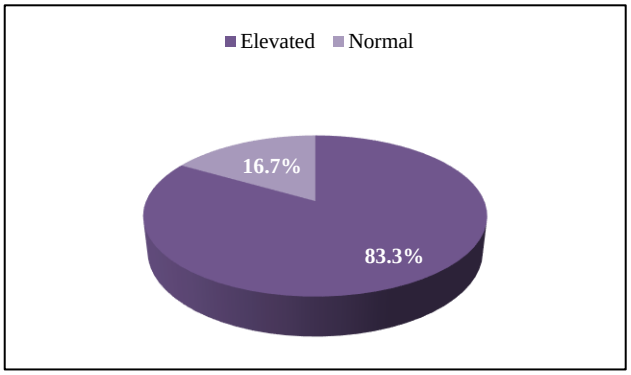

Figure 5: Percentage of elevated serum ADA levels in extrapulmonary tuberculosis.

Soft tissue involvement was the most common presentation of musculoskeletal tuberculosis (29.41%, 5 cases), followed by synovitis (23.52%, 4 cases), tenosynovitis (17.64%, 3 cases), osteomyelitis and pott's spine (11.76%, 2 cases each) and arthritis (5.88%, one case). Musculoskeletal tuberculosis showed male preponderance (58.88%, 10 cases) with male to female ratio being 1.7:1. Swelling was the most common presenting feature (82.35%, 14 cases), followed by pain (41.11%, 7 cases) and restricted mobility (17.64%, 3 cases). 23.52% (4 cases) of musculoskeletal tuberculosis had past history of tuberculosis and 11.76% (2 cases each) had associated HIV seropositivity and AFB positivity. Erythrocyte Sedimentation Rate was raised in 70.58% (12 cases) and Serum ADA levels (done for 15 cases) were raised in 86.66% (13 cases). Most common histological finding of musculoskeletal tuberculosis was well formed caseating epithelioid cell granulomas (88.24%), followed by non-caseating epithelioid cell granulomas (11.76%), scattered epithelioid cells (17.64%), and caseous necrosis alone (7.64%).

Table 4: Features of tubercular lymphadenopathy.

Features	No.of cases	Percentage (%)
Fever	117	63.6
Weight loss	112	60.8
Loss of appetite	110	59.8
Associated HIV seropositvity	54	29.3
Associated pulmonary tuberculosis	30	16.3
AFB positivity	55	29.9
Elevated erythrocyte sedimentation rate	157	85.32
*Elevated serum ADA levels	11	100

*Serum ADA levels done only in 11 cases.

Most common sites involved in abdominal tuberculosis were ileum and ileocaecal junction (25% each, 3 cases each), followed by appendix (18%, 2 cases), jejunum, colon, omentum and peritoneum (8%, 1 case each). Mean age of abdominal tuberculosis was 27.1years with female preponderance (67%, 8 cases) and M: F ratio being 1:2. Most common presentation being pain abdomen (75%, 9 cases) followed by distention of abdomen (16.67%) and constipation (8.33%). Majority of the lesions in abdominal tuberculosis were ulcerative (33.33%), followed by perforation, stricture and hypertrophic (16.67%, 2 cases each), and ulceroproliferative and tumor like (8.33%, 1 case each). Most common associated feature was ascitis (25%, 3 cases) followed by HIV sero positivity, pulmonary tuberculosis and extra pulmonary tuberculosis at other sites (16.67%, 2 cases each). Erythrocyte sedimentation rate was raised in 91.7% (11 cases). Serum ADA levels were done for 11 cases and were raised 90.9% cases (10 cases). Most common histological finding was well formed caseating epithelioid cell granulomas (83.34%).

Endometrium was the most common site involved by female genital tract tuberculosis (75%, 3 cases) followed by fallopian tubes and ovary (25%, 1 case). Mean age of tuberculosis of female genital system was 31.87years. Bleeding per vaginum being the most common presentation (75%, 3 cases) followed by pain abdomen, primary infertility and oligomenorrhoea (25% 1 case each). 1 case was associated with omental tuberculosis. 75% (3 cases) showed elevated serum ADA levels and all of them had elevated ESR. All the cases with elevated ESR showed elevated serum ADA levels. Majority of the cases had well-formed caseating epithelioid cell granulomas (75%) with rich lymphocytic infiltration.

