Starry sky sign: A prevalent sonographic finding in mediastinal tuberculous lymph nodes

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ABSTRACT
Background and Objectives: We report a prevalent finding in tuberculous lymphadenitis (TL): Starry sky sign, hyperechoic foci without acoustic shadows over a hypoechoic background. Materials and Methods: We retrospectively searched the database for a possible relationship of starry sky sign with a specific diagnosis and also the prevalence and accuracy of the finding. Results: Starry sky sign was found in 16 of 31 tuberculous lymph nodes, while none of other lymph nodes (1,015 lymph nodes) exhibited this finding; giving a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 51.6%, 100%, 100%, 98.5%, and 98.5%, respectively. Conclusion: Bacteriologic and histologic findings are gold standard in the diagnosis of tuberculosis, but this finding may guide the bronchoscopist in choosing the more pathologic node within a station and increase the diagnostic yield as it may relate to actively dividing mycobacteria.

Key words: Endobronchial ultrasound, mediastinum, tuberculosis

INTRODUCTION
Mediastinal lymph nodes are frequently involved in a number of diseases. Of these diseases, tuberculosis is one of the prevalent diseases in our country, despite aggressive control programs. In our institution, we perform endobronchial ultrasound (EBUS) in patients with mediastinal lymph node enlargement. During the procedures, we noticed an interesting finding in very limited number of the lymph nodes: Multiple hyperechoic foci without an acoustic shadow over a hypoechoic background which will be called as “starry sky sign” [Figure 1]. Thus, we searched the entire database in order to find out the relationship of the sign with a specific diagnosis and also, the prevalence and the relevance of the finding.

MATERIALS AND METHODS
We performed a retrospective analysis of patients who underwent EBUS for the diagnosis of mediastinal lymph nodes detected on computed tomography and specifically the patients who have diagnosed as tuberculous lymphadenitis (TL) with radiological, bacteriological, cytological, or surgical work up. The study was done at a single institution between May 2010 and October 2011. Technical procedures and materials were given elsewhere.[1] All images and available video files were retrospectively reviewed by three authors (IOA, NYD, and AY) who came to a consensus, and they were blinded to the results of EBUS-transbronchial needle aspirations (EBUS-TBNA). This analysis was approved by the Ethical Committee.
RESULTS

In total, we performed EBUS-TBNA in 451 patients with various indications and of which, 13 patients were TL, giving a prevalence of 2.8% in this selected population. A total of 31 lymph nodes were evaluated in the cases with TL (2.38 lymph nodes per patient). The mean age was 41 ± 19 years. Fifty-three percent of the patients (7/13) were male. The mean short axis length of the nodes was 17.92 ± 7.42 mm. On average, we did 3.1 aspirations per lymph node to prepare smears and cell blocks. The mean time of the procedures was 18.3 ± 6.1 min. The presence of the starry sky sign was evaluated in 1,015 lymph nodes of various etiologies other than TL. Of which, 195 lymph nodes were affected by sarcoidosis, 313 lymph nodes with malignancy, and 507 lymph nodes with other etiologies like normal lymph nodes, anthracosis, lymphoma, etc.

Figure 1. Some examples of sonographic appearances of tuberculous lymph nodes. Note the “starry sky sign”, hyperechoic foci without acoustic shadowing over a hypoechoic background in the lymph nodes

Starry sky sign was found in 16 of 31 (51.6%) tuberculous lymph nodes (those 16 lymph nodes were sampled from 7/13 patients with TL), while none of the remaining 1,015 nodes exhibited this finding. Thus, we reached a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 51.6%, 100%, 100%, 98.5%, and 98.5% for tuberculosis, respectively.

DISCUSSION

Not surprisingly, with its capabilities, EBUS can play a role in the diagnosis of intrathoracic lymphadenopathy. Apart from malignancies, granulomatous diseases are one of the main indications for EBUS. There are many reliable data about the diagnostic yield of EBUS in tuberculosis. Navani et al., studied the utility of EBUS-TBNA in patients with tuberculous intrathoracic lymphadenopathies and found that EBUS-TBNA was diagnostic of TB in 146 of 156 patients (94%, 95% confidence interval (CI) 88-97%).[2] In another retrospective analysis, Hassan et al., reported the accuracy, sensitivity, specificity, PPV, and NPV of EBUS-TBNA in 19 patients with intrathoracic isolated lymphadenopathy related to tuberculosis (in 24 patients suspected of tuberculosis) as 79%, 95%, 100%, 100%, and 80%, respectively.[3]

