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RESEARCH ARTICLE

EVALUATION OF TUBERCULOSIS IN HIV PATIENTS USING THE XPERT MTB/RIF ASSAY AND ITS RIFAMPICIN RESISTANCE PATTERN AT TERTIARY CARE CENTER IN NORTH INDIA

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ABSTRACT

Background: Tuberculosis (TB) is the most common opportunistic infection among people living with HIV. It is also the leading cause of death among people living with HIV. Patients with HIV-pulmonary tuberculosis co-infection are most likely benefitted by Xpert MTB/RIF Assay.

Aims & objective: Evaluation of Tuberculosis in HIV patients using the Xpert MTB/RIF assay and its rifampicin resistance pattern at tertiary care center in north India.

Material & methods: It was a cross sectional study conducted in a period of one year from 1st July 2015 to 30th June 2016 in the department of Medicine at Indira Gandhi Medical College and Hospital, Shimla. The study population included the HIV positive patients attending the ART clinic /Medicine OPD/Pulmonary Medicine OPD/admitted in Medicine ward. Out of these patients with HIV infection, the diagnosis of tuberculosis was established by further workup. Data collected was entered and analyzed in excel sheet, using appropriate statistical software and test of significance.

Results: Among 95 patients with HIV infection, the diagnosis of tuberculosis was established in 54 patients after further workup. The mean age of patients was 40.4 yrs. Out of 54 patients, 40 were males and 14 were females. Majority of the patients were from Shimla district i.e. 24 (44.4%). Fever (85%), pallor (81.5%), cough of more than 2 weeks (55%), Oral thrush (53.7%) and weight loss of more than 10% in the past 6 months (51%) were the most common symptoms of Patients on Presentation. Pulmonary tuberculosis (PTB) was found in 26 patients and extra-pulmonary tuberculosis (EPTB) in 28 patients. Nineteen (73.1%) out of twenty-six with pulmonary tuberculosis were gene xpert positive while Xpert MTB/RIF was positive in only five (17.85%) of the 28 patients with extrapulmonary tuberculosis.

Conclusion: This study has shown that Xpert MTB/RIF has remarkably increased the sensitivity of diagnosis of pulmonary TB than extrapulmonary TB.

INTRODUCTION

According to the Global Tuberculosis report 2014 of World Health Organization (WHO), Tuberculosis (TB) remains one of the world's deadliest communicable diseases that is caused by the bacterium *Mycobacterium tuberculosis* (MTB) (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1). Tuberculosis (TB) is the most common opportunistic infection among people living with HIV (Londhey, 2009). People living with HIV are 29 times more likely to develop active TB disease. Levels of plasma HIV RNA increase in the setting of active TB and decline in the setting of successful TB treatment.

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HIV patients have increased the risk for drug-resistant TB. There were an estimated 1.1 million new TB cases among HIV-seropositive patients globally in 2013. At least one-third of the 35 million people living with HIV worldwide are infected with latent TB. TB is also the leading cause of death among people living with HIV, accounting for some 360,000 deaths of HIV-associated TB (Longo Dan, 2015). Although smear microscopy is widely used for the rapid diagnosis of TB, it does not detect drug resistance and its sensitivity in individuals co-infected with HIV varies between 40 to 60%. This can result in a large number of cases of active TB disease going undiagnosed (Longo Dan, 2015 and Tb India, 2017). Patients with HIV-pulmonary tuberculosis co-infection cases are characterized by paucibacillary nature of the disease and AFB smear examination is usually negative. These subset of patients are most likely benefitted by Xpert MTB/RIF a novel

diagnostic modality detects *M.tuberculosis* as well as rifampicin resistance (http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf). The present study investigated symptomatic HIV patients with early suspicion of tuberculosis infection using Xpert MTB/RIF for the fast detection of tuberculosis and its rifampicin resistance at a tertiary care center.

Aims and Objectives

Evaluation of Tuberculosis in HIV patients using the Xpert MTB/RIF assay and its rifampicin resistance pattern at tertiary care center.

MATERIAL AND METHODS

Set up and design

Study Design: Cross sectional study.

Study Duration: Period of one year from 1st July 2015 to 30th June 2016.

Study Area: Department of Medicine at Indira Gandhi Medical College and Hospital, Shimla.

