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Sarcoidois: is it only a mimicker of primary rheumatic disease? A single center experience

Şenol Kobak, Fidan Sever, Oya Nermin Sivrikoz and Mehmet Orman

Abstract

Background: Sarcoidosis is known as a T helper 1 lymphocyte (Th1-Ly) mediated disease which can imitate or sometimes accompany many primary rheumatic diseases. The purpose of this study is to share the clinical, demographic and laboratory data of patients presenting with rheumatologic manifestations and diagnosed with sarcoidosis.

Methods: A total of 42 patients (10 men) were included in the study. The patients were admitted to the rheumatology outpatient clinic for the first time with different rheumatic complaints between November 2011 and May 2013 and were diagnosed with sarcoidosis after relevant tests. Clinical, demographic, laboratory, radiological and histological data of these patients were collected during the 18-month follow-up period and then analyzed.

Results: Mean patient age was 45.2 years (20–70 years) and mean duration of disease was 3.5 years (1 month–25 years). Evaluation of system and organ involvement revealed that 20 (47.6%) patients had erythema nodosum, 3 (7.1%) had uveitis, 1 (2.3%) had myositis, 1 (2.3%) had neurosarcoidosis, 32 (76.2%) had arthritis and 40 (95.2%) had arthralgia. Of the 32 patients with arthritis, 28 (87.5%) had involvement of the ankle, 3 (9.4%) had involvement of the knee and 1 (3.2%) had involvement of the wrist. No patient had cardiac involvement. Thoracic computed tomography scan showed stage 1, 2, 3 and 4 sarcoidosis in 12 (28.5%), 22 (52.4%), 4 (9.5%) and 4 (9.5%) patients, respectively. Histopathology of sarcoidosis was verified by endobronchial ultrasound, mediastinoscopy and skin and axillary biopsy of lymphadenopathies, which revealed noncaseating granulomas. Laboratory tests showed elevated serum angiotensin-converting enzyme in 15 (35.7%) patients, elevated serum calcium level in 6 (14.2%) patients and elevated serum 1,25-dihydroxyvitamin D concentrations in 2 (4.7%) patients. Serological tests showed antinuclear antibody positivity in 12 (28.5%) patients, rheumatoid factor positivity in 7 (16.6%) patients and anticyclic citrullinated antibody positivity in 2 (4.8%) patients.

Conclusion: Sarcoidosis can imitate or accompany many primary rheumatic diseases. Sarcoidosis should be considered not simply as an imitator but as a primary rheumatic pathology mediated by Th1-Ly. New studies are warranted on this subject.

Keywords: primary rheumatic disease, rheumatologic manifestations, sarcoidosis

Correspondence to:
Senol Kobak, Phd
Department of Rheumatology, Faculty of Medicine, Şifa University, Sanayi Cad. No. 7 Bornova, Izmir 35100, Turkey
senolkobak@yahoo.com

Fidan Sever, MD
Department of Chest Disease, Faculty of Medicine, Şifa University, Izmir, Turkey

Oya Nermin Sivrikoz, MD
Department of Pathology, Faculty of Medicine, Şifa University, Izmir, Turkey

Mehmet Orman, MD
Department of Statistics, Faculty of Medicine, Ege University, Izmir, Turkey

Introduction

Sarcoidosis is a systemic disease characterized by the reaction of noncaseating granulomas. It can involve a number of tissues and organs and its exact cause is not known [Newman *et al.* 1997]. Although its pathogenesis is not clear, activation of the cellular immune system and nonspecific inflammatory response occur with the influence of some genetic and environmental factors [Hofmann *et al.* 2008]. T helper 1 lymphocyte (Th1-Ly) and macrophage-derived proinflammatory cytokines trigger the inflammatory cascade