The value of ultrasound in tuberculous lymphadenopathy is commonly studied in cervical lymph nodes. Khanna et al., investigated the usefulness of sonography in differentiating cervical lymphadenopathy related to tuberculosis, lymphoma, and metastases.[4] They found that the ultrasonographic features of tuberculous lymph nodes were multiplicity, a fusion tendency of adjacent nodes, and a hypoechoic center with posterior enhancement. Additionally, they highlighted a common finding, strong internal echoes, which resembled calcification, in 52 of 62 patients (84%). Gupta et al., reported the value of imaging modalities (USG and CT) in 27 patients with tuberculous cervical lymphadenopathy. Sonography revealed hypoechoic (100%) and necrotic (100%) lymph nodes and other features, including sharp margins (70.4%), hilum (22.2%), abnormal surrounding tissue (85.2%), matting (37%), calcification (29.6%) and posterior enhancement (22.2%).[5] Haber et al., investigated sonographic findings in children with cervical lymph nodes related to atypical mycobacteria. In this study, the authors stated that sonography revealed ovoid lymph nodes with distinct margins.
showing strong echoes in four of 12 patients (33%). There have also been studies on abdominal tuberculosis. In one study on imaging features, Pereira et al., stated that lymph nodes form discrete or matted conglomerated masses, showing central hypoechoic areas. In another study, Malik and Saxena reported that of 37 patients with TL, most were hypoechoic, five (13.5%) had a hypoechoic central region and peripherally located echogenic regions, and two (5%) showed calcification.

With the introduction of old imaging modalities into new areas, researchers continue to provide reasonable answers to many questions. We used to know the appearance of tuberculous lymph nodes on CT images, with low resolution and little information. In a recent study from Germany, Fritscher-Ravens et al., investigated the utility of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in differentiating tuberculosis from sarcoidosis. They enrolled 72 patients with mediastinal lymphadenopathy; including 30 cases of sarcoidosis and 28 cases of tuberculosis (other cases included malignancy, abscess, and benign lymph nodes). They found that tuberculous lymph nodes were smaller than sarcoid nodes. Tuberculosis-related nodes were isoechoic to moderately hypoechoic and nonhomogeneous, and some showed hyperechoic areas without acoustic shadowing (nine of 28 patients, 32.1%). Seven of them (25.0%) exhibited acoustic shadows representing inactive calcified foci. The most recent study have been reported by Dhooria et al. They analyzed 165 patients (118 sarcoidosis and 47 tuberculosis) and 358 lymph node stations (270 sarcoidosis and 88 tuberculosis). Shape, margin, and presence of central hilar structure did not differ between groups; but in contrast, tuberculous lymph nodes were significantly more heterogeneous and exhibited coagulation necrosis sign. In multivariate analysis, heterogeneous echotexture and positive tuberculin skin test were the only independent predictors for the diagnosis of tuberculosis.

Finally, in a relevant study, Rana et al., reported a series of 42 patients with enlarged mediastinal lymphadenopathies, of whom 22 had tubercular lymph nodes. Hyperechoic foci in the lymph nodes were detected in 77.2% of the tubercular mediastinal lymphadenopathies and 5% of the patients with nontubercular lymphadenopathy (P = 0.00). In our series, a “starry sky sign”, which may represent granulomatus foci within the lymph nodes was detected in 51.6% of the patients with TL. This result was less than other studies, but there was confusion regarding acoustic shadows. We have only included images without shadows to differentiate them from calcification. Additionally, we highlight the high accuracy of this finding (none of the sarcoind, malignant, or normal lymph nodes showed this finding). Seven patients showed the finding and six of them were culture positive for Mycobacterium tuberculosis. So this may show the correlation of the finding with high bacillus load within the node.

Main strength of this paper is giving a very prevalent and relatively specific finding, starry sky sign, in tuberculous lymph nodes. This is, in particular, a very important finding as it does not present in any other diseases (like malignancy) in the study population, but remains suspicious until will be correlated in the future studies. There are certain limitations in the study. First, it is a retrospective analysis. Secondly, same investigators have performed the procedures and later, visual evaluations. Many other studies were conducted in the same manner, but actually this is not a great weakness as the data were evaluated blinded to the diagnoses.

Some other studies have reported the sonographic features as a diagnostic tool, but we still believe that these features may only guide the bronchoscopist in choosing more pathologic node in a particular station as they are usually exhibited in malignant disease. Microbiological and histological findings are the gold standard for the diagnosis of tuberculosis. This finding, of course, does not offer any diagnostic value, but may give additional information for choosing an affected lymph node. Choosing the more pathologic node within the same station may spare time and increase diagnostic yield. The starry sky sign should be investigated in other databases including various diseases and the true prevalence should be documented.

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