Study Population: The study population included the HIV positive patients attending the ART clinic /Medicine OPD/ Pulmonary Medicine OPD/admitted in Medicine ward from 1st July 2015 to 30th June, 2016.

Inclusion Criteria

- All HIV positive patients admitted in Medicine ward and attending ART clinic/Medicine OPD/Pulmonary Medicine OPD with any of following complaints i.e. fever, cough, night sweat, weight loss, shortness of breath .
- Age more than 18 yrs.

Exclusion criteria

- Those who didn't fulfill inclusion criteria.
- Those who didn't give consent.

Ethical Considerations: Only those patients who consented for study were included. Whole information regarding study kept confidential and anonymity maintained.

Study Methodology

- Informed written consent to be taken from all patients included in the study.
- The consent for HIV testing taken before collecting the sample from the patients as per National Program.

Serological Screening

Five milliliter of venous blood was collected by venipuncture and transferred aseptically from syringe into sterile test tube. The blood was allowed to clot for 3 minutes at room temperature and then clot was gently broken by using a sterile Pasteur pipette. Test tube was then centrifuged at 1200 G for 10 minutes to separate serum. Diagnosis of HIV was made as per national for HIV testing based on E.R.S.(ELISA rapid and

simple) using commercially available kits. CD4 cells count was done by fluorescent activated cell counter after the selection of patients according to inclusion criteria, relevant history was taken, physical and systemic examination was done. Then the patients were subjected to investigations including RBS, hemogram, CD4 count, renal functions tests, liver functions tests, chest X-rays and sputum smear microscopy at Direct Observed Treatment (DOT) Center, Xpert MTB/RIF, MGIT.

Diagnosis Of Tuberculosis Was Established By

- Isolating acid fast bacilli (AFB) from given specimen by Z.N. staining or Gene Xpert or culture.
- Histopathological demonstration of typical caseous granulomatous reaction.
- Clinical profile and response to ATT.
- Radiological features suggestive of tubercular lesions.
- Pleural/ascitic fluid analysis showing evidence of lymphocytic exudative effusion and CSF showing lymphocytic with hypoglycorrhachia (low CSF glucose).

Statistical analysis

Data collected was entered and analyzed in excel sheet, using appropriate statistical software and test of significance.

RESULTS

This was a cross sectional study conducted in the department of Medicine, IGMC Shimla from June 2015 to May 2016. We evaluated 95 HIV patients with symptoms suggestive of tuberculosis (e.g.a cough, fever, weight loss, night sweat, shortness of breath) from the department of Medicine, Pulmonary medicine, ART center. Out of these 95 patients with HIV infection, the diagnosis of tuberculosis was established in 54 patients after further workup.

Socio- Demographic Distribution

The mean age of patients was 40.4 yrs (median 39 yr, range 21-60 years). The majority (53.7%) of patients were in the age group of 31-40 years. Out of 54 patients, 40 were males and 14 were females. Majority of the patients were from Shimla district i.e. 24 (44.4%). Out of 40 male patients, 20 were driver by profession, 5 were shopkeeper, 5 were farmers, 2 were labourer, 3 were in private job and one was a factory worker. Out of 40 males, 39 were married and all were heterosexual. No patient in this study gave a history of intravenous drug abuse and blood transfusion, sharing of a razor blade, tattoo marks. On screening wives of 39 married males, nine (23.07%) were turned to be HIV positive. Out of total 14 female patients in our study, 13 female were housewives and one was a labourer. All females were married. Out of 14 females, seven had HIV positive spouse already. Husbands of three female died already and HIV status of husbands of four female was unknown. Out of 54 patients, 22 (40.7%) were undermatric, 15 (27.8%) were matriculated and 15 (27.8%) were illiterate. Two patients in our study were graduate (Table 1)

Symptoms of Patients on Presentation

Fever was present in 45 (83%), out of 54 the patients of TB and HIV patients in our the study. The cough of more than 2

weeks duration was present in 30 (55%) , weight loss of more than 10% in the past 6 months in 28 (51%), Shortness of breath in 20 (37%) ,night sweats in 18 (33.3) and Symptoms of neurological involvement in 6 (11.1%) of patients.