Mean age involved in male genital tract tuberculosis was 33.5 years. Scrotal pain was the most common symptom (100%, 4 cases), followed by scrotal swelling (75%, 3 cases). 25% (one case each) showed associated HIV seropositivity and AFB positivity and 50% (2 cases) showed elevated ESR. Serum ADA levels done for only two cases and was elevated in 1 case (50%). Majority of the cases had well-formed caseating epithelioid cell granulomas (75%, 3 cases) with rich lymphocytic infiltration.

Mean age of involvement of mammary tuberculosis was 37 years and all were females. Majority of cases presented with breast lump (75%, 3 cases) and discharging sinus (25%, 1 case). 25% cases were seropositive for HIV and 75% cases had elevated ESR. Serum ADA levels were done for 2 cases and both of them showed elevated levels (100%). All the cases with elevated serum ADA had elevated ESR and only 50% (1 case) of them had constitutional symptoms. Majority of the cases had well-formed caseating epithelioid cell granulomas (75%, 3 cases) with rich lymphocytic infiltration.

Ear and nose tuberculosis showed female preponderance with male to female ratio 1:2 and mean age of 25 years. Nose (inferior turbinate) was the most common site involved (66.66%) followed by ear (33.33%). Nasal discharge was the most common symptom (66.6%), followed by nasal obstruction (33.3%). All cases showed elevated ESR and only 66.66% cases showed elevated serum ADA levels. All the cases with elevated serum ADA levels showed elevated ESR. Caseating epithelioid cell granuloma, non-caseating epithelioid cell granuloma and poorly formed granuloma with scattered epithelioid cells were seen in 33.33% (1 case each). All the cases showed rich lymphocytic infiltration.

Mean age of involvement of cutaneous tuberculosis was 25 years and all were males. Common presentation was itchy erythematous lesion and plaque (50%). ESR and serum ADA levels were elevated in all cases. AFB positivity was seen in 50% cases. All the cases with elevated serum ADA levels showed elevated ESR and only 50% cases showed AFB positivity. Histological examination of all the cases showed caseating epithelioid cell granuloma with rich lymphocytic infiltration.

DISCUSSION

Extrapulmonary Tuberculosis continues to be major public health problem and an important cause of morbidity and mortality.[5]

Most studies found that lymph nodes, abdomen, bones, joints and genitourinary system as most common sites of involvement by EPTB.[5] Maltezou et al and the present study observed lymph node as most common site of involvement by EPTB and skin as the least common site of involvement.[6] There is no age predilection for EPTB and it is known to affect all age groups. Female preponderance is generally noticed by various studies including the present one and study by Kaur et al, owing to illiteracy, social exclusion, malnutrition and economic dependency with little access to health care.[1,3] Most studies observed low hemoglobin percentage as an associated (directly or indirectly) finding in patients with

tuberculosis. Sharma YR found 64% of his cases being anemic, where as 69.56% of cases were anemic in the present study. Anorexia, one of the important constitutional symptom of tuberculosis might be the cause for low hemoglobin percentage.[7] Various studies confirmed that immunodeficiency as most important predisposing factor for tuberculosis due to unchecked proliferation of M. tuberculosis bacilli.[8] Other predisposing factors include diabetes mellitus, chronic hepatitis and chronic renal dysfunction.[9] Factors such as lymphopenia, lymphocyte dysfunction including reduced interferon production, neutrophil dysfunction including defective chemotaxis, reduced bactericidal activity all predispose the individual to microbial infection including tuberculosis.[10]

Chakrabarti et al observed mild anemia, moderate anemia and severe anemia in 41.1%, 28.2% and30.7% of cases respectively, while it was 55%, 35.65% and 9.37% respectively in the present study.[11] Most of these anemias are multifactorial means both nutritional as well as due to anemia of chronic disease.[11] Chakrabarti et al observed leucocytosis and leucopenia in 23.1% and 12.9% of cases respectively, while it was 15.6% and 7,4% of cases respectively in the present study.[11] Neutrophilia was most commonly observed finding in the present study accounting for 37.4% of cases followed by lymphocytosis in 2.6% of cases and eosinophilia in 0.4% of cases. Chakrabarti et al found neutrophilia and lymphocytosis in 10.2% of cases each.[11] Chakrabarti et al observed thrombocytosis and thrombocytopenia in 2.5% and 17.9% of cases respectively, while it was 0.4% and 0.86% of cases respectively in the present study.[11]

