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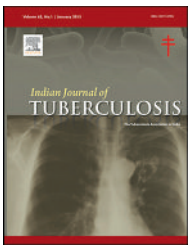

Original article

Role of percutaneous transpedicular biopsy in diagnosis of spinal tuberculosis and its correlation with the clinico-radiological features

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ABSTRACT

Introduction: Tuberculosis (TB) has long been an important cause of destructive lesions of spine in India. However the scenario is fast changing with atypical presentations and increasing reports of non-tubercular conditions. This poses a great diagnostic dilemma.
Aim: The present study is aimed at evaluating the diagnostic efficacy of percutaneous transpedicular needle biopsy and the correlation of the histology with clinico-radiological features.
Methods: Forty-one patients diagnosed of TB spine by magnetic resonance imaging (MRI) were revaluated of their clinical presentations, radiological and MRI features and underwent transpedicular needle biopsy under fluoroscopic guidance. Quality of the sample and radiological/MRI features between the tubercular and non-tubercular lesions were studied.
Results: A good sample obtained in 92.7% patients. Of these 28 patients had TB, 3 non-specific inflammatory lesion and 7 with other non-tubercular conditions (3 pyogenic, 3 metastasis, 1 multiple myeloma). Statistically there is no significant difference among the TB and non-TB groups in terms of vertebral involvement and MRI features. However risk of presentation with cord compression, cord changes and neurodeficit are higher with TB spine.
Conclusion: It is very difficult to differentiate between tubercular and non-tubercular pathology of spine on the basis of most of the clinical and MRI features. It is more difficult in early cases without any neurodeficit. Thus histopathological confirmation is must for further management and percutaneous needle biopsy is the best option considering the simplicity and minimally invasive nature of the procedure.

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1. Introduction

Of all the varieties of tuberculosis (TB), spinal TB has remained an elusive disease as the laboratory investigations can detect only half of them.[1] The clinical symptoms in spinal TB are non-specific often resulting in delayed diagnosis and serious morbidities.[2–4]

In developing countries with high prevalence of TB, spinal TB is often diagnosed and treated empirically based on the clinical and radiological criteria. But radiography cannot diagnose it until there is more than 50% decalcification of the vertebra.[1] The magnetic resonance imaging (MRI) on the other hand is a very sensitive tool in identifying the typical features of spinal tuberculosis including bone marrow oedema, endplate erosion, vertebral destruction, paravertebral collection, cord compression and cord changes but its specificity is very low.[5]

The chances of misdiagnosis are further accentuated due to the increasing incidence of atypical lesions, HIV co-infection and multidrug resistance TB.[1,2,6,7] Also with socioeconomic development and decreasing incidence of TB, ruling out non-tubercular pathologies like primary and secondary malignancies, fungal and bacterial infections, spondyloarthropathies and other granulomatous lesions of spine are becoming more important.

Therefore it has become imperative to have definitive diagnosis of TB. Biopsy done by open or percutaneous method will help in establishing the diagnosis with histopathological and microbiological analysis.[1,6,8] The percutaneous approach has distinct advantages of being simple, less morbid and a day care procedure.[9,10] However there are few studies evaluating the usefulness of percutaneous transpedicular biopsy (PTPB) in management of spinal TB.[1,3,6] In the present prospective study we aim to evaluate the efficacy of PTPB in diagnosing spinal TB and to correlate that with the diagnostic features in MRI.

2. Methods

From 2014 to 2016 all adult patients presenting with back pain were evaluated clinically. Patients who had clinical features suggestive of TB spine, i.e. >4 weeks of back pain, evening rise of temperature, loss of appetite/weight, night cries or neurodeficit were further evaluated by detailed clinical examination, radiography, haemogram (including ESR, CRP) and MRI. Patients who were diagnosed to have TB spine of dorsal or lumbar region on the basis of the MRI features, as reported by the radiologist were included in the study. Patients with known metastasis, lymphoma, multiple myeloma, immunodeficiency and other NTB granulomatous diseases were excluded from the study.

A total of 41 patients (19 males and 22 females) from age 19 to 65 years (mean 38.6) were selected for the study. In these patients the radiological features were further analysed. Various parameters used to study the MRI were (1) level of vertebra involved – dorsal (D1-D10), lower dorsal (D11, D12), lumbar (L1–L5) or any combinations, (2) number of segments involved–single, contiguous or multiple, (3) pattern of vertebral destruction, (4) spinal deformity, (5) discal involvement and (7) paraspinal soft tissue involvement. Details of the cord including cord compression, cord oedema, arachnoiditis, myelomalacia, cord atrophy or intradural granuloma were also noted.[5]

After evaluation, all patients had undergone PTPB under local anaesthesia. Based on MRI, the most affected region was selected for the biopsy. Under fluoroscopic guidance with the patient in prone position the bull's eye view of the pedicle was obtained in the AP view.[11] A stab incision was made on lateral border of the pedicle shadow and serrated tip bone cutting biopsy needle with core diameter of 3 mm (Uma Surgical, India) was used to advance up to the pedicle. After reaching the body, the trocar was withdrawn and the needle was advanced with slow rotating movements. A 20 ml syringe was kept at the other end of the needle during the advancement to create negative suction effect and minimise the loss of tissue during the withdrawal. If the sample was inadequate, repeat biopsy was done from the opposite side pedicle. The samples were then classified as per the 5 point macroscopic and 3 point microscopic scale by Aribas et al. and were sent for histopathology, scrape cytology and aerobic culture and sensitivity.[9,12]

After the final histopathological diagnosis, the patients were grouped into group 1 (TB spine), group 2 (non-tubercular diagnosis) and group 3 (non-specific chronic inflammatory lesion or patients in whom no abnormality was detected in histopathology). The MRI features of the group 1 and group 2 were compared. Statistical analysis was done using chi square test and odds ratio.

3. Results

As per the histopathology reports 28 patients were diagnosed with TB, 3 with pyogenic spondylodiscitis, 3 with metastatic adenocarcinoma, 1 with multiple myeloma and 3 with non-specific inflammatory lesion. In rest 3 patients no abnormality could be detected in the histopathology or culture. Thus the efficacy of PTPB in establishing a definitive diagnosis was 85.4%. Of the 28 patients of TB, 19 were treated conservatively with anti-tubercular chemotherapy (ATT) and bracing of spine and 9 with posterolateral decompression and fusion. Biopsy taken during surgery in these 9 patients confirmed to be TB. Two of the 3 non-specific inflammatory lesions had received ATT before presenting to us. All of these 3 were empirically treated with ATT and the symptoms improved. Two patients in our series had minor complications of haematoma formation which resolved with conservative management. There were no other major complications like neurological injury, prolonged bleeding, infection or pneumothorax.[13]

Details of clinical and MRI pictures are in Table 1. Examples of 3 non-tubercular cases were described in Figs. 1–4. Between tubercular and non-tubercular group there were no significant difference in the MRI picture in terms of level of involvement or number of segments involved. The paradiscal involvement was also seen in 3 non-tubercular patients including one with secondary metastasis. Also 7 patients of TB spine had involvement of single vertebral body. In TB spine the vertebral body had more severe affection resulting in destruction or collapse as compared to non-tubercular pathologies. Disc space narrowing was more specific to TB spine or pyogenic

Table 1 – The comparison of the MRI features of TB and non-TB patients.

	TB+	TB−	NTB+	NTB−	OR	*p*	χ^2	*p*
MRI features								
Dorsal or dorsolumbar involvement	19	9	3	4	1.58	0.21	10.1	0.12
Two contiguous vertebral involvement	16	12	3	4	1.8	0.4	2.45	0.65
Paradiscal involvement	18	10	3	4	2.4	0.27	1.13	0.57
Collection around vertebra	26	2	6	1	2.2	0.49	0.37	0.54
Disc space narrowing	19	9	3	4	2.8	0.21	1.52	0.47
Vertebral destruction or collapse	26	2	5	2	5.2	0.17	3.48	0.48
Deformity	18	10	2	5	4.5	0.10	3.03	0.22
Paraspinal soft tissue oedema	13	15	2	5	0.46	0.34	1.36	0.51
Cord compression	21	7	2	5	7.5	0.03	5.36	0.07
Cord changes	14	14	1	6	6	0.09	5.11	0.07
Clinical features								
Constitutional symptoms	22	6	5	2	0.68	0.51	0.16	0.69
Palpable abscess	9	19	0	7	–	–	4.21	0.12
Neurological deficit	19	9	2	5	5	0.08	8.72	0.07

TB+, number of TB patients having the corresponding feature; NTB+, number of non-tubercular patients having the corresponding feature; TB−, number of TB patients not having the corresponding feature; NTB−, number of non-tubercular patients not having the corresponding feature; OR, odds ratio; χ^2, Chi-square; *p*, corresponding *p* value.

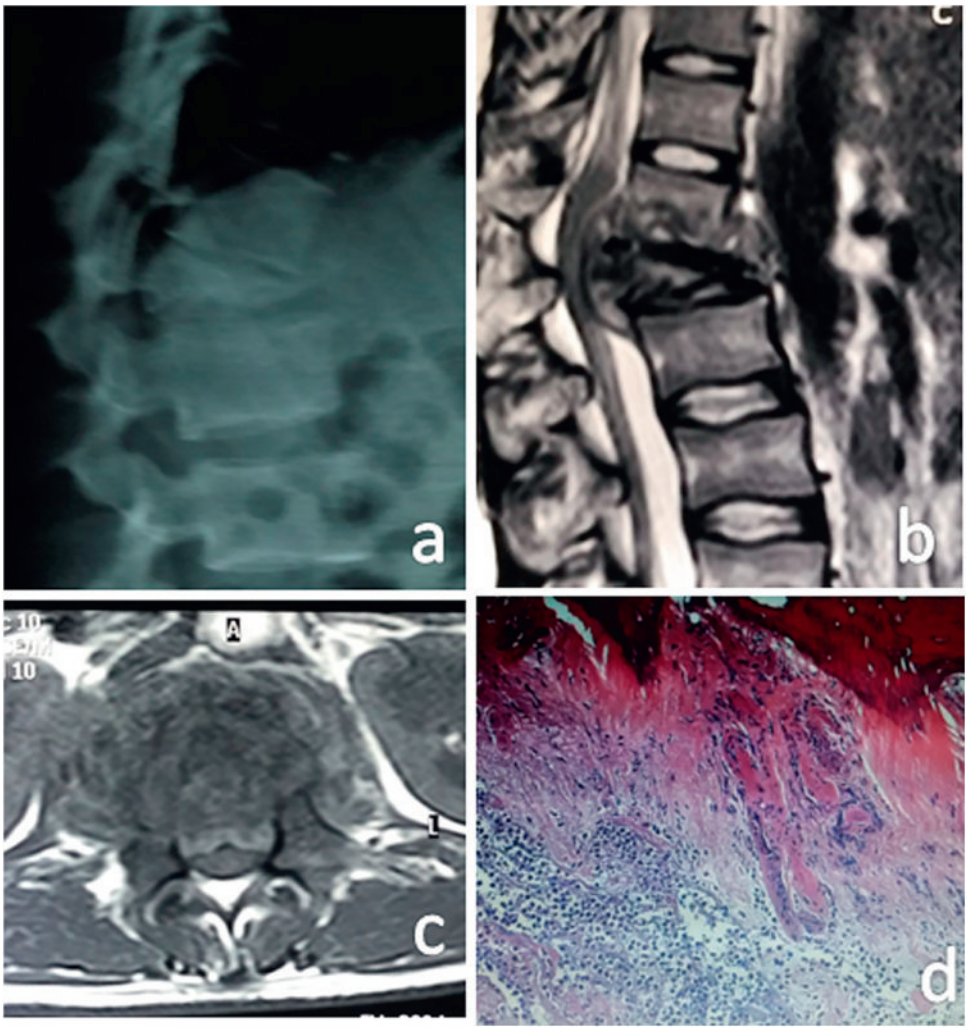

Fig. 1 – (a) Radiograph showing L1 vertebral body collapse with reduced disc space, (b) T2 MRI image with anterior epidural collection, (c) T1 MRI showing perivertebral oedema and collection, (d) histopathology with features of chronic pyogenic inflammation.

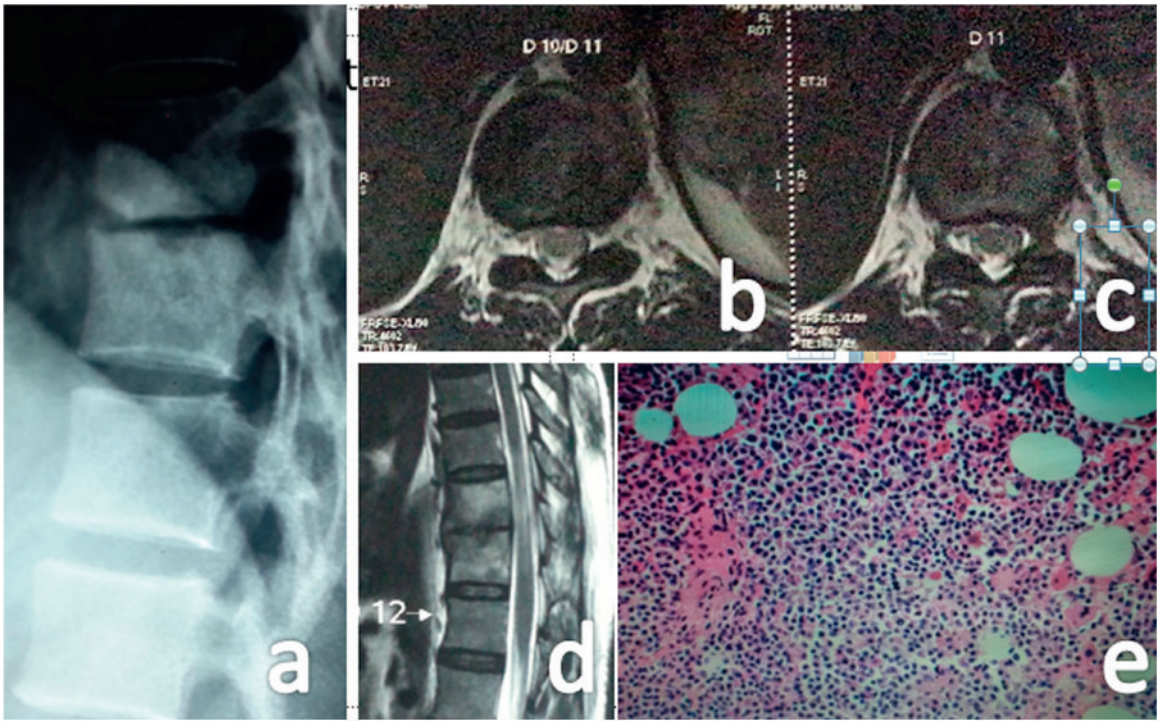

Fig. 2 – (a) D10-11 disc space reduction with endplate erosion, (b–d) MRI showing vertebral body oedema and patchy destruction, (e) histopathology with features of multiple myeloma.

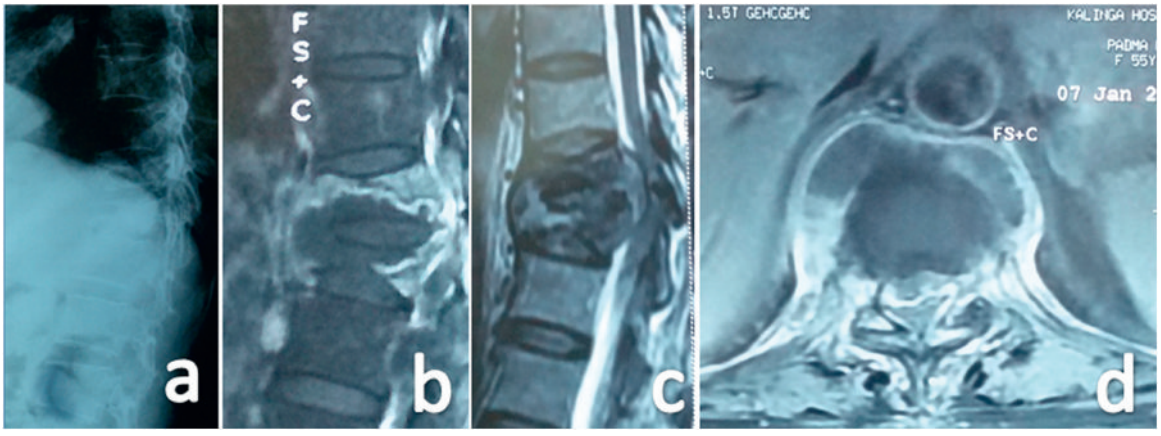

Fig. 3 – (a) Radiograph showing D7 vertebral body collapse, (b,c) sagittal MRI images showing vertebral body collapse, epidural collection with relative sparing of the disc space, (d) axial MRI image showing collection all-around vertebra. The culture of the aspirate in this patient grew *Staphylococcus aureus*.

spondylodiscitis. Collections around vertebra were more common in TB spine and were present all around anterior, paravertebral and epidural region. However 2 patients with secondary metastasis (one from stomach and one unknown primary) had paraspinal soft tissue mass that appeared like abscess.

The neurological involvement as per ASIA grading were (A-11 patients, B-3, C-2, D-3, E-9) in group 1 and (C-1, D-1, E-5) in group 2. Thus TB spine group had significantly more severe neurological deficit than the non-tubercular group.