Table 1. Socio- Demographic Distribution of The Patients

Variables	No. of Patients (N=54)	Percentage %
Age Distribution (In Years)		
18-30	3	5
31-40	2	53.7
41-50	16	29.6
>50	6	11.1
District wise Distribution		
Mandi	9	16.7
Solan	8	14.8
Bilaspur	6	11.1
Shimla	24	44.4
Sirmaur	2	3.7
Kinnaur	2	3.7
Kullu	1	1.9
Outside Hp	2	3.7
Occupation		
Driver	20	
Shopkeeper	5	
Farmer	5	
Govt Emp	4	
Labourer	3	
Factory Work	1	
Others	3	
Housewife.	13	
Educational Status		
Illiterate	15	27.8
Under Matric	22	40.7
Matriculate	15	27.8
Graduate	2	3.7

On general physical examination,pallor was the commonest finding present in 44 (81.5%) patients followed by Oral thrush 29 (53.7%), Lymphadenopathy 8 (13.8%). On clinical examination of the chest, 19 (35.2%) had the clinical feature of pleural effusion followed by consolidation in 15 (27.8%). On examination of abdomen, four (7.4%) had splenomegaly, two(3.7%)had hepatomegaly and two(3.7%) had ascites.On clinical examination of nervous system, three (5.6%) patients had features of meningismus.

Table 2. Distribution of Patients According to clinical Presentation

Symptoms	No. Of Patients (N=54)	Percentage %
Fever	45	83
Cough (More Than 2 Weeks)	30	55
Weight Loss	28	51
Sob	20	37
Night Sweats	18	33.3
Neurological Complaints	6	11.1
Clinical Findings		
Pallor	44	81.5
Oral Thrush	29	53.7
Pleural Effusion	19	35.2
Consolidation	15	27.8
Lymphadenopathy	8	13.8
Splenomegaly	4	7.4
Hepatomegaly	2	3.7
Meningismus	3	5.6
Ascites	2	3.7

Investigations

Investigations revealed elevated erythrocyte sedimentation rate (ESR) in 52 (96.29%) patients. 28 out of 54 (51.85%) patients had ESR between 21-50, followed by 17 (31.48%) had in the

range of 51-100 and seven (12.96%) patients had ESR above 100 mm 1st hr. X-Ray chest was done in all the 54 patients. Abnormal radiographical findings were observed in 44 patients.Nineteen X-Rays showed pleural effusion,followed by pulmonary infiltrates in seventeen, fibrosis in three, miliary shadows in two, cavity in two and hilar lymphadenopathy in one patient. On ultrasonography abdomen splenomegaly and ascites were found in four patients each. Abdominal lymphadenopathy and hepatosplenomegaly were found in two patients each.Hepatomegaly was found in one patient. Computerised Tomography (CT) head was done in 1 one patients and was suggestive of hydrocephalus. Contrast enhanced computerized tomography (CECT) chest and abdomen was done in five patients.It showed necrotic lymph nodes in four patients, lesion in Right upper lobe suggestive of infective etiology in two patients,miliary tuberculosis in one patient. Hepatosplenomegaly with multiple granulomatous lesion in spleen in one patient. MRI brain was done two patients, one showed hydrocephalus and other showed basilar meningitis (Table 3).

Table 3. Distribution of Patients According to various investigations

Esr (Mmlst Hr)	No. of Patients (n=54)	USG Findings	No. of Patients (n=13)
<20	2	Splenomegaly	4
21-50	28	Ascites	4
50-100	17	Lymphadenopathy	2
>100	7	Hepatosplenomegaly	2
Cxr Findings	No. Of Patients(n=44)	Hepatomegaly	1
Pleural Effusion	19	CECT Findings	
Pulmonary Infiltrates	17	Necrotic lymphadenopathy	No. of Patients(n=12)
Fibrosis	3	Chest infiltrates	4
Miliary Lesson	2	Multiple granuloma spleen	2
Cavity	2	Hepatosplenomegaly	1
Hilar Lap	1	Miliary TB	1

