Sarcoidosis

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KEYWORDS

• Sarcoidosis • Granulomas • Tumor necrosis factor • HLA • EBUS-TBNA
• Steroid-sparing • Corticosteroids • Infliximab

KEY POINTS

- Sarcoidosis is a diagnosis of exclusion. In most patients, it requires a biopsy demonstrating non-necrotizing granulomas and no exposure to other agents known to induce granulomatous inflammation.
- Asymptomatic organ involvement that is not readily apparent on routine blood tests, electrocardiogram, or ophthalmologic examination is unlikely to be clinically important, and extensive screening tests to "stage" sarcoidosis are not generally necessary.
- Sarcoidosis will spontaneously remit in up to two-thirds of patients within 5 years of onset. There are insufficient data to support the hypothesis that early treatment increases the prospects for resolution to warrant routine empiric therapy in all patients.
- Corticosteroids have been traditionally used to treat acute, severe manifestations of sarcoidosis; for chronic or refractory disease, steroid-sparing alternatives may be considered.

INTRODUCTION

Sarcoidosis is a highly variable multisystem syndrome characterized by granulomatous inflammation in affected organs. The pathogenesis of sarcoidosis involves an interaction between a putative triggering antigen, probably inhaled, and a susceptible host. The exact causative agent or agents remain unknown. The incidence, severity, and clinical phenotypes of sarcoidosis are influenced by race, ethnicity, gender, and age. In the United States, African Americans are afflicted more often and more severely than are whites. However, the manifestations in any single patient are unpredictable, so that clinicians must actively tailor diagnostic testing, follow-up, and therapy for each individual.

EPIDEMIOLOGY

Sarcoidosis occurs worldwide, with the highest ascertained incidence rates reported in northern European and African American females. A survey conducted in a health maintenance organization in the Detroit, Michigan, area reported age-adjusted

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incidence rates of 10.9 per 100,000 white population and 35.5 per 100,000 black population, based on diagnosis during usual health care.[1] Using these data, it has been estimated that the lifetime risk for developing sarcoidosis is 0.85% in US whites and 2.4% in US blacks.[1] A geographically broader study, the Black Women's Health Study, enrolled 59,000 black women in the United States.[2] The annual incidence of sarcoidosis in that group was calculated to be 71 per 100,000, with a peak of 92 per 100,000 in women aged 40 to 49 years. In addition to susceptibility, race influences disease phenotype, with blacks far more likely to exhibit chronic disease, multiple organ involvement, and morbidity.

It is important to note, however, that the reliability of disease incidence or prevalence estimates may be tenuous. For example, in the US military, sarcoidosis is much more common in recruits from the southeastern states and less common in those from the southwest region.[3,4] In Japan, sarcoidosis is more common in the northern part of the country.[5] Therefore, incidence estimates from any given region are unlikely to be generalizable. Second, because many cases are clinically silent, most cases of sarcoidosis are probably not recognized. For example, in an autopsy study from northeast Ohio, the prevalence rate was estimated to be 320 per 100,000, a 10-fold higher rate than that predicted by death certificate data from the same period.[6] In countries with population-based mass chest radiographic (CXR) screening programs, approximately 50% of the diagnoses of sarcoidosis are made in asymptomatic individuals.[7]

CAUSE AND PATHOGENESIS

The cause of sarcoidosis remains unknown. Based on epidemiologic evidence, it is generally believed that development of sarcoidosis requires exposure to an environmental antigen(s). This hypothesis is supported by several observations, including studies of disease incidence, reports of case-clusters in small populations, transmission by organ transplantation, and the worldwide reproducibility of intradermal granulomatous reactions only in patients with sarcoidosis after the injection of sarcoidosis lymph node homogenate (the Kveim-Siltzbach test).[8]

Infectious agents have long been suspected as possible causes of sarcoidosis, but early studies failed to yield convincing support for various organisms. Using molecular techniques, there are now accumulating data suggesting that immune responses to mycobacteria or *Propionibacterium acnes* may contribute to the disease.[9–11] Based on analogy with a similar granulomatous lung disease, chronic beryllium disease, it is tempting to speculate that there may be more than one etiologic agent capable of causing sarcoidosis. Therefore, it seems likely that development of a sarcoidosis reaction to a triggering antigen depends on a combination of genetic polymorphisms, the status of the host immune system, and the exposure itself.

Besides a relevant exposure, there are substantial data delineating a role for genetic polymorphisms in the susceptibility and phenotype of sarcoidosis. This topic was reviewed recently in detail elsewhere.[12] One example of the importance of genetics comes from a registry-based study of 210 affected twin pairs in Denmark and Finland.[13] Monozygotic twins had an 80-fold increased susceptibility for development of sarcoidosis versus population controls, compared with only a 7-fold increased chance in dizygotic pairs. A range of other studies have reported similar increased heritable risk.[14,15]

Much of the data suggest that the genetic effect on disease risk or severity depends on human leukocyte antigen (HLA) genes governing the expression of the type II major histocompatibility complex on antigen-presenting cells.[12,16] These observations fit well with the current concepts of disease pathogenesis, reserving a central role for activation of antigen-specific oligoclonal $CD4^+$ T cells by major histocompatibility