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DIAGNOSTIC CHALLENGES AND CLINICAL PROFILE OF SPINE TUBERCULOSIS – AN EXPERIENCE FROM MEDIUM SIZED HEALTH CARE CENTER, SOUTH INDIA

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ABSTRACT

Introduction: Skeletal tuberculosis accounts for 10-35% of Extra-Pulmonary Tuberculosis (EPTB) and 3% of all cases of tuberculosis. Spine is involved in about 50% cases of skeletal tuberculosis. The diagnosis of Spine TB in the developing world until recently has been carried out by clinical presentation and neuroimaging modalities like X-ray/CT/MRI. Until the molecular era, the diagnostic tests at laboratories had mostly remained less contributory with low reliability and accuracy. The objective of the study was to review the spinal cases of TB and present an overview of the different methods of microbiological diagnosis in patients with Spine TB at our center.

Methodology: Retrospective study (April 2016 – April 2019) of all consecutive patients suspected with pyogenic or Spine TB was undertaken with relevant clinical details. With the radiological screen the probable TB patients were sampled (tissue, pus, abscess fluids and exudates) and were processed for ZN stain, Culture (conventional), Xpert RIF/MTB assay (at reference lab) and Histopathology. Anti-Tubercular Therapy (ATT) was administered to all definitive cases with or without surgery.

Results: A total of 26 patients of Definite TB were identified out of 42 suspected. The mean age was 47 years (14-78 range). Fever (n=17) and pain (n=18) were most common symptoms reported by over 80% of the patients. The twenty-six patients characteristically had positive radiological changes in MRI. Lumbar (n=6)and thoracic (n==6) vertebrae were equally involvedand over 50% (n=14) had two or more vertebral involvement. All 26 spine samples were negative for Acid Fast Bacilli (AFB) by ZN staining. Individually, the positive detection rate by Xpert MTB/RIF was 88% (n=23), by HPE was 65% (n=17) and by culture was 42% (n= 11) respectively. XpertMTB/RIF was 82.3% sensitive and 64% specific when compared with Histopathological Evidence (HPE) alone and the sensitivity and specificity rose up 81% on comparing with cross HPE and or culture.

Conclusion: Improved case detection of Spine TB was noted by using Xpert MTB/RIF assay at our center. We recommend Xpert MTB/RIF molecular test as the first-line investigation at laboratories for all the suspected cases of Spine TB and for confirmation when the clinical and MRI findings are inconclusive or unavailable. Staining and culture have proved less contributory. Age-old Histopathological evidence may no longer be viewed as a reference standard and needs more evaluation. Small and medium sized hospitals may gradually scale-down the Spine TB processing by AFB stain, and consider establishing on-site molecular infrastructure.

Key words: Spine Tuberculosis, Diagnostic Challange, Clinical Profile.

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INTRODUCTION

Skeletal tuberculosis accounts for 10–35% of Extra-Pulmonary Tuberculosis (EPTB) and 3% of all cases of tuberculosis. Spine is involved in about 50% cases of skeletal tuberculosis followed by hip

and knee. Spinal tuberculosis is the destructive form of skeletal TB and is one of the main pathologies seen in spinal and general Orthopaedic units in the developing world. The exact incidence and prevalence of spinal tuberculosis however in many parts of the world are not known as many cases go unreported. In countries with a high burden of pulmonary tuberculosis, the incidence is expected to be proportionately high. Aggravating the problem is raising MDR TB, treatment non-compliance and invasion by HIV. [1-4]

India, with a high burden of global TB, has been steering the Revised National Tuberculosis Control Program (RNTCP)forever three decades with over 14,000 designated microscopy centres and regional, state and national level Reference laboratories providing culture and drug sensitivity test (DST) and molecular diagnostic services. [5,6] While this strategy primarily focuses on Pulmonary TB, the diagnostic care is yet to satisfactorily reach out to EPTB patients. There have been no concrete guidelines for the diagnosis of EPTB or the diagnosis of Spine TB in the developing world. Diagnosis is typically carried out by clinical presentation along with systemic constitutional manifestation, evidence of past exposure to TB or concomitant visceral TB, and neuroimaging modalities like X-ray/CT/MRI. Deep seated infections are likely to be missed out during this diagnosis.

