Sarcoidosis Epidemiology, Clinical Presentation, Small Fiber Neuropathy, and Options Beyond Prednisone

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Sarcoidosis—a disease characterized by granulomas that can affect any organ but most commonly affect the lungs—may be caused by interplay of environmental factors and genetic susceptibility. Eva M. Carmona Porquera, MD, PhD, Mayo Clinic, Rochester, Minnesota, USA, described the epidemiology of sarcoidosis, as well as the genetic and environmental factors that may be involved. Patients with sarcoidosis may have a genetic predisposition, as there is a familial relative risk of 4.7 [Rybicki BA et al. *Am J Respir Crit Care Med.* 2001] and, depending on the study, up to 17% of patients have a positive family history. African Americans are more likely to develop sarcoidosis and experience more severe disease with extrapulmonary manifestations, whereas Japanese patients experience a greater rate of cardiac sarcoidosis. The course of the disease can be predicted by class II major histocompatibility complex alleles; presence of HLA-DRB1*03 predicts spontaneous resolution, whereas *14 and *15 indicate a chronic course. Class II HLA glycoproteins influence the T-cell response because they are directly involved in antigen presentation; thus, a change in the shape of the peptide-binding groove can affect antigen binding and presentation.

Environmental factors have been identified as possible causative agents for sarcoidosis. Infectious agents such as mycobacteria and propionibacteria have been associated with sarcoidosis, as well as noninfectious agents such as insecticides, silica, or talc. For example, a proposed mechanism by which mycobacterial antigens can cause granuloma formation is due to chronic inflammation and fibrosis as a result of the inability to clear aggregates formed during the immune response in the genetically predisposed host [Chen ES et al. *Am J Respir Crit Care Med.* 2010].

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Marc A. Judson, MD, Albany Medical College, Albany, New York, USA, discussed the clinical presentation of sarcoidosis. Sarcoidosis can affect any organ, with varying severity—from asymptomatic to life-threatening. Disease that is acute or subacute is often reversible; however, chronic sarcoidosis and acute cardiac sarcoidosis can be life-threatening. Lung involvement occurs in almost 90% of patients, with the skin, eyes, and liver involved in ≥20% of cases [Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis.* 2012].

Pulmonary sarcoidosis most typically affects the upper two-thirds of the lung and involves the bronchovascular bundles, subpleura, intralobular septa, and lymph nodes. In sarcoidosis that involves the skin, maculopapules, subcutaneous nodules, infiltration of scars, and lupus pernio can occur, as well as nonspecific erythema nodosum and rash. Lacrimal gland involvement occurs in ≤88% of patients with sarcoidosis, presenting as keratoconjunctivitis sicca, and can be biopsied for differential diagnosis. Uveitis, an inflammatory disorder of the cells in the anterior chamber or vitreous cavity of the eye, can occur as well.

Cardiac involvement occurs in a quarter of cases. Although cardiac sarcoidosis accounts for a lower percentage of sarcoidosis-related deaths than that of pulmonary sarcoidosis, it can be more suddenly fatal. Importantly, 80% of patients with cardiac sarcoidosis are asymptomatic. Cardiac sarcoidosis can cause conduction disturbances, arrhythmias, congestive heart failure, valvular dysfunction, pericarditis, and ventricular aneurysm. The underlying cause of cardiac sarcoidosis is believed to involve, at least in part, abnormal calcium metabolism.

Daniel A. Culver, DO, Cleveland Clinic, Cleveland, Ohio, USA, discussed small fiber neuropathy and fatigue in patients with sarcoidosis. Sensory symptoms of sarcoidosis can include pain, restless legs syndrome, sheet intolerance, and paresthesias [Hoitsma E et al. *Curr Opin Pulm Med.* 2010]. Autonomic symptoms can include sweating abnormalities, flushing, palpitations, irritable bowel symptoms, sicca symptoms, orthostasis, and sexual dysfunction. Currently, the underlying

mechanism that causes small fiber dropout in sarcoidosis is unknown.

Fatigue occurs in 60% to 80% of patients with sarcoidosis, even among those with resolved sarcoidosis and no evidence of active disease. The treatment of fatigue can include cognitive behavioral therapy, exercise such as yoga or dance, weight loss, and selective serotonin reuptake inhibitors, as well as treatment of the disease itself.

Nadera J. Sweiss, MD, University of Illinois Hospital and Health Sciences System, Chicago, Illinois, USA, described treatments for sarcoidosis when prednisone therapy fails. Corticosteroids are effective and induce a rapid response but are associated with substantial side effects. If corticosteroids fail to resolve sarcoidosis, cytotoxic agents such as methotrexate, leflunomide, azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporine can be considered. In addition, cytokine modulators such as thalidomide, infliximab, adalimumab, rituximab, golimumab, and ustekinumab may be considered, as well as antimicrobials such as hydroxychloroquine and minocycline.

However, Dr Sweiss noted that cytotoxic agents are not as effective as corticosteroids and a longer duration of therapy is required to elicit a response; she added that in various studies, the relapse rate of sarcoidosis with corticosteroids, methotrexate, and infliximab ranged from 62% to 88%. In addition, second-line agents can have substantial side effects. For example, in a 1995 study, methotrexate caused histologic liver toxicity in 15% of patients.

In a multicenter randomized trial, patients with chronic sarcoidosis with pulmonary involvement who were treated with infliximab experienced minimal added benefit to corticosteroid treatment [Judson MA et al. *Respir Med.* 2014]. A small prospective study established the safety of rituximab but did not designate efficacy as an end point; thus, it cannot be recommended as a first- or second-line agent [Sweiss NJ et al. *Eur Resp J.* 2014].

The most effective therapy for sarcoidosis is corticosteroids; however, second-line therapies may be beneficial for patients. In addition, newer targeted therapies are under evaluation to determine if they provide added benefit for patients with chronic sarcoidosis.