4. Discussion

In the present study most common clinical features were back pain (100%) and constitutional symptoms (54%) which were slightly higher than the previous studies. This could be due to back pain being an initial criterion for selection in to the study.[14–16] But it was non-specific. On the other hand presence of clinically palpable gibbus, abscess and neurological deficit were more common in TB spine than non-tubercular pathologies.

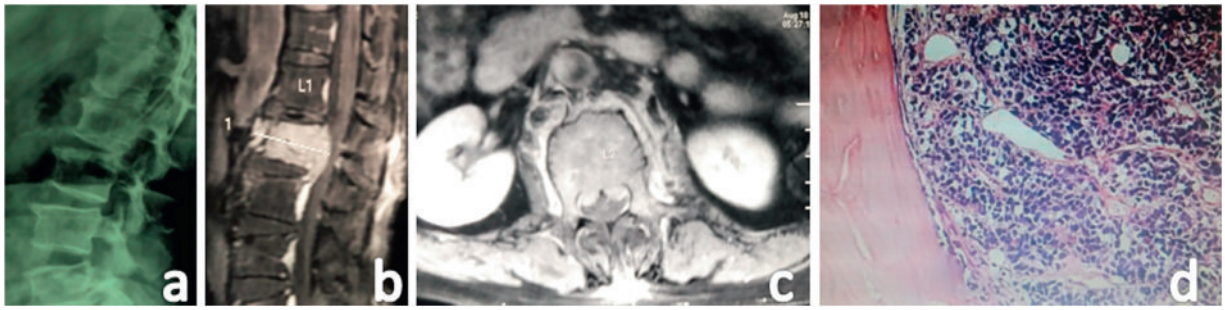

Fig. 4 – (a) Wedging of the L2 vertebral body in radiograph, (b) vertebral body oedema with relative sparing of disc space, (c) perivertebral collection all-around body, (d) histopathology showing features of metastatic adenocarcinoma.

Hyperintensity of the body in T2 weighted images was the most consistent MRI feature seen in all of our cases. It was also the most common observed feature in previous studies. Vertebral body destruction and perivertebral abscesses were next common features.[3,5,14–16] Presence of a thin smooth walled abscess was the most specific feature of TB spine. Gupta et al. had suggested a direct correlation of epidural abscess with the neurodeficit which improved accordingly with recovery.[18] Discal involvement and disc space narrowing were seen in 67% of cases and was comparable to previous studies.[3,5,14–16] This was in contrast to the general assumption of 'discal sparing' as a common finding in TB spine.[4,17] Cord involvement including compression and cord changes were also more common to TB spine. However exact comparison of MRI features amongst various studies was difficult owing to the variation in the stage of presentation and neurological deficit (Table 2). Also the MRI picture may change in presence of atypical myobacteria, immunodeficiency and post-antitubercular chemotherapy.[1,2]

In the present study the accuracy of PTPB in providing a definitive diagnosis was 85.4% which is comparable to previous literatures (74–92%).[9,11,13,19–22] The accuracy of the PTPBs done under image intensifier were also similar to those done under CT guidance. Nourbaksh et al. in a meta-analysis found no significant difference between them.[20] There are several advantages of PTBP over open biopsy like being less expensive, less morbid and less chance of spillage of pathological tissue out of vertebra.[13,19] Jelineck et al. compared various approaches for the percutaneous biopsy and found that the transpedicular route provides the safest route and gives better results than the paraspinal approach.[23] However PTPB may not be that useful in cervical spine pathologies and those affecting the part of the vertebral body that lies immediately anterior to spinal canal.[21] Seven patients (20%) in the present study were wrongly diagnosed as TB in MRI but PTPB assisted histopathological analysis helped in identifying the non-tubercular pathology and had an impact on the management. This reduced the unnecessary use of ATT, the adverse drug reactions and helped in early identification of the true pathology and prompt management.

Various factors can affect the accuracy of PTPB. It was found better in cases of female patients, thoracic levels, whole vertebral body involvements, soft lesions or neoplastic conditions but less accurate for partial vertebral body involvements, sclerotic lesions or infective pathologies.[9,21,24,25] There are various methods that can be employed to improve the accuracy. Macroscopic and microscopic comparison of various needles showed that PTPB with a larger inner diameter gives better tissue samples with minimal crushing effect.[13,26] Also needles with serrated edges give

Table 2 – Comparison of MRI finding of the present and the previous studies.

MRI features	Present	Gracia[3]	Sivalingam[4]	Jain[5]	Thammaroj[14]	Khalid[15]	Zaidi[16]	Gupta[18]
	(Percentage of the patients in each study having the corresponding MRI feature)							
T 2 hyper intense body	100	95	–	100	67	95	100	100
Paradiscal involvement	64	80	–	–	87	–	65	–
Vertebral abscess	–	85	37	–	54	–	–	–
Paraspinal abscess	71	65	45	100	75	92	92	–
Epidural abscess	82	50	–	86	83	74	78	93
Subligamentous spread	54	40	–	92	66	90	–	–
Body destruction/collapse	92	70	–	–	41	62	36	–
Discal hyperintensity in T2	71	80	None	98	88	84	77	–
Disc space narrowing	67	60	None	88	50	68	–	–
Kyphosis	64	25	–	50	–	52	–	40
Cord compression	75	65	32	75	–	70	64	69
Cord oedema	50	–	11	22	80	–	2	75
Posterior elements	–	–	54	–	–	86	18	–
Neurodeficit	57	–	–	24	–	62	–	80

better results as compared to those with bevelled edges.[11,19,24] However more care has to be taken while using the larger needles as it can increase the chances of inadvertent pedicular violation and damage to the spinal cord and roots. This is more so important in cases of upper thoracic vertebra where the sagittal diameter may be only 4 mm.[19] In this study we had used a needle with 3 mm core inner diameter with good accuracy and without any obvious pedicular violations. Intra-operative scrape cytology is another easy and cheap addition to enhance the efficacy of the PTPB and can give quick results. It can help in identifying the false negative results intra-operatively, and the biopsy can be repeated at the same time.[9] The samples of PTPB can also be used for the culture sensitivity and DNA PCR technologies to identifying specific organisms that help in further management.[1,6]

5. Conclusion

Diagnosis of TB spine can be difficult with clinico-radiological parameters only. Presence of thin walled perivertebral abscess is the only MRI feature specific for TB spine. Considering poor specificity of MRI, additional tissue diagnosis methods are needed before starting antitubercular chemotherapy. PTPB under image intensifier is a safe and effective method to get the tissue in TB spine for histopathological and microbiological analysis. In the present study using this method we could identify 20% non-tubercular pathologies wrongly diagnosed as TB spine and avoided the additional misery of the patients. However this study has few limitations. First, the number patients are less specially in non-tubercular group. A larger number could have helped in understanding the difference in the clinical and MRI features better. Secondly we could not use the DNA PCR technology which could have further helped us in improving the diagnostic yield.

Conflicts of interest

The authors have none to declare.

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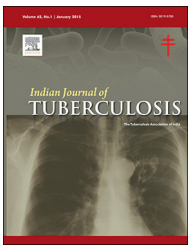

Original article

A study on procedural delay in diagnosis and start of treatment in drug resistant tuberculosis under RNTCP

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Background: Multi-drug-resistant TB (MDR-TB) has become a significant public health problem and an obstacle to effective TB control. Rapid diagnostic tests for anti tubercular drugs sensitivity have significantly reduced total time in initiation of treatment. Still there is a significant gap between MDR diagnosis and start of category IV treatment. Delay in establishing the diagnosis may cause disease progression, transmission, lost to follow up and death. This study was planned to assess the actual delay from day one of sputum examination to the day of initiation of category IV in operational settings.

Methodology: MDR-TB suspected patients attending the Respiratory medicine department, JLNMC, Ajmer from June-15 to July-16 were followed from sputum examination to sample deposition for drug sensitivity testing (LPA/CBNAAT) to MDR detection to category IV initiation, for assessment of procedural delay at various steps.

Results: LPA group (371 patients): Sputum smear to LPA deposition mean duration was 8.02 days, LPA deposition to LPA result upload mean duration was 3.78 days, LPA deposition to patients received LPA reports mean duration was 21.73 days and reports received to PMDT site admission (if drug resistant) mean duration was 3.61 days. Total time duration in category IV initiation was 32.63 days.

CBNAAT group (50 patients): Sputum smear to CBNAAT deposition mean duration was 6.70 days, CBNAAT deposition to CBNAAT result upload mean duration was 1.13 days, CBNAAT deposition to patients received CBNAAT reports mean duration was 6.53 days and reports received to PMDT site admission (if R-resistant) mean duration was 3.8 days. Total time duration in category IV initiation was 12.4 days.

Conclusion: Major delay seen on part of receiving sensitivity reports indicates the need to stress upon field staff motivation, appropriate training, sensitisation and expert counselling.

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1. Introduction

Tuberculosis has been a major cause of suffering and death since time immemorial, thought to be one of the oldest human diseases.[1] Tuberculosis, despite the availability of effective diagnostic, preventive and curative strategies, ranks alongside HIV as a leading cause of death.[2,3] The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multi-drug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective TB control.

Multi-drug resistant TB (MDR-TB) is defined as *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin with or without resistance to other drugs. The prevalence is found to be at a low level in most of the countries, where it has been studied. Data from studies conducted by NIRT (erstwhile TRC Chennai) and NTI Bangalore, have found MDR-TB levels of 1% to 3% in new cases and around 12% in re-treatment cases.[4,5] Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, a level that has changed little in recent years. India and the Russian Federation, which combined with China, contribute to almost 54% of the estimated global burden of MDR-TB.[2,3]

In 2014 India achieved complete geographical coverage for diagnostic and treatment services for multi-drug resistant TB. In 2013, 248,000 cases of TB were tested for drug resistance and 35,400 were found to have either MDR or rifampicin resistant TB.[6] Although the proportion is small, the number of persons with MDR TB is sizeable in numbers. If left undiagnosed or poorly treated, MDR-TB patients often live and suffer for months to years before succumbing to the disease; hence transmission of MDR can continue, amplifying MDR in the community.[8] Even in HIV seronegative patients, treatment of MDR TB has been difficult and may only give response rates of the order of 50% with a high mortality rate with persistent positive culture.[7]

MDR TB suspects from Revised National Tuberculosis Control Program (RNTCP), i.e. category I failures, category II failures, follow up smear positive cases, retreatment cases (smear positive and negative), HIV-TB co infected cases and contacts of MDR TB patients are being subjected to sputum Mycobacterial culture and drug susceptibility test (DST) at the Intermediate Reference Laboratories (IRLs) and some accredited private labs. Under the DOTS Plus strategy, a standard treatment regimen (STR) is being followed. The regimen includes injection kanamycin (K), levofloxacin (LVFX). Ethionamide (ETA), cycloserine (CLY), pyrazinamide (Z) and ethambutol (E). P-amino salicylic acid (PAS) is included in the regimen as a substitute drug if any of the bactericidal drugs (kanamycin, levofloxacin, pyrazinamide and ethionamide) or any two bacteriostatic drugs (ethambutol and cycloserine) are not tolerated.

A detailed protocol for follow up and monitoring the treatment efficacy and adherence is in place. Result from DOTS plus pilot sites have shown good treatment success rates.[9]

1.1. Problem statement

PMDT status in India (Since inception of PMDT).[6,10]

Year	Total MDR suspect	Total MDR confirmed	Total MDR started on category IV
2011	22,695	6069	4217
2013	248,000	35,400	20,700

Thus there is a huge difference between MDR diagnosed patients and patients for which category IV treatment was started.

The first constraint to be identified in implementing DOTS plus was delay of months in obtaining a laboratory diagnosis of MDR-TB.[11] These delay could lead to continuing transmission of infection to others. There may be further amplification of resistance associated with clinical deterioration and death due to delayed initiation of adequate management. Delay in mobilising the patients in the field, delay in referral of patients from the periphery to the PMDT site, Poor coordination at the PMDT site in receiving and initiating treatment of eligible patients and non-availability of beds could be possible reasons for delayed treatment initiation.

PMDT site, Ajmer is situated at JLN Medical College, Ajmer. The IRL (Intermediate Reference Laboratory) for state of Rajasthan is also situated at STDC, Ajmer only, within the same campus. Still, we come across similar situations of delayed diagnosis of suspected MDR TB cases.

As per PMDT guidelines, LT (Lab Technician) and STLS (Senior TB Laboratory Supervisor) are the first person who may first know the relapse, treatment failure or follow up positives. It is therefore their responsibility prima facie to ask these patients to get drug sensitivity testing (DST) done by LPA/CBNAAT immediately. In practice it is found that they do not advise DST for these patients nor they collect/deposit sputum for DST at their own. Moreover, it has also been found that they do not receive LPA/CBNAAT/culture reports in time from IRL either personally or they do not visit the IRL site for the reports in time which might delay the start of treatment for these patients.

Despite clear cut guidelines healthcare workers are not aware of anti TB treatment regimen for these patients awaiting DST results. Therefore, this study was planned to evaluate such factors responsible for delay in diagnosis of MDR TB and to formulate a better strategy to improve the deficit.

1.2. Aims and objectives

1. To assess the average delay in patients seeking care for drug resistant tuberculosis at various steps in management.
   (a) Period between the day of MDR Suspect and Deposition of Sputum for LPA/CBNAAT or Pleural fluid/pus/lymph node aspirate for CBNAAT.
   (b) Period between submission of sample for LPA/CBNAAT and results upload.
   (c) Period between submission of sample for LPA/CBNAAT and receipt of report to the patient.
   (d) Period between receipt of report and start of treatment for MDR-TB (admission at PMDT Site).
2. To assess the various factors for such delay in start of treatment.
3. To assess the treatment received between these periods.
4. To formulate a better strategy to reduce the period between diagnosis and start of treatment for such patients.

2. Material and methods

This study was carried out on all MDR-TB suspected patients attending the Department of Respiratory medicine, JLN Medical College, Ajmer for drug resistance evaluation and patients being admitted at PMDT site to start Cat IV regimen between a period from 1 June 2015 to 31 July 2016.

These patients were evaluated in the following manner including history and lab reports to assess the possible factors responsible for delay in the diagnosis and start of treatment for Drug resistant TB.

(a) What was the criteria to suspect patient as MDR?
(b) Any anti tubercular treatment taken in past or not.
(c) Date of sputum examination and dispatch of report.
(d) The person who advised for LPA/CB-NAAT.
(e) When was LPA/CBNAAT deposited?
(f) What was the result of LPA/CBNAAT/culture?
(g) When was the report uploaded on site?
(h) When was the report received to patient?
(i) Who reported result to the patient?
(j) When he/she got admitted to PMDT Site?
(k) What treatment did he/she receive while waiting for sensitivity result?

3. Results

In this study samples from 371 MDR Tuberculosis suspected patients were sent to Intermediate Reference Laboratory, Ajmer, where these were investigated for anti tubercular drugs sensitivity (isoniazid and rifampicin) by molecular line probe assay (LPA) while samples from 50 patients were evaluated by cartridge based nucleic acid amplification test (CB-NAAT) for rifampicin sensitivity (Tables 1A, 1B, 2, 3A, 3B and 4–6).

4. Discussion

Following factors did not appear to influence time elapsed in their treatment for both the groups.

- Geographical distribution of patients.
- Gender and age of the patients.
- Place of residence.
- Educational status.
- MDR suspect category of patients.
- Past history of anti tubercular treatment.

Table 1A – MDR suspect category in study population (LPA) (*n* = 371).

	No. of patients	Percentage
Contact MDR (Cont. MDR)	1	0.3%
Defaulter (DF)	120	32.3%
Failure (Fail)	13	3.5%
Follow up positive (FU+)	56	15.1%
Relapse (Rel)	181	48.8%
Total	371	100.0%

Table 1B – MDR suspect category in study population (CBNAAT) (*n* = 50).

	No. of patients	Percentage
Smear negative treatment interrupted (Sm-t/t int)	13	26.0%
Pulm. + extra pulm.TB (PTB + EP-TB)	3	6.0%
Extra pulmonary TB (EP-TB)	10	20.0%
TB-HIV	1	2.0%
Smear negative re-treatment (Sm-Re t/t)	23	46.0%
Total	50	100.0%

Similarly studies done by Naidoo et al.[15] (January 2008–December 2012), Rifat et al.[14] (September 2012–April 2013) and Jacobson et al.[13] (culture based study) (2007–2011) could not find any significant association between age and gender variation of patients and time elapsed for their diagnosis and treatment initiation.

In their study Rifat et al.,[14] also could not find any relationship with urban–rural status, educational status of the patients and time to treatment. Zhang et al.,[17] (January 2010–May 2012) also could not find any association of education level with treatment delay in their study which included most of the patients of education level below high school.

However we found a statistically significant association between educational status of patients of CBNAAT group and time elapsed for their diagnosis (from sputum smear examination to patients received CBNAAT/culture reports) (p-value 0.01; significant). The reason for getting this association may be due to small number of patients (50) we could enrol for our CBNAAT study group in compare to LPA study group (371).

In study by Rifat et al.,[14] also no any relation in their previous treatment outcome and time to treatment at present was found. Any influence of previous anti tubercular treatment episode on patients' time to initiation of category IV treatment was also not found.

In LPA study group when patients results were awaited, 8 (2.2%) patients were continued on category I, 200 (53.9%) patients received category II, 26 (7%) patients were taking private anti tubercular treatment. 121 (32.6%) patients were not receiving any anti-tubercular treatment while treatment status for 16 (4.3%) patients was not traceable.

