Safety and diagnostic yield of endobronchial ultrasound-guided lymph node biopsy in children and adolescents with suspected tuberculosis

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February 6, 2021

Abstract

Referring to a literature review published recently in this Journal, we report a single-center case series of 45 children and adolescents (age 2-17 years) with suspected tuberculosis (TB) and negative microscopy on repeated sputum or gastric aspirate samples. All subjects underwent flexible airway endoscopy including bronchoalveolar lavage (BAL) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) without adverse events. Among 41 subjects with a final TB diagnosis, Mycobacterium tuberculosis was detected by PCR and/or culture in 20 (49% bacteriological confirmation) with 11 cases relying exclusively on results from TBNA samples. Only 7 of 17 positive culture results related to sputum (17% confirmation rate), and 9 of 17 on the combination of sputum and BAL (22%) respectively. The sampling site of a person's first positive culture was TBNA in 13 of 17 cases (76%). Bacteriological confirmation was essential for diagnostic accuracy and tailored treatment based on individual drug susceptibility testing. We therefore recommend the inclusion of bronchoscopy and EBUS-TBNA in a comprehensive diagnostic protocol for smear-negative pediatric TB suspects.

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Refers to: Review by Madan et al. in Jan. 2021 issue of *Pediatr Pulmonol* (ref. 2)

In part presented as free communication at the annual congress of the German-Swiss-Austrian Society for Pediatric Pulmonology (GPP e.V.) in March 2018

Sources of support: None

Word count: 991

ABSTRACT

Referring to a literature review published recently in this Journal, we report a single-center case series of 45 children and adolescents (age 2-17 years) with suspected tuberculosis (TB) and negative microscopy on repeated sputum or gastric aspirate samples. All subjects underwent flexible airway endoscopy including bronchoalveolar lavage (BAL) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) without adverse events. Among 41 subjects with a final TB diagnosis, *Mycobacterium tuberculosis* was detected by PCR and/or culture in 20 (49% bacteriological confirmation) with 11 cases relying exclusively on results from TBNA samples. Only 7 of 17 positive culture results related to sputum (17% confirmation rate), and 9 of 17 on the combination of sputum and BAL (22%) respectively. The sampling site of a person's first positive culture was TBNA in 13 of 17 cases (76%). Bacteriological confirmation was essential for diagnostic accuracy and tailored treatment based on individual drug susceptibility testing. We therefore recommend the inclusion of bronchoscopy and EBUS-TBNA in a comprehensive diagnostic protocol for smear-negative pediatric TB suspects.

To the editor:

Flexible airway endoscopy is not part of the recommended diagnostic routine for tuberculosis (TB) in children and adolescents. Most pediatric pulmonologists will only perform it on an individual case basis either for sampling bronchoalveolar lavage (BAL) from areas of localized infiltration or for resecting endobronchial granuloma in cases with atelectasis. This may contribute to the low bacteriological confirmation rate in pediatric cases, although mycobacterial detection remains a diagnostic standard for active TB and a prerequisite for drug susceptibility testing (DST). Specific challenges in children and adolescents include the notoriously low sensitivity and specificity of symptoms and radiological abnormalities, technical issues around sputum or gastric aspirate sampling and the lower pathogen density in children's respiratory samples. Furthermore, thoracic lymphadenopathy occurs frequently in pediatric TB with minor or no obvious pulmonary affection. As a targeted approach, transbronchial needle aspiration (TBNA) guided by endobronchial ultrasound (EBUS) has been addressed by an ERS statement on interventional bronchoscopy in children[1] and a recent literature review [2]summarizing smaller case series. We sought to evaluate the safety and diagnostic yield of a comprehensive endoscopic investigation including EBUS-TBNA in a prospective pediatric cohort.

Forty-five children and adolescents (mean age 12 years; range 2-17) with suspected TB were investigated at our regional center between 2014 and 2020. Sputum was collected from 37 subjects, in part after nebulized hypertonic saline, and gastric aspirate from eight younger children. Bronchoscopy was considered when repeated samples were microscopically negative for acid-fast bacilli. The study group consisted of 8 preschoolers (2-5 years), 10 schoolchildren (6-11 years) and 27 adolescents (12-17 years); 36 were foreign-born with a wide range of Eastern European, African or Asian nationalities. Diagnostic work-up had been triggered by suspicious symptoms in nine patients, by health screening of asylum seekers in 20 patients and by active case finding after exposure to infectious TB in 16 patients. DST results were available for 16 of 19 contact persons, with multiple or extensive resistance in five index cases.