Chronic inflammation suppresses heamatopoeisis with resultant pancytopenia and stimulates hyperplasia of mononuclear phagocytic system with resultant trapping of free iron and extravascular haemolysis.[11]

ESR was elevated in 83% of the cases which was consistent with study done by Karim et al.[6] ESR is the most important laboratory parameter of systemic inflammation. Cytokines such as interleukin-6, tumor necrosis factor and interleukin-1 stimulate the liver to produce acute phase reactant proteins (fibrinogen, immunoglobulin, haptoglobulin, CRP and others) which increase the dielectric constant in the blood allowing the erythrocytes to form rouleax and increasing the velocity of their descent in the tube. The ESR is thus an indirect measure of systemic inflammation which has been criticized as being neither sensitive nor specific but is nonetheless widely used.[11]

Tang et al, Tripathi et al and present study found well-formed caseating epithelioid cell granuloma as predominant histolgic pattern.[12,13] Next common histologic patterns were non caseating granulomas and poorly formed granulomas. In EPTB, pathological findings and histological detection of acid fast bacilli in tissue is two way to support or confirm the presence of disease. Despite wide use of smear microscopy for acid fast bacilli in ZN stained smears in the diagnosis of EPTB, it has limitations due to low and variable sensitivity and specificity values. EPTB cases more often are smear negative than pulmonary tuberculosis.[6,14] Acid fast bacilli positivity was seen in 25.65% of the cases in present study which was comparable with the study done by Nassaji et al who found AFB positivity in 26.1% cases.[14]

Serum Adenosine Deaminase levels were done for 54 cases and of which 45 cases showed elevated levels. The cut off value for serum Adenosine Deaminase was taken as 14U/L.[15,16] It acts in the proliferation and differentiation of lymphocytes especially T lymphocytes. It acts in the maturation of monocytes and transforming them to macrophage. It is significant indicator of active cellular immunity.[15] Serum ADA levels are increased in diseases due to intracellular micro-organisms. ADA is produced after alveolar macrophages are infected by Mycobacterium tuberculosis and is determined in the serum during active pulmonary tuberculosis. Lymphocytes, particularly T lymphocytes have significant role in the control of M. Tuberculosis infection in which lymphocyte turn over increases.[16]

Table 5: Correlation of elevated serum ADA levels with other parameters in tubercular lymphadenopathy.

Parameter	No of cases	Percentage
Constitutional symptoms	11	100
Elevated ESR	11	100
HIV Positivity	2	18.2
AFB positivity	0	0

Tubercular lymphadenopathy is the most common form of EPTB. Various studies including the present study, study by Rajasekaran et al and Karim et al observed cervical group as most common site for tubercular lymphadenopathy and fever with multiple lymph nodes involvement with matting as common presentation.[6,17] There are two specific pathologic criteria for identifying tuberculous lymphadenitis-caseation and granuloma formation. Caseation has been found to be more specific and sensitive.[17] In the present study typical granuloma formation and caseation was seen even in HIV positive cases representing an early phase of immunosupression. All patients with elevated serum ADA levels (11 cases) had constitutional symptoms and raised ESR (100%), but none of them showed AFB positivity (Table 5).

Musculoskeletal tuberculosis usually results from trauma with reactivation of dormant bacilli.[18,19] In the present study ESR was raised in 70.58% cases and serum ADA levels (done for 15 cases) were raised in 86.66% (13 cases). 53.8% (7 cases) and 69.2% (9 cases) of patients with elevated serum ADA levels respectively had

constitutional symptoms and raised ESR, but none of them showed AFB positivity (Table 6).

Table 6: Correlation of elevated serum ADA levels with other parameters in musculoskeletal tuberculosis.

Parameter	Number of cases	Percentage
Constitutional symptoms	7	53.8
Elevated ESR	9	69.2

Abdominal tuberculosis can be primary or secondary.[20] Various studies including study by Amarapurkar et al and the present study observed ileum and ileoceacal junction as frequent sites of involvement by abdominal tuberculosis and less common sites being peritoneum, appendix and jejunum.[21] Most studies including Islam MB et al and present study found female preponderance.[22] Present study as well as study by Karim et al found pain abdomen as the most common symptom (75% cases).[6] Distension of abdomen was the second most common symptom in the present study accounting for 16.66% which was near to the study done by Amarapurkar et al.[21] Constipation was the third most common symptom. Most studies including Amarapurkar et al, Karim et al and the present study found ulcerative lesion as the most common type of abdominal tuberculosis and other less common presentations include ascites, hypertropic lesion, stricture and perforation.[6,21] Elevated ESR was seen in 91.7% of cases in present study which was consistent with study done by Amarapurkar et al.[25] HIV seropositivity was seen in 16.67% of cases whereas none of the other studies showed HIV seropositivity. In the present study 100% (10 cases), 90% (9 cases) and 10% (1 case each)of patients with elevated serum ADA levels respectively had elevated ESR, constitutional symptoms, and associated HIV seropositivity and pulmonary tuberculosis (Table7) but none had AFB positivity.