In CBNAAT study group when patients results were awaited, 4 (8%) patients received category I, 28 (56%) patients received category II, 3 (6%) patients were taking private anti tubercular treatment. 15 (30%) patients were not receiving any anti tubercular treatment.

Zhang et al.,[17] found in their study that 56.8% patients were treated with first-line drugs during their delay before initiating category IV treatment. Similarly 56.1% patients of LPA group and 64% patients of CBNAAT group received first line drugs while awaiting sensitivity results in our study.

4.1. *Gap between sputum smear and LPA/CBNAAT deposition*

Mean gap between sputum smear and LPA deposition (n = 371) was 8.02 days (range 1–154 days) while standard deviation (SD) was 12.870.

Table 2 – Who advised for LPA/CBNAAT.

	No. of patients (LPA)	Percentage	No. of patients (CBNAAT)	Percentage
Medical College (Med Colg)	322	86.8%	47	94%
Medical Officer (MO)	36	9.7%	2	4%
Private (Pvt)	1	0.3%	0	0
Senior Treatment Supervisor (STS)	12	3.2%	1	2%
Total	371	100.0%	50	100%

Table 3A – Result of LPA/culture (*n* = 371).

Result	No. of patients	Percentage
HR-resistant	71	19.1%
HR-sensitive	68 + 1 (culture)	18.6%
R-resistant, H-sensitive	60	16.2%
R-sensitive, H-resistant	34 + 1 (culture)	9.4%
NTM (by culture)	1	0.3%
Culture negative	2	0.5%
On solid culture	5	1.3%
LPA report not received (–)	55	14.8%
Died when LPA report awaited (*)	51	13.7%
*Solid (died when solid culture report awaited)	6	1.6%
Not traceable (?)	16	4.3%
Total	371	100.0%

Table 3B – Result of CBNAAT/culture (*n* = 50).

Result	No. of patients	Percentage
R-resistant	5	10%
R-sensitive	10	20%
Culture negative	2	4%
On solid culture	12	24%
CBNAAT report not received (–)	8	16%
Died when CBNAAT report awaited (*)	9	18%
* Solid (died when solid culture report awaited)	4	8%
Total	50	100%

Table 4 – Who reported results (LPA/CBNAAT/culture).

Who reported results	No. of patients (LPA/culture)	Percentage	No. of patients (CBNAAT/culture)	Percentage
Medical College (Med colg) DOTS plus site	174	73.1%	14	82.3%
Medical Officer (MO)	27	11.3%	2	11.7%
Senior Treatment Supervisor (STS)	37	15.5%	1	5.8%
Total	238	100%	17	100.0%

Table 5 – Treatment offered in this period in study population (LPA/CBNAAT).

Treatment offered	No. of patients (LPA)	Percentage	No. of patients (CBNAAT)	Percentage
Cat I	8	2.2%	4	8%
Cat II	200	53.9%	28	56%
Private (Pvt)	26	7.0%	3	6%
None	121	32.6%	15	30%
Not traceable (?)	16	4.3%	0	0
Total	371	100.0%	50	100%

Mean gap between sputum smear and CBNAAT deposition ($n = 40$) was 6.70 days (range 2–52 days) while standard deviation (SD) was 8.395.

Thus there was a difference of 1.32 days in mean delay of sputum smear to LPA or CBNAAT deposition but this difference is not statistically significant (p-value 0.37, not significant).

Table 6 – Comparative analysis (LPA v/s CBNAAT).

	N	Mean (days)	SD	t-value	p-value
Gap between sputum smear and LPA deposition	371	8.02	12.870	0.88	0.37
Gap between sputum smear and CBNAAT deposition	40	6.70	8.395		
Gap between LPA deposition and LPA result upload	233	3.78	3.596	8.7225	**0.0001**
Gap between CBNAAT deposition and CBNAAT result upload	15	1.13	0.743		
Gap between LPA deposition and culture result upload	5	65	3.082	2.9021	**0.0440**
Gap between CBNAAT deposition and culture result upload	2	61	0		
Gap between LPA deposition and patient received LPA report	233	21.73	24.735	8.2139	**0.0001**
Gap between CBNAAT deposition and patient received CBNAAT report	15	6.53	3.461		
Gap between LPA deposition and patient received culture report	5	124.8	52.627	2.6889	0.0547
Gap between CBNAAT deposition and patient received culture report	2	61.5	0.707		
Gap between LPA report received and admission	131	3.61	5.710	0.16	0.87
Gap between CBNAAT report received and admission	5	3.80	2.387		
Total time delay in initiation of category IV (LPA)	131	32.63	24.741	6.73	**0.0001**
Total time delay in initiation of category IV (CBNAAT)	5	12.40	4.669		

'*p*' values have been shown in bold where it is significant i.e. < 0.05.

- **Provider delay** has been defined as time between visiting a provider to visiting designated diagnostic centre for testing which is equivalent to gap between sputum smear to LPA/CBNAAT deposition in our study. Also in our study maximum numbers of LPA as well as CBNAAT were advised at medical college level so we may expect a lesser delay at this step.

In a study by Yagui et al.[12] provider delay observed was >6 days which is similar to our study though that was sputum culture based study. In a study by Natt et al.[16] provider delay observed was 20.74 days which was also a sputum culture based study. In study done by Rifat et al.[14] conducted in Bangladesh provider delay was 4 weeks.

4.2. *Gap between LPA/CBNAAT deposition and LPA/CBNAAT/Culture result upload*

Mean gap between LPA deposition and LPA result upload ($n = 233$) was 3.78 days (range 1–38 days); standard deviation was 3.596. Mean gap between LPA deposition and culture result upload ($n = 5$) was 65 days (range 60–68 days); standard deviation was 3.082.

Mean gap between CBNAAT deposition and CBNAAT result upload ($n = 15$) was 1.13 days (range 0–2 days); standard deviation was 0.743. Mean gap between CBNAAT deposition and culture result upload ($n = 2$) was 61 days (Min. and Max. 61 days); standard deviation was 0.

So there was a difference of 2.65 days in LPA deposition to LPA result upload and CBNAAT deposition to CBNAAT result upload mean gaps and this difference is statistically highly significant (p-value <0.001). Also there was a difference of 4 days in LPA deposition to culture result upload and CBNAAT deposition to culture result upload mean gaps and this difference is also statistically significant (p-value 0.04, significant).

- **Laboratory turnaround time** has been defined as time from date of sputum collection to date result was available in the laboratory. It is equivalent to LPA/CBNAAT deposition to their reports upload gap in our study.

Here it should be stressed that 133 (35.8%) patients in LPA group (including 16 not traceable patients) and 33 (66%) patients in CBNAAT study group were those for whom sensitivity results were not available or their samples were on solid culture. As our data shows the promptness of IRL in the processing of samples, preparing results and upload them. This clearly indicates the non-alertness on the side of Medical officers, STS, STLS and field staff.

In a study by Naidoo et al.[15] median laboratory turnaround time observed was 1 day in the Xpert MTB/RIF-based algorithm. While it was 54 days in culture based algorithm in the study done by Yagui et al.[12] These observations are quite close to that of our study.

4.3. *Gap between LPA/CBNAAT deposition and patient received LPA/CBNAAT/culture report*

Mean gap between LPA deposition and patients received LPA reports ($n = 233$) was 21.73 days (range 1–161 days); standard deviation was 24.735. Mean gap between LPA deposition and patients received culture reports ($n = 5$) was 124.8 days (range 70–195 days); standard deviation was 52.627.

Mean gap between CBNAAT deposition and patients received CBNAAT reports ($n = 15$) was 6.53 days (range 1–14 days); standard deviation was 3.461. Mean gap between CBNAAT deposition and patients received culture reports ($n = 2$) was 61.5 days (range 61–62 days); standard deviation was 0.707.

In our study after sample deposition patients received their CBNAAT reports 15.2 days (mean) earlier than LPA reports and this difference is statistically highly significant (p-value <0.001). Culture reports were received 63.3 days earlier in CBNAAT group than LPA group, but this difference was not statistically significant (p-value 0.054, not significant).

- **Diagnostic delay** has been defined as time between the diagnostic sample provided to date the result is available to the patient which is equivalent to our gap between LPA/CBNAAT deposition and patients getting their reports. 133 (35.8%) patients in LPA group (including 16 not traceable patients) and 33 (66%) patients in CBNAAT study group could not receive their sensitivity results in our study.

In a study in Brewelskoof hospital, Worcester, South Africa, Jacobson et al.,[13] found diagnostic delay for LPA of 27 days. Similarly in a study by Naidoo et al.[15] in South Africa diagnostic

delay was 24 days for LPA algorithm which is close to our observation while it was <1 day for CBNAAT algorithm. A huge difference from our CBNAAT algorithm here clearly indicates the need for earlier dispatch and informing the patients about their results in our region. Also significant number of patients could not receive their sensitivity results in both LPA and CBNAAT groups.

In a study by Rifat et al.,[14] in Bangladesh a diagnostic delay of 5 days was observed for patients evaluated by LPA and Gene Xpert. In other studies by Singla et al.,[11] diagnostic delay was 5 months (culture method), 2.8 months (BACTEC); by Natt et al.,[16] 24.75 days (culture based) delay; by Yagui et al.,[12] 54 days (culture based) delay was observed in their studies.

4.4. *Gap between report received and admission at PMDT site in study population (LPA/CBNAAT)*

There was a mean delay of 3.61 days (range 0–38 days) from patients received LPA reports to being admitted at PMDT site if drug resistant (n = 131) with standard deviation (SD) of 5.710.

Mean delay from CBNAAT report receiving to admission at PMDT site (n = 5) was 3.8 days (range 1–7 days) and standard deviation (SD) 2.387 was there for R-resistant patients.

A difference of 0.19 days was found between mean delays of MDR/R-resistant patients getting admitted at PMDT site after getting their CBNAAT or LPA reports. This difference was statistically not significant (p-value 0.87).

- **Treatment initiation delay** has been defined as time between the date of diagnosis and the date of treatment initiation. It is similar to our study's gap from reports receiving to admission at PMDT site.

In study by Naidoo et al.,[15] (2008–2012) this delay was 14 days (LPA) and 10 days (CBNAAT). In study by Yagui et al.,[12] (2004) it was 10 days (LPA and Gene Xpert). In study by Jacobson et al.,[13] (2007–2011) it was 20 days (LPA) and 19 days (conventional DST). So we got a lesser delay in this step which would have been due to the fact that most of the patients who were resistant to HR or R alone received their reports at PMDT site itself and were immediately advised admission on the next admission day. Immediate response by M.O. or local S.T.S. may be the other factors.

Natt et al.,[16] (2011–2013) observed a mean delay of 15.45 days in receiving reports of C/DST to referral of patients to DOTS-plus sites and a delay of 2.44 days from referral of patients to DOTS-plus sites to initiation of category IV regimen. Treatment initiation delay of 33 days and 3.3 months were observed in other studies done by Yagui et al.,[12] (2004) and Singla et al.,[11] (2002–2006) respectively.

4.5. *Total time delay in initiation of Cat IV in study population (LPA/CBNAAT)*

Average time delay in initiation of category IV in LPA algorithm (n = 131) was 32.63 days (range 7–184 days) with standard deviation of 24.741.

Average time delay in initiation of category IV in CBNAAT algorithm (n = 5) was 12.4 days (range 6–17 days) with standard deviation of 4.669.

So we observed that patients who were evaluated by CBNAAT for drug sensitivity had a lesser total delay of 20.23 days in comparison to LPA group resistant patients being put on category IV regimen. And this different was statistically highly significant (p-value <0.001).

- **Health system delay** has been defined as time between visiting a provider to start of treatment. It was derived by adding provider delay, diagnostic delay and treatment initiation delay. It is equivalent to total time delay in initiation of category IV in our study.

Total delay in initiation of category IV of 24 days (by LPA) in study by Jacobson et al.,[13] and 43 days (by LPA) and 17 days (by CBNAAT) in study by Naidoo et al.,[15] were observed in their studies. These observations were close to our findings.

Though in other studies a total health system delay of 2–5 months[11,12,14,16] were observed in different countries but in all these studies patients' drug sensitivity was done by sputum culture, so greater delay was obvious.

5. Conclusion

- Since the introduction of rapid diagnostic tests for detection of anti tubercular drugs sensitivity, total time in initiation of treatment has significantly reduced from months to days.
- This study was planned to assess the actual delay from day 1 of sputum smear examination to the day of initiation of category IV regimen for these patients in operational settings as they were investigated for drug sensitivity by the tests whose standard reporting time is just 2–3 days (LPA) and 3 h (CBNAAT).
- In our study 85–95% of patients LPA and CBNAAT were advised at medical college level and again around 75–80% of these results were reported at the same level. It clearly indicates the reluctance of STS, STLS, Medical officers and field staff for their duty. There should be an intensive training and supervision for these workers. Also decentralisation of these investigations is needed for easy access.
- LPA reports status was not known for 133 (35.8%) patients and CBNAAT reports status was not known for 33 (66%) patients. It includes those patients for whom reports were not received or sputum was put on solid culture and further results not reported or non-traceable patients. Early dispatch of these reports up to root level is strongly needed. Use of electronic media and Internet should be encouraged for this purpose. Apart from patient, the report must also be communicated to treating physician, STS at the same time.
- 57 (15.3%) patients from LPA group and 13 (26%) patients from CBNAAT group died while awaiting sensitivity results probable cause being the delay in diagnosis and inadequate treatment. To overcome such loss criteria A, B and C must be dissolved and every patient of tuberculosis must be investigated for drug resistance on day 1.
- About one-third of the patients in both LPA and CBNAAT study groups were not receiving any anti tubercular treatment. Most of them must be those whom sensitivity results were awaited. It again shows the poor coordination

between field staff and patients. All care providers need to be sensitised by the guidelines to treat such patients.
- Greatest delay in diagnosis and initiation of treatment was seen on part of delay in receiving LPA and CBNAAT reports which again indicates insensitivity and non-alertness on the side of STS, STLS, Medical officers and field staff. Staff motivation, appropriate training, sensitisation and expert counselling are the needs of the hour.

6. Solutions

- Same sputum smear sample should be subjected to LPA/CBNAAT as that for smear examination.
- Proper training of M.O./STS/STLS regarding history taking, clinical evaluation and immediate referral of suspected cases.
- Use of social media/SMS/smart phones for immediate reporting in local languages.

7. Limitations of our study

This study was an observational study conducted at a tertiary care centre and patients enrolled in this study must be coming regularly here for follow up and also they must be regularly being enquired for their LPA/CBNAAT deposition and to collect their reports. So generalisation of observations of this study at large level is not possible and actual scenario in the periphery at large level will be certainly worse.

PROFORMA

S. No.
Name : Age : Sex :
Address :
Telephone number :
DTO-E-mail with Mobile number :
Category of patient-Relapse/Defaulter/Failure/Contact of MDR/HIV/Follow up positive/Smear neg t/t interrupted/Smear neg re-treatment/EP-TB/ Others.

History of Past ATT:

Treatment Episode	Month/Year of Treatment	Drugs and Duration	Source (RNTCP/Pvt.)	Response

Date of Sputum smear examination and result :
- Lab No. :
- DMC :

Who advised for LPA/CBNAAT-LT/STS/STLS/Local Medical Officer/DTO/at Medical College	
Date of Submission of sample for LPA/CBNAAT	
LPA/CBNAAT/Culture Report	
Date of Reporting from IRL (upload)	
Date of Receipt of report to patient.	
Who Reported - STS/STLS/ MO/DTO/ Medical College	
Date of Admission at PMDT Site (if resistant)	
Treatment offered during this period	
Patient Related Factors: ➢ Literacy Status ➢ Accessibility-Telephone/Emails ➢ Personal Delay	

Conflicts of interest

The authors have none to declare.

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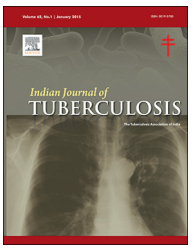

Original article

Cartridge based nucleic acid amplification test is superior in diagnosing lymphnode tuberculosis

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ABSTRACT

Background: The role of Cartridge based Nucleic Acid Amplification test (CBNAAT) in the diagnosis of lymphnode TB which helps in reducing the mortality and morbidity by early identification and initiating treatment at the earliest. Also helps in identify the drug resistance among tubercular lymphnodes cases.

Patients and methods: A prospective clinical study was performed in 101 suspected lymph node tuberculosis patients. The results of FNAC and/or excision biopsy of lymphnode samples obtained by CBNAAT were compared with direct smear microscopy for AFB bacilli, cytology and their combination considering AFB culture as gold standard.

Results: A total of 101 patients were evaluated of which 74 subjects (73.3%) were CBNAAT positive for TB. Among the CBNAAT positive cases, 57 were aged above 16 years, 38 were females, equal number (37) had single and multiple lymphnodes, 46 had less than 1 cm size lymphnodes, 69 had lymphnode in neck region, 65 had chest X-ray normal. Among CBNAAT positive 74 subjects, 53 subjects (71.6%) were positive for AFB direct smear, 64 subjects (86.48%) were cytology consistent with TB and their combination were positive for TB in 71 subjects (95.94%) and 71 subjects (95.94%) were positive by AFB culture and 3 cases (0.04%) showed Rifampicin resistance.

