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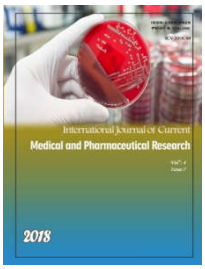

TRANSESOPHAGEALBRONCHOSCOPIC ULTRASOUND- GUIDED FINE-NEEDLE ASPIRATION (EUS-B-FNA) IN PEDIATRIC MEDIASTINAL LYMPHADENOPATHY: A CASE SERIES, AND COMPREHENSIVE REVIEW OF LITERATURE

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ABSTRACT

Background and Aims -Transesophagealbronchoscopic ultrasound-guided fine needle aspiration (EUS-B-FNA), performed using an endobronchial ultrasound (EBUS) bronchoscope is a useful modality for diagnostic evaluation of mediastinal lymphadenopathy. Most of the literature on EUS-B-FNA is limited to adults, with limited studies describing safety and utility in children. We describe a case series of EUS-B-FNA in the pediatric population, with a comprehensive review of literature.
Methods - Three children under the age of 8 years underwent EUS-B-FNA of mediastinal lymp-nodes, with microbiological and histopathological evaluation.
Results - EUS-B-FNA was done successfully without any complications. A definitive diagnosis was obtained in all the patients with no significant adverse effects.
Conclusions - This case series illustrates the role of EUS-B -FNA in the pediatric population, as a feasible, safe and successful minimally invasive procedure.

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the preferred diagnostic modality for benign and malignant mediastinal lymph node (MLN) enlargement in adults[1,2] and children[3,4]. Transesophageal bronchoscopic ultrasound- guided fine-needle aspiration (EUS-B-FNA), where the EBUS scope is introduced into the esophagus to sample MLN's is gaining wider acceptance in both adult[5, 6] and pediatric practice[4, 7, 8] in certain specific situations.

There are few studies on EUS-B-FNA in pediatrics[4, 7, 8], and limited recommendations exist for its use in children, with respect to indications, application across various age groups, safety and procedure details. We describe a case series which highlights these aspects, with a review of current literature on EUS-B-FNA in pediatrics.

Patients and methods

Case 1

A 7 year school going female presented with persistent fever, dry cough, weight loss and anorexia for 3 months. There was no history of chest pain, wheezing, hemoptysis, or contact with tuberculosis (TB). On examination, she was underweight [weight and height 17 kg and 118 cm respectively (10- 25% for age)], with no significant peripheral lymphadenopathy. The respiratory rate was 22/min, pulse rate 110/min, and oxygen saturation at room air (SpO2 -RA) was 97%. Systemic examination was normal. Chest radiograph (CXR) showed mediastinal widening and tuberculin skin test was negative.

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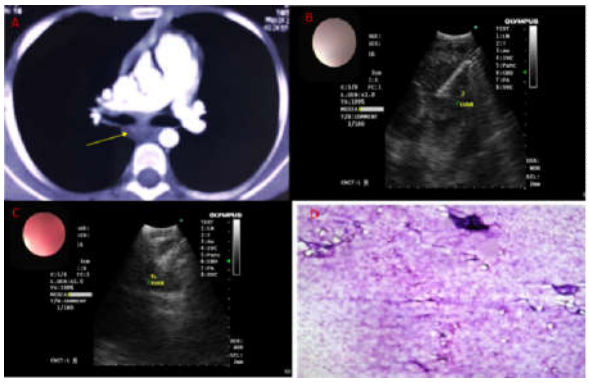

Figure 1 Contrast enhanced computed tomography (CECT) of thorax shows A. Enlarged station 7 (Yellow Arrow), B. & C. The TBNA needle in the target lymph nodes (Station 7 & 4L), D. H & E histologic section showing necrotising granulomatous lesion.

Computed tomography (CT) scan of the thorax showed multiple enlarged mediastinal lymph nodes (MLN) at the lower right and left paratracheal and subcarinal lymph node stations (Fig 1A). Tissue diagnosis was needed, and MLN sampling was discussed.

