SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2010; 27; 5-6 © Mattioli 1885

Ultrasound endoscopy (EBUS, EUS) as a sophisticated tool for morphological confirmation of Sarcoidosis: do we need to find new answers for an old quest?

V. Poletti, Sara Tomassetti
Department of Diseases of the Thorax, Pulmonology Unit, Ospedale GB Morgagni, Forlì, Italy

The diagnosis of Sarcoidosis is mainly based on clinical and radiological findings but- up to day- in the clinical practice morphological confirmation is still obtained (1). Clinical aspects are, "per se", typical in a minority of cases (Lofgren syndrome is a well known example) but they become more specific if imaging findings, and especially lymph nodes enlargement, are taken into account. Lymphadenopathy is the most common intrathoracic manifestation of sarcoidosis and sarcoidosis itself is the most common interstitial lung disease associated to enlarged lymph nodes. Studies based on chest radiography have shown that they occur in 75-80% of patients at some point in their illness. Lymph node enlargement is usually seen in the right paratracheal, aortopulmonary window, hilar, and tracheobronchial regions). In one series of 150 patients with sarcoidosis and an abnormal chest radiograph, about 30% had bilateral hilar lymphadenopathy (BHL) alone, 30% had BHL with right paratracheal adenopathy, and 30% had BHL with bilateral paratracheal adenopathy (2). Diseases in which -usually bilateral- hilar and mediastinal lymphoadenopathy are one of the main imaging features are numerous: infection [tuberculosis especially in HIV-positive patients, fungi, brucellosis, tularemia, plaque, antrax, infectious mononucleosis, cat-scratch disease, viral or mycoplasma infection (mainly in children)], neoplasm (epithelial tumors, lymphoma, leukemia, mesothelioma, other rare tumors), occupational (silicosis, chronic berilliosis), Castleman disease, amyloidosis, drugs (phentoin), immune reconstitution syndrome, other rarities. However in West World Countries the pretest probability of the disease -having clinical data and radiographic findings as the only support- is very high and in many such cases a need for pathologic sample is not strictly required for clinical management and decision making. CT adds information regarding the parenchymal aspects (micronodules with periplymphatic distribution and involving mainly the upper lobes, the presence of the "galaxy sign") and the peculiar lymph nodes calcification. This investigative tool may increase the diagnostic confidence and help to spare the patient a biopsy. On the contrary, settings in which biopsy remains mandatory, even if imaging findings may suggest a diagnosis of sarcoidosis, are represented by patients presenting with lung infiltrates and/or enlarged hilar mediastinal PET positive lymph nodes with a neoplasm present in their clinical history or by HIV positive subjects. At last the balance between clinico-radiologic diagnosis and the need of confirmation by the finding of well-formed noncaseating granulomas in one or more affected organ systems or tissues, with appropriate additional studies to exclude other causes of granulomas depends on the side effects expected and the disconforts related to the invasive procedure adopted and the confidence with which Clinicians take their decision mainly on the basis of the clinic-radiologic information. The result is that in the clinical practice -up today- mininvasive procedures are still part of the diagnostic work-up of patients with suspected sarcoidosis. Flexible bronchoscopy provides a number of options to obtain diagnostic material from the pulmonary parenchyma, airways, or mediastinal lymph nodes (3). Transbronchial biopsy of the lung parenchyma is particularly useful, with a yield of 60 to 95%, depending on the radiographic stage of the disease and the number of biopsy specimens.

Even when pulmonary parenchymal involvement is not grossly visible on plain chest radiography (e.g., in radiographic stage 1 disease), transbronchial lung biopsy is positive in more than 60% of patients. Biopsy of the bronchial mucosa (endobronchial biopsy) may sometimes demonstrate noncaseating granulomas, particularly when mucosal nodularity is seen on visualization of the airways through the bronchoscope. Transbronchial needle aspiration (TBNA) performed through the bronchoscope can also aspirate diagnostic cellular material from enlarged mediastinal lymph nodes. Finally, bronchoalveolar lavage, which samples the inflammatory cell population within the lung, is not diagnostic for sarcoidosis but, actually in less then 50 per cent of cases, may characteristically show an increased proportion of lymphocytes, with the ratio of $CD4^+$ to $CD8^+$ cells typically being elevated to greater than 3.5 : 1. An interesting observation that became widely accepted after introduction into routine clinical practice of aspiration bioptic procedures (mainly transbronchial needle aspiration) was that non-necrotizing granulomas may be recognized easily also in cytological preps (smears, cell block preps) (4). The diagnosis of Lymphoma -a good competitor for the differential diagnosis- may be more controversial although the use of flow cytometry, molecular biology techniques and immunohistochemistry on cell block preps may provide enough information for a definitive diagnosis or robust data for a diagnosis of lymphoma without any further specification. TBNA can provide a morphological confirmation in patients with Sarcoidosis in less then 70% of patients with Stage I or Stage II disease, being subcarinal lymph nodes, right paratracheal space and the hilum the more accessible sites (5). This approach is guided by CT scan findings: lymph node puncture is performed only if enlarged lymph nodes are present; its diagnostic yield decreases significantly when the minor axis of the lymph node is less then 2 cm. The introduction of real time ultrasound guided biopsy/aspiration through esophagoscope (EUS) or bronchoscope (EBUS) has increased the diagnostic yield of this approach rendering surgical biopsy (mainly through mediastinoscopy) obsolete and definitively contraindicated to confirm a diagnosis of sarcoidosis. Recently, it was shown that EBUS-TBNA had a 30% higher yield to find nonnecrotizing granulomas as compared to blind TBNA (6). The same results were recently reported using EUS (7). In this issue Eckardt J et al (8) confirm these data. The study was conducted in an unselected group of patients with enlarged hilar and/or mediastinal lymph nodes or with parenchymal infiltrates in which TBNA or other bronchoscopic procedures (TBB and BAL) previously carried out were inconclusive. The prevalence of sarcoidosis was 14% (43/308 patients). Thirty-three (77%) were diagnosed with EBUS. This study formally confirms what is an observation made -not so unfrequently- by those who use transbronchial oe transesophageal endoscopic ultrasonography: lymph nodes considered normal only on the basis of their size as assessed by CT may actually be infiltrated by pathologic tissue. Furthermore this study reinforce the question: should we continue to do a bronchoscopy or should we better do or refer for immediate endoscopic ultrasound when thoracic sarcoidosis is suspected? The "answer my friends is still blowing in the wind". The only way to stop the wind and catch the answer is:

1. To assess if the clinic-radiologic diagnosis of Sarcoidosis is feasible; what are the characteristic that allow to make this diagnosis with an acceptable degree of certainty.

2. In cases in which the clinic-radiologic profile appears not so typical randomized controlled trials with a direct comparison between these different procedures should be performed

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