CD4 was done in all 54 patients. Out of these 16 (29.6%) had CD4 count was below 50, eleven (20.4%) had between 51-100, eleven (20.4%) had been between 101-150, seven (13%) had between 151-200,five(9.3%) had between 201-250,three (5.6%) had between 251-500 and one (1.9%) had above 500 cells/ul. Out of 54, 21 (38.9%) patients were on ART. Pulmonary tuberculosis (PTB) was found in 26 patients and extra-pulmonary tuberculosis (EPTB) in 28 patients.Out of 26 cases of pulmonary tuberculosis, six had disseminated form and out of 28 patients of extrapulmonary case, five had disseminated tuberculosis. So out of 54 cases, eleven (20.4%) patients had disseminated tuberculosis. All except one patient with disseminated tuberculosis had CD4 count below 200 /cumm. Out of fifty-four,prior history of tuberculosis was present inten (18.51%) patients. Seven(26.9%) out of twenty-six with pulmonary tuberculosis were sputum smear positive on Zeihl-Neelsen staining. All patients with sputumsmear-positive tuberculosis had CD4 count below 200cells/cumm. Nineteen (73.1%) out of twenty-six with pulmonary tuberculosis were gene xpertpositive.

Sixteen (61.5%) with Xpert MTB/RIF positive tuberculosis had CD4 count below 200cells/cumm. Seven patients out of total twenty-six patients, which were negative for both smear for AFB and gene xpertas well, were diagnosed on the basis of clinical symptomatology, chest X-ray findings, raised ESR andresponse to treatment.

Table 4. Distribution of Patients According To CD4 Count

CD4 Count	CD4 Count In All Patients (n=54)		CD4 Count In PTB/EPTB Patients (n=54)		CD4 Count in PTB patients. (n=26)		CD4 Count in Gene Xpert +/- patients (n=26)		CD4 Count in EPTB patients (n=28)			
	No.	%	PTB (n=26)	EPTB (n=28)	Sputum (+) (n=7)	Sputum (-) (n=19)	Gene Xpert (+) (n=19)	Gene Xpert (-) (n=9)	TB LAP n=9	CNS n=4	PLEF (n=9)	ABD (n=6)
<50	16	29.7	8	7	3	5	5	3	2	1	3	3
51-100	11	20.4	5	6	3	2	4	2	2	1	2	0
101-150	11	20.4	4	6	1	4	4	1	2	1	2	1
151-200	7	13	3	4	0	3	3	2	2	1	1	1
201-250	5	9.3	3	2	0	3	2	1	0	0	0	1
251-500	3	5.6	3	2	0	1	1	0	1	0	0	0
>501	1	1.9	0	1	0	0	0	0	0	0	1	0

All Xpert MTB/RIF positive cases except one were positive on Mycobacteria Growth Indicator Tube (MGIT) and Lowenstein-Jensen (LJ) medium. Out of 19 XpertMTB/RIF positive patients only two were rifampicin resistant. Thus the detection of acid fast bacilli by Xpert MTB/RIF increased by 2.7 times as compared to sputum smear microscopy. The commonest form of extra pulmonary tuberculosis in this study was tubercular lymphadenitis and pleural effusion in nine (32.14%) patients each, followed by abdominal tuberculosis in six (22.2%) and CNS tuberculosis in four (14.8%) patients. (Table 4).

DISCUSSION

Tuberculosis remains a major public health problem, particularly in low and middle-income countries. Over 95% of TB deaths occur in low and middle-income countries. Tuberculosis is the most common opportunistic infection in HIV-positive patients. Globally, about one-third of HIV-positive patients are co-infected with TB. About 5% of new TB cases in India occur in people HIV with infection (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1). TB is a leading killer of HIV-positive people in 2015 (Southwick, 2007). Through altering the clinical and bacteriological presentations, HIV infection has contributed to the delay in diagnosing active TB disease, which leads to the increased morbidity, mortality and enhancement of the rate of transmission within communities (Golub, 2005; Wood, 2007 and Davis, 2010). In our study, a total of 95 patients were evaluated, and HIV-TB co-infection was diagnosed in 54 (56.84%) patients.