Table 7: Correlation of elevated serum ADA levels with other parameters in abdominal tuberculosis.

Parameter	Number of cases	Percentage
Constitutional symptoms	09	90
Raised ESR	10	100
HIV positivity	01	10
Pulmonary TB	01	10

Female genital tract tuberculosis is usually secondary to tuberculosis infection elsewhere in the body and is an important cause of infertility.[2] Hatami et al and present study observed endometrium as the most common site of female genital tract tuberculosis and less common sites include fallopian tube and ovary.[23,28] Common presentations include lower abdominal pain or pelvic pain, or alterations in the menstrual pattern.[2] About 11% women with genital TB may be asymptomatic and are usually discovered incidentally during sterility studies.[24] Though dominant histologic pattern seen was granulomas with caseation necrosis, sometimes they may be non-necrotizing because of continuous shedding of stratum functionalis during menstruation.[25] All cases with raised serum ADA levels showed elevated ESR which was not found in other studies.

Male genital system tuberculosis commonly affects the epididymis due to its rich blood supply and is due to direct hematogenous spread.[26] Tuberculous epididymitis may be the first presentation of genitourinary tuberculosis in males and involves testis by direct extension.[27] Most studies found 4th decade as most common age group affected and pain and swelling in scrotum as the common presentation.[28] 75% of cases (3 cases) had typical histology but only 25% (1 case) showed AFB positivity. 50% (2 cases) showed elevated serum ADA levels and ESR.

Mammary tuberculosis is most commonly secondary to tuberculosis elsewhere in the body or is due to reactivation of dormant bacilli lodged in tissue macrophages of breast. Primary tuberculous mastitis is extremely rare. Lymphatic spread by retrograde extension from axillary lymph nodes is considered to be the most common mode of spread.[2] Women are at increased risk during their reproductive years.

Table 8: Correlation of elevated serum ADA levels with other parameters in mammary tuberculosis.

Parameter	Number of cases	Percentage
Constitutional symptoms	1	50
Elevated ESR	2	100

Most studies including Khanna et al and the present study found lump and discharging sinuses as the most common presentation.[29] Khanna et al observed raised ESR in 77% of cases which was comparable with the present study.[29] In the present study HIV seropositivity was seen in 25% of cases which was not seen in other studies. In the present study serum ADA levels were done in 2 cases and all showed elevated levels, but were normal in other studies. In the present study 100% (2 cases) and 50% each (1 case each) of patients respectively with elevated serum ADA levels had elevated ESR and constitutional symptoms and HIV sero positivity but none had AFB positivity (Table 8).

Ear and Nose tuberculosis excluding laryngeal forms, is exceptional and constitutes only 2-6% of EPTB and 0.1-1% of all forms of tuberculosis.[30] Nasal septal tuberculosis is a rare and is usually secondary to tuberculosis of lung, larynx and facial lupus. Common presentations include nasal bleeding, nasal obstruction and nasal discharge.[30] Associated pulmonary tuberculosis was seen in 33.3% (1 case) of cases in our study whereas

which was not seen in any of the studies. In the present study elevated ESR was seen in 66.6% (2 cases) cases while it was 33.3% cases in study by Chandra et al in the present study serum ADA levels were raised in 66.6% (2 cases) of cases. 100% (2 cases) and 50% (1 case) of patients with elevated serum ADA levels had elevated ESR and associated pulmonary tuberculosis respectively but none had AFB positivity.[30]

Table 9: Correlation between typical histology (caseating epithelioid cell granulomas), elevated ESR, AFB positivity, elevated serum ADA levels and HIV seropositivity.