Case 2

A 1 year 8 month toddler presented with acute dyspnea with wheezing for one day. There was no other significant history. The respiratory rate was 56/min, pulse rate 160/min, and SpO2 -RA 88%. She was neuro-developmentally appropriate for her age with normal growth parameters, and no significant peripheral lymphadenopathy. Respiratory examination showed bilateral wheeze. CT thorax showed multiple enlarged MLN at the right and left paratracheal and subcarinal locations with no other abnormalities (Fig 2 A, B). The differential diagnosis included either lymphoma or TB, and an accurate diagnosis was essential.

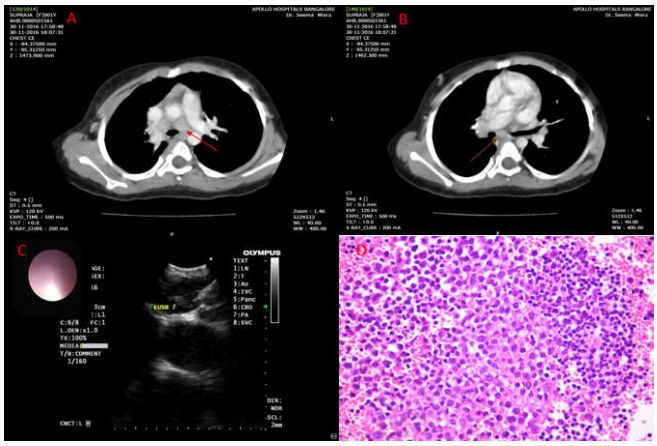

Figure 2 CECT of thorax shows A. Enlarged station 7 (Red Arrow), B. Enlarged station 4L (Brown Arrow), C. The TBNA needle in the target lymph node (Station 7), D. H & E histologic section (40X) showing atypical lymphoid cells arranged in diffuse sheets.

Case 3

A 6 year school going female presented with acute onset of nodular swellings on both shins, diagnosed as erythema nodosum. There was no history of fever, loss of weight or anorexia. On general physical examination, she was age appropriate with normal growth parameters [weight and height 23 kg and 120 cm (75- 90% for age) respectively] with no significant peripheral lymphadenopathy.

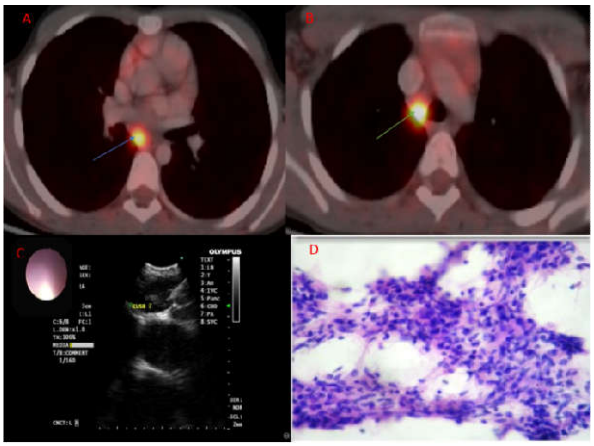

Figure 3 Positron emitted tomography of thorax shows A & B. Enlarged station 7 (Blue Arrow) and station 4R (Green Arrow) with significant uptake, C. The TBNA needle in the target lymph node (Station 7), D. H & E histologic section (40X) Shows epithelioid cells with interrupted lymphocytes.

Systemic examination was normal. Investigations including complete hemogram and C-reactive protein were normal. The tuberculin test was 22 mm (positive) and CXR showed significant MLN. Positron emitted tomography (PET) of the chest showed enlarged MLN, with significant uptake at the right paratracheal and subcarinal stations (Fig 3 A). A procedure was planned to obtain tissue diagnosis.

Plan and Technique

This is a retrospective analysis of data collected at Apollo hospitals, Bangalore, between 1stJanuary 2017 to 31stDecember 2017. The Institutional Ethics Committee waived the requirement for informed consent. However, standard procedural consent was obtained from all subjects (and their guardians) according to the institutional practices.

In all the above situations, the possibilities for tissue diagnosis included minimally invasive sampling of the MLN with EBUS-TBNA or EUS-B-FNA, or surgical sampling with mediastinoscopy or video-assisted thoracoscopic surgery (VATS). The advantages and disadvantages of each procedure were discussed in detail with the parents of the children. Case 2 was not a candidate for EBUS-TBNA due to both: a) small tracheal size precluding the safe passage of an EBUS scope and b) significant baseline hypoxemia (SPO2 -RA 88%).