Conclusion: CBNAAT is a rapid diagnostic tool having sensitivity of 93.42% with specificity of 86.96% and positive predictive value of 95.95% and having comparable results with AFB culture and more sensitive than other investigation procedures. Thus it can be a rule in test for lymphnode TB.

1. Introduction

Tuberculosis (TB) is an infectious disease caused predominantly by *Mycobacterium tuberculosis* complex. India accounts for one fifth of the global TB burden. It is estimated that annual incidence of tuberculosis globally is 8.70 million and annual incidence in India is 2.20 million.[1]

Extrapulmonary tuberculosis (EPTB) is defined as tuberculosis of organs other than the lungs. Accounts for 10–15% of all

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types of tuberculosis and up to 53–62% of cases of TB in HIV-positive individual.[2] Lymph node TB is the commonest form accounting for 58% of new extrapulmonary tuberculosis cases,[2] of which tuberculous cervical lymphadenopathy is a common disease accounting for 75.24%.[2]

Diagnosis of lymph node TB is difficult because of the pauci bacillary nature of the extra pulmonary tuberculosis. Diagnosis is based on either culture-positive specimen from the extrapulmonary site; or histological evidence; or strong clinical evidence consistent with active extrapulmonary tuberculosis disease. The average turn-around time for smear microscopy is 1–2 days. The gold standard for the diagnosis of active tuberculosis is to perform culture test. Conventional culture techniques can take 3–8 weeks on solid media, 1–2 weeks in broth media.[3] Current methods to diagnose smear negative TB and multidrug resistant TB are slow and cumbersome. Nucleic acid amplifications techniques such as PCR gives result much faster but still take some days and are much less specific and more sensitive.[4]

Newer diagnostic test like Cartridge Based Nucleic Acid Amplification Test (CBNAAT) [GeneXpert] is a novel integrated test for the diagnosis of tuberculosis and rapid detection of RIF resistance in pulmonary and extra pulmonary specimens obtained from possible tuberculosis patients. CBNAAT requires less than 2 h (walk away test) with sensitivity of 95% and specificity of 98% in sputum samples but its use in lymph node TB is supported by limited data.[4] CBNAAT is a nucleic-acid amplification test for (1) the detection of MTB complex DNA in sputum or concentrated sputum sediments and (2) the detection of RIF resistance associated mutations of the *rpoB*gene.[5] It integrates and automates sample processing, nucleic acid amplification and detection of the target sequences using real-time PCR and reverse transcriptase PCR. As the cartridges are self-contained, cross-contamination between samples is eliminated.[6]

World health organization (WHO) endorses Gene Xpert MTB (*Mycobacterium tuberculosis*)/RIF (Rifampicin) may be used as a replacement test for usual practice (including conventional microscopy, culture and/or histopathology) for testing of specific non-respiratory specimens, lymph nodes and other tissues from patients presumed to have extra pulmonary TB.[4,7]

Effective control of tuberculosis requires rapid detection and early treatment of patients with active disease so as to interrupt further spread into the community. In recent years the prevention, diagnosis and treatment of TB has become more complicated because of 2 factors changing the epidemic: HIV associated TB and multidrug-resistant TB. With the advent of new molecular diagnostics; CBNAAT offers a major breakthrough against these limitations.[5]

The present study focused on the utility of performing CBNAAT assay over the other investigation tools to diagnose lymph node tuberculosis and reducing the gap time between diagnosing and starting the treatment efficiently.

2. Material and methods

All consecutive registered Lymph node tuberculosis suspect patients under RNTCP from 1st December 2014 to 31st August 2015 in Kingsway chest clinic of Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, New Delhi who met our inclusion and exclusion criteria were taken up as study group. The enrollment were done both through out-patient department (OPD) and indoor, irrespective of age and sex.

With taking into consideration of exclusion criteria sample size was calculated using the formula for study $(Z^2 \times p \times q)/d^2$. With reference to previous study (), we expected that sensitivity of cartridge based nucleic acid amplification test in the diagnosis of Lymphnode tuberculosis correlating their findings with Gold Standard AFB culture (p) = 93.5%, with the precision error of estimation (d) = 0.07 (or 7%), and alpha = 0.05, a sample size was calculated to be 50.

During the study duration, 101 patients suspected of having lymph node TB were enrolled in the study. Written informed consent was taken from all patients. All patients were thoroughly examined and a standard proforma was filled and a record of their history, clinical examination and diagnostic investigations were made. The results were tabulated, p-value and k-value was calculated to know the significance of the results and this is implied on various parameters and compared between the test under evaluation with gold standard to know the sensitivity, specificity and positive predictive value pattern.

2.1. *Patient inclusion criteria*

1. All patients who had given informed consent for their inclusion in the study and willingness to undergo diagnostic evaluation.
2. All suspected New lymph node tuberculosis patients irrespective of age and gender, who were registered under RNTCP, Kingsway camp chest clinic, RBIPMT.
3. Patients who were relatively stable, ambulatory and cooperative.

2.2. *Patient exclusion criteria*

1. All moribound and ill patients.
2. All patients who were not willing to give consent.
3. All patients who turned out malignant lymphadenopathy.

2.3. *Sampling technique*

Detailed demographic and clinical data was recorded and after taking informed consent from each Tubercular lymph node suspect, the following tests were done:

FNAC of the lymph node sent for:

- Cytology
- AFB direct smear (Ziehl Nielsen staining)
- AFB culture (Liquid culture)
- Cartridge based nucleic acid amplification test

AFB culture was done at Intermediate Reference Laboratory, State TB Training & Demonstration Center, NDTB centre, Delhi.

Cartridge based nucleic acid amplification test was done at Department of Pulmonary Medicine, RBIPMT, Delhi.

At the end of the study diagnostic yield of cartridge based nucleic acid amplification test was compared with respect to other investigation tools (as mentioned above) and culture in diagnosis of tubercular lymphadenopathy and the yield of this novel diagnostic modality to diagnose tubercular lymphadenopathy was assessed by utilizing appropriate statistical tests.

Ethics: The study was carried out after obtaining approval from the Institutional Human.

Ethics Committee: An informed written consent was obtained from all the patients. Patients willingly volunteered were enrolled in study. All patients had freedom of opting out of study at any point of time during study.

2.4. *Statistical analysis*

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean ± SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. The sensitivity, specificity, PPV, NPV and accuracy were also calculated to analyze the diagnostic accuracy of cartridge based nucleic acid amplification test in the diagnosis of Lymph node tuberculosis and the findings were correlated with AFB culture. For all statistical tests, a p value less than 0.05 was considered to be statistically significant.

3. Results

The result of FNAC of lymph node direct smear compared with CBNAAT as depicted in Table 1. Out of 45 FNAC of lymph node AFB D/S negative patients 24 were CBNAAT negative and 21 were CBNAAT positive. Out of 54 FNAC of lymph node AFB D/S positive patients 1 was CBNAAT negative and 53 were CBNAAT culture positive. The difference in results were not statistically significant.

The result of FNAC of lymph node cytology compared with CBNAAT as depicted in Table 2. Out of 22 FNAC of lymph node cytology non-suggestive of TB patients 15 were CBNAAT negative and 7 were CBNAAT positive. Out of 68 FNAC of lymph node cytology suggestive of TB patients 4 were CBNAAT negative and 64 were CBNAAT positive. The difference in results were not statistically significant.

The result of combination of FNAC of lymph node direct smear and cytology compared with CBNAAT as depicted in Table 3. Out of 24 FNAC of lymph node AFB D/S + cytology not consistent with TB patients 21 were CBNAAT negative and 3 were CBNAAT positive. Out of 75 FNAC of lymph node AFB D/S + cytology consistent with TB patients 4 were CBNAAT negative and 71 were CBNAAT positive. The difference in results were not statistically significant.

The results of FNAC of lymphnode CBNAAT was compared with AFB culture as depicted in Table 4. Out of 25 CBNAAT negative patients 20 were AFB culture negative and 5 were AFB

Table 1 – Comparison of FNAC of lymph node AFB direct smear with CBNAAT.

FNAC of lymph node AFB D/S	N	Lymph node	
		CBNAAT (k value – 0.535)	
		Negative	Positive
Negative	45	24	21
Positive	54	1	53
Total	99	25	74

FNAC: fine needle aspiration cytology, AFB D/S: acid fast bacillus direct smear, CBNAAT: cartridge based nucleic acid amplification test.
N – absolute number of subjects.

Table 2 – Comparison of FNAC of lymph node cytology with CBNAAT.

FNAC of lymph node cytology	N	Lymph node	
		CBNAAT (k value – 0.653)	
		Negative	Positive
Not suggestive of TB	22	15	7
Suggestive of TB	68	4	64
Total	90	19	71

FNAC: fine needle aspiration cytology, CBNAAT: cartridge based nucleic acid amplification test.

Table 3 – Comparison of FNAC of lymph node AFB direct smear + cytology with CBNAAT.

FNAC of lymph node AFB D/S + cytology	N	Lymph node	
		CBNAAT (k value – 0.810)	
		Negative	Positive
Not consistent with TB	24	21	3
Consistent with TB	75	4	71
Total	99	25	74

FNAC: fine needle aspiration cytology, AFB D/S: acid fast bacillus direct smear, CBNAAT: cartridge based nucleic acid amplification test.

Table 4 – Comparison of FNAC of lymph node CBNAAT with AFB culture.

FNAC of lymph node CBNAAT	N	Lymph node	
		AFB culture	
		Negative	Positive
Negative	25 (24.8%)	20	5
Positive	74 (73.3%)	3	71
Repeat	2 (2%)	0	2
Total	101 (100%)	23	78

FNAC: fine needle aspiration cytology, CBNAAT: cartridge based nucleic acid amplification test, AFB: acid fast bacillus.

Table 5 – Comparison of FNAC of lymph node AFB direct smear + cytology + CBNAAT with AFB culture.

FNAC of lymph node AFB D/S + cytology + CBNAAT	N	Lymph node	
		Culture	
		Negative	Positive
Not consistent with TB	22	18	4
Consistent with TB	79	5	74
Total	101	23	78

FNAC: fine needle aspiration cytology, AFB D/S: acid fast bacillus direct smear, CBNAAT: cartridge based nucleic acid amplification test.

culture positive. Out of 74 CBNAAT positive cases, 3 were AFB culture negative and 71 were culture positive.

The result of combination of FNAC of lymph node direct smear, cytology and CBNAAT compared with AFB culture as depicted in Table 5. Out of 22 FNAC of lymph node AFB D/S + cytology + CBNAAT non-consistent with TB patients 18 were AFB culture negative and 4 were culture positive. Out of 79 FNAC of lymph node AFB D/S + cytology + CBNAAT consistent with TB patients 5 were AFB culture negative and 74 were culture positive.

Comparison of various parameters with individual tests and their combination as depicted in Table 6. On comparing the individual tests and respective combination in terms of various parameters as shown in the table, sensitivity pattern increased with combination with decline in specificity. The sensitivity, specificity and positive predictive value of CBNAAT was comparably similar with other tests and the combination.

4. Discussion

This study aimed to evaluate role of Cartridge Based Nucleic Acid Amplification test (CBNAAT) in diagnosis of tubercular lymphadenopathy in comparison to the gold standard AFB culture and the most commonly done test AFB direct smear and cytology. 101 patients were enrolled in our study.

In this study 56.5% of FNAC of lymph node samples were AFB direct smear positive accounting for sensitivity of 66.67%, specificity of 91.30% and positive predictive value of 96.30% which showed comparable sensitivity and specificity with a study by Ozkutuk et al.[10] showed the sensitivity of 41.8% and specificity of 99% in lymph node AFB direct smear samples.

In this study 68.3% of FNAC of lymph node samples were cytology consistent with TB accounting for sensitivity of 89.3%, specificity of 88.24% and positive predictive value of 97.10% which showed comparable sensitivity and specificity with a study by Tadesse et al.[11] which showed sensitivity of 80% and specificity of 57.8%. This may be due to increased sample size compared to reference studies, endemicity of TB in our country and also being a tertiary referral center patients with suspected LN-TB are referred for diagnosis at the earliest to our center, the location and amount of mutation may affect test sensitivity.

In this study 73.3% of FNAC of lymph node samples were CBNAAT positive accounting for sensitivity of 93.42%, specificity of 86.96% and positive 66 predictive value of 95.95% which was comparable with various studies. A study by Tadesse et al.[11] showed sensitivity of 87.8% and specificity of 91.1%. A study by Ozkutuk et al.[10] showed sensitivity of 73.9%, specificity of 98.6% and PPV of 79.6%. A study by Ioannidis et al.[8] showed sensitivity of 100% specificity of 91.6% and PPV of 50%. A study by Chang et al.[9] showed sensitivity of 80.4% and specificity of 86.1%. A study by Denkinger et al.[12] showed sensitivity of 83.1% and specificity of 93.5%. So comparing with various studies, our study showed comparable sensitivity, specificity and PPV in the diagnosis of lymph node TB. This may be due to increased sample size compared to reference studies.

In this study when comparing CBNAAT with AFB culture in AFB direct smear negative and positive patients, the difference in the results were not statistically significant. When comparing CBNAAT with AFB culture in cytologically consistent and non-consistent with TB patients, the difference in the results were not statistically significant. CBNAAT was equally effective in the diagnosis of lymph node TB when compared with AFB culture hence, former can be applied in all the settings for rapid diagnosis.

In this study additional 3 patients were picked up by the CBNAAT when compared with AFB culture.

In this study the average time duration between sample collection and availability of report in our center in majority was less than 2 days for CBNAAT, AFB direct smear, cytology and for AFB culture in majority was >8 weeks. Though CBNAAT is a walk away test (result within 2 h) delay may be often due to laboratory operations issues, including limited staff, practices of batching specimens, and other logistical

Table 6 – Comparison of the individual tests and respective combinations in terms of various parameters.

		N	AFB D/S	CYT	CBNAAT	AFB D/S + CYT	AFB D/S + CYT + CBNAAT
		101	101	101	101	101	
Comparison of various parameters with individual tests and their combination	Sensitivity (%)		66.67	89.33	93.42	92.31	94.87
	Specificity (%)		91.30	88.24	86.96	82.61	78.26
	Positive predictive value (%)		96.30	97.10	95.95	94.74	93.67
	Negative predictive value (%)		44.68	65.22	80.00	76.00	81.82
	Accuracy (%)		72.28	89.13	91.92	90.10	91.09

FNAC: fine needle aspiration cytology, AFB D/S: acid fast bacillus direct smear, CBNAAT: cartridge based nucleic acid amplification test, CYT: cytology.

Table 7 – Comparison of CBNAAT positive patients with various parameters.

Parameters in tubercular lymphadenopathy cases	Present ('n' out of 74 CBNAAT positive cases)	%
1. Age >16 years	57	77%
2. Gender – Females	38	51.35%
3. Socio economic status – upper lower class	65	87.83%
4. Family history of TB – absent	69	93.24%
5. Previous history of TB	34	45.94%
6. Lymph node number, size, site	Single = multiple = 37, <1 cm = 46, neck region = 69	50%, 62.1%, 93.24%
7. Sputum AFB direct smear – negative	67	90.54%
8. Chest X-ray – normal	65	87.83%
9. FNAC of lymph node AFB direct smear – positive	53	71.6%
10. FNAC of lymph node cytology – consistent with TB	64	86.48%
11. FNAC of lymph node AFB D/S + cytology – consistent with TB	71	95.94%
12. FNAC of lymph node AFB culture	71	95.94%

FNAC: fine needle aspiration cytology, AFB D/S: acid fast bacillus direct smear, CBNAAT: cartridge based nucleic acid amplification test, TB: tuberculosis.

barriers such as inefficient specimen referral and transport networks.

CBNAAT positive patients are compared with various parameters as shown in Table 7.

Out of 74 CBNAAT positive cases, 71.6% were positive for AFB direct smear, 86.48% were cytology consistent with TB, 95.94% positive by AFB culture. Thus CBNAAT is a rapid diagnostic tool having comparable results with AFB culture and more sensitive than other rapid investigations like AFB direct smear and cytology. Thus can be a rule in test for lymph node tuberculosis.

NTM being a major differential diagnosis not identified by CBNAAT, which clearly identifies MTB complex only and thus is a ruling test for TB.[8]

5. Conclusion

CBNAAT is optimal for the diagnosis of Lymph node tuberculosis with sensitivity of 93.42%, specificity of 86.96%, positive predictive value of 95.95% in the present study and also comparable results with gold standard AFB culture when compared with various parameters which increase the yield of CBNAAT in specific subgroups of patients and helps in identification and initiation of treatment at the earliest.

The diagnosis of lymph node tb is based on the combination of multiple tests; among them, the main role of the culture is once more confirmed with the potential of CBNAAT being high in ruling in, but suboptimal in ruling out lymph node TB. Among the rapid tests investigated here, CBNAAT's sensitivity scored twice as high in comparison with microscopy thus doubling the proportion of rapid diagnoses with important effect on the patient's outcome.

Conflicts of interest

The authors have none to declare.

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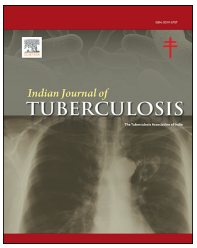

Review article

Byssinosis and tuberculosis amongst "home-based" powerloom workers in Madhya Pradesh State, India

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ABSTRACT

Background: Byssinosis is an occupational lung disease observed among workers exposed to cotton, flax, and hemp dust. The severity and extent of Byssinosis are well recognised in the high-income countries and control measures have been implemented to prevent the disease. In India, there are conflicting evidence on burden estimation of the disease, followed by inadequate prevention and control of Byssinosis.

