Diagnostic Modalities in Sarcoidosis: BAL, EBUS, and PET

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ABSTRACT

Advances have been made in minimally invasive diagnostic procedures in sarcoidosis, including bronchoalveolar lavage (BAL), endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA), and positron emission tomography (PET). Several independent groups found almost identical predictive values of the CD4:CD8 ratio in BAL for the diagnosis of sarcoidosis. A CD4:CD8 ratio greater than 3.5 shows a high specificity of 93 to 96% for sarcoidosis, but the sensitivity is low (53 to 59%). EBUS-TBNA is a safe and useful tool for diagnosing sarcoidosis stage I and II with a sensitivity of 83 to 93% and a specificity of 100%. Novel imaging techniques have been explored, such as PET using L-[3-^{18}F] fluoro-α–methyltyrosine (^{18}F-F MT), which is more specific for malignancy than ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET. The combined modality of FMT-PET with FDG-PET could successfully discriminate sarcoidosis from malignancy. These recent developments including novel biopsy procedures and novel imaging techniques could be of value to diagnosing sarcoidosis.

KEYWORDS: Bronchoalveolar lavage (BAL), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), positron emission tomography (PET), sarcoidosis, diagnosis

Sarcoidosis is a multisystemic disease of unknown etiology characterized by the formation of noncaseating epithelioid cell granulomas. The diagnosis of sarcoidosis is based on the following: (1) a compatible clinical and/or radiological picture, (2) histological demonstration of noncaseating granulomas, and (3) exclusion of other diseases capable of producing a similar histological or clinical picture. Making an accurate diagnosis requires a multimodality approach that combines clinical, radiological, and bioptic evaluation.[1,2] Recently, there have been advances in minimally invasive diagnostic procedures, including bronchoalveolar lavage (BAL), endobronchial ultrasonograpy-guided transbronchial needle aspiration (EBUS-TBNA), and positron emission tomography (PET), which are reviewed in this article.

BRONCHOALVEOLAR LAVAGE

BAL has become increasingly popular as a low-risk investigational tool with wide application in the clinical assessment and research of interstitial lung diseases (ILDs).[3,4] It is safe, minimally invasive, and can provide useful information for the diagnosis of sarcoidosis. The characteristic findings in BAL for sarcoidosis are a normal or only mildly elevated total cell count with a

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predominance of lymphocytes, usually a normal percentage of eosinophils and neutrophils, and an absence of plasma cells and foamy alveolar macrophages.[5,6] An increase in lymphocytes can be found in 90% of patients with sarcoidosis at the time of diagnosis, independent of the stage of sarcoidosis. Patients with active disease tend to have higher lymphocyte counts than those with inactive sarcoidosis but the range is wide, and BAL may be normal in 10 to 15% of patients. In late or advanced sarcoidosis, neutrophils may also be increased as well as the mast cells.[7] Some studies demonstrated that an increased neutrophil count in BAL obtained from newly diagnosed patients with sarcoidosis may indicate unfavorable prognosis.[8,9] Patients with primary extrathoracic sarcoidosis may show a typical finding of sarcoidosis on BAL even when imaging studies are normal.[10]

BAL lymphocytosis is not specific for sarcoidosis because it is seen in many other disorders, including hypersensitivity pneumonitis, nonspecific interstitial pneumonitis (NSIP), or organizing pneumonia. When interpreting the BAL cell differentials in regard to the differentiation of sarcoidosis versus other disorders, a combination of several features is important, not just a single parameter. The aforementioned other disorders with a BAL lymphocytosis usually show, in contrast to sarcoidosis, an additional increase in neutrophils, eosinophils, and mast cells. Therefore, a computer program for BAL data was established by Drent et al.[11,12] This program allows differentiating between three major ILDs using a discriminate analysis of logistic regression, with excellent accuracy.

The importance of the CD4:CD8 ratio has been debated because of the high variability in sarcoidosis.[13] Only ~55% of patients show an increased CD4:CD8 ratio at the time of diagnosis. The ratio is even decreased to below 1.0 in 15% of individuals with sarcoidosis. Nevertheless, several independent groups found almost identical predictive values of the CD4:CD8 ratio for diagnosing sarcoidosis (Table 1). A CD4:CD8 ratio greater than 3.5 shows a high specificity of 93 to 96% for sarcoidosis, although the sensitivity is low, with a value of 53 to 59%.[14–17] The specificity of the ratio was higher than the specificity of transbronchial biopsy in one of these studies.[14] The CD4:CD8 ratio is especially high in patients with Löfgren syndrome and acute sarcoidosis. In inactive disease, the ratio is usually in the normal range. These studies reached similar conclusions: in patients with a clinical/radiological picture typical of sarcoidosis, an elevated CD4:CD8 ratio in BAL may confirm the diagnosis and obviate the need for confirmation by additional biopsy.