Site of EPTB	Typical histology	↑ ESR	AFB positivity	↑ Serum ADA levels	HIV seropositivity
Lymph node (184 cases)	82.06% (151 cases)	85.32% (157 cases)	29.9% (55 cases)	*100%	29.3% (54 cases)
Musculoskeletal (17 cases)	88.24% (15 cases)	70.58% (12 cases)	29.41% (5 cases)	**86.66%	11.76% (2 cases)
Abdominal (12 cases)	83.34% (10 cases)	91.7% (11 cases)	-	***90.9%	16.67% (2 cases)
Female genital system (4 cases)	75% (3 cases)	75% (3 cases)	-	75% (3 cases)	
Male genital system (4 cases)	75% (3 cases)	50% (2 cases)	25% (1 case)	50% (2 cases)	25% (1 case)
Mammary (4 cases)	75% (3 cases)	100% (4 cases)	-	****100% (done for 2 cases)	25% (1 case)
ENT (3 cases)	100% (3 cases)	66.66% (2 cases)	-	66.66% (2 cases)	-
Skin (2 cases)	100% (2 cases)	100% (2 cases)	50% (1 case)	100% (2 cases)	-
Total= 230 cases					

Note: * serum ADA levels done in only 11 cases, ** serum ADA levels done in only 15 cases and 13 were positive, *** serum ADA levels done only in 11 cases and 10 were positive, **** serum ADA levels done in only 2 cases and all are positive.

Table 10: Correlation between cases of EPTB with raised serum ADA levels and other parameters (ESR and AFB).

Number of cases of EPTB with raised serum ADA levels	Elevated ESR (%)	AFB positivity in ZN stained smears
Tubercular lymphadenitis (11 cases)	100% (11cases)	0
Musculoskeletal tuberculosis (13 cases)	69.2% (9 cases)	0
Abdominal tuberculosis (10 cases)	100% (10 cases)	0
Female genital tract tuberculosis (3 cases)	100% (3 cases)	0
Male genital tract tuberculosis (2 cases)	100% (2 cases)	50% (1 case)
Mammary tuberculosis (2 cases)	100% (2 cases)	0
Ear and nose tuberculosis (2 cases)	100% (2 cases)	0
Skin (2 cases)	100% (2 cases)	0

Cutaneous tuberculosis represents 1.5% of all cases of EPTB. The development of cutaneous TB depends on several factors such as immune status of patient, route of infection, past sensitization with TB and socio-economic status.[31] Various studies found male preponderance.[38] Itchy erythematous lesion and plaque were seen in 50% of cases each in the present study. ESR and serum ADA levels were elevated in all cases in the present study. Acid Fast Bacilli positivity was seen in 50% of cases in the present study whereas it was seen in only 13% of cases in study by Mathur et al.[31] In the present study 100% (2 cases) and 50% (1 case) of patients with elevated serum ADA levels had elevated ESR and AFB positivity respectively. Typical histology, raised ESR and raised serum ADA levels were seen in majority of cases of tubercular lymphadenitis (82.06%, 85.32% and 84.61% respectively), musculoskeletal tuberculosis (88.24%, 70.58% and 86.66% respectively), abdominal tuberculosis (83.34%, 91.7% and 90.9% respectively), mammary tuberculosis (75%,100% and 100% respectively), cutaneous tuberculosis (100%, 100% and 100% respectively) and female genital tract tuberculosis (75%,75% and 75% respectively) (Table 9). Only minority of EPTB (25.65%) had AFB positivity. Most cases (91.11%) of EPTB with raised serum ADA levels showed elevated ESR but only 2.22% (1 case) were

positive for AFB (Table 10). Though AFB is gold standard it is not always positive, but raised serum ADA levels and raised ESR in the presence of strong clinical suspicion or in the presence of typical histology are most valuable surrogate parameters in arriving at diagnosis of EPTB and early institution of therapy.

Although nonspecific, recording of constitutional symptoms, ESR, along with serum ADA levels is more valuable in the diagnosis of EPTB which most often paucibacillary and AFB negative.

CONCLUSION

Both histopathology (including cytological smears) showing caseation necrosis with granulomas and AFB positivity in ZN stained smears are most specific and "independent "diagnostic parameter and still be considered as "gold standard". ESR and serum ADA levels are more sensitive and less specific Though AFB is gold standard it is not always positive. But raised serum ADA levels and raised ESR in the presence of strong clinical suspicion or in the presence of typical histology with negative for acid fast bacilli, are most valuable surrogate parameters in arriving at diagnosis of EPTB.

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