The parents preferred minimally invasive sampling over surgical sampling as an initial modality. Though EBUS-TBNAcould have been done for cases 1 and 3, it would have been technically challenging. This is because the larger EBUS scope carries the risk of desaturation as it occupies majority of the tracheal lumen, and sampling difficulties can also compromise the yield. In such a situation, the parents opted for the safer EUS-B-FNA, which does not come with a risk of significant desaturation due to esophageal access.

EUS-B-FNA was done for all the cases after informed consent. In consultation with the anesthesiologists, the procedure was planned with local anesthesia and conscious sedation, with intravenous midazolam and fentanyl. General anesthesia (GA) was reserved as a secondary option, which is the usual practice with esophageal procedures such as upper gastrointestinal endoscopy in children. EUS-B-FNA was performed in the supine position with supplemental nasal oxygen with the patient breathing spontaneously. The EBUS scope (Olympus BF-UC180F convex probe, 6.9 mm outer diameter) was advanced into the esophagus and enlarged MLN were seen at

stations 7 (subcarinal, case 1-3) and 4L (left paratracheal, case 1 and 2). A 22G EBUS-TBNA needle was used for sampling. An average of three aspirates were obtained from each lymph node (Fig 1 B, C, 2 C, and 3 B). Slides for cytopathology were prepared from the aspirated material, microbiology was sent as clinically indicated, and cell blocks were prepared as needed. Rapid onsite evaluation (ROSE) was done in all the cases. The average procedure time varied from 15 - 20 minutes. The patients remained hemodynamically stable, with no significant desaturation during or after the procedure. The patients were observed as per standard recovery protocols, and except for case 2 who was admitted earlier, the procedures were done on a day care basis. All the patients were followed for a period of 4 weeks, for any procedure related complications.

RESULTS

EUS-B-FNA was done successfully without any complications in all the patients. The material was classified as 'adequate' when the aspirate showed lymphocytes, 'diagnostic' when the needle aspirate yielded a specific diagnosis, and 'inadequate' when the needle aspirate was neither diagnostic nor showing lymphocytes. The diagnostic yield was 100% in all the cases (Table 2). Of the three cases, case 1 and 3 had necrotizing granulomatous lesions on ROSE (Fig 1 D, 3 C), with staining for acid fast bacilli (AFB) positive, establishing a diagnosis of lymphnode tuberculosis. Xpert MTB/RIF test done on the aspirate flush was positive for Mycobacterium tuberculosis in both cases, with no rifampicin resistance, thus making an additional diagnosis of drug-sensitive tuberculosis.

Transient hypoxemia was noted in case 2, who had pre-existing hypoxemia, which was managed by supplemental oxygen. (Table 3)

Table 3 Complications

Patient Complications	Patient 1	Patient 2	Patient 3
Transient hypoxemia	No	Yes	No
Difficulty or pain during feeding	No	No	No
Chest pain	No	No	No
Fever	No	No	No

DISCUSSION

This case series illustrates the role of EUS-B -FNA in the pediatric population, as a feasible, safe and successful minimally invasive procedure. EUS-B-FNA in the adult population has been used as a diagnostic modality not only in staging and molecular diagnosis of lung cancer, but also for the diagnosis of other conditions such as TB, sarcoidosis and lymphoma[5, 6, 7, 8].

The application of EBUS for pediatric MLN sampling was a landmark advance, but came with some limitations. The use of the current adult EBUS scope (Olympus BF-UC180F convex probe, 6.9 mm outer diameter) for performing EBUS-TBNA in children was first reported by Wuzrel *et al* in 2009 in a 13-year old adolescent diagnosed as sarcoidosis[9].