Design/methods: We did a cross-sectional study to assess the prevalence of Byssinosis in "home-based" power-loom workers in Mominpura, an administrative ward of Burhanpur Municipality with 2800 population in the state of Madhya Pradesh, India. 290 adults working from "home-based" power loom units were randomly selected, profiled and screened for Byssinosis like symptoms with the help of a semi-structured questionnaire and simple hand-held peak expiratory flow monitor. For epidemiological purposes the symptoms were classified based on Schilling's classification. Chest x-rays were done for selected subjects. Sputum smear microscopy for detecting TB was done for those who had Byssinosis like symptoms.

Results: Prevalence of Byssinosis among "home based" powerloom workers was found to be 98% [n = 283, 95 CI (95.65–98.96)]. Peak expiratory flow rate (PEFR) was reduced in 44% (n = 124), of which 81 (29%) had more than 50% PEFR reduction, and of these, 69 (29%) were in early stage of Byssinosis (Grade 0.5). 11% of study participants who had Byssinosis like symptoms, also had TB.

Conclusions: Byssinosis is highly prevalent in "home-based" power loom units in Madhya Pradesh. Adequate advocacy on awareness and prevention; prompt diagnosis and linkages to treatment services in "home-based" power loom units are urgently required to address Byssinosis at an early disease stage.

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1. Introduction

'Byssinosis' is an occupational lung disease, a type of pneumoconiosis, which is observed among workers exposed to cotton, flax, and hemp dust.[1] Three essential factors for developing clinical pneumoconiosis are[2] – 1) Exposure to specific substance, 2) Particles of appropriate size (1–5μm), and 3) Exposure for a sufficient lengthy of time (usually around 10 years). Byssinosis is a case in point as it is associated with the occupational history to exposure of 2–10 years or more than 10 years of cotton and other dusts of appropriate size by processing cotton in textile mills, which is by far the largest industry in developing countries of South Asia, thereby, risking textile workers of developing Byssinosis.[3,4] In the early phases of Byssinosis, acute reversible symptoms such as wheezing, chest tightness and shortness of breath, increased respiratory distress to physical activity[5,6] are the clinical manifestations.

The characterization of Byssinosis primarily has been based on respiratory symptoms as well as the clinical grading by Schilling[7]. The disease may progress to a stage in which symptoms are present throughout the workweek and may eventually result into chronic and irreversible stage of obstructive pulmonary disease.[6,8]

The severity and extent of Byssinosis are well recognised in the developed countries and control measures have been implemented to prevent the disease.[9] However, in developing countries like India, conflicting prevalence estimates exists among textile mill workers. A review of the earlier studies on Byssinosis suggests a low prevalence of the disease in most of the Indian textile mills.[10] Another study in three textile mills in Ahmedabad in India suggests that the prevalence of Byssinosis is not low among the workers in the spinning departments.[3] India has a large textile industry, including "home-based" units, employing 35 million workers (including ~ 35% of all factory workers), who are at risk of cotton dust exposure. "Home-based" units, the premises where the workers reside, typically with poor ventilation, are still being used to produce cloths in many parts of India from obsolete powerloom machines and the burden of Byssinosis in such settings is yet to be estimated. Also, the recommended heath-based occupational exposure limits are far exceeded and without any safety measures in such "home based" units.

This study was undertaken to assess the prevalence of Byssinosis among "home based" powerloom weavers in Mominpura, an administrative ward in Burhanpur in the state of Madhya Pradesh, India.

2. Methods

2.1. Setting

'Mominpura', an administrative ward of 'Burhanpur' municipality, in the state of Madhya Pradesh in India. Burhanpur, is one of the largest hubs for 'home-based' powerloom with around ten thousand power-loom machines and over forty thousand power-loom weavers. 'Burhanpur' municipality is dominated by minorities living in ill-ventilated houses, which are also used to run obsolete power loom machines. Over 80% of population of Mominpura have begun weaving at an early age of 15 years.

2.2. Study design

This is a cross sectional study conducted in 2013.

2.3. Study population and sampling size

Our sampling frame is 2800 population as per the voters list of the Mominpura ward in 2013 state legislative assembly elections. The sample size of 290 adults was calculated for the study purpose based on the assumption that 30% of the population employed will have the respiratory symptoms of Byssinosis. The sample size was estimated with an absolute precision of +/- 5% (with 95% confidence interval). A line list was prepared from the voter's list and 290 persons, who had worked in the power looms continuously for two years or more, were selected randomly.

2.4. Data collection

The randomly selected 290 individuals were administered a structured questionnaire to assess their respiratory health, and information on occupational lung health status using schilling parameter; smoking and occupational history to exposure: 2–10 years or >10 years; and their demography were collected between September to October 2013 by trained project personnel. Peak expiratory flow rate (PEFR) was measured using a simple peak flow meter [PEFR Normal Range: 300–400 L/min]. Three readings were obtained from each of the respondents on Saturdays (Friday being a holiday for the weavers) 2–4 hours after exposure and the highest of all the readings was taken as the average measure of PEFR. Those having symptoms related to occupational lung disease like Byssinosis were subjected to Chest X-Ray (CXR) to determine further lung disorders and sputum smear microscopy for detecting pulmonary TB. A panel of physicians and radiologists, identified by the International Union Against Tuberculosis and Lung Disease (The Union), defined abnormalities in the CXRs (shadow and infiltration) for reaching towards a conclusive diagnosis of Byssinosis. Anybody was free to withdraw at any stage. Monitoring of data collection through periodic field visits by the Principle Investigator (PI) was done to ensure quality assurance.

2.5. Data entry and analysis

EpiData software version 3.1 was used for quality data capture and version 2.2.2.183 (EpiData Association, Odense, Denmark) for univariate and bivariate analysis. Data was double entered and validated before using for analysis.

3. Ethics

The study participants were provided with the relevant information about the study and a written consent was obtained from them. Individuals less than 18 years of age were

Table 1 – Characteristics of "home based" powerloom workers (N = 290) in Mominpura ward, Burhanpur, Madhya Pradesh.

Characteristics		*N (%)*
Age group (yrs)	18–24	34 (12)
	25–34	54 (19)
	35–44	82 (28)
	45–54	72 (25)
	>55	47 (16)
	Not recorded	1 (0.3)
Sex	Male	210 (72)
	Female	59 (20)
Marital status	Married	210 (72)
	Unmarried	45 (16)
	Widower/widow	3 (1)
	Not recorded	32 (11)
Smoking	Yes	163 (56)
	No	100 (34)
	No response	27 (9)
Smoking more than 10 sticks/day	Yes	41 (25)
	No	78 (48)
	No response	44 (27)
Duration of exposure to Cotton dust (years)	2–10	44 (15)
	>10	239 (82)
	No response	7 (2)

excluded from the study. Confidentiality of the data set was assured. Names and other personal identifiers were not used in the database for analysis. Ethics approval for the study was obtained from the Union's Ethics Advisory Group (EAG number: 62/13) after all the queries raised by the EAG were addressed satisfactorily.

4. Results

Median age of the participants was 40 years [IQR 32–50]. The male to female ratio was 3.6:1 (Male, 210: Female, 59). Of all the study participants, 77% were married, 56% were smokers and 82% were exposed to cotton dust for more than 10 years (Table 1). The prevalence of Byssinosis among "home based" powerloom workers was found to be 98% [n = 283, 95 CI (95.65–98.96)].

Of 283 who had Byssinosis, 239 (84%) were in Grade 0.5, 32 (11%) in Grade 1, 8 (3%) in Grade 2 and 4 (2%) in Grade 3. PEFR was reduced in 44% (n = 124) (Table 2). Of those having Byssinosis in whom PEFR was reduced, 81 (29%) had more than 50% of PEFR reduction, and of these, 69 (29%) were in early stage of Byssinosis (Grade 0.5). CXRs were done in 124 participants, of which only 8% (22) had abnormal CXRs (Table 2). 11% (30/283) of study participants who had Byssinosis like symptoms, also had TB.

5. Discussion

This is the first community based prevalence study in India among "home based" powerloom setting suggesting very high prevalence. Our study found that prevalence of Byssinosis didn't differ much by smoking and non-smoking; by demographic characteristics of the participants, and therefore, cotton dust seems to be the main driver for developing Byssinosis in "home-based" powerloom setting in the community. Only small proportions of the exposed study participants had abnormal CXRs, suggesting that CXRs are not necessary for the diagnosis of Byssinosis.

Majority of the participants (84%) had only occasional chest tightness on the 1st day of the working week (Grade 0.5). The peak expiratory flow rate (PEFR), a rough measurement of the degree of obstruction in the airways, was reduced in almost half the subjects. Most of the workers with reduced PEFR were in the early stage of Byssinosis. This finding is of great public health importance as it reinforces the need for early diagnosis of Byssinosis at a reversible disease stage, and early linkages with preventive and rehabilitative measures for adequately alleviating occupational health condition of power-loom workers as a public health response. This preventive measure can be achieved by wearing protective clothing and a face mask and implementing industrial dust control measures.[11]

Our finding suggests ~11% of participants having Byssinos like symptoms also have other chronic lung ailments like TB. This finding supports a similar finding by Seboxa et al, 1994; that there is a strong association between Byssinosis and TB.[12] Screening of TB among those having occupational health condition like Byssinosis is must for early identification of TB cases.

This study had certain limitation. ByssinosisByssinosisWe couldn't do CXRs and Pulmonary Function Tests, especially forced expiratory volume in the first second (FEV1) of all the participants due funding limitations, and couldn't know the effect of FEV1 due to change in work shifts (symptoms on first and other days of the working week) as per the Schilling's criteria. This calls for a large community based multi-centric prevalence study among "home-based" powerlooms by addressing the aforementioned short-coming, enabling to conclude on the national estimates of Byssinosis among "home-based" power loom units.

Table 2 – Assessment of PEFR and Chest X-ray among those 'home-based' powerloom workers who had Byssinosis.

Screening Tools	Parameter	Grade 0.5		Grade 1		Grade 2		Grade 3		Total	
		N = 239	%	N = 32	%	N = 8	%	N = 4	%	N = 283	%
PEFR	>50% reduction	69	29	9	28	2	25	1	25	81	29
	30–50% reduction	14	6	4	13	1	13	2	50	21	7
	<30% reduction	19	8	2	6	0	0	1	25	22	8
	Normal	137	57	17	53	5	63	1	25	160	57
CXR	Normal	83	35	13	41	3	38	3	75	102	36
	Abnormal	19	8	2	6	0	0	1	25	22	8
	Not done	137	57	17	53	5	63	1	25	160	57

6. Conclusion and recommendation

Since early Byssinosis is reversible, adequate advocacy on awareness and prevention; prompt diagnosis and linkages to treatment services in "home-based" power loom units needs to be enforced. Measuring PEFR by a simple hand-held device is a feasible screening tool to rule out Byssinosis in a resource constrained setting. Screening of TB among those having Byssinosis like symptoms should be routinely done.

There is an opportunity for the Government of India to formulate a comprehensive policy framework on prevention, treatment, rehabilitation, compensation and follow-up in line with the earlier recommendation for silico-TB.[13]

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.01.001.

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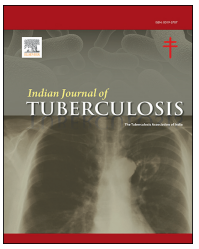

Review Article

Gastric tuberculosis

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ABSTRACT

Tuberculosis of the stomach is an extremely rare manifestation of *Mycobacterium tuberculosis* infection and mimics gastric carcinoma in its presentation. Most of our knowledge about this rare disease comes from case reports and there are only a few case series published on this disease and thus the majority of the part remains uncovered. Diagnosis is made commonly only after a major surgery. Endoscopy and guided biopsy are the diagnostic modality of choice. Surgery is indicated in cases which present with complications. Patients respond well to antituberculous therapy. The authors encountered 4 cases of gastric tuberculosis over 5 years. This study summarises the available literature and gives comprehensive update on this rare disease.

1. Introduction

Gastric tuberculosis is a rare manifestation of gastrointestinal tuberculosis. This pathology often gets misdiagnosed because the presentation mimics gastric carcinoma. Barkhausen, in 1824,[1] was the first to describe this rare entity. Broders described a case of multiple gastric tuberculous ulcer in 1917.[2] In 1913, Good was the first to report an analysis of gastric tuberculous cases.[3] In most of the studies on gastrointestinal tuberculosis and short series of gastric tuberculosis, this pathology has never been described in detail. Even in regions with high prevalence of tuberculosis, involvement of stomach is extremely rare not only in isolation but also in association with involvement of other parts of gastrointestinal tuberculosis or as a secondary manifestation to pulmonary tuberculosis. Most of our knowledge about this rare entity comes from individual case reports as there are only a few case series on this pathology. The authors encountered 4 cases of gastric tuberculosis over 5 years. This study summarises the available literature and gives comprehensive update on this rare disease.

2. Methods

In a PUBMED search of English language articles from 1950 till now, using the MeSH terms "tuberculosis" and "stomach" in combination with each other and with "epidemiology", "presentation", "pathology", "biologic behaviour", "endoscopy", "imaging", "resection", "antituberculous therapy" and "prognosis", 4 small case series, and 53 case reports of gastric tuberculosis have been identified. All resulting titles, abstract, and full text, when available were read and kept for reference.

2.1. *Epidemiological features*

Tuberculosis is a worldwide health problem with a high prevalence in developing countries and abdominal

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tuberculosis is the third most common extrapulmonary manifestation of tuberculosis (TB) comprising approximately 12% cases of extrapulmonary tuberculosis (EPTB) and 2–3% of all cases of tuberculosis, ileocaecal region being the most common site followed by peritoneum and mesentery.[4] EPTB is more common in immunocompromised host.[5] Tuberculous involvement of the stomach has been reported to occur in 0.5%–3% of all cases of gastrointestinal tuberculosis.[6,7] Incidence of gastroduodenal tuberculosis is 0.5%[8] and isolated gastric tuberculosis is even rare, comprising 0.1–2% of all cases of TB. In HIV positive patients with pulmonary tuberculosis, gastric TB constitutes <1% of cases in non-endemic areas.[9] It has been reported that the incidence of gastric tuberculosis was found in only 0.03 to 0.21% of all routine autopsies, and in 0.3 to 2.3% of autopsies of patients with known concurrent pulmonary tuberculosis.

Gastric tuberculosis has been reported to be more common in males as compared to females with a ratio of 2.8:1.[11] Youngest reported patient is 15 years old while the oldest is 81 years old[12] and majority of the patients fall within the age range of 15–62 years.[11]

2.2. *Pathology*

Gastric tuberculous lesions may form an ulcer, a nodular hypertrophic mass or ulcerohypertrophic lesion or rarely an abscess.[6,13,14] Cases with nodular hypertrophic lesions may mimic carcinoma (Fig. 1). Ulcers are the most common type of lesions which may be single or multiple. Ulceration of the pyloric region on the lesser curvature is the most common pathological finding. Ulcerative lesions are irregular with a necrotic base which may extend deep into perforation or fistula formation with adjacent organ, most commonly transverse colon.

The granulomatous inflammatory lesion may involve the mucosa, submucosa or serosa.[6] The granulomas may be confluent and typically shows central caseation with langerhans giant cells and lymphocytes but they may be non-caseating also. In such ill formed granulomas without necrosis, presence of acid fast bacilli is diagnostic. Demonstration of acid and alcohol fast bacilli is pathognomonic, though not commonly seen, then bacterial cultures are important for diagnosis. Regional lymph nodes are frequently enlarged, thus need to be examined carefully, as they commonly contain granules which are not readily seen in gastric wall itself.[6]

2.3. *Etiopathogenesis*

Gastric tuberculosis can be due to primary or secondary infection, usually secondary to pulmonary infection or as a part of multifocal gastrointestinal tuberculosis or miliary tuberculosis. Primary and isolated gastric TB is a rare occurrence and it is usually associated with immunodeficiency state and pulmonary tuberculosis. Mitchell and Bristol[15] reported that with moderate pulmonary tuberculosis, the frequency of developing gastric tuberculosis increases by 4.5% and by 25% in patients with severe disease. Based on the mode of involvement and involvement of stomach in isolation or in association with other organ systems (Table 1), gastric tuberculosis can be classified into the following:

(1) Local, with isolated involvement of stomach in the form of primary complex with caseation of the associated celiac lymph nodes.
(2) Gastric tuberculosis developing secondary to pulmonary tuberculosis due to swallowing of bacilli.
(3) As a part of multifocal involvement of gastrointestinal tract.
(4) Miliary tuberculosis, as a part of generalized tuberculosis resulting in involvement of stomach as well. This is most commonly seen in immunosuppressed patients.

