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Review

Diagnostic criteria for sarcoidosis

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ABSTRACT

Sarcoidosis is a multiorgan system disease that often presents insidiously. The diagnosis is often made fortuitously upon routine chest radiography or that done for other reasons. Blacks are more commonly affected than whites and age of onset is typically adolescents to young adults. Lung involvement is common and symptoms may include cough, dyspnea and chest pain. Extrapulmonary symptoms may include the skin, joint and eye findings. Bilateral hilar adenopathy is the classic finding on chest radiograph. Anemia or other cell line deficiencies, elevated liver enzymes, hypercalciuria, and EKG abnormalities may also be present. Angiotensin converting enzyme levels may be elevated but are not diagnostic. Histopathological confirmation of noncaseating granulomas is essential for diagnosis. It is generally performed through a biopsy of the most peripheral site possible, although transbronchial biopsy is commonly required. Finally, other possible etiologies must be evaluated and differentiated with a particular emphasis on tuberculosis due to the multiple overlapping symptoms and findings. Newer techniques such as proteomics and transcriptional gene signatures may contribute to the understanding of the pathophysiology of sarcoidosis, and may even serve as diagnostic tools in the future.

Contents

1. Introduction

Sarcoidosis is a multisystem disease that primarily affects adolescents and adults most commonly between the ages of 10 and 40. The overall prevalence of sarcoidosis appears to be between 10 and 20 per 100,000 people. It is characterized by the presence of noncaseating granulomas in the lymph nodes, lung, skin, joint or eyes. The onset is often insidious, and in children, it is particularly asymptomatic. In symptomatic pediatric patients, extra-pulmonary manifestations are more commonly observed, in contrast to adults [1]. There is a significant geographical and racial variation. It is 3–4 times more common in blacks compared to whites and familial clustering has been reported [2]. The lifetime risk of sarcoidosis in African Americans is 2.4%, compared to 0.8% for whites. Blacks also seem to have more acute and aggressive disease compared to whites.

Making the diagnosis under the age of 5 years is rare, as the prevalence in this age group is only about 0.06 per 100,000. By the mid-teenage years of 14–15, the prevalence has climbed to about 1 new patient per 100,000 and the clinical presentation is similar to that of adults [3]. Females have a higher incidence than males [4].

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2. Diagnostic criteria

Sarcoidosis is a very heterogeneous disease, both in terms of presentation and severity. The pathophysiology of sarcoidosis is unclear, but it is likely that a heterogeneous set of triggers leads to the formation of noncaseating granulomas throughout multiple organ systems in genetically susceptible individuals. There appears to be a predilection for the lungs, but other sites can be involved. The presence of different phenotypes renders it difficult to develop clear and concise diagnostic criteria for sarcoidosis. Moreover, little is known about endotypes in sarcoidosis, so there is little success in linking diagnostic testing to pathophysiologic characteristics of the disease. At the present time, the diagnosis of sarcoidosis is based on a combination of clinical, radiographic and histological features. In addition, elimination of other etiologies in the differential diagnosis must be accomplished to make the correct diagnosis of sarcoidosis.

3. Clinical features consistent with sarcoidosis

The clinical history is of critical importance in establishing a diagnosis of sarcoidosis. As sarcoidosis has been reported to occur following exposure to certain "toxic" or "chemical" agents, a comprehensive occupational and environmental history may be helpful. Sarcoidosis has been associated with heavy metal exposures such as beryllium and its salts (Salem Sarcoid), although the American Thoracic Society criteria list berylliosis as a separate entity [4]. In some cases, the trigger is not clearly defined. Firefighters who responded to the collapse of the World Trade Center have a higher incidence of sarcoid-like pulmonary disease, and this may be a result of exposure to an unidentified substance [5]. Sarcoidosis has also been linked to infectious agents such as *propionibacterium* and *mycobacterium* [4]. Finally, there is clearly a genetic component to the pathophysiology of sarcoidosis, since certain HLA alleles appear to confer susceptibility to sarcoidosis, such as HLA DR 11, 12, 14, 15 and 17, while others confer a protective effect, such as HLA DR1, DR4, and possibly HLA DQ*0202 [6].

A history of present illness should elicit pulmonary symptoms of sarcoidosis, including cough, dyspnea or chest pain. Lung involvement occurs in over 90% of cases [7]. Though dyspnea may be a presenting symptom of sarcoidosis, approximately 50% of sarcoidosis patients tolerate strenuous exercise without dyspnea, and only 1 in 7 patients will notice that they tend to walk slower than others [8]. Rarely there may be involvement of the upper airway with symptoms of hoarseness, dysphagia, laryngeal paralysis, and upper airway obstruction [9]. Constitutional symptoms such as low-grade fever, malaise and weight loss may be present in a third of patients [4]. Extrapulmonary symptoms may be reported, including the skin (rashes, plaques), joint (arthritis) or eye findings (changes in vision, iridocyclitis). Patients may have noticed lumps due to lymphadenopathy. Rarely, a history of facial swelling, facial droop, abdominal pain or diarrhea may be elicited.