The laboratory diagnosis of Spine TB has for long had remained as supportive with low reliability. Direct smear examination of material by Ziehl–Neelsen (ZN) stain yields a positive result for tubercle bacilli only if the sample contains more than 10,000 bacilli/ml, thus, decreasing the sensitivity. Incidence for conventional (LJ) positive cultures for acid-fast bacilli (AFB) in osteo-articular Tuberculosis lesion has ranged between 40- 88% due to pauci-bacillary load (Masood 1992)[7,8]. However, the newer automated cultures of M. tuberculosis has shown promising results but takes 10-14 days and is carried out only in reference labs under RNTCP and at fewer private laboratories. WHO policy included Xpert MTB/ RIF nucleic acid amplification test for the initial diagnosis of EPTB in 2013. The newer 2016 updated policy conditionally states that Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having EPTB and simultaneously emphasizes the need for microscopy, culture and DST for monitoring treatment. This test has better accuracy than a smear and is performed faster than cultures. At most tertiary care levels, histological evidence such as finding caseating granulomas complements the diagnosis of Spine TB. Despite this advancement in diagnostics, it is not uncommon for the spine specialist to stumble upon negative test, result discrepancies and encounter the diagnostic challenges. The objective of the study was to review the spinal cases of TB and present an overview of the different methods of microbiological diagnosis in patients with Spine TB (with special reference to GeneXpert) at our center.

METHODOLOGY

The study was conducted at St. Martha's Hospital, Bangalore, a hundred-year-old missionary run medium sized tertiary health center with 500 beds, mostly serving below poverty line patients. Retrospective study of the charts of over two years (April 2016-19) of 43 consecutive patients suspected with Spine TB was undertaken and demographic and relevant clinical details were collected. Spine OP and IP clinics at hospital receives about 1000 and 150 patients per year respectively.

Sampling of all 'suspected cases' included spine tissue, pus, abscess fluids and exudates being processed for Acid Fast Smear (ZN stain), culture, Xpert MTB/RIF and HPE. The hospital lodges a RNTCP run DOTS center and AFB diagnostic microscopy is covered as the screen under the Memorandum of Understanding. All the samples were processed with Conventional LJ at our laboratory and positive growth sent to the state reference center for automated cultures (MGIT, Biomeruix) for confirmation. Hospital outsourced GeneXpert molecular proceedings to local accredited laboratory till 2017 and to state reference laboratory from 2017 after the wide spread escalation of XpertMTB/RIF in the country. ATT (Anti Tubercular Therapy) is administered to all definitive cases of Spine TB. The regimen

followed is 2-3 months of HRZE +9-10 months of HR with or without surgery. Treatment extends to 24 months for MDR positive patients. For HIV positive patients, it is ART + 14 months of ATT. Details of surgical intervention (if) carried out were noted. The hospital follows a protocol to follow-up the patients until their cure. The patients were followed up for 6 months after termination of therapy by clinical and radiological evaluation. Cure was defined as no suggestive radiological evidence by the end of 6 months of post ATT. Both the outpatients and inpatients of all age groups were included in the study. Approval of hospital management was obtained with patient's informed consent.

A case of 'Suspect TB' was defined as patient presenting symptomatically with TB or signs suspicious of TB or pyogenic spine on examination at the first encounter. A case of 'probable TB' was defined as patients with clinical and radiologic evidence of inflammation of one or more vertebrae and/or discitis pending microbiologic evidence and/ or histopathological and/or clinical and radiologic response to anti-TB therapy without the laboratory evidence. A case of 'definitive TB' was defined as Microbiologic evidence of least one of the following: -a) isolation of M. tuberculosis in blood/ bone, bone marrow/ deep soft tissues and/or (paravertebral, epidural or psoas) abscess specimens by cultureb) positive microscopy (Ziehl–Nielsen staining) for acid-fast bacilli from bone/ bone marrow/ deep soft tissue and/or (paravertebral, epidural or psoas) abscess or any sterile body tissue; or c) positive PCR for M. tuberculosis complex. D) And/or a Histopathological evidence of caseating granulomas.

As the positive result by PCR was the most recent addition for the microbiological evidence of Spine TB at the hospital, the sensitivity, specificity and predictive values were determined using with the HPE for definite TB as the reference and culture with HPE as composite reference standard. Simple descriptive analysis was carried out to characterise the study population. Categorical data were quoted as proportions with 95% CI.