The possible reasons for rarity of gastric tuberculosis are absence of gastric mucosal lymphoid tissue, high acidity, bactericidal property of gastric acid, relatively rapid gastric transit time due to continuous motor activity of stomach resulting in rapid passage of organism through the stomach, and intact gastric mucosa also attributes to local immunity of gastric wall.[5,6,16]

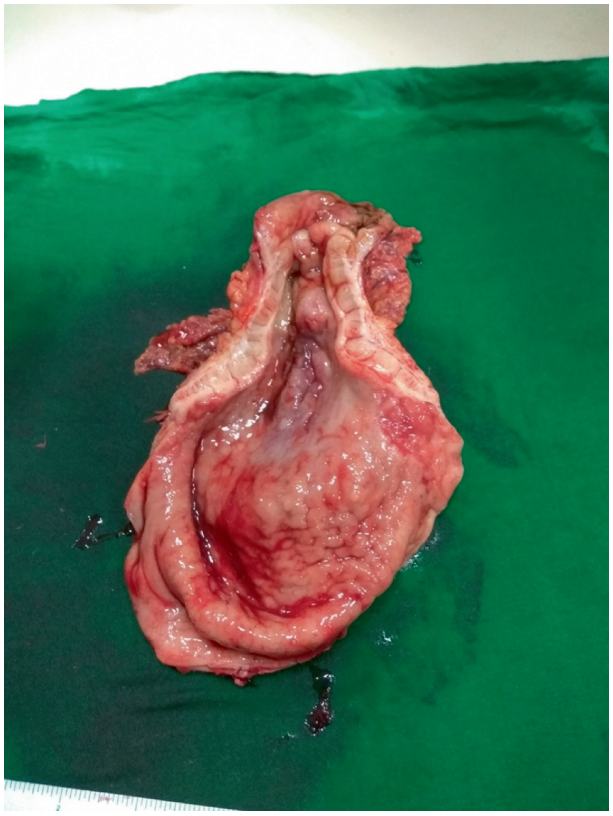

Fig. 1 – Resected specimen of stomach showing antral nodular hypertrophic tuberculous lesion.

Table 1 – Type of involvement in previously published case reports and series.

Type of involvement	Number of cases
Primary gastric tuberculosis	26
Secondary to pulmonary tuberculosis	12
In association with involvement of other parts of gastrointestinal tract	3
HIV positive cases	2

The most common site of gastric TB is lesser curvature near prepyloric region because of presence of lymphoid follicles at this site. Also, this is the most common site for acid peptic ulcers, thus resulting in mucosal breach at this site. Tuberculous infection reaches stomach following mucosal breach through ulcers, gastritis, erosions and echymosis. Diffuse involvement of stomach is rare and only one case has been reported. Cardia and fundus have also been found to be involved in 2 and 1 case respectively.[17–19] Gastro-esophageal junction has also been reported to be involved in 1 case.[20]

Gastric TB has also been reported in association with gastric carcinoma and it has suggested by Guntani et al[21] and Chowdhary et al[22] that gastric cancer can develop in about 10% of cases of gastric TB. Immunocompromised state associated with gastric cancer further acts as a predisposing factor for gastric TB.

The possible routes of tuberculous infection of stomach are[5,23]:

(1) direct infection of the mucosa in presence of predisposing factors due to swallowing of bacilli rich sputum resulting in direct mucosal invasion,
(2) direct spread through tuberculous lesions in contiguous organs,
(3) haematogenous spread is considered to be the most common route of spread as tuberculous lesions in stomach are most commonly located in submucosal layer,
(4) retrograde lymphatic spread or adjacent celiac lymph nodes, lymphatic spread occurs by transluminal transport of the bacilli to the submucosal lymph nodes with subsequent colonization of lymph nodes and the formation of granulomas, and
(5) superinfection of an ulcer or malignancy.

Main causes of isolated or primary gastric tuberculosis are: (1) ingestion of unpasteurised milk infected with bovine TB or (2) a severely immunocompromised condition (constituting high risk groups) such as HIV infected individuals, immigrants from endemic areas, immunocompromised patients with transplantation or patients on prolonged steroid therapy.[10,24] Other high risk groups include elderly patients with diabetes, alcohol abusers, intravenous drug abusers.

2.4. *Clinical features*

There are no specific clinical features of gastric TB. Patients usually present with vague gastrointestinal symptoms, nonspecific upper abdominal pain is the most common complaint followed by epigastric discomfort described as intermittent and squeezing in nature and mild to moderate in intensity. Patients experience constitutional symptoms of tuberculosis such as anorexia, weight loss, night sweats, evening rise of temperature, fatigue, weakness, and shortness of breath. Depending on the location and the type of lesion, patient may present with features of gastric outlet obstruction such as vomiting, weight loss, distension of upper abdomen after eating food. As these cases mimic gastric malignancy, often create a diagnostic dilemma. Patients may also present with haemetemesis and malena. In literature, 10 cases have been reported with haemetemesis. Other rare presentations which have been reported are perforation, gastrocolic and gastrobronchial fistulae.[25] Six cases have been reported with perforation due to gastric tuberculosis. Severe pain is a feature of perforation, a case of retroperitoneal perforation has also been reported.[26] Patients may present with intermittent dyspepsia[27] and in such cases diagnosis often gets delayed as the clinical presentation is similar to that of peptic ulcer.[14] It may coexist with peptic ulcer disease, one such case has been reported.[25] Involvement of other parts of gastrointestinal tract further add to confusion[27] and it is the most common cause of missed diagnosis as occurrence of Tb is rare in stomach. Common presentations of this rare pathology are shown in Table 2.

Nayyar et al[5] reported a case of tuberculous gastric abscess and the patient presented with epigastric pain and persistent fever. Malena,[19] haematochezia,[28] diarrhoea, dysphagia and pyrexia of unknown origin[6] has also been reported in the literature. On examination, anaemia is a common feature. Patients may have hypertrophied antrum which is felt as a mass in epigastric region. Presence of large mass is a rare occurrence.

Out of our 4 cases, gastric tuberculosis was a part of military tuberculosis in 2 cases, 1 patient had an isolated hypertrophic nodular mass while 1 patient had a nodular mass with perigastric lymph nodes.

2.5. *Diagnosis*

Diagnosis of gastric tuberculosis is difficult because of its rare occurrence. Clinical features, epidemiology, imaging and biochemical studies support the diagnosis of gastric tuberculosis but the definitive diagnosis requires demonstration of *Mycobacterium tuberculosis* (MTB) on histologic examination.[29] Das and Shukla[30] reported that only 50% of cases are diagnosed accurately because tuberculosis of stomach is often not considered in the diagnosis. In majority of the reported cases, diagnosis was made postoperatively after histopathological examination of the resected specimen as the preoperative diagnosis is often hampered by negative biopsies.[27]

2.6. *Role of imaging studies*

X-ray chest should always be done in cases suspected to have gastric tuberculosis as this pathology is secondary to pulmonary TB in most of the cases, so, x-ray chest can diagnose coexisting pulmonary TB. Mukherji and Singhal[31] reported

Table 2 – Various presentations of gastric tuberculosis.

Different presentations	Number of cases
Gastric outlet obstruction	16
Haemetemesis	10
Perforation	6
Mimicking- gastric cancer	5
-Gastrointestinal stromal tumor	1
Tuberculous gastritis	2
Non-healing gastric ulcer	2
Pyrexia of unknown origin	1
Abscess	1

that in up to 20% of cases, chest X-ray may show pulmonary tuberculous lesion.

X-ray abdomen may show a dilated fluid filled stomach in cases with gastric outlet obstruction due to lesions in the antrum.

2.7. Ultrasonography (USG)

USG shows pyloric mass as hypodense area, it can also show enlarged mesenteric, celiac and para-aortic lymph nodes.[8] Ascitis and peritoneal thickening is also seen on USG.

2.8. Endosonography (EUS)

Sharma et al[32] suggested that EUS is a good modality for lesion characterization. It is also helpful in obtaining a sample for cytology and polymerase chain reaction (PCR).[8] Nayyar et al[5] recommended EUS guided biopsy as it makes diagnosis faster and easier.

2.9. Contrast enhanced computed tomography (CECT) of abdomen

In a case reported by Arabi et al, CECT showed antral hypodense lesions, multiple enlarged mesenteric lymph nodes, ascitis and peritoneal thickening.[8] In most of the cases, CT shows only diffuse thickening of gastric wall. Espinoza-Rios et al[33] reported a case of multisystemic tuberculosis in which CT scan showed marked gastric dilatation due to extrinsic compression from lymphadenopathies (Fig. 2). In another case, CECT of abdomen showed thickening of lesser curvature just below gastroesophageal junction.[5]

2.10. Role of polymerase chain reaction

Kim et al[24] suggested that PCR testing of biopsy tissue helps in diagnosing tuberculosis and also allows exclusion of crohn's disease. Moghadam et al[34] has reported a sensitivity of 27–75% and specificity of 100%. Settbas et al[35] has concluded that PCR assay is one of the most helpful study as results can be obtained within 48 hours, so, it allows early diagnosis.

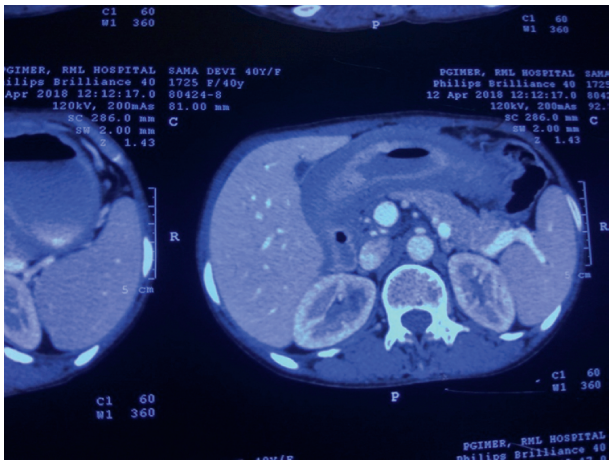

Fig. 2 – CECT showing diffuse homogenous wall thickening of stomach and enhancing mesenteric, para-aortic and celiac lymph nodes.

2.11. Role of fine needle aspiration cytology (FNAC)

FNAC can be obtained from a hypertrophied mass lesion under USG guidance or from the gastric lavage. Nussinson et al[36] reported that acid fast bacilli were found in the gastric juice and a positive culture for TB was obtained on gastric lavage. FNAC can also be obtained from enlarged caseating lymph nodes.[37]

2.12. Role of endoscopy

Upper gastrointestinal endoscopy has an important role in locating and diagnosing gastric lesions. Gastric tuberculous lesions are often seen as a submucosal lesion or an ulcer located at lesser curvature near antrum (Fig. 3). Tuberculous ulcer may be giant, irregular shape, solitary or multiple. Because of submucosal location, it is important to take deeper biopsy bits to diagnose gastric tuberculous lesions. PCR and histopathological examination can then be done on tissue bits. Gastric endoscopic picture is often confusing with gastric carcinoma as the lesions appear as an ulcerated mass or infiltrative mass in the antrum. Kalac et al[38] reported a case in which endoscopic findings were suggestive of pangastritis. Bleeding ulcer or site can also be detected on endoscopy. Rao et al[11] concluded that endoscopic biopsy has a poor yield because majority of the lesions are submucosal in location and quite often endoscopic biopsies fail to include the submucosa. Jain et al[39] suggested a role of endoscopic brush cytology and diagnosis was made in 7 out of 10 cases using brush smears in his study. Nayyar et al[5] reported a case of tuberculous gastric abscess and endoscopy showed atrophic gastric mucosa in body and enlarged folds with friable mucosa and lacy reticular pattern in fundus. Biopsy in this case was suggestive of active gastritis in the fundus with chronic inactive gastritis and lymphoid hyperplasia in the body, biopsy and PCR were negative for MTB and MTB grew from the gastric aspirate culture after 13 days.

Diagnosis of gastric tuberculosis was made in 3 of our cases on endoscopic guided biopsy while one patient underwent radical surgery and diagnosis was made postoperatively.

2.13. Other diagnostic modalities

Colonoscopy should also be a part of investigations whenever gastric tuberculosis is suspected because ileocaecal region is the most common site of tuberculous pathologies in gastrointestinal system and the coexistence of tuberculosis at two sites has been reported in the literature. Barium meal study is non-specific and may show narrowing of pylorus or the presence of an ulcer.[11]

Haematological and biochemical examination and tuberculin test are non-specific. It is important to rule out H pylori infection with rapid urease test in patients suspected to have gastric tuberculosis. Araujo et al[40] suggested role of some antigens secreted by *M. tuberculosis* such as CPF-10, ESAT-6, 27 kDa, and 38 kDa in diagnosing tuberculosis but their role has not been proven yet. These antigens induce the production of IFN-gamma, TNF-alpha and nitric oxide.

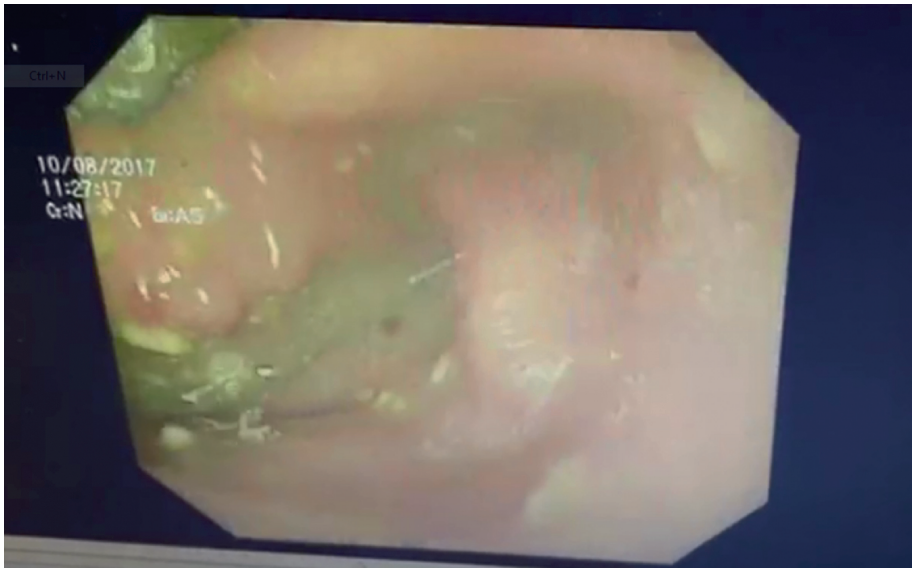

Fig. 3 – Endoscopy showing submucosal lesions in the antrum.

2.14. *Differential diagnosis*

The important differential diagnosis include gastric carcinoma, lymphoma, crohn' disease, peptic ulcer disease, syphilis and sarcoidosis. Presence of constitutional symptoms and a past history of pulmonary tuberculosis or tuberculosis contact are helpful in differentiating from other pathologies. The diagnosis essentially relies on endoscopy and histopathology. Crohn's disease, sarcoidosis and syphilis show non-caseating granulomas on pathological examination. Preoperatively it is often difficult to differentiate gastric tuberculosis from malignancy because of submucosal location of lesions on lesser curvature in the antral part of the stomach. CT scan in patients with lymphoma shows multiple enlarged lymph nodes at various levels. In literature, only 2 cases of coexisting gastric tuberculosis and malignancy have been reported and 1 case has been reported in association with acute myeloid leukaemia.

2.15. *Treatment*

The treatment of gastric tuberculosis depends upon the symptoms, and clinical presentation and presence of complications. All the stages and presentations respond well to conventional four drug antituberculous treatment (ATT) for 9–12 months. Treatment regime consists of isoniazid (5 mg/kg BW/day), rifampicin (10 mg/kg BW/day), ethambutol (20 mg/kg BW/day), pyrazinamide (30 mg/kg BW/day) for 2–4 months, subsequently isoniazid and rifampicin for 6–12 months.[11,41] This has been reported to be effective resulting in rapid resolution of inflammation and symptoms. Short course treatment also results in resolution of gastric mass and ulcer. In addition to initiation of standard ATT, each presentation and any associated complication need to be addressed. So, management ranges from symptomatic treatment to operative intervention in elective or emergency setting depending on patient's condition. Patients may present with gastritis, bleeding, perforation, or gastric outlet obstruction. Salpeter et al[6] concluded that surgical intervention is not essential for cure unless acute complication is present. Perforation is the only complication which needs to be managed surgically while other complications can be managed conservatively.

Gastric outlet obstruction secondary to tuberculosis makes the case more challenging as drug delivery is compromised. For patients with gastric outlet obstruction, treatment options are:

(I) Endoscopic balloon dilatation of pyloroduodenal stricture
(II) Operative intervention: (1) gastric resection with reconstruction, (2) gastric bypass procedures

Endoscopic balloon dilatation is the ideal procedure for cases diagnosed on time and thus avoids major surgery and morbidity. Balloon dilatation is an effective and safe option for acute obstruction and it is recommended as the first line therapy for gastric outlet obstruction due to tuberculosis. ATT should be initiated with dilatation procedure.[5]

Majority of the reported cases have been managed surgically because diagnosis of tuberculosis was not made preoperatively. Gastric resection with gastrojejunal anastomosis is preferred in cases where diagnosis cannot be made preoperatively and the malignancy is kept as differential diagnosis. For cases in which diagnosis is made preoperatively, gastric bypass procedures are done. Gastrojejunostomy is preferred over pyloroplasty because intense fibrotic reaction around pyloroduodenal area precludes safe pyloroplasty.[8,42]

For perforation peritonitis due to gastric tuberculosis, surgery is the mainstay of therapy after initial resuscitation. Out of 6 reported cases with gastric perforation, distal gastrectomy was performed in 5 cases and in only one case conservative approach with primary closure was done. Patients with haemetemesis usually respond to conservative treatment and out of 10 reported cases, wedge gastrectomy was performed in 2 cases.