Table 1 Details of EUS-B-FNA Procedure in the Diagnosis of Mediastinal Lymphadenopathy

Patient	Age (Months)	Sex	Position for Eus-B-Fna	Number of Mln Accessed	Size of the Node Station (mm)	Number of Pass per node	Sedation	Duration of Procedure in Minutes
1	84	F	Supine	1	7 – 14.7	3	Conscious sedation	15
2	20	F	Supine	2	4L -17.1 7 - 11.9	3	Conscious sedation	20
3	72	F	Supine	2	4L -16.5 7 - 11.6	3	Conscious sedation	15

Table 2 Diagnostic yield

Patient	Rose	TBNA AFB Smear	TBNA AFB Culture	Gene Expert/ Rifampicin Resistance	Immunohistochemisrty
1	NGL	Positive		Positive for MTB/Negative	Not done
2	Small round cell tumour	Negative	Negative	Negative	Diffuse large B cell lymphoma, cells strongly positive for CD45 and CD20, Ki67 proliferation index of 70%
3	NGL	Positive		Positive for MTB/Negative	Not done

ROSE –Rapid onsite examination, TBNA –Trans bronchial needle aspiration, AFB – Acid fast bacilli, NGL – Necrotizing granulomatous lesion, MTB – Mycobacterium tuberculosis

The cytopathology in case 2 showed a small round cell tumor suggestive of lymphoma, or metastatic neuroblastoma (Fig 2 D). Immunohistochemistry done using the cell block confirmed diffuse large B cell lymphoma (DLBCL), CD45 and CD20 positive, and a Ki67 proliferation index of 70%. No significant complications were encountered during or after the procedure.

Gilbert *et al*' then described performance characteristics of EBUS-TBNA in 21 children (age 13.7 ± 4.1 years). Of the 21 children, only one was aged < 7 years (1.5 years), which required GA to accommodate the EBUS scope. It became clear that EBUS in the younger age group came with considerable challenges, which laid the foundation for EUS-B-FNA in this population.

Table 4 Studies Describing the Use of Endoscopic Ultrasound (EUS)/ Esophageal ultrasound-bronchoscopic fine needle aspiration (EUS-B-FNA) for Diagnosis of Mediastinal Lymphadenopathy in the Pediatric Population

Author (year)	Publication type	Number of patients	Age Range (years)	Diagnostic yield	Diagnoses
Attila et al. (2009)a,13	Retrospective study	5	7–15	1/5	Lymphoma
Madan et al. (2015)8	Case report	1	3	1/1	Tuberculosis
Dhooria et al (2016)b, 4	Retrospective study	13	< 12 years – 11 13-17 years - 2	6/13	Not specified
Mehta R et al (2017)7	Case report	1	1.8	1/1	Lymphoma

All studies employed the adult EBUS scope except the study marked by alphabet "a" which is a EUS-based study. "b - 1/13 case underwent both EBUS and EUS-B-FNA for diagnosis.

What are the difficulties with EBUS in smaller children?EBUS/TBNA cannot be used in all ages due to the following limitations:

a) Below a certain age (approximately < 6 to 8 years), the size and position of the larynx and the cricoid size are incongruous with the size of the currently available EBUS scopes[12, 13].
The adult EBUS scope has an insertion tube diameter of 6.9 mm, which restricts its use in very small children, typically less than the age of < 6-8 years[12, 13, 14].

b) Certain technical issues also arise. In small children, when done under GA, the EBUS scope is preferably passed through an artificial airway such as a laryngeal mask airway or endotracheal tube. The minimum required size of the conduit required to pass the EBUS scope are either the LMA 2.0 (I Gel LMA) or the endotracheal tube of 8.5 mm (internal diameter), both of which are not useful in smaller children (<6 to 8 years).

c) Technically, if the EBUS scope can be passed through the vocal cords across the fixed cricoid cartilage into the trachea in smaller children, it occupies a major part of the cross-sectional area of the trachea[10, 11]. The resulting inability to ventilate can rapidly lead to hypoxemia and hypercarbia, making the procedure both unsafe and compromising yield. This can be a major issue, when there is associated events such as secretion build up, oozing of blood, and when multiple passes in multiple stations need to be done. This restricts the use of the EBUS scope in small children, such as the age group described in this case series.

