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Current Perspectives in the Diagnosis of Sarcoidosis

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COLUMN ARTICLE

Introduction

Sarcoidosis occasionaly emerges as a diagnostic dilemma for the pulmonary clinician. Diagnosis of sarcoidosis is never secure despite the designated identification criteria [1]. If the clinical presentation is characteristic for the disease as in certain specific syndromes such as Löfgren's or Heerfordt syndrome, diagnosis can be reached on clinical grounds without tissue biopsy [2]. Otherwise, histopathologic confirmation for granulomatous inflammation is imperative in at least two organs for definite diagnosis as sarcoidosis is a multisystemic disease. Since the granulomatous inflammation is associated with many other diseases, a thorough differential diagnosis is required for the final diagnosis of sarcoidosis. The disease is a diagnostic challenge for the pulmonary clinician because the symptoms or the laboratory findings are never specific enough to warrant the diagnosis. Identification requires pathologic tissue examination from involved organs although the granulomas alone are not sufficient for diagnosis that the presence of a consistent clinical syndrome and a characteristic evolutionary outcome are necessary eventually. Isolated extrapulmonary sarcoidosis occurs in approximately 3% to 5% of the patients. Definite diagnosis may not be feasible in some patients in whom sarcoidosis presents with an isolated organ involvement that requires several years of follow up to ensure the final diagnosis of sarcoidosis while another organ involvement may develop as short as six months that facilitates the diagnosis [3,4].

Diagnostic approach for sarcoidosis

Confidence level for sarcoidosis has evolved from definite to highly probable diagnosis since unconditional precision may not be feasible [5]. Identification of sarcoidosis can not be done on the basis of clinical and radiologic profile of the patient because the same clinical profile may occur in many other diseases such as tuberculosis, fungal infection, hypersensitivity pneumonitis and lymphoma. Even the presence of granulomatous inflammation in a single organ with associated clinical manifestations is not adequate for final diagnosis since other granulomatous diseases may share similar clinical features. A compatible clinical and radiologic presentation, pathologic evidence of non-caseiting granulomas in at least two organs and the exclusion of other disease that emerge with identical clinical or radiologic findings are requried for final diagnosis.

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Sarcoidosis is a complex disease that requires a diagnosis of exclusion. Because the presentation, clinical, laboratory and the radiologic manifestations are versatile and variable, every patient should be evaluated on a case to case basis using a different diagnostic approach. Half of the patients are diagnosed within three months of initial presentation while in approximately 10% of the cases the definitive diagnosis is delayed up to two years due atypical presentations or variable clinical profiles [6]. The confidence level in a diagnosis of sarcoidosis has been revised from definite to highly probable diagnosis of sarcoidosis since absolute diagnostic certainty may not be feasible in many patients [5]. Consequently, the confidence level of diagnostic accuracy has been designated as highly probable, probable, possible, or unlikely [7] even though this approach is still equivocal. Highly probable confidence level reveals a consistent clnical profile, multisystemic involvement with a positive pathology. Probable confidence level includes patients with a consistent clinical presentation with a supportive pathology from presenting and asymptomatic organ. In possible confidence level of diagnosis there is a suggestive clinical profile with an unobtainable supportive pathology. Unlikely confidence level reveals a suggestive clinical presentation with an incompatible or an absent pathology [3,7].

The diagnostic pathway for sarcoidosis is inexplicit. The patients may be asymptomatic, may present with an isolated single organ involvement, or with an extrapulmonary organ disease may dominate the clinical picture. The most common lung symptoms of presentation are dyspnea and dry cough. Arthralgia and fatigue are other common systemic symptoms. Skin rashes are frequent manifestations of skin involvement while blurred vision and red eye are mostly associated with ocular sarcoidosis. In ocular involvement, anterior uveitis is the most common compartment occuring in 35% while ocular involvement is the presenting symptom in 15% of the sarcoidosis patients [8,9]. Clinicians should bear in mind that presence of nonspecific skin lesions, lupus pernio or erythema nodosum and uveitis of unidefined etiology may the initial manifestation of sarcoidosis.