The physical exam may reveal several findings supportive of a diagnosis of sarcoidosis; however none of the findings are specific to sarcoidosis. Pulmonary examination may reveal wheezing, but crackles are unlikely [8]. Ophthalmological evaluation may reveal exudates or vasculitis. Because of the morbidity associated with ocular manifestations, ophthalmological referral for slit-lamp exam to identify uveitis, retinal vasculitis, conjunctivitis, glaucoma or cataracts, is strongly recommended. Head and neck examination may reveal parotid or salivary gland swelling, and a neurologic examination may reveal facial or ocular palsies. Neurologic and ocular symptoms are more common in women. Cardiac arrhythmias have been reported. A quarter of patients will have hepatomegaly and 1 in 5 will have splenomegaly. Rarely splenomegaly may lead to pancytopenia. Joints should be examined closely for signs of arthritis. Dermatologic findings on exam may be variable but can manifest as erythema nodosum, a maculopapular rash of the face and neck, waxy pink lesions on the face, trunk or extensor surfaces, or plaque like lesions [10]. Peripheral adenopathy occurs in 40% of patients and may provide a target for biopsy to confirm the diagnosis from a histologic standpoint.

4. Laboratory and radiographic studies in the diagnosis of sarcoidosis

Laboratory tests to support the diagnosis include complete blood count (CBC), electrolytes, BUN/Cr, liver enzymes, alkaline phosphatase, calcium, urinalysis including urinary calcium and creatinine, immunoglobulins and angiotensin converting enzyme (ACE). The CBC may show leukopenia, anemia, thrombocytopenia or pancytopenia. Liver enzymes, alkaline phosphatase and immunoglobulins may be elevated. Hypercalciuria is defined as urinary calcium to creatinine ratio of >0.2 for normal patients over the age of 2 years with relatively normal body mass index. Men are more likely to have difficulties with calcium homeostasis than women and an elevated urinary calcium/Cr ratio is more common than hypercalcemia. Elevated ACE is not diagnostic due to false-positives. However, it is found to be elevated in over 75% of cases of sarcoidosis lending further support to the diagnosis [6].

Conduction abnormalities may be seen on electrocardiogram due to sarcoidosis ranging from benign arrhythmias to high-degree heart block [4]. Pulmonary function testing (PFT) may show a restrictive pattern with a decreased forced vital capacity (FVC), but FVC is normal in over two-thirds of patients. Additionally, as sarcoidosis progresses, a diffusion impairment may arise [6]. This may lead to hypoxemia that can be exacerbated by exercise. Bronchoalveolar lavage may detect a decrease in CD8 cells, an increase in CD4/CD8 ratio, and low levels of neutrophils and eosinophils (less than 1%) [11].

Often sarcoidosis is asymptomatic and approximately 50% of cases come to light incidentally by chest radiograph. Classically, there is bilateral hilar adenopathy on chest radiograph and this may be found incidentally as the presenting "symptom" of sarcoidosis. Parenchymal opacities may be present, but pleural involvement is rare [7]. Lung involvement may be staged according to radiographic presentation. Features of Stage I include hilar adenopathy without other opacities (Fig. 1). Hilar adenopathy with reticular opacities are seen in Stage II disease. Stage III findings include resolving hilar adenopathy but persistent reticular opacities (Fig. 2). In Stage IV disease, there is no hilar adenopathy, but reticular opacities and evidence of volume loss can be seen. Finally, chest radiography (Fig. 3a) and CT scan in stage V show bilateral lung nodules that may even be mistaken for metastases,

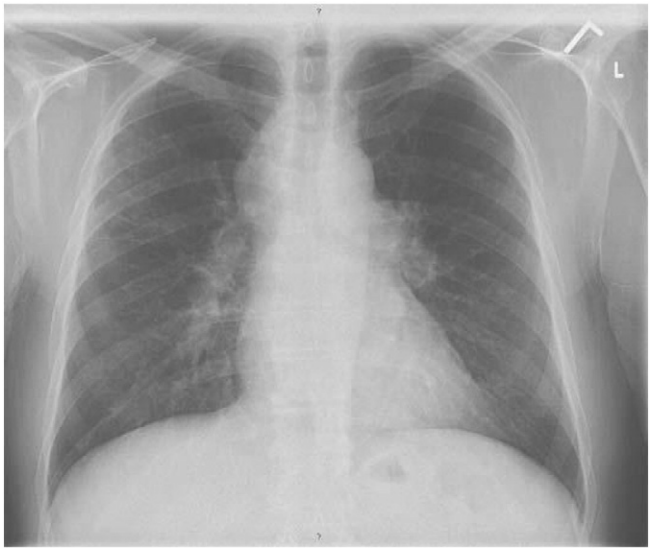

Fig. 1. Stage 1 sarcoidosis: Hilar adenopathy without parenchymal lung disease. Reproduced with permission, Baughman RP. Pulmonary sarcoidosis. Clin Chest Med. 2004; 25 [3]:521-307 [7].