Original Article

Pediatric mediastinal tuberculosis: Exploring the diagnostic precision of endobronchial ultrasound and ancillary investigations

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ABSTRACT

Background: Mediastinal Tuberculosis (TB), although a common presentation of TB in children, has a very low rate of microbiological confirmation. This is because of the difficulty in acquiring appropriate tissue samples for microbiological confirmation. Endobronchial ultrasound (EBUS) and esophageal ultrasound with a bronchoscope (EUS-B) offer a safe, effective, and minimally invasive modality of sampling in these children. We present our institutional experience on EBUS/EUSB and the various ancillary investigations for mediastinal TB. **Methods:** This is a single-center retrospective study among children who underwent EBUS/EUS-B for a mediastinal nodal lesion. The primary objective of the study was to analyze the diagnostic accuracy of histopathology and various microbiological investigations, through EBUS/EUS-B guided TBNA, in the diagnosis of mediastinal TB. The secondary objective was to ascertain the safety of EBUS/EUS-B. **Results:** A total of 50 children underwent EBUS/EUS-B at our center, of those 26 (17 girls, mean age 11.7 years) were diagnosed with mediastinal TB. Fever was the most common presenting symptom (85%) and only seven children (26%) had a concomitant pulmonary involvement. The diagnostic performance of various investigations was as follows: Acid-fast bacilli (AFB) smear (sensitivity - 86.6%, specificity - 82.9%, NPV-93.5%, PPV - 68.4%), Xpert Ultra (sensitivity -100%, specificity - 68.5%, NPV - 100%, PPV - 57.7%), and cytology (sensitivity - 100%, specificity - 82.9%, NPV - 100%, PPV - 71.4%). A microbiological confirmation was attained in 81% of the children. There were no major complications in any of the procedures. **Conclusion:** EBUS/EUSB is an effective and safe investigation for the diagnosis of mediastinal TB in children.

KEY WORDS: Endobronchial ultrasound, esophageal ultrasound with a bronchoscope, mediastinal TB, pediatrics

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INTRODUCTION

Tuberculosis (TB) is one of the major health concerns in India, which constitutes one-fifth of the world's total TB burden.[1] Although mediastinal adenopathy is a common presentation of TB in children, microbiological confirmation of the same is achieved only in a third of the children.[1] This is because of the absence of concomitant pulmonary involvement in a large proportion of children with mediastinal TB, leading to reduced yield in a gastric

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aspirate,[2] or even a broncho alveolar lavage (BAL).[3] Traditionally, procuring a nodal sample required surgical access, which was often deemed invasive. This often leads to a presumptive diagnosis of TB, overlooking the possibility of a more sinister diagnosis such as a malignancy.[4] Convex probe endobronchial ultrasound with trans bronchial needle aspiration (EBUS-TBNA) and EUS-B, offers a safe and minimally invasive alternative for the evaluation of mediastinal adenopathy. Although, a standard diagnostic tool for mediastinal adenopathy in adults, the literature on pediatric EBUS is limited to a handful of case series demonstrating its utility and safety in children.[5–8] Diagnosis of TB relies upon various investigations such as a Microscopy for AFB, gene xpert MTB/RIF ultra (Xpert Ultra), Mycobacterium Tuberculosis (MTB) cultures, and histo pathological examination (HPE). As each investigation has its drawbacks, TB diagnosis often relies on combining these investigations.[9] This study aims to present our experience with the use of EBUS/EUS-B, more specifically the various diagnostic investigations, in pediatric mediastinal TB.

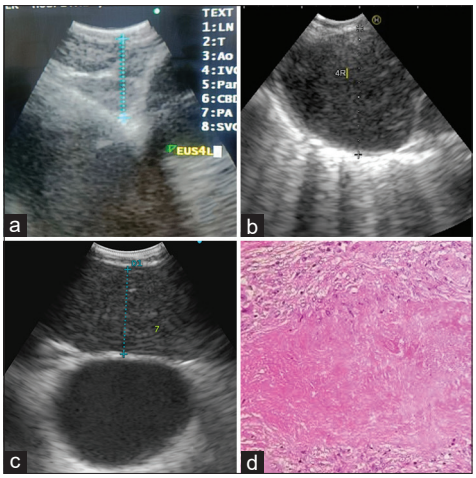

Figure 1: (a) Station 4L node visualized in a 9-month-old infant via EUS-B. (b) Station 4R node visualized via EBUS in an 8-year-old girl. (c) Station 7 node visualized via EUS-B in a 12-year-old girl. (d) Section showing necrotizing granulomatous inflammation, composed of a central necrotic zone surrounded by epithelioid histiocytes and lymphocytes