The clinical, laboratory and the radiologic manifestations are not specific enough to warrant a definitive diagnosis of sarcoidosis. The diagnosis is based on a compatible clinical presentation with consistent radiologic findings, presence of non-caseiting granulomas in tissue biopsy samples in at least two organs and the exclusion of other granulomatous diseases in differential diagnosis. Sarcoidosis constitutes a diagnostic challenge for the pulmonary clinician thereby its identification may occasionally be extremely formidable or delayed. Furthermore, genetic variations associated with sarcoidosis may pose another difficult aspect of the disease because they promote atypical clinical manifestations as well as an aberrant disease course. The best diagnostic pathway is the evaluation of patients on a case to case basis because no single clinical presentation, radiologic finding or an algorithm is adequately specific enough for the diagnosis of the individual sarcoidosis patient.

Sarcoidosis is defined in histopathological terms as a disease characterised by the presence several affected organs and tissues of non-caseating epithelioid-cell granulomas, proceeding either to resolution or to conversion into hyaline connective tissue. Definite diagnosis is dependant upon the compatible clinical, radiological and laboratory findings. Support of histopathology required varies greatly from case to case. Though histology from one site cannot in itself establish the diagnosis of sarcoidosis, a generalised disease, detailed histological study of biopsy tissue makes an important and often essential contribution. In many instances, complete lack of necrosis, an intact reticulin pattern and failure to demonstrate infective agents permit an unequivocal statement of compatibility with this diagnosis; however, a compatible clinical picture and absence of evidence of known causes of local granulomatous reactions or of other generalised granulomatous diseases are required for definite diagnosis. Inflammatory and granulomatous reactions with dense superficial and deep lymphocytes, eosinophils and plasma cells are usually observed. Typical histopathologic pattern states that there may be a little necrosis, the follicular pattern of the granuloma may be less than perfect and exclusion of known infectious etiology like tuberculosis [10]. Non-caseating epithelioid granulomas with tightly packed epithelioid cells, Langhans giant cells and lymphocytes (T cells), usually in interstitium adjacent to bronchioles and around and within vessel walls, pleura and connective tissue septa are dominant features of sarcoidosis.

Hyalinization, diffuse interstitial fibrosis, fibrinoid necrosis, fibrosis within granulomas, intra and extracellular inclusions may be present. Also Schaumann bodies, calcium and protein inclusions inside the Langhans giant cells as part of a granuloma; asteroid bodies (small, intracytoplasmic, eosinophilic star shaped structure also present in tuberculoid leprosy, berylliosis and atypical facial necrobiotic xanthogranuloma) basophilic laminated rounded conchoidal structures consisting of laminated concentrations of calcium and protein along with stellate inclusions within the giant cells in 60% of the granulomas may ocur in sarcoidosis. Hamazaki-Wesenberg bodies, PAS (+) inclusions within large lysosomes containing hemolipofuscin may also be present [1,11]. Neither of these findings is specific for sarcoidosis and may be encountered in many other granulomatous diseases. Definite diagnosis requires confirmation of non-caseiting granulomas in two organs associated with a compatible clinical profile. Pathology is never adequate for the diagnosis of sarcoidosis on its own.

Difficulty of diagnosis most often arises if the patient presents without lung disease or with a single organ involvement. Even if the single organ involvement includes lung, a diagnostic dilemma arises because many lung diseases may lead to non-caseified granulomatous inflammation in the lung and histopathologic confirmation for granulomatous inflammation is imperative in at least two organs for definite diagnosis. The best approach in such cases is to follow up the patient every three or four months to identify the involvement of another organ. Involvement of a second organ usually occurs in the following six months [4] and may provide the definite diagnosis by the biopsy of the aforementioned organ. Bronchial or transbronchial biopsy from the normally visible bronchial mucosa may also provide the diagnosis in most of hte patients. Another approach in single organ disease is the detection of other sites of involvement by PET / CT that may identify sites of granulomatous inflammation, involved organs or available biopsy sites. Clinicians may also perform blind biopsy of the salivary glands or muscle, especially the gastrocnemius muscle [12] in cases of single organ disease. Another biopsy site is skin areas with lesions suspicious for sarcoidosis. Detection of uveitis in such patients makes the diagnosis of sarcoidosis probable. The presence of high serum or urinary calcium are other significant clinical markers for sarcoidosis. Negative tuberculin test supports the diagnosis of sarcoidosis and is present in paproximately 80% of the patients. Hypergammaglobulinemia is another crucial laboratory criteria for diagnosis. It should not be forgotten that the laboratory findings may only support the diagnosis but never constitute the final diagnosis.

