Sarcoidosis – moving to the new standard of diagnosis?

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Summary. In this article, the most recent literature data regarding the diagnosis of sarcoidosis have been reviewed. The diagnosis of sarcoidosis can be reliably established when there is a compatible clinical/radiological picture together with pathologic evidence of noncaseating epithelioid cell granulomas. Pathologic specimens can be obtained by conventional bronchoscopy with endobronchial, transbronchial lung biopsy, bronchoalveolar lavage, and recently introduced endoscopic ultrasound techniques (endoscopic ultrasound-guided fine-needle aspiration, EUS-FNA, and endobronchial ultrasound-guided transbronchial needle aspiration, EBUS-TBNA) or surgical procedures such as thoracotomy, thoracoscopy, and mediastinoscopy. The place and value of EBUS-TBNA or EUS-FNA in diagnosis of sarcoidosis are discussed.

Sarcoidosis is a systemic granulomatous disease of unknown etiology (1). Now the diagnosis of sarcoidosis is established when there is a compatible clinical/radiological picture together with pathologic evidence of noncaseating epithelioid cell granulomas. In case of suspected sarcoidosis, biopsy specimen should be obtained to confirm the diagnosis and to exclude the malignant disease, tuberculosis, and histoplasma infection. The only clinical situation when diagnosis of sarcoidosis can be confirmed reliably without biopsy is Löfgren syndrome. Otherwise biopsy should be done.

It is clear that biopsy specimen should be obtained from the most easily accessed place. Although the lung is most commonly involved, there is no single diagnostic test. Thoracic lymphadenopathy can be seen in up to 85% of cases (2). Bronchoscopy with transbronchial lung biopsy, conventional transbronchial needle aspiration, and endobronchial biopsy, bronchoalveolar lavage (BAL) are used (3–5). BAL alone is not an adequate and accurate method for diagnosis of sarcoidosis. The diagnostic yield is only 47% (6). Flexible bronchoscopy with transbronchial lung biopsy is the initial procedure of choice. The procedure is cheap and can be safely performed on an outpatient basis. The diagnostic yield is about 65% (40–90%) reported in case series (7). That means that one-third of bronchoscopies remains nondiagnostic. Currently, cervical mediastinoscopy is advised as the next step, when increased mediastinal or hilar lymph nodes are detected. However, mediastinoscopy is a highly invasive, costly procedure, which requires general anesthesia, and causes complications in 2–3% of cases (8). However, this is still a gold standard for establishing a morphological diagnosis. There is a room for the new diagnostic technique to increase the diagnostic yield in sarcoidosis and to avoid surgical procedure.

Development of linear echoendoscopes and subsequent procedures (endoscopic ultrasound-guided fine-needle aspiration, EUS-FNA, and endobronchial ultrasound-guided transbronchial needle aspiration, EBUS-TBNA) opened a new diagnostic possibility for sarcoidosis. Both procedures are safe diagnostic techniques and allow real-time echoscopic node investigation and sampling. EBUS-TBNA enables reaching multiple lymph node stations including paratracheal (stations 2, 4), subcarinal (station 7), and hilar nodes (stations 10 and 11). EUS-FNA is a good tool for investigating and reaching the left and lower mediastinal and paraesophageal (4L, 5, 7, 8, 9) stations (9). “Blind” TBNA was performed only by 27% of chest physicians (10) due to the lack of real-time monitoring of the needle movement (11).

Since 2002, EUS-FNA and EBUS-TBNA have spread throughout the interventional pulmonology centers of the world. There is only one endoscopic ultrasound center where EBUS-TBNA and EUS-FNA procedures are performed in Lithuania (Hospital of Kaunas University of Medicine). Fig. 1 shows a chest CT scan (lung and mediastinal windows) of 26-year-old woman with sarcoidosis. Fig. 2 depicts EBUS-guided lymph node aspirate (right paratracheal station) with Giemsa staining that shows an epithelioid cell granuloma. The procedure was performed with a curvilinear scanning ultrasound bronchoscope (Olympus, BR UC160F OL8) connected to an ultrasound unit (ALOKA α5-10).
EBUS-TBNA in diagnosis of sarcoidosis was prospectively evaluated in five clinical studies. Wong et al. (12) included 65 patients with clinical and radiological findings suggestive of sarcoidosis and enlargement of lymph and/or mediastinal nodes more than 1 cm. In 56 cases, the final diagnosis of sarcoidosis was confirmed by positive cytological results, and mediastinoscopy was done in 5 cases. Thoracoscopy was done in one case. Three patients were followed up clinically. EBUS-TBNA was diagnostic for sarcoidosis in 91.8% of cases. The negative predictive value in this study was 11%. Garwood et al. (6) included 50 patients with suspected sarcoidosis. Forty-five patients had radiological and clinical signs suggesting sarcoidosis. EBUS-TBNA demonstrated noncaseating granulomas in 41 (85%) of 48 patients with final diagnosis of pulmonary sarcoidosis. Patients with a negative EBUS-TBNA results underwent further histologic biopsy or were followed up clinically. According to this study, EBUS-TBNA had a sensitivity of 85% and negative predictive value of 12.5%. Oki et al. (13) investigated 15 patients with clinical and radiological findings suggestive of sarcoidosis and enlargement of lymph or mediastinal nodes (>1 cm). TBNA was performed in all cases. Diagnostic performance of EBUS-TBNA and TBNA was 93.3% and 94%, respectively. What was really important, there were no major complications reported in all these studies.