MATERIALS AND METHODS

This is a single-center retrospective study. We included all children who underwent EBUS/EUS-B during a 3-year study period (June 03, 2020 to June 2023). Ethical clearance for the same was obtained from the Institutional Ethics Committee. Data regarding the age, sex, clinical features, nodes sampled, complications, and cytological and microbiological investigations of the children who underwent the procedure were collected from the hospital database. In children with a parenchymal lesion, EBUS/EUS-B was considered only when a respiratory sample (sputum, gastric aspirate, or a BAL) did not provide a microbiological confirmation of TB. EBUS/EUS-B was performed by trained pediatric pulmonologists from our unit. Signed consent from the parent/guardian was obtained before the procedure. The nodes to be sampled were mapped using a contrast-enhanced computerized tomography (CECT) chest, before the procedure. The procedure was carried out in our bronchoscopy suite, under general anesthesia. The airway was secured using a laryngeal mask airway for EBUS or an endotracheal tube in case of an EUS-B. EBUS/EUS-B was done using a convex probe EBUS scope (BF-UC 180F, external diameter 6.9 mm, working channel diameter 2.2 mm with a 7.5 MHz transducer, Olympus Medical Systems, Tokyo, Japan), and lymph node sampling was done using Olympus ViziShot EBUS-TBNA 21G needle [Figure 1]. Each node was sampled with 3–5 passes, with 10–20 jabs per pass. A negative pressure suction of 10 mmHg was applied during each pass. Rapid-on-site evaluation (ROSE), was not performed routinely. Aspirated material was smeared onto glass slides and fixed with alcohol for cytology. For molecular investigations, samples were obtained by flushing the contents of the needle with sterile saline. Microscopy for AFB was done using Ziehl-Neelsen stain on the cytology specimen, nucleic acid amplification test (NAAT) using Xpert Ultra, and MTB cultures using BacT/Alert MP (Bio Merieux, Durham, NC). A diagnosis of TB was made if one of the under-listed criteria were fulfilled.

1. A microbiological confirmation from the lymph node sample, either with a smear for AFB, Xpert Ultra, or an MTB culture.
2. A cytology consistent with the diagnosis of TB (granulomatous inflammation with or without necrosis), where alternative diagnoses have been reasonably ruled out and a clinical improvement had been documented after starting therapy for TB.

Statistical analysis was performed using IBM SSPS software version 21. Descriptive variables were described as frequency/percentages when categorical and mean ± standard deviation when continuous. Parameters such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), along with their confidence intervals were calculated using standard formulas to assess the diagnostic utility of the tests performed for detection of TB. MTB culture was considered the reference test. McNemar test was employed to assess the comparability of the new tests against the reference test, MTB culture. The test statistic was calculated based on the differences in the discordant pairs and a *P* value was obtained to determine if the observed difference is statistically significant, typically using a significance level of 0.05.

RESULTS

During the study period, 51 children underwent EBUS/EUS-B at our institute. One child underwent EBUS for a non-nodal pathology and was excluded. The remaining

50 children were taken for analysis. The mean age of the children in our study was 10 years (9 months- 17 years). A diagnosis was achieved through EBUS/EUS-B in 38 of the 50 children, with a diagnostic yield of 76%. Of them, 26 children (52%) were diagnosed with mediastinal TB, whereas the diagnosis in the rest included, sarcoidosis (n = 6, 12%), lymphoma (n = 3, 6%), and chronic granulomatous disease (CGD) (n = 2, 4%). Of the children with mediastinal TB, the mean age at presentation was 11.6 years, with a female predominance (n = 17, 65%). The youngest child to undergo the procedure was a 9-month-old [Figure 1a]. Presenting symptoms included fever (n = 22, 85%), cough (n = 9, 35%), and weight loss (n = 14,54%) [Table 1]. Concomitant pulmonary involvement was seen in 7 of the 26 children (27%). None of the children were on empirical anti tubercular therapy (ATT) at the time of the procedure. EBUS was performed in 20 children; whereas, EUS-B was done in 6. EUS-B was preferred with children <6 years and in children with respiratory distress. Each child had, on average, 2.5 nodes sampled with the most common being station 7 (n = 22) and station 4R (n = 17) [Figure 1b and c]. The mean size of the node, on the ultrasound was 1.85 cm (±0.7 cm). An adequate sample was obtained in all children. No major or minor complications were observed during or in the immediate post-procedure period.