Bhagywati Devi et al (Bhagyabati, 2005), also reported HIV-TB co-infection in 55% of their patients. Ghiya et al (Ghiya, 2009), similarly reported HIV-TB co-infection in 49.2 % of HIV cases in their study. Our study included only symptomatic patients and most of them were referred cases due to lack of rapid and sensitive diagnostic facilities at peripheral hospitals. This may explain the higher incidence of TB in these HIV patients coming to our tertiary care center. The majority of patients (68.9%) in our study were in the age group of 31 to 40 years. Kamath et al (Kamath, 2013), also reported similar age group of 31 to 45 years in 61.3% of patients in their study. The majority of patients i.e. 70.07% were males. About 75.3% and 81.3 % of HIV-infected patients were male in the study by Kamath et al (Kamath, 2013), and Sharma et al (Sharma, 2015), respectively. Males were more commonly affected than females due to their occupational (like drivers) requirements and need to travel to distant places in the country for their business. In our study, 50 % of the total male patients were driver by occupation and all females were housewives.

In our study, the mode of transmission was heterosexual in all the patients. None of our patients had a history of intravenous drug abuse, blood transfusion, and tattoo or razor cuts. The majority of patients gave a history of extramarital heterosexual contacts and had visited roadside commercial sex workers. The heterosexual mode was the only mode of transmission in our study because of the low prevalence of intravenous drug abuse. It is also a common practice to use blood products after screening for transmissible infection. Unprotected multiple heterosexual contacts with professional sex workers have been demonstrated as a prominent mode of HIV transmission, followed by intravenous drug abuse, blood transmission, and vertical transmission. In the Ghiya et al (Ghiya, 2009), study, the most common mode of transmission was heterosexual (65%), followed by blood transfusion (13.8 %), vertical transmission (9.8%) and unknown (10.6%). Only one male patient in our study was unmarried. All the female patients were married in the present study. Out of 54 cases of tuberculosis in the present study, past history of tuberculosis was documented in 16 % of cases. Ghiya et al (Ghiya, 2009), documented the history of tuberculosis in 14.2% of cases in their study. It can be safely assumed that these cases were more likely to have developed reactivation of tuberculosis as HIV-induced immunosuppression eventually took its toll. In the present study, pulmonary tuberculosis was diagnosed in 26 (48.14%) patients and extrapulmonary tuberculosis in 28 (51.85%) patients. Eleven (20.37%) of 54 patients had disseminated tuberculosis. Singhal et al (Singhal, 2011), found the ratio of pulmonary tuberculosis and extrapulmonary tuberculosis of 1:1. However, Sharma et al¹³ reported a predominance of extrapulmonary TB with 372 (63.8%) patients of extrapulmonary TB and 211 (36.2%) patients of pulmonary TB. Ghiya et al.⁵² had reported disseminated tuberculosis in 23.1 % of their cases.

Fever was the commonest symptom at presentation and was present in 45 (83%) patients. It was associated with a cough in 30 (55%) patients and weight loss in 28 (51%) patients. Bhagyawati et al (Bhagyabati, 2005), evaluated 55 HIV-TB co-infected patients and reported fever and cough in 100 % and 47.5% of cases respectively. The finding in our study was comparable to study done by Kumar et al (Kumar, 2002), Ahmed et al. (Zuber, 2005), and Gautam et al. (Gautam, 2014), Chest X-ray was done in all the patients. Following findings were noted: pleural effusion in 19 (35.18%) patients, followed by pulmonary infiltrates in 17 (31.84%) patients, pulmonary fibrosis in three, cavity and miliary shadows in two (3.7%) patients each. Hilar lymphadenopathy was seen in one (1.85%) patient. This finding was consistent with a study done by Kumar et al (Kumar, 2002). Eleven patients (20.04%) in our study group had disseminated tuberculosis and all the patients had CD4