and granulomas are formed as a result of tissue permeability, cellular influx and local cell proliferation [Chen and Moller, 2008]. Identification of noncaseating epithelioid cell granulomas is an essential pathological finding in sarcoidosis [Smith *et al.* 2008]. Epithelioid cells are transformed to bone marrow monocytes with marked secretory activity. Increased active CD4 T lymphocytes have been shown in sarcoid tissues. While these lymphocytes are diffusely increased in the granulomatous lesion, a small amount of CD8 T-Ly, B cells, plasma and mast cells were found in the outer part of the granuloma [Kataria and Holter, 1997]. Varying prevalence, clinical findings and course of disease among different races and ethnic groups indicate that sarcoidosis is a heterogeneous disease [Rybicki *et al.* 1997]. It is more common in women and often develops when patients are in their forties. In the USA, the incidence of sarcoidosis is 10.9/100,000 in white people while this rate goes up to 35.5 in African Americans with a more severe course of disease [Milman and Selroos, 1990]. Sarcoidosis can imitate or accompany many primary rheumatic diseases [Gumpel *et al.* 1967; Pettersson, 1998]. The rate of musculoskeletal system involvement is 15–25% [Spilberg *et al.* 1969]. In this study, we shared the clinical, demographic and laboratory data of 42 patients who presented to our outpatient clinic with different rheumatologic complaints and were diagnosed with sarcoidosis after relevant examinations.

Materials and methods

A total of 42 patients (10 men) were included in the study. The patients were admitted to the rheumatology outpatient clinic for the first time with different rheumatic complaints between November 2011 and May 2013 and were diagnosed with sarcoidosis after relevant tests were performed. Comprehensive rheumatologic anamnesis was obtained from all patients; the findings of systemic examination and locomotor system examination were recorded. According to anamnesis of the patients, we understood that only one patient was diagnosed with sarcoidosis 25 years ago, but had not had any complaints until admission to our hospital. Diagnostic, laboratory, serological and imaging tests were carried out. Tissue samples collected with endobronchial ultrasound (EBUS), mediastinoscopy and skin and axillary lymphadenopathies biopsies were used for histopathological verification of sarcoidosis and diagnosis was made upon identification of noncaseating granulomas by the pathologist. Clinical, demographic, laboratory, radiological and histological data for these patients were collected during the 18-month treatment and follow-up period and then analyzed.

Statistical analysis

Crosstabs were created for data analysis and the χ^2 test or Fisher's exact test was used. The threshold level for statistical significance was determined as 0.05.

Results

The mean patient age was 45.2 years (20–70 years) and the mean duration of disease was 3.5 years (1 month–25 years). Evaluation of system and organ involvement revealed that 20 (47.6%) patients had erythema nodosum, 3 (7.1%) had uveitis, 1 (2.3%) had myositis, 1 (2.3%) had neurosarcoidosis, 32 (76.2%) had arthritis and 40 (95.2%) had arthralgia. Of the 32 patients with arthritis, 28 (87.5%) had involvement of the ankle, 3 (9.4%) had involvement of the knee and 1 (3.2%) had involvement of the wrist. No patient had cardiac involvement. Thoracic computed tomography scan showed stage 1, 2, 3 and 4 sarcoidosis in 12 (28.5%), 22 (52.4%), 4 (9.5%) and 4 (9.5%) patients respectively (Table 1).

A possible relationship between different clinical and laboratory findings was investigated: arthritis and Erythema nodosum (EN) ($p = 0.003$), arthritis and erythrocyte sedimentation rate (ESR) ($p = 0.01$), and stage 1 sarcoidosis and C-reactive protein (CRP) ($p = 0.004$) were statistically significant. Histopathology of sarcoidosis was confirmed by EBUS, mediastinoscopy and skin and axillary laparoscopic (LAP) biopsy, which revealed noncaseating granulomas. Laboratory tests showed elevated levels of serum angiotensin-converting enzyme (ACE) in 15 (35.7%) patients, elevated serum calcium in 6 (14.2%) patients and elevated serum 1,25-dihydroxyvitamin D concentrations in 2 (4.7%) patients. Serological tests showed antinuclear antibody (ANA) positivity in 12 (28.5%) patients (speckled in 9, nucleolar in 2 and sentromer in 1 patient), rheumatoid factor (RF) positivity in 7 (16.6%) patients and anticyclic citrullinated antibody positivity in 2 (4.8%) patients. Laboratory tests at the time of the initial visit revealed elevated ESR and increased CRP levels in 25 (59.5%) and 23 (54.7%) patients respectively. Three patients in our cohort had coexistence with another rheumatic disease