After appropriate risk assessment and consent/ assent, all subjects underwent flexible bronchoscopy through the largest possible laryngeal mask airway under general anesthesia. Following inspection and bronchoalveolar lavage, EBUS (EXERA II BF-UC180F, Olympus, Hamburg, Germany) served to visualize thoracic lymph node stations with sampling of nodes >10 mm by repeated TBNA (ViziShot 22G, Olympus). Tissue specimens were minced and suspended in phosphate buffer for both fluorescence microscopy using auramine-O stain and for molecular diagnostics of *Mycobacterium tuberculosis* DNA and resistance-conferring mutations in the *rpoB* , *inhA* ,*katG* , *embB* and *gyrA* genes. Mycobacterial cultures in liquid (Mycobacterial growth indicator tubes, Becton Dickison, Sparks MD, USA) and solid media (Loewenstein-Jensen and Stonebrink plates) were incubated at 30/ 37 degrees for 8 weeks.

In line with previous reports [2-5] and contrary to most pediatricians' intuition, investigation with a flexible EBUS-scope of 6.9 mm outer diameter including a convex-array ultrasound transducer and needle aspiration under assisted ventilation was universally feasible and well tolerated by all our patients, even toddlers of 12 kg body weight. During endoscopy and 24-hour follow-up monitoring, no patient experienced complications such as dyspnea, fever, hypoxemia, bleeding, sustained coughing, pain, pneumothorax or feeding difficulties.

After reviewing all diagnostic findings, an alternative diagnosis was established in four subjects (one each with post-infectious lobar bronchiectasis, chronic suppurative bronchitis with segmental atelectasis, mucoid impaction with retention pneumonia and cryptogenic organizing pneumonia). The remaining 41 patients were started on antituberculous combination treatment according to guidelines and DST results from an index case where available.

Microscopic evaluation was negative in all additional respiratory specimens but BAL and TBNA from one patient in this smear-negative cohort. After a median of 15 days, cultures from 17 subjects grew *Mycobacterium tuberculosis* . In three additional cases, TB was confirmed by positive PCR testing (two sputum samples, one BAL and one TBNA). Thus, total bacteriological confirmation rate amounted to 20 of 41 patients (49%). Only seven of these cases would have been diagnosed based on sputum samples alone (confirmation rate 17%), all gastric aspirates were culture-negative. BAL cultures were positive in four cases, two had positive sputum cultures as well (combined confirmation rate 9 of 41 = 22%). Processing of TBNA samples yielded 14 positive cultures and four positive PCR results. In 11 of 20 cases with bacteriological confirmation (55%), mycobacterial infection was exclusively secured by lymph node biopsy. The sampling site of an individual's first positive culture was TBNA in 13 of 17 cases (76%), sputum in three (18%) and BAL in one (6%). The detailed patterns of samples and test results are specified in table 1 .

All isolates were fully susceptible using phenotypic and molecular methods. Medication could be changed to oral first-line drugs in the case of a 6-year-old Chechnian girl upon growth of a sensitive strain from the TBNA-based culture after 14 days. After previous treatment for pulmonary disease in her home country, she had been diagnosed with paratracheal lymph node TB and empirically started on a second-line regimen including intravenous amikacin.

EBUS-guided TBNA is an established diagnostic tool in adults, but still infrequently applied in pediatric respiratory medicine due to the requirement of a large-diameter bronchoscope. Our single-center experience in 45 consecutive subjects, the largest case series reported to date, expands current evidence on the procedure's efficacy and safety as recently reviewed by Madan et al.[2] Our use of EBUS and lymph node biopsy almost tripled the bacteriological confirmation rate in comparison to sputum- or gastric aspirate-based testing alone. Bronchoscopic BAL only increased the confirmation rate by a factor of 1.3 relative to standard testing, and additional TBNA resulted in a further doubling of the diagnostic yield. More than half of our cases were only confirmed by results from the TBNA sample, and the first positive culture was based on TBNA in 76% of cases.

These findings were important for establishing a timely and definite diagnosis, excluding drug-resistant TB and guiding long-term management. We therefore recommend the inclusion of bronchoscopy and EBUS-TBNA into a comprehensive diagnostic protocol for smear-negative pediatric patients with suspected TB.

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`EBUS-TBNA Ped Pulmonol - Table 1.pdf` available at https://authorea.com/users/394046/articles/507524-safety-and-diagnostic-yield-of-endobronchial-ultrasound-guided-lymph-node-biopsy-in-children-and-adolescents-with-suspected-tuberculosis