Heron et al evaluated the contribution of the integrin CD103, expressed on $CD4^+$ T-lymphocytes in the BAL fluid to diagnose sarcoidosis in a cohort of 56 patients with sarcoidosis.[18] The combined use of the $CD103^+CD4^+$:$CD4^+$ ratio (<0.2) with either the BAL $CD4^+$:$CD8^+$ ratio (>3) or the relative BAL/peripheral blood $CD4^+$:$CD8^+$ ratio (>2) could discriminate sarcoidosis from other ILDs with a sensitivity of 66% and a specificity of 89%.

Welker et al aimed to quantify how the likelihood for a given diagnosis changes with the knowledge of the BAL cell differentials and the CD4:CD8 ratio.[19] They found that, when lymphocytes were combined with the ratio, the probability of sarcoidosis was doubled if the ratio was high. They were able to demonstrate an added informative value of the CD4:CD8 ratio, especially in sarcoidosis and hypersensitivity pneumonitis (HP).

However, also in HP, the assessment of the CD4:CD8 ratio in BAL has given contradictory findings. It is a general belief that in HP the CD4:CD8 ratio is decreased. More recent studies, however, found that the ratio may be decreased, normal, or increased.[20,21] The ratio is usually higher in chronic than in acute or subacute HP.[20] Therefore, a high CD4:CD8 ratio does not rule out the diagnosis of HP. The complete profile of the BAL cell differential has to be considered, including morphological features such as the heterogeneity of alveolar macrophages, the presence of activated lymphocytes, plasma cells, and a mild granulocytosis as features strongly favoring HP over sarcoidosis. This is very similar to the histopathologic assessment where nonnecrotizing granulomas are seen in both diseases,

Table 1 Predictive Value of CD4:CD8 Ratio in Bronchoalveolar Lavage for the Diagnosis of Sarcoidosis

Study	CD4:CD8 Ratio	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Costabel et al 1988[14]	>3.5	53	93	75	85
	>5.0	47	98	89	84
Winterbauer et al 1993[15]	>3.0	67	89	86	74
	>4.0	59	96	94	71
Thomeer, Demedts 1997[16]	>3.0	64	89	73	84
	>4.0	55	94	82	82
Korosec et al 2010[17]	>3.3	70	88	na	na

na, not available.

whereas additional morphological features are different and discriminate the granulomatous inflammation of sarcoidosis from HP in most cases.

Another caveat is BAL in the elderly. The BAL CD4:CD8 ratio increases with age,[22] and elevated BAL CD4:CD8 ratios are not unusual in patients with idiopathic pulmonary fibrosis (IPF), which is a characteristic "geriatric" lung disease.

ENDOBRONCHIAL ULTRASONOGRAPHY

Transbronchial lung biopsy (TBLB) has a long-standing tradition as one of the preferred diagnostic methods for pulmonary sarcoidosis,[1] with a diagnostic yield of ~70% (range 40 to 90).[23,24] Potential complications of pneumothorax and bleeding must be considered.[25,26] Conventional transbronchial needle aspiration (TBNA) is also a useful diagnostic procedure for pulmonary sarcoidosis, with diagnostic yields similar to TBLB.[27,28]

The recent development of linear echoendoscopes has opened new diagnostic possibilities for pulmonary sarcoidosis. Transesophageal ultrasound-guided fine-needle aspiration (EUS-FNA) and bronchoscopic EBUS-TBNA are both safe, minimally invasive, and give real-time information for aspirations.[29] Recent studies using transesophageal EUS-FNA in patients with suspected pulmonary sarcoidosis cited diagnostic yields of 82 to 86%,[30,31] with sensitivities of 89 to 100% and specificities of 94 to 96%.[32,33]

The diagnostic yield of real-time EBUS-TBNA has been reported to be 83 to 93%,[25,26,34–37] with a specificity of 100% (Table 2). No complications with EBUS-TBNA were reported in these studies, which included only patients with suspected sarcoidosis and enlarged hilar or mediastinal lymph nodes on CT. The value of EBUS-TBNA in patients with normal-sized lymph nodes is unknown. Moreover, the prevalence of sarcoidosis was very high (92 to 98%) (see Table 2), limiting the power of the studies.