Another diagnostic difficulty arises in the diagnosis of sarcoidosis-related comorbid diseases. Cardiac disease, pulmonary hypertension and cerebral sarcoidosis are the major comorbid diseases of sarcoidosis. Because cardiac sarcoidosis accounts for approximately 13 - 25% of sarcoidosis relevant deaths, identification of cardiac involvement is one of the most crucial aspects of sarcoidosis [13]. Cardiac sarcoidosis incidence is about 5% and 11% among the patients [14]. Non-invasive tests like ECG, Holter and echocardiogram revealed that 40% of outpatients had cardiac sarcoidosis while half of these patients were asymptomatic [15]. Clinically apparent cardiac sarcoidosis is observed only in a minority of patients. Approximately one fourth of patients with systemic sarcoidosis had myocardial involvement identified by autopsy [16]. Diagnosis of cardiac disease is extremely crucial because these patients usually have a poor prognosis with a less than 2 years of survival following signs and symptoms myocardial involvement. Cardiac involvement accounts for approximately 25% of deaths from sarcoidosis and is the second leading cause of death from sarcoidosis [17]. In cases of equivocal cardiac involvement, PET/CT may be the hallmark for the diagnosis of definite cardiac disease by detecting high FDG uptake in sites with granulomatous inflammation. PET/CT may also accurately determine the myocardial the biopsy sites thereby facilitating a definite diagnosis [18-21]. PET/CT is currently considered the hallmark of diagnosis in patients with suspected cardiac sarcoidosis.

Another important aspect of sarcoidosis is pulmonary hypertension that appears as as a diagnostic dilemma in most of the patients. The first clue to diagnosis is the unexplained dyspnea. Clinicians should know that dyspnea of sarcoidosis associated pulmonary hypertension may not correlate with the pulmonary function tests or the radiologic stage of sarcoidosis [22]. The 6MW test is a useful screening

test for pulmonary hypertension. The 6MW distance is usually less than 450 meters in most of the patients [23-26]. However, it should be noted that there are other factors associated with sarcoidosis such as fatigue, airway disease and muscle involvement that may decrease the 6MW distance. Echocardiography is useful non-invazive diagnostic test for pulmonary hypertension. Pulmonary angiography is the most accurate and definitive method for the diagnosis of pulmonary hypertension. Pulmonary angiography also differentiates between arterial and venous pulmonary hypertension. In the absence of lung disease, transthoracic echocardiogram appears to be the most reliable non-invasive screening test for pulmonary hypertension. On the other hand, low FVC, TLC and DLCO may be useful to support the diagnosis of SPH while the correlation between pulmonary hypertension and lung function tests is poor [27]. Cerebral involvement by granulomas can easily be diagnosed by brain CT or MR in patient with previous sarcoidosis. Otherwise cerebral biopsy is required for diagnosis.

CONCLUSIONS

A definite diagnosis of sarcoidosis can only be reached if non-caseified granulomatous inlammation is demonstrated in at least two organs with a compatible clinical profile. In the presence of certain specific syndromes such as Löfgren's or Heerfordt syndrome diagnosis can be confirmed clinically without organ biopsy. Transbronchial and bronchial biopsy can provide diagnostic tissue in up to 93% of the cases even with a normal appearing mucosa. In patients with single organ sarcoidosis or without lung involvement, the diagnosis may be accomplished after a follow-up period if a second organ involvement arises. For patients with suspected sarcoidosis blind biopsies from various organs including muscle, salivary glands or skin may be performed for final diagnosis. PET/CT is the hallmark of sarcoidosis diagnosis to demonstrate active granulomatous inflammation. It may show unidentified organ involvement clinically in cases where histopathologic verification is required for definite diagnosis. This imaging modality also shows activity of active parenchymal disease and fibrosis of lung sarcoidosis thereby facilitating diagnostic biopsy. PET/CT is also very useful to demonstrate myocardial sarcoidosis which is the most difficult organ for diagnosis. Nowadays, PET/CT appears to be the most properous imaging modality in patients with difficult or equivocal sarcoidosis diagnosis due to its trenchancy in detecting active granulomatous inflammation and biopsy sites thereby revealing occult organ involvement.

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