Table 1. Demographic, clinical and laboratory features in patients with sarcoidosis.

Features	Patients, *N* = 42
Age, mean (years)	45.2
Disease duration, mean (years)	3.5
Sex (women/men)	32/10
Erythema nodosum	20 (47.6%)
Uveitis	3 (7.1%)
Myositis	1 (2.3%)
Neurosarcoidosis	1 (2.3%)
Arthritis	32 (76.2%)
Elevated serum ACE level	15 (35.7%)
ANA positivity	12 (28.5%)
RF positivity	7 (16.6%)
Stage 1	12 (28.5%)
Stage 2	22 (52.4%)
Stage3/4	4/4 (9.5%)

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; RF, rheumatoid factor.

(ankylosing spondylitis, systemic sclerosis and Sjögren's syndrome). As for the patients' treatment approaches, 17 patients had short-term treatment with low-dose corticosteroids, 5 patients used hydroxychloroquine (HQ), 1 patient used azathioprine (AZT), 1 patient used methotrexate (MTX), 2 patients used colchicum dispert (CD) and 35 patients used nonsteroidal anti-inflammatory drugs (NSAIDs). Musculoskeletal system complaints were rapidly controlled and lung findings also regressed markedly.

Discussion

Sarcoidosis is a systemic granulomatous disease with unknown etiology and multiple organ involvement, which is mediated by Th1-Ly. The disease primarily starts with pulmonary findings, however extrapulmonary involvement and rheumatologic manifestations are also common. Sarcoidosis can imitate or accompany many rheumatological diseases. It most commonly presents with connective tissue diseases such as primary Sjögren's syndrome, systemic lupus erythematosus and scleroderma but clinical findings which are reminiscent of vasculitis or spondyloarthritis are also seen [Chatham, 2010]. In our cohort three patients also had other rheumatic disease (ankylosing spondylitis, systemic sclerosis and Sjögren's syndrome). These patients were diagnosed according to New York, American College of Rheumatology and American-European Study Group (AESG) criteria respectively. Two different joint involvement patterns (acute/chronic) are seen in 15–25% of patients with sarcoidosis. Acute arthritis is more common and unilateral/bilateral ankle, knee and wrist involvement is usually observed. There can be certain accompanying constitutional symptoms such as weakness and fever, as well as generalized arthralgia.

Chronic sarcoid arthritis is less common, seen with generalized disease and is prevalent in black people. It involves joints such as the knee, feet, wrist, ankle, metatarsal phalangeal and proximal interphalangeal. The condition may lead to Jaccoud's type deforming arthropathy or joint destruction [Visser *et al.* 2002]. Sarcoidosis should be considered first in the case of bilateral acute arthritis of the ankle. In our series, 40 patients had arthralgia, 25 patients had bilateral arthritis of the ankle and 3 patients had unilateral involvement of the ankle. Only 2 cases developed chronic sarcoid arthritis.

Erythema nodosum is a type of panniculitis that is seen with different infections, drugs or rheumatic pathologies. It is a significant symptom of sarcoidosis and is accompanied by acute arthritis with an incidence of up to 75% in some races [Pettersson, 2000]. In our series, this condition was observed in 12 patients at the time of initial admission to hospital and in 47.6% of patients during the entire course of the disease.