count below 200 cells/cumm. This is in accordance with the study done by Attili *et al* (Attili, 2005) in which they found 40 out of 163 (24.53%) patients had disseminated tuberculosis. Out of 26 pulmonary tuberculosis patients, seven (26.92%) were diagnosed by smear microscopy, nineteen patients (73.07%) were diagnosed by Xpert MTB/RIF assay, seven patients were diagnosed on the basis of radiological features and response to anti-tubercular treatment. All 19 patients except one which was diagnosed by Xpert MTB/RIF, were confirmed by MGIT and LJ culture. Out of 19 Xpert MTB/RIF positive patients only two were rifampicin resistant. The commonest form of extrapulmonary tuberculosis in our study group was tubercular lymphadenitis and pleural effusion diagnosed in nine patients (32.14%) each, followed by abdominal tuberculosis in six patients (21.42%) and CNS tuberculosis in four patients (14.28%). Ahmed *et al*⁶ reported tuberculous lymphadenopathy and pleural effusion in 18% and 14% of the extra-pulmonary tuberculosis patients respectively. All four patients with CNS tuberculosis in our study had tubercular meningitis. CSF analysis was suggestive of tubercular etiology in four patients and Xpert MTB/RIF was positive in two patients. MRI of one patient showed basilar meningitis. Nine patients in our study group had tubercular lymphadenitis which was diagnosed on the basis of Xpert MTB/RIF assay of lymph node aspirate, FNAC, and lymph node biopsy. Out of nine patients, one was Xpert MTB/RIF positive of lymph node aspirate, two had a necrotic lymph node on imaging (mediastinal and retroperitoneal).

Rest of the patients were diagnosed on the basis of granulomatous and necrotic lymphadenitis and response to anti-tubercular treatment. Eight out of nine patients with tubercular lymphadenopathy had CD4 count below 200 cells/cumm. Xpert MTB/RIF was positive in only five (17.85%) of the 28 patients with extrapulmonary tuberculosis as compared to 19 (73.07%) patients of pulmonary tuberculosis. This study has shown less utility and benefits of Xpert MTB/RIF in extrapulmonary tuberculosis which may be due to the difficulty in getting adequate sample e.g. lymph node aspirate, CSF, pleural fluid. Moreover; the sensitivity of Xpert MTB/RIF is low in body fluids than in sputum. The another salient feature of our study was that the prevalence of extrapulmonary tuberculosis was higher as compared to pulmonary tuberculosis as reported in earlier studies. This difference may be due to the fact that patient of extrapulmonary tuberculosis were more commonly referred to the tertiary care center due to unavailability of diagnostics facilities in the peripheral hospitals.

Summary and Conclusion

The study revealed following features. The most common affected age group was 31-40 years. Males were affected more than females. The most common affected professional group was of drivers. Unprotected multiple heterosexual contacts were found as a most common mode of HIV transmission. Out of 95 patients for symptoms, tuberculosis was diagnosed in 54 (56.84%) patients. Fever, weight loss, and cough were the commonest symptoms on presentation. Anemia was found in 43 patients (79.62%) and ESR was raised in 52 (96.29%) patients. Out of the fifty-four patients with HIV-TB coinfection 27 patients (49.99%) had CD4 cell count < 100/cumm and 38 patients (70.36%) had CD4 cell count < 200/cumm. This shows that tubercular co-infection is more common in HIV-infected with advancing immunosuppression. Pulmonary

Tuberculosis was found in 26 patients and extra-pulmonary tuberculosis in 28 patients. Eleven patients had disseminated form of tuberculosis. Out of 26 pulmonary tuberculosis patients, seven (26.92%) were diagnosed by smear microscopy, nineteen patients (73.07%) were diagnosed by Xpert MTB/RIF for sputum, seven were diagnosed on the basis of radiological features and response to treatment. So Xpert MTB/RIF increased detection of sputum positive tuberculosis by 46.15%. The commonest form of extrapulmonary tuberculosis in our study group was tubercular lymphadenitis and pleural effusion. Xpert MTB/RIF has helped to diagnose only 5 (17.85%) patients out of 28 patients with extrapulmonary tuberculosis as compared to 19 (73.07%) cases of pulmonary tuberculosis. This study has shown that Xpert MTB/RIF has remarkably increased the sensitivity of diagnosis of pulmonary TB than extrapulmonary TB, may be due to difficulty in getting adequate non respiratory invasive samples e.g. lymph node aspirate, CSF, pleural fluid. Also, the sensitivity of Xpert MTB/RIF has been reported low in body fluids than sputum.

Thus Xpert MTB/RIF has a definite role in early detection of pulmonary tuberculosis among patients suffering from HIV disease. But due to low sensitivity in diagnosis of extra pulmonary tuberculosis with Xpert MTB/RIF, the diagnosis of extrapulmonary tuberculosis also depends upon cytological and biochemical analysis of fluid, histopathological examination and ZN staining of tissue coupled with radiological features and response to antitubercular therapy.

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