RESULTS

Of the suspected 42 patients, 26patients of were identified as Definite TB. The mean age was 42 years (14-78 range).The mean duration of symptoms had an average 116 days (1- 6.5 months). Seven patients had pre-existing conditions such as Diabetes, IHD etc. Most patients (over 80%) reported with fever(n=22)and pain (n=17). Neural involvement such as tingling, numbness (n=8), paraplegia (n=4) and kyphosis (n=3) were seen in patients. Nine patients had sputum samples positive by GeneXpert amongst which two were also positive by culture and ZN staining. Only four cases showed pulmonary involvement on chest X-ray. Rest of the results with ESR, CRP and leucocyte counts are tabulated in Table 1.

Table 1: Demographic characteristics, clinical symptoms and laboratory findings of Definite TB patients (n=26) at presentation

Characteristics	**Value**
MeanAge	42(14-78) years
Sex, M/F	13/13
Pulmonary Koch positive*	9
Comorbidities	15
Hypertension/Diabetes/CVD/ IHD/anaemia	12
Chronic smokers/Gutkha chewer	3
Clinical symptoms	
Pain	17
Fever	22
Swelling over the back	3
Neurodeficeits	8
Paraplegia	4
kyphosis	3
Constitutional symptoms	12
Median Laboratory findings (range)	
Leucocyte count ($\times 10^3/\mu l$)	6350 (1450-16430)
Haemoglobin level(g/dl)	12.6 (9-15.1)
ESR(mm/hr)	62 (12-141)
CRP**(mg/dl)	10.3 (0.5-232)

*Pulmonary Koch diagnosed either by ZN stain/ culture or GeneXpertor by combination

**CRP was not done in 5 patients

All the patients were screened for HIV and HBs Ag as per the hospital protocol and were negative. Lumbar and thoracic vertebrae involvement was common (n=6) and 77 % (n=20) had over two vertebral involvement. Eleven patients had disc space involvement (Table 2).

Table 2: Imaging characteristics of Spinal TB (n=26) of definite TB patients	
Location	**n (%)**
Cervical	2
Thoracic	6
Cervico-thoracic	1
Thoracolumbar	3
Lumbar	6
Lumbosacral	3
Cervical, thoracic & Lumbar	3
Sacral	1
Skipped lesion(T, L), SI joint	1
No. of Vertebra involved	
1	4
2	14
3	5
4	1
SI Joint	1
Image findings	
Disc space involvement	11
Disc space involvement with paravertebral/paraspinal abscess	9
Paravertebral/paraspinal abscess only	3
Epidural compression with disc space involvement/abscess/combination	4

All 26 spine samples were negative by ZN staining. Individually, the detection rate by Xpert MTB/RIF was 88.4% (n=22), by HPE was 65.3% (n=17) and by conventional culture was 42% (n=11) respectively. XpertMTB/RIF was 82.3% sensitive and 64% specific when compared with HPE alone and specificity rose up to 81% on comparing with cross HPE and or culture (Table 3).

Table 4: GeneXpert performance at the center for detecting TB				
Reference standard	**Sensitivity % (n)**	**Specificity %(n)**	**PPV % (n)**	**NPV %(n)**
HPE only	82.3 (14/17)	64 (16/25)	61 (14/23)	15.7 (3/19)
HPE and/ or culture	81 (17/21)	81 (17/21)	81 (17/21)	19 (4/21)

Note: Patient negative by all three tests(n=1, by culture, HPE, Xpert TB) is excluded from the analysis. For abscess fluid(n= 3), two patients had undergone curettages/ extractionswhileHPE was taken as negative for analysis purpose for one patient.

Gene Xpert results were available from 72 hours- 7 days, HPE reports by 7 days, while culture results took a median of 30 days. All patients received ATT as per the hospital protocol. Nine patients underwent percutaneous biopsy, while 15patients underwent posterior instrumentation with / without decompression/bone grafting /corpectomy/ cage fixaton/plating with biopsy. Purified protein derivative (PPD) testing and INF-Y assay was not carried out in any patients. Twenty five patients had complete cure with normal MRI and ESR/ CRP levels (previously elevated values) on follow-up after completion of treatment, and implants in situ while one patient expired with multi-organ failure and septic shock. One patient with SI joint involvement grew Multi Drug Resistant (MDR) TB with Rifampicin and low level resistance to INH but achieved complete cure with extended 2nd line ATT with Quinolones and Aminoglycosides for 4 months. The remaining 16 suspected patients were treated with antibiotics for pyogenic spine, one of whom turned out to be a case of 'Probable TB' (negative by smear, culture, molecular diagnosis), but recovered with ATT based on radiological and clinical findings.