Of the diagnostic tests for TB, AFB smear was positive in 19 children (73%), Xpert Ultra in 21 (81%), and MTB culture in 15 children (58%), whereas, all children (100%) had a necrotizing granulomatous inflammation on cytology [Table 1]. Figure 2 shows a Venn diagram of the relationship between these investigations [Figure 2]. As compared to the gold standard MTB culture, the AFB smear had a sensitivity of 86.5%, a specificity of 82.9%, a PPV of 68.4%, and an NPV of 93.5%. The *P* value by Mc Nemar test was 0.289 indicating that there was no significant difference between the sensitivity or specificity of AFB in comparison with culture. Xpert Ultra had a sensitivity of 100%, specificity of 82.9%, PPV of 71.4%, and NPV of 100%, whereas, cytology had a sensitivity of 100%, specificity of 68.5%, PPV57.7%, and an NPV of 100%. A comparison of discordant outcomes of the tests against the reference test, culture showed *P* value of 0.031 for Xpert Ultra and 0.001 for cytology. These indicate the superior performance of Xpert Ultra and cytology in comparison to culture. A microbiological confirmation of TB was achieved in 21 of the 26 children (81%) [Table 2]. All had a Rifampicin sensitive TB. Procedural complications were encountered in 12 children (46%). This was mostly minor including transient hypoxia (n = 4, 15%) and minor bleeding (n = 10, 38%). Only one adolescent had persisting hypoxia where EBUS was aborted and was converted into an EUS-B. All bleeding events were minimal and did not require additional intervention, and there were no instances of pneumo-mediastinum. At the time of writing, all but two children had completed the course of ATT and had clinical improvement on follow-up.

Table 1: Clinical features and laboratory findings of children who were diagnosed with mediastinal TB

Clinical features	
Fever	22 (85%)
Weight loss	14 (54%)
Weight loss	9 (35%)
Fast breathing	6 (23%)
Investigations	
AFB	19 (73%)
Gene Xpert Ultra	21 (80.7%)
Cytology	26 (100%)
TB culture	15 (58%)

DISCUSSION

Mediastinal lymphadenopathy constitutes around 4% of all pediatric TB cases.[1] Used widely in adults, EBUS offers a minimally invasive yet effective tool for sampling mediastinal nodes.[10] Wurzel *et al.*,[11] first described the use of EBUS in the pediatric age group, where they used the same for the diagnosis of sarcoidosis in a 13-year-old. Because then multiple reports and case series have been published describing its use in various pediatric mediastinal pathologies.[3,6,12] The challenge with doing an EBUS in children lies in negotiating the large EBUS scope (6.9 mm outer diameter) into the relatively smaller trachea. This has been partly solved by introducing the EBUS scope through the esophagus, a technique called EUS-B.[13] Although a conventional TBNA has been described in a 9-month-old infant,[12] the youngest reported child to undergo an EBUS/EUS-B was a 20-month-old toddler who underwent sampling of nodal station 4L, yielding a diagnosis of lymphoma.[14] The youngest in our cohort was a 9-month-old infant who presented with a parenchymal lesion and mediastinal adenopathy (station 7), where a BAL was unyielding. The child was subjected to EUS-B sampling of the lymph nodal stations 7 and 4 L, which resulted in a diagnosis of TB. Although EUS-B has been demonstrated for sampling of lymph node

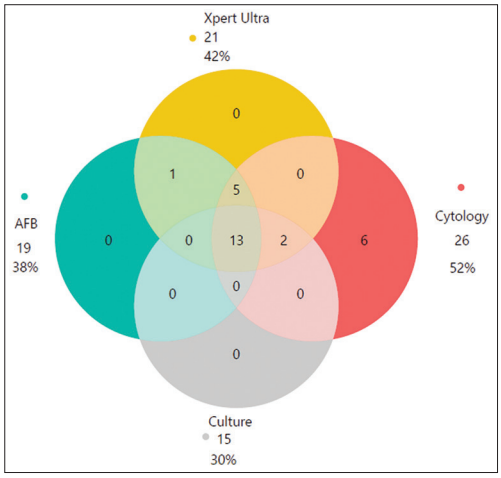

Figure 2: A Venn diagram representing the overall between the four investigations utilized in the diagnosis of mediastinal Tuberculosis. AFB- Acid Fast Bacilli; Xpert Ultra- Gene Xpert MTB/RIF Ultra

Table 2: Tabulation of the precision of various investigations used in the diagnosis of mediastinal TB

