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Concomitant sarcoidosis and a connective tissue disease: Review of the clinical findings and postulations concerning their association

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Summary
Introduction: Known causes of granulomatous inflammation must be excluded before the diagnosis of sarcoidosis can be secured. We explored the possibility that connective tissue diseases (CTDs) could be a cause of granulomatous inflammation through an analysis of patients cared for in 2 medical centers and a review of the medical literature.
Methods: Patients with both a diagnosis of sarcoidosis and a CTD were identified at two medical centers. In addition, a literature search identified reported cases of patients with both diagnoses.
Results: We identified 15 patients at 2 medical centers plus 53 previous reported patients in the medical literature (total = 68) with diagnoses of both sarcoidosis and a CTD. The patients were predominantly female. Scleroderma was the most common CTD. Only 2/59 (3%) with chest radiographs recorded had fibrocystic (stage 4) disease. In 48/67 (72%) patients where the time of diagnosis was recorded, sarcoidosis was diagnosed simultaneously or after the CTD. Sarcoidosis in only one organ ("isolated sarcoidosis") was associated with sarcoidosis being diagnosed simultaneously or after the CTD ($p = 0.0001$).
Conclusions: These data suggest that a significant portion of patients with CTDs and sarcoidosis

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may actually not have the latter disease. Rather, the CTD may "cause" granulomatous inflammation. Alternate explanations for these findings include that sarcoidosis and/or the connective tissue disease was misdiagnosed in these patients. The diagnosis of a concomitant connective tissue disease and sarcoidosis must be made with extreme caution.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology.[1] To that end, all alternative granulomatous diseases need to be excluded before the diagnosis of sarcoidosis can be secured.[2,3] These diseases include infections from mycobacteria and fungi,[1] occupational diseases such as chronic beryllium disease,[4] and lymphoma.[1]

Connective tissue diseases are not generally recognized as being a cause of granuloma formation. However, many case reports and very small case series have suggested that there is an association between connective tissue diseases and sarcoidosis. Although no epidemiological analysis of such an association has been undertaken, it is extremely unlikely that a patient would develop both diseases concomitantly given their prevalence. We undertook a retrospective analysis of patients with concomitant sarcoidosis and a connective tissue disease at two medical university centers. It is important to emphasize that we did not perform an epidemiological analysis of the association between sarcoidosis and connective tissue diseases. Rather, we aimed to characterize the clinical presentation and characteristics of patients with a history of both diseases. In addition, we reviewed the medical literature to identify and describe patients who were previously reported to have both conditions.

Methods

This study was conducted at the Medical University of South Carolina (MUSC) and Albany Medical College (AMC). It was approved by the Institutional Review Boards at both institutions. At MUSC, ICD-9 codes were examined and patients were identified who were coded as having sarcoidosis as well as one of the following diseases: systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, dermatomyositis, polymyositis, psoriatic arthritis, rheumatoid arthritis, and undifferentiated connective tissue disease. At AMC, patients were identified using established sarcoidosis and rheumatology clinical databases. At both AMC and MUSC, patients were identified over a 10-year period of time.

The patients identified by ICD-9 coding were considered to have a history of sarcoidosis if, upon medical chart review: (1) there was documented tissue confirmation of noncaseating granulomas on biopsy of one or more organs; (2) alternative causes of granulomatous inflammation were reasonably excluded[1]; and (3) the presence of clinical signs or symptoms consistent with sarcoidosis were present.[2] Only such patients could be entered into the AMC and MUSC sarcoidosis databases. Involvement of an organ with sarcoidosis was determined by using the ACCESS organ assessment instrument.[5]

The patients identified by ICD-9 coding were considered to have a history of a connective tissue disease if, upon medical chart review, they fulfilled standard criteria for these diagnosis.[6–21]

Only patients fulfilling the above criteria for both a history of sarcoidosis and a connective tissue disease were included in this analysis. Patients were not required to have these two diseases concurrently. Data were collected retrospectively and included: age, race, year of diagnosis of sarcoidosis, year of connective tissue disease diagnosis, biopsy data, radiographic findings, and pulmonary function testing. The diagnosis of sarcoidosis and a connective tissue disease were classified as "simultaneous" if they were the diagnoses related to symptoms and/or clinical findings that occurred concurrently. Scadding stages[22] of sarcoidosis were determined by reports of chest radiographs or chest computed tomography scans. Sarcoidosis organ involvement was determined on the basis of the A Case Control Etiology of Sarcoidosis Study (ACCESS) organ assessment system.[5]

Patients with concomitant sarcoidosis and a connective tissue disease who had been described in the medical literature were identified via Medline and PubMed database searches through October 1 2012 using the following terms, sarcoidosis, rheumatoid arthritis, scleroderma, systemic sclerosis, lupus, systemic lupus erythematosus, dermatomyositis, polymyositis, Behcet's syndrome, mixed connective tissue disease, overlap syndrome, Wegener's granulomatosis, granulomatosis with polyangiitis, microscopic polyangiitis, psoriatic arthritis, Reiter's syndrome, reactive arthritis. All manuscripts identified by this method were evaluated to determine if the reported clinical data supported concomitant diagnoses of sarcoidosis and a connective tissue disease.

Results

We identified 15 patients (8 at MUSC, 7 at AMC) with concomitant sarcoidosis and a connective tissue disease (Table 1). The patients were all female. Systemic lupus erythematosus (4/15, 27%), scleroderma (4/15, 27%), rheumatoid arthritis (3/15, 20%) accounted for the connective tissues diseases found in 11 of the 15 patients (73%).

Table 2 shows the clinical features of sarcoidosis in our cohort. The lung was the most common organ involved, followed by the skin, peripheral lymph node, eye, and liver. The most common Scadding stage at the time of sarcoidosis presentation was stage 1 (bilateral hilar adenopathy without parenchymal infiltrates). Only 1/15 (7%) patients had stage 4 (fibrocystic) disease. Four patients in our cohort had evidence of only one organ involvement with sarcoidosis: mediastinal lymph node (3 patients), peripheral lymph