Table 3: Samples processed in laboratory by different diagnostic tests						
Total number of patients with suspected Clinical history and/or Radiological changes of TB (Probable TB)	**Pyogenic spinal involvement (Non-TB/ bacterial)**	**MTP positive by any one of the three tests (Definitive TB)**	**MTB detected by ZN stain (microscopy positive)**	**MTB grown in conventional LJ (culture positive)**	**Gen Xpert assay positive (molecular test positive)**	**MTB detected by histopathology (HPE positive)**
42	16	26	0	11	23	17

DISCUSSION

Arriving at the diagnosis of Spine TB poses a challenge to treating clinicians at medium sized health care centers across the country in the absence of a defined protocol. Diagnosis thus gets based on strong clinical and radiological suspicion in TB endemic areas. Until recently, the closest available literature for early detection or decision-making algorithms of spinal tuberculosis was from Association of Physicians of India (API)[9] and from WHO[10].The samples processed at our laboratory showed high smear (zero detection rate) and culture negativity results with poor yield. Result tracing was difficult as samples were initially out sourced for molecular tests at multiple places. In the later days, the results of molecular tests sent to state reference laboratory would take anywhere beyond 72hours to 7 days while the running test time would only take 4-6 hours. There was also a longer time in receiving the automated culture reports from reference center (over a month) sent for confirmation. Peripheral hospitals which submit the samples to the pool of samples at reference laboratories promptly needs to follow up for the results till the end. For chronic diseases such as TB, continuity of care is challenging unless followed up.

The Index TB guidance by the Central Ministry of Health at all levels of health care has been introduced with evidence-informed practices for suspecting, diagnosing and managing various forms of EPTB including Spinal TB making a special mention to molecular tests[11]. Molecular evidence around the use of PCR based tests such as Xpert MTB/RIF in Spinal TB have been used often nowadays despite wide sensitivity and specificity ranges. Literature quotes sensitivity from 61 to 90% and specificity from 80 to 90% for spine TB[12-14]. The observed positive rate of 88% in this study seems satisfactory. Xpert MTB/RIF had its sensitivity and specificity of 81%and the lower-side-value may be attributed to false negatives from culture and HPE- perhaps suggesting that age-old HPE may no longer be viewed as a reference standard. However, Jain AK et al found a PCR positive rate of 98% in osteo-articular samples, smear and culture positivity of 12% but 100% positivity for HPE[15]. This probably indicates that the accuracy of histopathological evidence needs further understanding and more evaluation in the coming years.

Higher sample numbers which would have added weight to the results is noted to be the limitation of the study. Retrospective chart reviews invariably carry some degree of selection bias and we acknowledge the same. Nevertheless, we recommend MTB/RIF assay as the first-line investigation at laboratories for all the Probable TB cases and to gradually scale-down the processing by AFB stain. WHO attests this in Standard for TB care in India and has already set up next generation usage of MTB/RIF ultra assay, it needs to be seen to what extent this will be implemented in EPTB[16, 17].Medium sized laboratories may well start establishing their own molecular infrastructure on site.

Contrary to most literature, Spinal TB was noted to be more in the elderly population in this study(46%were over 50 years) as put forward by the Alavi et al[18].The duration of symptoms (pain and fever predominantly) varied to months as stated by Colmenero JDand colleagues [19]. The non-specific constitutional symptoms were also not predominant as is mostly seen with Spinal TB patients. Multiple vertebral involvements (suggestive haematogenous spread) were seen in over 70% of the patients which again calls for rapid diagnosis and early initiation of therapy. Positive MRI findings in Spine TB are well documented in literature; findings were favorable for diagnosis in this study like other studies [20-23]. As up to 38% (n=10) of the patients in this study had pulmonary involvement, it becomes important for the spine surgeons to screen patients for pulmonary involvement as well to curb the TB transmission rates in the population.

CONCLUSION

Improved and faster case detection was noted by using Xpert MTB/RIF assay than the culture and histopathology tests. We hence recommend the use of the same as the first-line investigation at laboratories for all suspected Spine TB cases and

to gradually scale-down the processing by AFB staining and conventional culture. The results of the study may be used to improve existing Spinal TB diagnostics at medium sized hospitals by assessing the usefulness of the tests in their own set-ups and pickon the most optimal and accurate one. Age-old HPE may no longer be viewed as a reference standard and needs further evaluation.

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CONFLICT OF INTEREST

None

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