3. Conclusion and recommendations

Gastric TB is a rare pathology, though easily curable with conservative approach and ATT if diagnosed correctly on time but often requires surgery not only for management but also for diagnosis. To be able to diagnose gastric TB case and manage this pathology and its associated complications, the authors recommend.

1. Consider the diagnosis of gastric TB in a patient with non-specific symptoms such as nausea, upper abdominal discomfort in association with constitutional symptoms of tuberculosis with a history of pulmonary tuberculosis or tuberculosis contact or in a patient who is from a region with high prevalence of TB. Though an uncommon entity, the first definite way is to keep such a case in the list of differential diagnosis.
2. Endoscopic biopsy and histopathological examination is the best way to diagnose it. When there is strong clinical suspicion, endoscopic biopsy should be repeated and PCR also needs to be done for diagnosis.
3. There are no specific features of gastric TB on imaging studies but EUS and CECT should always be done as they help in ruling out the most important differential diagnosis i.e. carcinoma.
4. Try and make all efforts to diagnose it before surgery as the disease and its complications respond well to conservative approach and ATT. This reduces morbidity and surgery related complications in such patients.
5. Gastric perforation always needs surgical management while other complications can be managed effectively with less invasive procedures.
6. If the diagnosis could not be made pre-operatively, then in such a case intra-operative frozen biopsy is of great help in guiding about limited or radical resection.

Conflicts of interest

The authors have none to declare.

Author contribution

All the authors have contributed in study design, data collection, data analysis and critical analysis. All the authors have approved the final version of the manuscript and all the authors agree to be accountable of the work.

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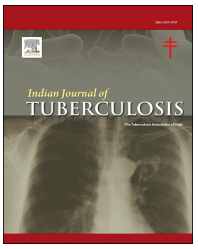

Correspondence

A rare case of coexistence of allergic bronchopulmonary aspergillosis (ABPA) and active pulmonary tuberculosis- Role of CBNAAT in ABPA evaluation

Sir,

Allergic bronchopulmonary aspergillosis (ABPA) first described by Hinson et al in 1952 is an immune-mediated inflammatory disease caused by hypersensitivity to *Aspergillus fumigates* that occurs predominantly in patients with underlying chronic airway disorders like bronchial asthma & cystic fibrosis [1,2]. In India pulmonary tuberculosis (PTB) is one of the most common chronic pulmonary infections. Among tubercular patients most of the reported cases of ABPA are among previously treated patients [3] and the others are cases of ABPA misdiagnosed as pulmonary tuberculosis [4]. The occurrence of ABPA in patients with active pulmonary tuberculosis has been rarely reported. Here we present a rare case of 80 years old male patient in which active pulmonary TB and ABPA were present simultaneously. This was possible only because of use of Cartridge based nucleic acid amplification test (CBNAAT) to rule out active pulmonary TB during ABPA evaluation.

A 80 year old male farmer presented to our chest clinic with complaints of cough with brownish expectoration, chest pain, and dyspnea on exertion (mMRC grade I progressing to mMRC grade III) since last 6 months. He was a non smoker and denied any past h/o antitubercular therapy, diabetes mellitus or any other significant medical illness. He also denied any drug intake, addiction or recent travel history. On examination patient was normotensive with heart rate of 96/min and respiratory rate 20/min. On chest auscultation there were bilateral diffuse rhonchi. Examination of other systems was unremarkable. A chest radiograph revealed opacity in the right lower lobe (Fig. 1). His hemogram revealed eosinophilia with absolute eosinophil count of 3500 cells/microL. A sputum sample for acid fast bacilli(AFB) was negative. His spirometry had moderate obstruction with significant post bronchodilator reversibility suggestive of bronchial asthma. Considering his clinical picture and high local prevalence of ABPA, he was further evaluated. Intradermal test with A.fumigatus elicited strong type I hypersensitivity reaction. The total serum Ig E and Aspergillus fumigatus specific Ig E levels were 9880IU/mL (normal <295IU/mL)and 9.92kUA/L(normal <0.1kUA/L) respectively. HRCT of the thorax showed centrilobular nodules and tree in bud opacities in bilateral lower lobes (Fig. 2). Patient was thus diagnosed as a case of ABPA . As a part of routine institutional practice for all patients with abnormal chest radiology & negative sputum smear for AFB, his sputum sample was sent for Cartridge based nucleic acid amplification test (CBNAAT)/ gene Xpert analysis. The CBNAAT detected presence of rifampicin sensitive mycobacterium tuberculosis. The sputum was sent for culture which later confirmed the growth of Mycobacterium tuberculosis The patient was started on antitubercular treatment with 4 drugs namely

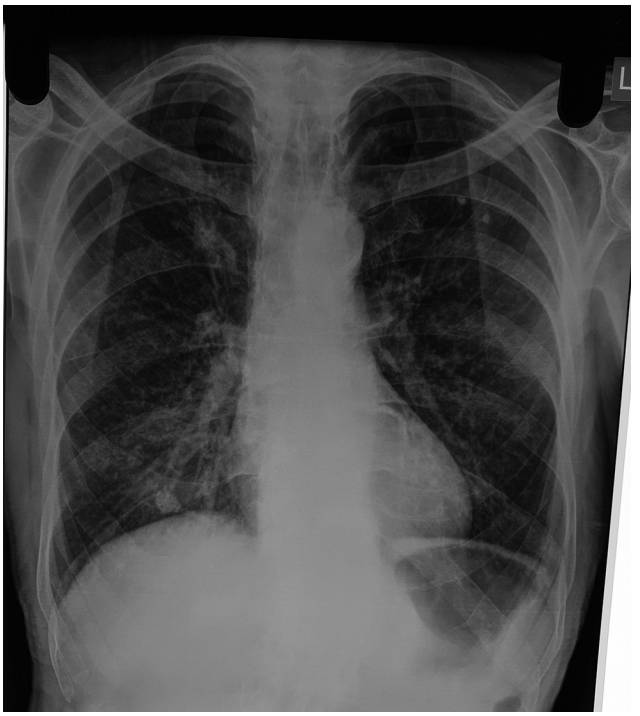

Fig. 1 – Chest X ray PA showing opacity in right lower zone.

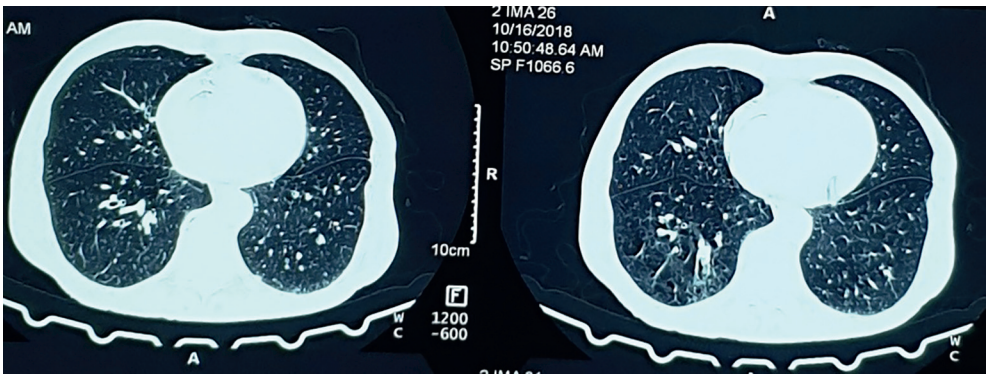

Fig. 2 – HRCT Thorax showing centrilobular nodules & tree in bud opacities in bilateral lower lobes.

isoniazid, rifampicin, pyrazinamide & ethambutol according to weight for PTB. He was also prescribed prednisolone at dose of 0.75 mg/kg for 6 weeks, 0.5 mg/kg for next 6 weeks, then tapered by 5 mg every 6 week with a plan to continue for a total duration of 9 months for ABPA. The patient showed marked clinical improvement in his condition. The total serum IgE after 3 months of treatment decreased to 3964 IU/mL and peripheral blood eosinophilia resolved. The patient is under regular follow up at our chest OPD.

This case brings into focus the importance of satisfactorily ruling out PTB while evaluating cases of ABPA .ABPA which was once considered rare is now being frequently diagnosed because of increased awareness among physicians & availability of better technology. However before starting steroids for treatment of ABPA, pulmonary tuberculosis needs to be ruled out satisfactorily. A simple sputum smear examination for AFB is not enough as it may miss paucibacillary disease. CBNAAT for MTB which was once very expensive and rarely available test that can detect very low MTB load (as low as 130-150 colony forming units per ml) especially in sputum smear negative patients, is now available free of cost at all district hospitals under RNTCP .It should be used in all ABPA cases to rule out active PTB before starting steroids to prevent dissemination of underlying PTB.

ABPA frequently complicates the disease process in bronchial asthma and cystic fibrosis patients. There are few case reports of ABPA developing in old treated PTB patients but It has been rarely reported in patients with active pulmonary TB. To our knowledge this is second case reported in which active PTB and ABPA are present concurrently. The only other case was reported by Min et al. [5]. With increasing awareness about ABPA & widespread availability of CBNAAT for MTB detection we expect more such cases will be reported in future.

To conclude, ABPA is a relatively common but underdiagnosed disease which may be coexistent with active pulmonary TB & is not restricted to old treated tubercular patients. Pulmonary tuberculosis should be carefully evaluated in patients with ABPA, particularly in high TB prevalent country like ours. CBNAAT for MTB should be used to rule out PTB in all ABPA patients before starting treatment with corticosteroids.

Conflicts of interest

The authors have none to declare

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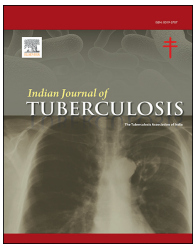

Correspondence

Front loading sputum microscopy: Honing the diagnosis of pulmonary tuberculosis

Dear Editor,

Tuberculosis (TB) is an immense public health problem that causes ill health among millions of people every year. India accounts for one-fifth of the global TB burden, with about 1.75 million incident cases reported in 2016 and 33,820 drug resistant TB patients were notified additionally.[1]

To overcome the burden of pulmonary TB, India is implementing WHO endorsed Directly Observed Treatment Short Course (DOTS) strategy under Revised National Tuberculosis Control Programme (RNTCP). Although newer technologies have been developed, the microscopic examination of sputum specimen has been the mainstay of TB case detection for over 100 years and is likely to remain the primary tool for the laboratory diagnosis of TB in resource constrained nations for a longer duration. Microscopy is rapid, inexpensive and easy to perform than other technologies. A positive sputum smear is indicative of high risk of transmitting infection to others.

In existing RNTCP guidelinesTB suspects are required to submit a spot sputum sample and another early morning sample. This requires atleast two visits and does not take patient convenience or cost into account. About 50% patients abandon the diagnostic procedure by failing either to submit a second specimen or to receive results and are called as "diagnostic defaulters". These diagnostic defaulters may spread the disease in the community.[2]

WHO has indicated that "same day microscopy" or the "front loading" method of specimen collection should be done according to a phased implementation plan. As per this scheme a TB suspect has to submit two sputum samples one hour apart on first day of visit. Two smears are prepared, assessed and report is generated on the same day.[3] This procedure saves multiple visiting for the diagnosis of TB inturn reduces economic burden and thus will lead to lesser drop-out rate. An expert group formed by WHO compared "front loading" method with "spot-morning" sputum smears and found almost same sensitivity and specificity. They also noted a drop-out of 2% in "front loading" method in compare of 5.8% drop-out in "spot-morning" method.[4]

Studies have shown greater bacillary load and higher sensitivity rates in morning samples than spot samples.[5] Therefore large scale multi-centric pragmatic trials need to be performed to establish diagnostic accuracy, as this same day microscopy can help to initiate therapy on the same day and can save time as well as resources of the patients.

Optimization of front loading sputum microscopy for increasing its rate of detecting pulmonary TB cases and reducing drop-out rate of patients from the diagnostic procedure is highly important. Since the reported has to be generated on same day, it will need reorientation of existing staff in the diagnostic microscopy centers (DMCs). The DMCs and the primary health centers (PHCs) will require internet facilities so that the reports are transferred immediately. An external quality assurance protocols need to be devised and tested which can monitor the quality of front loading sputum microscopy. With these changes, this method will go a long way in achieving India as a TB free nation.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.01.003.

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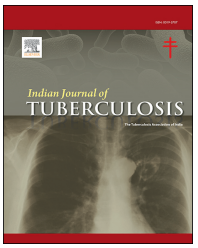

Case report

Mycobacterium avium-intracellulare septic arthritis of the sternoclavicular joint in an immunocompetent host; a three-year follow-up

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ABSTRACT

A 34 year-old lady was referred for rheumatology review by the orthopaedic team for further investigation of chronic left sternoclavicular joint pain. No preceding event such as trauma, injury or infection had occurred. A rheumatology workup turned out to be negative for an inflammatory arthropathy. After extensive investigations including blood tests, an MRI scan, a CT scan, and a bone scan, and in consultation with the orthopaedic team, the affected joint was biopsied and tested for mycobacterium avium-intracellulare infection. The results came back as positive and the patient was started on anti-mycobacterial treatment. We report the diagnosis, management and 3-year follow-up of this unique case. This highlights an uncommon and often misdiagnosed cause of septic arthritis caused by mycobacterium avium-intracellulare infection. To our knowledge this is the first confirmed sternoclavicular mycobacterium avium-intracellulare infection in an immunocompetent host reported in the literature.

1. Background

Joint mycobacterium avium-intracellulare (MAI) infection is a rare cause of infectious arthritis. It may present with clinical features similar to inflammatory monoarthritis and can involve any joint of the body. This non-typical presentation may be challenging for the physician, may delay the diagnosis and can even lead to the mistaken administration of immunosuppressive treatment with disastrous effects on the infected joint. Therefore, it is important that all physicians are aware of this uncommon, yet significant cause of septic arthritis.

2. Case presentation

A 34 year-old female health care assistant was referred to rheumatology by the orthopaedic team in February 2015, due to

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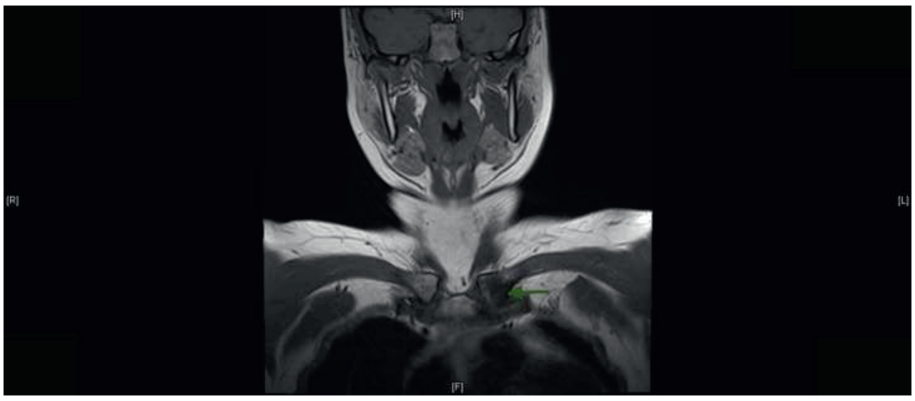

Fig. 1 – MRI scan: Abnormal signal present in T1W image in the proximal clavicle as well as the adjacent sternum (green arrow). No obvious soft tissue proliferation identified and no adjacent lymph enlargement.

a two-year history of left sternoclavicular joint pain. The pain was predominantly in the middle and medial part of the left clavicle. There was no preceding event such as trauma, injury or infection. On detailed history, she mentioned constitutional symptoms such as fatigue, feeling unwell and having intermittent drenching sweats for the past three years. She had tried various NSAIDs for the pain with some short-term relief. Her travel history included visiting Egypt and Morocco 2–3 years ago and working in Morocco for a short period. Her employment also included working in a local charity daycentre, which reported a tuberculosis breakout 4–5 years ago. She had never smoked and had alcohol only occasionally. On physical examination there was mild diffuse tenderness in the left clavicular region near the sternoclavicular joint. There was no obvious asymmetry or swelling over the sternoclavicular joint and there was near normal range of movements in all directions. Examination of the small joints did not reveal any synovitis or any soft tissue swelling. She had been extensively investigated by the orthopaedic team who could not find any orthopaedic cause to explain these symptoms.

3. Investigations

Initial blood test showed normal full blood count ESR 30 mm/h and CRP of 26 mg/L. Immunology showed negative ANA, anti-CCP antibodies and rheumatoid factor. HIV, CMV, Hepatitis B and C screen was negative. Serum ACE, C3 and C4 levels were normal. Urate levels, immunoglobulins and serum protein electrophoresis were also normal and there was no Bence - Jones protein in the urine. The initial chest X-ray was reported as normal.