Tournoy et al. (14) have recently published the results of large diagnostic algorithm implementation trial for sarcoidosis. A total of 137 patients were included. Bronchoscopy was done for 121 patients with establishing the definite diagnosis of sarcoidosis in 57 cases (42%). In 72 cases, EUS-FNA/EBUS-TBNA was performed, yielding a definite diagnosis in 47 (59%). The sensitivity of endoscopic ultrasound after negative bronchoscopy was 71%. Endoscopic ultrasound prevented a surgical procedure in 47 of the 80 patients. The trial clearly indicates the place for endoscopic ultrasound in the algorithm of sarcoidosis diagnosis.

EBUS-TBNA was used for diagnosis of sarcoidosis and had a yield of 82% and sensitivity of 89–94% by assessing noncaseating granulomas in mediastinal nodes. Anema et al. (15) included 51 patients with suspected stage I and II sarcoidosis. Less than three-fourths (71%) of these patients underwent nondiagnostic bronchoscopy.

Additionally recently 50 patients with hilar and/or mediastinal adenopathy and a clinical suspicion of sarcoidosis were included into the clinical study where 24 patients were randomized to undergo EBUS-guided TBNA and 26 to undergo TBNA using a standard 19-gauge needle (16). The primary outcome measure of diagnostic yield was 53.8% vs. 84.3% in favor of the EBUS-guided TBNA group, an absolute increase of 29.5%. After blinded research pathology review, diagnostic yield was 73.1% vs. 95.8%, in favor of the EBUS-guided TBNA group, an absolute increase of 22.7%. Sensitivity and specificity were 60.9% and 100%, respectively, in the standard TBNA group, and 83.3% and 100%, respectively, in the EBUS-guided TBNA group (absolute increase in sensitivity, 22.5%). The diagnostic yield of EBUS-guided TBNA is superior to TBNA.
using a standard 19-gauge needle for sampling of mediastinal lymph nodes in patients with a clinical suspicion of sarcoidosis.

It can be seen from the published studies that all investigators used EBUS-TBNA and EUS-FNA after conventional diagnostic methods and finally the gold standard – surgical procedure – to check negative (noninformative) cases. Most authors hypothesized that EBUS-TBNA and EUS-FNA can prevent surgical diagnostic procedures and especially mediastinoscopy.

During diagnosis of sarcoidosis, clinicians do not want such surgical reference tests as thoracotomy, thoracoscopy, mediastinoscopy, or even clinical follow-up. Nevertheless, diagnosis should be established definitively especially in cases when the treatment with steroids is planned. Now it is clear that EBUS-TBNA and EUS-FNA have their place in diagnosis of sarcoidosis, but where? The first option is that it could be used after conventional bronchoscopy with endobronchial and transbronchial lung biopsy with BAL after negative results. The second option – it could be used in experienced centers as an initial investigation tool when the diagnosis of sarcoidosis is most likely (in the absence of identifiable malignancy, lymphoma, tuberculosis, or fungal infection). However, no randomized clinical trials that compared conventional bronchoscopy (arm 1) with endoscopic ultrasound (arm 2) have been carried out to date. The same situation can be observed in patients with lung cancer where only few studies were done with head-to-head comparison (17, 18).

In March 2009, a large international randomized clinical study “Trial for the Diagnosis of Sarcoidosis (GRANULOMA)” was started (19). This study is currently recruiting the participants. This phase III study investigates two different diagnostic strategies for patients with suspected stage I/II pulmonary sarcoidosis. Primary outcome measures are to assess the role of endosonography (EBUS/EUS-FNA) in demonstrating noncaseating granulomas in comparison with conventional bronchoscopy (TBLB+EBB). Investigators are going to recruit 300 patients. We hope that the results of this clinical study will help us to answer the raised questions and let us change our diagnostic strategy in sarcoidosis.

Raktažodžiai: sarkoidozė, endoskopinis ultragarsas, EBUS, EUS.

Santrauka. Straipsnyje pateikia literatūros apžvalga apie naujausius sarkoidozės diagnostikos metodus. Sarkoidozės diagnozė nustatoma patikimai, kai nustatomi aikščios šios ligos klinikiniai ir radiologiniai požymiai bei turint morfologinį nenekrotizuojančių granuliomų patvirtinimą. Mėgins morfologiniam tyrimui gali būti paimamas atliekant bronchoskopiją su endobrončine, transbrončine plaučių audinio biopsija, bronchoalveoliniai lavažų (BAL) taikant naujus endoskopinių ultragarsinių tyrimo metodus (EUS ir EBUS) arba chirurginiu būdu (mediastinoskopija, torakotomija, torakoskopija). Straipsnyje aptarta, kaip turėtų būti taikomos EBUS ir EUS tyrimai.

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