Garwood et al demonstrated that the yield of EBUS-TBNA exceeded 80% at five passes, with no further increase in yield after seven passes.[25] The yield was highest in stage I, followed by stage II, and lowest in stage III disease. Oki et al obtained the same performance with EBUS-TBNA and TBNA in a small cohort of 15 patients,[34] Tremblay et al performed a randomized, controlled trial of standard TBNA versus EBUS-TBNA involving 26 and 24 patients, respectively, and found that the diagnostic yield of EBUS-TBNA was superior by 30%.[35]

The major difference between EUS-FNA and EBUS-TBNA is the ability to access lymph nodes. It is frequently difficult for EUS-FNA to access the hilar nodes and nodes anterolateral to the trachea, which are more commonly involved in sarcoidosis.[26,34] Annema et al reported that the assessment of fibrotic lymph nodes in stage II sarcoidosis using EUS-FNA was difficult.[31]

A recent multicenter trial involving 15 centers showed an additional value of endoscopic ultrasound (EUS or EBUS) after a first negative bronchoscopic study (with endobronchial and transbronchial biopsies) in patients with suspected sarcoidosis.[38] The diagnostic yield of the EUS study was 71%. The problem with this trial is, however, that the diagnostic yield of the bronchoscopic study was only 45%, which is at the lower end of what has been reported before.

POSITRON EMISSION TOMOGRAPHY

^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) can be of value for evaluating systemic inflammatory activity[39] and is more sensitive than gallium scanning,[40–42] particularly in the detection of extrapulmonary involvement. Its sensitivity in detecting active sarcoidosis sites reaches 80 to 100%. Teirstein et al demonstrated in 137 patients with sarcoidosis that FDG-PET scans were of value in detecting occult diagnostic biopsy sites in patients with sarcoidosis.[43] Teirstein et al also demonstrated that a positive uptake in FDG-PET was found in two thirds of patients with radiographic stage II and III sarcoidosis, whereas negative uptake in FDG-PET was common in patients with radiographic stage 0, I, and IV sarcoidosis. These findings suggest that FDG-PET may be able to assess the reversible activity in patients with sarcoidosis. The limitation of FDG-PET is that a false-positive uptake in FDG-PET could be observed in patients with other granulomatous diseases, infections, and neoplasms.[43]

Table 2 Diagnostic Effectiveness of Endobronchial Ultrasonography-Guided Transbronchial Needle Aspiration in Sarcoidosis

Study	*N*	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Prevalence
Wong et al 2007[26]	65	92	100	88	44	98
Oki et al 2007[34]	15	93	100	100	50	93
Garwood et al 2007[25]	50	85	100	100	13	98
Tremblay et al 2009[35]	50	83	100	na	na	92
Nakajima et al 2009[36*]	38	91	100	100	50	92

*Retrospective study; all others prospective.
na, not available.

L-[3-^{18}F] fluoro-α–methyltyrosine (^{18}F-F MT), an amino-acid analog, is accumulated in tumor cells solely via an amino-acid transport system, suggesting its higher specificity for evaluating malignancy as compared with ^{18}F-FDG. Kaira et al demonstrated in 24 patients with sarcoidosis that the use of an FMT-PET in combination with an FDG-PET may be of value to distinguish sarcoidosis from malignancy.[44] In lung cancer, an increased uptake was seen on FDG-PET in 94% and on FMT-PET in 88% of patients, whereas sarcoidosis lesions were positive only on FDG-PET, and always negative on FMT-PET.

Ohira et al studied the sensitivity and specificity of FDG-PET and cardiac magnetic resonance imaging (MRI) [high signal intensity on T2-weighted imaging (T2WI) or delayed enhancement] for diagnosing cardiac involvement in 21 patients with sarcoidosis.[45] These authors demonstrated a sensitivity of 88% and a specificity of only 39% for FDG-PET, and of 75% and 77% for cardiac MRI, respectively. A positive correlation between positive findings on FDG-PET and elevated serum angiotensin-converting enzyme (ACE) levels was also demonstrated. Based on these results, cardiac MRI is preferred over FDG-PET as a noninvasive and nonradioactive method to diagnose cardiac involvement in sarcoidosis. There are anecdotal reports about the value of FDG-PET for diagnosing neurosarcoidosis[46–49] or ocular involvement.[50]

Keijsers et al demonstrated that changes in FDG-PET imaging during infliximab treatment in sarcoidosis patients correlated with signs of clinical improvement to a considerable extent, which supports the hypothesis that FDG uptake represents disease activity.[51] The same group showed that FDG-PET correlated with the BAL CD4:CD8 ratio and neutrophils, suggesting that FDG-PET represents this specific cell profile in BAL.[52]

CONCLUSION

The current diagnostic problem with sarcoidosis is the absence of a single confirmatory diagnostic test. Recent developments including novel biopsy procedures and novel imaging techniques could become promising tools to facilitate the diagnosis of sarcoidosis.

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