	TB culture			Chi-square (*P*)	*P* by McNemar's test
	Positive *n* (%)	Negative *n* (%)	Total *n* (%)		
AFB smear					
Positive	13 (86.6%)	6 (20.9%)	19 (38%)	21.54	0.289
Negative	2 (13.4%)	29 (79.1%)	31 (62%)	(<0.000)	
Total	15	35	50		
Sensitivity		86.7%			
Specificity		82.9%			
NPV		93.5%			
PPV		68.4%			
Xpert Ultra					
Positive	15 (100%)	6 (20.9%)	21 (42%)	29.52	0.031
Negative	0	29 (79.1%)	29 (58%)	(<0.000)	
Total	15	35	50		
Sensitivity		100%			
Specificity		82.9%			
NPV		100%			
PPV		71.43%			
Cytology					
Positive	15 (100%)	11 (31.4%)	26 (52%)	19.78	0.001
Negative	0	24 (58.6%)	24 (48%)	(<0.000)	
Total	15	35	50		
Sensitivity		100%			
Specificity		68.6%			
NPV		100%			
PPV		57.7%			

AFB: Acid fast bacilli, PPV: Positive predictive value, NPV: Negative predictive value

stations 4L and 7,[15] we were able to sample a large 4R node of size 24.5 mm, which had a retrotracheal extension.

The overall diagnostic yield of EBUS/EUS-B in our series was 76%. This is higher than a recent meta-analysis, that observed a pooled diagnostic yield of 61% for EBUS in children.[7] TB was the most common diagnosis, similar to the other Indian studies.[8] Although cultures are considered the gold standard, relying on cultures alone will likely underestimate TB.[16] Hence other investigations are relied upon, mainly cytopathology and NAAT. All children in our series had cytology showing necrotizing granulomatous inflammation, consistent with TB, similar to observations made in adult studies.[17] Although cytology has excellent sensitivity and NPV, its specificity remains low (68.5% in our study), diminishing its utility as the sole diagnostic marker.[16] In our series, two children with persistent mediastinal adenopathy having necrotizing granuloma and negative microbiological evidence for TB were diagnosed with CGD for further evaluation. Nodal involvement is a common occurrence in CGD with a recent multicentric study describing its occurrence in 25% of the children.[18] However, a microbiological diagnosis was achieved in only a third of those children. In the two children in our cohort, as all microbiological investigations were negative, they were started on empirical trimethoprim-sulfamethoxazole and voriconazole following which regression of the nodes was observed. ATT was not started given the absence of supportive evidence apart from cytology. As a routine in our unit, we evaluate for CGD in all children with granulomatous lymphadenopathy, without microbiological confirmation of TB, before starting ATT.

As compared to Mohan *et al*.,[17] we observed a higher sensitivity (100% vs. 88.8%) and PPV (71.4% vs. 53.3%) for NAAT. Various adult studies mention sensitivities between 61% and 98%.[16] This could be attributed to using Xpert Ultra in our series, which is known to improve the sensitivity of TB detection by 45%, over Xpert, in lymph nodal TB.[19] The specificity for NAAT is lower in Indian studies, as compared to Western studies which mention a high specificity of 97–100%.[16,20] This could be because of two reasons. The first of that could be attributed to our use of cultural positivity as the gold standard. This is in contrast to studies that employed a composite clinic-pathological diagnostic criterion as the reference standard.[20] The second could be attributed to the endemicity of TB in India, where NAAT-positive and culture-negative cases are highly likely to have TB as opposed to an alternative diagnosis. Overall, we were able to achieve a microbiological confirmation, through EBUS/EUS-B, in 81% of the cases. Geweniger *et al*.,[3] in their use of EBUS in adolescents, had a microbiological confirmation of TB in 73% and a multicentric study in adults had a microbiological confirmation of 62%.[9]

EBUS/EUS-B is usually a daycare procedure. Although moderate sedation is generally preferred in adults for EBUS, few studies have observed better diagnostic yield with deeper sedation.[21] As an institutional protocol, all pediatric EBUS/EUS-B are done under general anesthesia with a pediatric anesthesiologist. Apart from the one child where EBUS was converted to an EUS-B given persisting hypoxia, there was no major complication.

Smaller sample sizes, single-centric data, and the retrospective nature of our research protocol are the

limitations of our study. Although the costs involved and the expertise required limit the universal adoption of EBUS/EUS-B in evaluating pediatric mediastinal pathologies, our study outlines the precision of various investigations via EBUS/EUS-B for the diagnosis of mediastinal TB.

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Conflicts of interest
There are no conflicts of interest.

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