MAYO CLINIC

Pulmonary Sarcoidosis: Diagnosis and Treatment

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CME Activity

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Dr Carmona is a coinvestigator in a RESAPH study, a registry for patients with sarcoidosis and pulmonary hypertension.

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Abstract

Sarcoidosis is a chronic granulomatous disease of unknown cause that is seen worldwide and occurs mainly in patients between the ages of 20 and 60 years. It can be difficult to diagnose because it can mimic many other diseases including lymphoproliferative disorders and granulomatous infections and because there is no specific test for diagnosis, which depends on correlation of clinicoradiologic and histopathologic features. This review will focus on recent discoveries regarding the pathogenesis of sarcoidosis, common clinical presentations, diagnostic evaluation, and indications for treatment. This review is aimed largely at general practitioners and emphasizes the importance of differentiating pulmonary sarcoidosis from its common imitators.

 ■ Mayo Clin Proc. 2016;91(7):946-954

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Sarcoidosis is a multisystem disease that predominantly affects individuals between the ages of 20 and 60 years. The incidence is about 10 per 100,000 in a predominantly white population but up to 3 to 4 times higher in African Americans. Sarcoidosis is frequently encountered first by primary care physicians when evaluating patients with nonspecific symptoms such as cough or dyspnea and not uncommonly also encountered incidentally during routine evaluations. Because its cause is unknown and there is no standard test for its diagnosis, sarcoidosis remains a diagnosis of exclusion. It can mimic many illnesses and therefore is included in the differential diagnosis of many pulmonary and systemic processes. Skilled clinical reasoning is required to

Mayo Clin Proc. ■ July 2016;91(7):946-954 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.004
www.mayoclinicproceedings.org ■

ensure that the correct diagnosis is made in a cost-effective and timely manner.

The etiology of sarcoidosis remains unknown despite decades of effort, including notably the ACCESS (A Case-Control Etiologic Sarcoidosis Study) project, a case-control study of over 700 matched case and control pairs. This study investigated occupational and environmental factors as well as infection and genetic associations, but a plausible cause could not be identified.[1] Despite the absence of a definitive cause, it is widely held that the pathogenesis of sarcoidosis involves exposure to an environmental or nonenvironmental agent(s) in a genetically susceptible individual. This combination triggers the activation of components of the immune system and the formation of nonnecrotizing granulomas, the hallmark lesions of sarcoidosis. Depending on unknown genetic aberrations or immune system defects, the granulomatous reaction either resolves or persists as chronic inflammation leading ultimately to fibrosis. Different combinations of exposures and host defects likely determine the multiple phenotypes seen in sarcoidosis.

This review summarizes the recent discoveries regarding the pathogenesis of sarcoidosis, most common clinical presentations, diagnosis, and indications for treatment of pulmonary sarcoidosis. This review is mainly aimed at general practitioners and emphasizes the importance of differentiating pulmonary sarcoidosis from its common imitators, particularly when treatment fails.

PATHOGENESIS

The pathogenesis of sarcoidosis still remains an enigma despite the first documented cases being described in the late 1800s by Hutchinson and Boeck. One of the largest efforts to identify a common causative agent was the ACCESS study, and although no unifying exposure was clearly identified, this study has been key in recognizing some occupations (raising birds, automobile manufacturing, teaching school, cotton ginning, and work involving radiation, organic dust, gardening, and building material exposure) and certain exposures (insecticides, molds and mildew, central air conditioning, and birds) that are more frequently associated with the development of sarcoidosis.[2] Interestingly, when infectious agents were sought, positive blood culture results and serologic test rates were similar in patients and controls. Nevertheless, given the pathologic resemblance of sarcoidosis to granulomatous infections, some of the most investigated environmental factors have been infectious agents. Among these factors, antigens from typical and atypical mycobacteria, *Propionibacterium*, viruses, and various fungi have been hypothesized as initial triggers of the granulomatous reaction.[3] Some of these microbial antigens, also known as pathogen-associated molecular patterns, are likely triggers of the innate immune response, leading to granuloma formation in the susceptible host.[4] Therefore, the absence of increased positive culture results in patients compared with controls does not completely exclude infectious organisms or associated antigens as potential triggers because it could be the exposure, and not necessarily the infection, that elicits the sarcoid reaction in the predisposed patient. Similarly, other pathogen-associated molecular patterns derived from toxins and chemical compounds as well as damage-associated molecular patterns such as human heat shock proteins could potentially trigger granuloma formation in the susceptible host.[5] Chen et al[4] also suggested that the acute phase response agent, serum amyloid A, triggered by mycobacterial infection can form insoluble aggregates with some of the mycobacterial antigens, which can then activate the immune response via toll-like receptors contributing to the granuloma formation.

Once the innate immune response has been activated, antigen-presenting cells process the antigen and present the peptide to HLA class II molecules, which can then be recognized by specific T-cell receptors. It is known that certain HLA alleles are associated with disease severity. For instance, patients with *HLA-DRB1*03* experience higher rates of disease resolution within 2 years than those without *HLA-DRB1*03*, while those with *HLA-DRB1*14* and *HLA-DRB1*15* tend to have a more chronic course.[6] Some HLAs may also predict disease pattern as illustrated by the association of *HLA-DRB1*0401* with eye involvement or *HLA-DPB1*0101* with abnormal calcium metabolism.[7] Furthermore, patients with sarcoidosis who have *HLA-DRB1*0301* and *HLA-DRB3*0101* have an accumulation of T cells expressing a specific T-cell receptor clone (AV2S3+), suggesting a clonal expansion of $CD4^+$ T cells to a particular