Muscle involvement can present with three different clinical forms: acute, chronic and nodular type [Fayad *et al.* 2006]. It is usually asymptomatic and histological verification is made with muscle biopsy. In our series, we identified myositis in one patient and controlled the symptoms with corticosteroid and MTX treatment.

Sarcoidosis is diagnosed using clinical findings, identification of noncaseating granulomas and exclusion of other causes [Lofgren, 1953]. The general approach includes performing a biopsy with at least one invasive method and pathological confirmation in all cases in whom sarcoidosis is suspected. Transbronchial lung biopsy is used for diagnosis in many cases. The need for a biopsy is discussed for patients presenting with Löfgren's syndrome. In our series, tissue biopsies were collected using different methods to confirm the diagnosis of sarcoidosis. EBUS, skin and axillary LAP biopsy were performed on 34 patients, 2 patients

and 1 patient, respectively. Histopathological presence of noncaseating granulomas was shown in all of these patients. No biopsy samples were collected in five patients because they had presented with typical Löfgren's syndrome.

Different biochemical and serological changes can be identified in patients with sarcoidosis [Selroos, 1986]. High ESRs and CRP elevation can be detected during acute sarcoidosis. RF and ANA positivity can be seen in 15–38% and 8–10% of patients respectively. In our series, we found increased ESR, elevated CRP, RF positivity and ANA positivity in 25 (59.5%), 23 (54.7%), 7 (16.6%) and 12 (28.5%) patients respectively. Elevated serum calcium and 1,25-dihydroxyvitamin D levels can be observed in patients with sarcoidosis. Active macrophages are responsible for the hydroxylation of 1,25-dihydroxyvitamin D3 and increase the absorption of calcium in the gastrointestinal system, resulting in hypercalcemia (10%) and hypercalciuria (40%) [Sharma, 1996]. These findings are more common in chronic sarcoidosis. In our series, six patients had elevated serum calcium and two patients had elevated serum 1,25-dihydroxyvitamin D. Elevated serum ACE levels are seen in 40–90% of patients with sarcoidosis; it is considered to be synthesized from the epithelioid cells and alveolar macrophages found in the granulomas [Lieberman, 1975]. Elevated serum ACE level was associated with chronic arthritis and generalized disease and it was identified in only half of the patients with Löfgren's syndrome. Since it is also observed in other granulomatous diseases, elevated serum ACE level is not specific for the diagnosis of sarcoidosis. In our series, 15 (35.7%) patients had elevated serum ACE level.

The method of treatment for sarcoidosis is not clear yet. NSAIDs are sufficient for mild and acute disease while corticosteroids can be used for chronic systemic pulmonary and extrapulmonary disease. However, it has been shown in one study that when remission is achieved with corticosteroids, relapse rates are much higher than spontaneous remission [Iannuzzi *et al.* 2007]. Low-dose corticosteroids and basic drugs such as MTX, cyclosporine A and AZT are used for chronic arthropathy [Schutt *et al.* 2010]. New biological drugs have recently been tried to treat sarcoidosis. In our series, we controlled the disease with NSAIDs and low-dose corticosteroids as first-line therapy. In patients whose condition did not respond, we used AZT in one patient, MTX in one patient, CD in two patients and HQ in five patients.

In conclusion, we pooled the data of 42 patients who presented to our outpatient clinic for the first time with rheumatic complaints and were diagnosed with sarcoidosis after relevant tests. The low number of patients prevents generalizations about the rheumatological manifestations of sarcoidosis. Nonetheless, it should be noted that similar findings have been found in the literature. Delayed or incorrect diagnosis is possible since sarcoidosis can imitate rheumatological diseases. Therefore, it should always be considered for differential diagnosis in patients presenting to a rheumatology physician with musculoskeletal system complaints. Sarcoidosis should be considered not simply as an imitator but as a primary rheumatic pathology mediated by Th1-Ly. New studies are required in this area.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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