An MRI scan of the clavicles showed the presence of abnormal signal in the proximal clavicle as well as in the adjacent sternum. The left sternoclavicular joint was not abnormally widened compared with the opposite side, but there was very slight irregularity of the articular surface of the clavicle. There was abnormal signal present in the proximal clavicle as well as the adjacent sternum. No obvious soft tissue proliferation identified and no adjacent lymph enlargement. Appearance suggested to represent acute pathology, and possible low grade infection (Fig. 1). The radiologist suggested that a CT scan would be more helpful for the accurate evaluation of the bony cortex on each side of the joint. The CT scan showed well marked sclerosis at the proximal end of the left clavicle, as well as the adjacent manubrium (Fig. 2). The scan was discussed with the radiologist and it was suggested that as the articular ends of contiguous bones on either side of joint were involved, then arthritis is the possibility and a stress fracture would be less likely. And in case of monoarticular involvement infection has to be the first differential in a young patient, and degenerative arthritis in the elderly

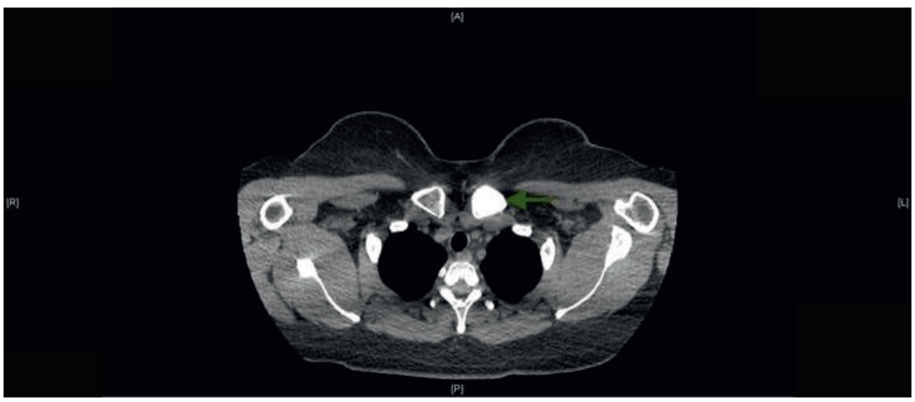

Fig. 2 – CT scan: Well marked sclerosis at the proximal end of the left clavicle, as well as the adjacent manubrium (arrow). No abnormal bone erosive changes detected and no other significant abnormality identified. The right side is normal.

ones. So much of sclerosis of the articular margin of clavicle was also unusual for inflammatory arthritis. A bone scan showed focal increased uptake at the left sternoclavicular joint confirming the presence of inflammation (Fig. 3). Although SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome was very unlikely from a rheumatology point of view, the typical "bull's head" appearance of SAPHO was not evident on the bone scan.

4. Outcome

The patient was re-referred to the orthopaedic team for a biopsy of the left proximal clavicle under regional anaesthesia. The surgically obtained bone specimen was examined microbiologically and histopathologically. The biopsy consisted of scanty bone and periosteum. There was a sparse infiltrate of lymphocytes and plasma cells within the marrow spaces which was of doubtful significance. There was no evidence of malignancy. Mycobacterial cultures were reported as positive for MAI. Bacterial cultures were negative. All cultures from the synovial fluid were also negative.

In July 2015, the patient was referred to the respiratory and infectious diseases team, and she was started on rifampicin (600 mg daily), clarithromycin (500 mg twice daily), and ethambutol (15 mg/kg once a day).

She was followed up regularly by the Respiratory team for a total of 2 years and 6 months since the initiation of anti-

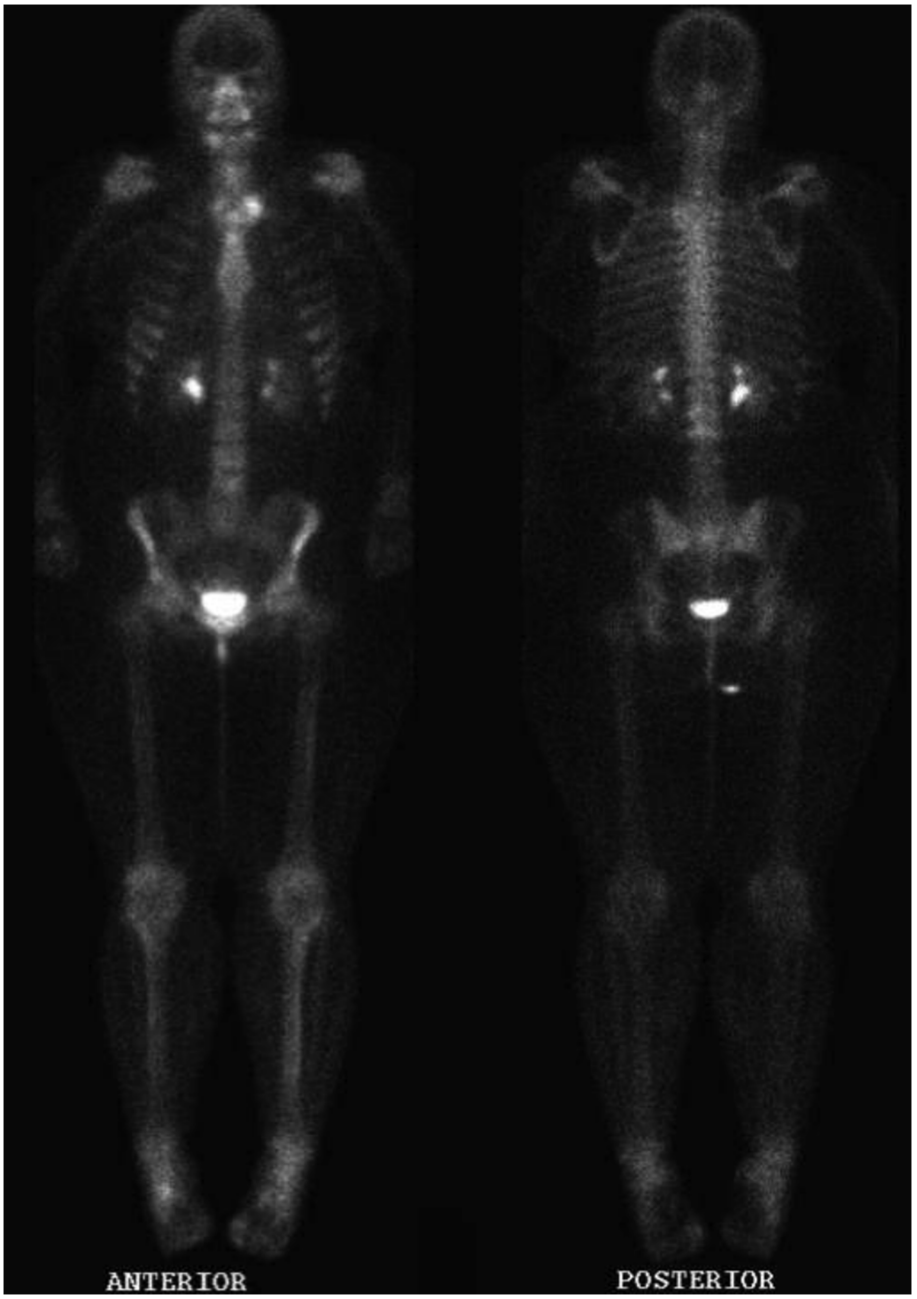

Fig. 3 – Bone scan: There is focal increased uptake at the left sternoclavicular joint on both phases of imaging, particularly on delayed imaging. No further significant focal abnormality is identified.

mycobacterial treatment (July 2015–January 2018), with remarkable improvement of her clinical symptoms. During this period she had repeated MRI scans to monitor for radiologic improvement. Despite the complete resolution of her constitutional symptoms, her last MRI scan showed periarticular bone marrow oedema, no joint effusion and normal surrounding soft tissues without synovial swelling. Although she completed her course of antibiotics in January 2018, she is going to be followed up regularly as an outpatient.

5. Discussion

Mycobacterium avium-intracellulare is usually associated with pulmonary infection in adults, cervical lymphadenitis in children, and disseminated infection in children and adults.[1] Localised MAI infection is rare, most commonly occurring in immunocompromised patients, such as those with HIV infection, receiving immunosuppressant drugs or having received prior intra-articular corticosteroid injection in the affected joint.[2–4] It is rare for immunocompetent hosts to be affected.[1,5]

Osteoarticular mycobacterial infections, such as TB and MAI infection, can be often misdiagnosed in the initial stages due to lack of awareness or presentation at uncommon sites. The diagnosis rests on culture of the synovial fluid. A synovial biopsy and culture of surgically obtained specimens may be indicated if the diagnosis is unclear after initial investigations.[6] The often insidious nature of the infection may lead to a delay in the diagnosis for many years.[7,8] The most commonly affected joint is the knee.[2,9]

Septic arthritis due to MAI is extraordinarily rare with only a few cases reported.[10–20] There have been cases of MAI arthritis masquerading as inflammatory arthritis initially treated with disease modifying anti-rheumatic drugs.[21] The so called SAPHO syndrome was within the differential, however, while the widely used criteria described by Benhamou et al[22] refer to the exclusion of infections, non-tuberculous mycobacterial infection has not been recognized as an important differential diagnosis of SAPHO syndrome.[23] Our patient's presentation mimicked an inflammatory arthropathy and this highlights the importance of taking a detailed history including occupation and recreational interests. Excluding infectious causes of inflammatory arthritis is vital because immunosuppressive treatment can have potentially disastrous consequences.

The treatment of extra-pulmonic, localised joint disease, a combination of excisional surgery (or surgical debridement) and chemotherapy is usually performed.[24] The recommended drug regimen for these infections is the same as for MAI pulmonary disease. Whether a three-drug regimen alone in this setting would be adequate, or the optimal duration of treatment, are not known.[24] In this case of sternoclavicular MAI infection, a 2-year and 6 months, three-drug antibiotic regime has led to remarkable clinical improvement. However, some radiographic abnormalities have persisted and the patient is being followed up regularly.

To our knowledge, this is the first case of sternoclavicular joint MAI infection described in the literature. Most of the reported cases of MAI arthritis, including the current sternoclavicular MAI infection, responded well to the anti-mycobacterial treatment.

6. Declaration from authors

The authors declare that there is no conflict of interest regarding the publication of this paper.

Learning points

- Patients with general constitutional symptoms and monoarthritis should be considered to have chronic infection until proven otherwise.
- MAI arthritis can present with symptoms similar to inflammatory monoarthritis. Disease modifying anti-rheumatic drugs, should never be started without having firmly excluded septic arthritis.
- A multidisciplinary approach involving the rheumatology and the orthopaedic team is needed in order to safely and effectively make the right diagnosis. Surgically obtained specimens may be the only way to diagnose MAI arthritis.

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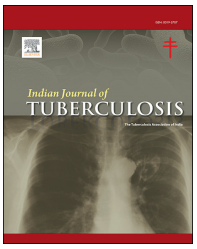

Case report

Panhypopituitarism- An unusual presenation of tuberculous meningitis

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ABSTRACT

Pituitary gland involvement is a very rare entity of central nervous system tuberculosis. Tubercular meningitis (TBM) is a chronic meningitis on hypothalamic-pituitary axis which causes high morbidity and mortality hence it is the most dreaded form of extra pulmonary tuberculosis. Here we report a case of 24 year old female presenting with three months history of fever and headache along with altered sensorium since four days. There was also complain of secondary amenorrhea and generalised apathy. Neuroimaging revealed subependymal tuberculomas with meningitis and obstructive hydrocephalus. Cerebrospinal fluid (CSF) examination was also suggestive of tubercular meningitis. Endocrinological investigations showed multiple hormonal deficiencies manifesting as pituitary hypothyroidism, hypocortisolism, hypogonadotropic hypogonadism, and hypoprolactinemia. Antituberculosis treatment was started, and it led to significant improvement in the general condition of the patient.

1. Introduction

Panhypopituitarism is a condition of inadequate or absent production of anterior pituitary hormones. There are various aetiologies causing hypothalamic-pituitary insufficiency (HPI), among them important ones are pituitary tumors (including craniopharyngioma), postoperative and post-radiotherapy states, vascular conditions, snake bite, head injury, and autoimmune diseases such as hypophysitis.[1] Now, infectious/inflammatory conditions become important cause as well. HPI causing infectious agents are *Mycobacterium tuberculosis* and non-mycobacterial agents such as bacteria, fungi, spirochetes, viruses, and protozoa.[1] TBM causes both endocrinological as well as structural abnormalities.

Among all space occupying lesions tuberculosis accounts for 20% in Indian scenario.[2] Meninges, cerebrum, and cerebellum are common sites of central nervous system (CNS) tuberculosis while brainstem, basal ganglia, and thalamus are rare ones.[3] In Indian scenario study and data on hypopituitarism are very few despite estimated total prevalence of pituitary disorders to 4 million in the year 2000.[4] Often hypopituitarism is missed because it follows smoldering course unless it has an onset with pituitary apoplexy.[5] Cardiovascular events are leading cause of increased mortality in hypopituitarism.[5] Hence it is important for early diagnosis and treatment of hypopituitarism in patients at high risk.

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2. Case report

A 24-year-old married female was admitted with chief complaints of fever and headache for past three months and altered sensorium for last four days. History of amenorrhea was there for past three months and urinary pregnancy test was negative. Informed consent was obtained from relatives for examination. On examination, she was febrile. Glasgow coma scale (GCS) was E2V2M3 but vital was stable. Neck rigidity and Kernig's sign was positive. All other systemic examinations were within normal limit. Papilledema was absent on fundoscopy.

Lab investigations showed hemoglobin (Hb) of 13.4 g/dl, total lecocyte count (TLC) 16300 cells/mm3, neutrophils 88% and lymphocytes 10%, sodium (Na) 138 mmol/l, potassium (K) 3.87 mmol/l. On CSF examination there was 120 cells/Cmm, polymorphs 10%, lymphocytes 90%, protein 329 mg/dl and sugar 63 mg/dl (corresponding blood sugar was 140 mg/dl). Adenosine deaminase (ADA) was 23.9 IU/L. This CSF examination was suggestive of tuberculous meningitis. For menstrual irregularity, thyroid profile was done which showed free tri-iodothyronine (fT3) 1.21 pg/ml, free thyroxine (fT4) 0.86 ng/dl, thyroid stimulating hormone (TSH) 0.02 ulU/ml. Serum leutinizing hormone (LH) was zero. Serum follicle stimulating hormone (FSH) 0.58 mlU/l, serum prolactin (PRL) was 4.18 ng/ml. All these parameters were in lower side of normal range. Thus hormone profile was suggestive of pituitary dysfunction. Contrast-enhanced magnetic resonance imaging (MRI) of the brain done which showed tuberculoma with meningitis and obstructive hydrocephalus. Few ring enhancing lesions with minimal perifocal edema in bilateral cerebellar hemispheres and left temporal lobe. Anatomically pituitary gland was normally visualised. She was started on intravenous dexamethasone and oral antitubercular treatment (ATT), which included oral isoniazid, rifampicin, pyrazinamide, and ethambutol.

2.1. *Differential diagnosis*

There are a number of inflammatory, granulomatous or neoplastic, traumatic or radiation injuries which involves the hypothalamic–pituitary axis and may lead to panhypopituitarism. Others are genetic defects of various types which also may be possible causes of syndromic and non syndromic isolated/multiple pituitary hormone deficiencies. Defective anterior pituitary function may also be due to unexplained gonadal dysfunctions, developmental craniofacial abnormalities, newly discovered empty sella and previous pregnancy-associated hemorrhage or blood pressure changes like Sheehan syndrome.

2.2. *Treatment*

Patient was given intravenous dexamethasone and oral antituberculosis treatment (ATT), which included oral isoniazid 5 mg/kg body weight, rifampicin 10 mg/kg body weight, pyrazinamide 25 mg/kg body weight and streptomycin 15 mg/kg body weight along with pyridoxine supplementation (20 mg/day). Hormone replacement therapy was not needed as patient was improving on antitubercular treatment.

2.3. *Outcome and follow-up*

She showed gradual improvement in sensorium and discharged after one week on ATT and tapering dose of oral prednisolone. She is continuing her medication but due to financial constraints hormonal profile could not be repeated.

3. Discussion

This case is important because there is paucity of information regarding clinical spectrum of hypopituitarism from India scenario. We report the clinical profile of hypopituitarism from a tertiary center in North India. Tuberculoma or exudates around sellar region may be the cause of hypothalamic-pituitary axis dysfunction due to tuberculosis. Hematogenous route is the main mode of spread of extra cranial source of tuberculosis to reach in meninges and brain parenchyma.

Radiological manifestations of tuberculous meningitis are of various types. Leptomeningeal and basal cisternal enhancement, focal infarcts and tuberculomas are usual findings of Contrast-enhanced MRI of the brain. Obstructive hydrocephalous accounts for 85% of tuberculous meningitis. Till date exact pathogenesis of hydrocephalus in tuberculous meningitis is unclear and probably it is due to adhesive meningeal reaction, obliteration of archnoid villi themselves or exudation in the subarachnoid space and cisterns of the base of the brain, around optic chiasma, interpeduncular, and prepontine cisterns.[6]

Panhypopituitarism in neurological tuberculosis is very rare entity. In tuberculous meningitis incidence of endocrine dysfunction is 77%[2] headache (91%), visual symptoms (46%), anterior pituitary hypo function (58%), hyperprolactinemia (23%), diabetes insipidus (11%).[2] In case of our patient hypogonadotropic hypogonadism, pituitary hypothyroidism, hypoprolactinemia, and hypocortisolism suggests the possibility of panhypopituitarism.

Pituitary tuberculosis is treated on the basis of clinical and radiological findings, although histopathological confirmation is suggested by many of authors. ATT response, clinical presentation, and serial imaging findings differentiates pituitary tuberculosis and neoplastic conditions. Transphenoidal approach may be used for histopathological confirmation when there is no real threat to the life or vision of the patient, but it is very rarely done.[3]

Conflicts of interest

The authors have none to declare.

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