EUS-B-FNA emerged as an effective alternative due to these technical issues with using the large EBUS scope in small children. Table 4 describes articles/case reports describing EUS-B-FNA as a diagnostic modality in the pediatric population. The advantages of EUS-B-FNA include ease of procedure, reduced requirement for general anesthesia, and diminished chances of hypoxemia and hypercarbia as the airway is not compromised. Stations such as the left paratracheal MLN (4L), which can occasionally be challenging with EBUS, can easily be accessed by EUS-B-FNA. All the patients in this case series underwent EUS-B-FNA which is gaining wider acceptance not only in adult pulmonology[1, 2, 5, 6] but also in pediatric practice.[7, 8]

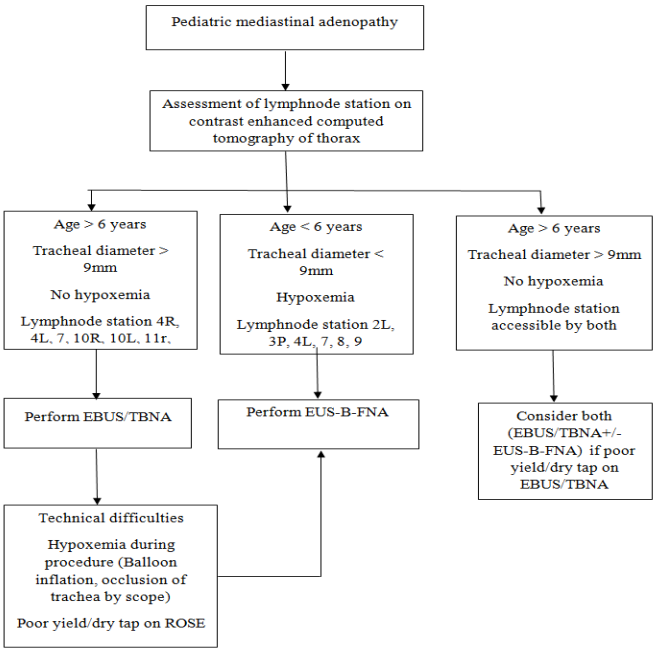

Figure 4 Proposed algorithm for guiding choice of EBUS-TBNA and EUS-B-FNA in children with mediastinal lymphadenopathy.

In terms of yield, adequate material was obtained by EUS-B-FNA in all the patients (3/3). Diagnostic material was obtained in all the cases to categorically make a diagnosis of either TB or lymphoma. The use of EUS-B-FNA in our case series obviated the need for more invasive testing such as a mediastinoscopy or surgical biopsy, thus leading to early expedited treatment. No major procedure related complications were reported in our case series, thus highlighting the safety of the procedure. Reviewing other literature, in the series by Gilbert[3] and Goussard, [10]there were no significant complications. Dhooria *et al*[4] in their series reported only minor complications with transient hypoxemia in one patient, similar to our series, which improved with supplemental oxygen.

Clinical infection or sepsis after EUS-FNA is infrequent. In the series by William *et al*[15] and Eloubeidi *et al* (672 adult patients) [16] who had EUS-FNA for a variety of lesions, sepsis was reported only in 3 patients. Dhooria *et al*[4] with 13 pediatric patients had no major or minor complications post - procedure. Thus, prophylactic antibiotics are not recommended before a EUS-FNA of solid lesions. For cystic-appearing lesions along the gastrointestinal tract, antibiotic prophylaxis for prevention of cyst infection is recommended.[18]

The limitations of EUS-B-FNA include lack of access to all MLN stations. It provides access to stations 2L, 3p, 4L, 7, 8, and 9, with anterior and hilar stations more accessible with EBUS-TBNA. In addition, the pulmonologist needs to be familiar with esophageal intubation, which is actually an advantage due to absence of the cough reflex. In EUS-B-FNA, there is no endo-image visualization, and scope insertion is done on clinical grounds. Ultrasound images guide the rest of the procedure, similar to transesophageal ultrasound done by cardiologists. EUS-B-FNA is not difficult to perform, and has a shallow learning curve.

In conclusion, our series re-iterates safety, feasibility and success of EUS-B-FNA with the currently available EBUS scope in pediatric patients with mediastinal lymphadenopathy, and reviews the current literature on the concept. The procedure has a good diagnostic yield and excellent safety profile, and can potentially circumvent invasive procedures such as mediastinoscopy/VATS. EUS-B-FNA extends the ability of the current EBUS scope to sample MLN in the younger age group safely and effectively. A suggested decision tree for the use of EBUS-TBNA vs EUS-B-FNA in pediatric MLN sampling is outlined in Figure 4. Further studies are required to more precisely define the role of this entity in pediatric MLN sampling.

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