Ther Adv Musculoskel Dis
2016, Vol. 8(6) 220–224
DOI: 10.1177/1759720X16670598

The clinical characteristics of sarcoid arthropathy based on a prospective cohort study

Senol Kobak, Fidan Sever, Ozan Usluer, Tuncay Goksel and Mehmet Orman

Abstract

Background: Sarcoidosis is known as a Th1-mediated disease, which can mimic many primary rheumatologic diseases or sometimes co-exist with them. Clinical characteristics of sarcoid arthropathy are not well described and the studies reported in the literature so far are mostly based on data from referrals. The aim of this study was to evaluate the incidence and clinical characteristics of sarcoid arthropathy.

Methods: All our patients were prospectively evaluated in our rheumatology outpatient center from 2011 to 2015. A total of 114 (32 male) patients with sarcoidosis who were admitted to our clinic were included in the study. Clinical, demographical, laboratory, radiological and histological data of these patients obtained during 4-year follow-up and treatment period were compiled and analyzed.

Results: The mean patient age was 48.1 years (range, 20–82 years), and the mean disease duration was 40.5 months (range, 1–300 months). Sarcoid arthritis was observed in 71 (62.3%), and arthralgia in 106 (92.9%) patients. Out of the 71 patients with arthritis, 61 (85.9%) had involvement of ankle, 7 (9.8%) knee, 2 (2.8%) wrist, MCP and PIP joints, and 1 (1.4%) had shoulder periarthritis. Oligoarthritis (two to four joints) was the most common pattern followed by monoarthritis and polyarthritis. Arthritis and erytjhema nodosum and arthritis and female sex was found to be correlated ($p = 0.03$ and $p = 0.001$). Again, in patients with arthritis, even higher levels of CRP/ESR as well as ANA and RF positivity were observed ($p = 0.03$, $p = 0.01$, $p = 0.01$, and $p = 0.02$, respectively). A total of 11 patients had another rheumatic pathology concurrent with sarcoidosis.

Conclusions: Inflammatory arthritis occurs in a majority of patients with sarcoidosis. Acute arthritis with bilateral ankle involvement is the most common pattern of sarcoid arthropathy. Sarcoidosis can mimic many primary rheumatic diseases or may coexist with them. Sarcoidosis should be considered not only as a mimicker but also as a Th1-mediated primary rheumatologic pathology.

Keywords: arthropathy, incidence, sarcoidosis

Correspondence to:
Senol Kobak, MD, PhD
Department of Rheumatology, Faculty of Medicine, Istinye University, LIV Hospital, Istanbul, Turkey
senolkobak@gmail.com

Fidan Sever, MD
Department of Chest Diseases, Faculty of Medicine, Sifa University, Izmir, Turkey

Ozan Usluer, MD
Department of Chest Surgery, Suat Seren Chest Diseases Hospital, Izmir, Turkey

Tuncay Goksel, MD
Department of Chest Diseases, Faculty of Medicine, Ege University, Izmir, Turkey

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

Introduction

Sarcoidosis is a systemic disease of unknown etiology, which can involve many tissues and organs and is characterized by a noncaseating granuloma reaction [Newman *et al.* 1997]. Although the pathogenesis is still not entirely clear, activation of the cellular immune system and nonspecific inflammatory response can occur with the effects of some genetic and environmental factors [Hofmann *et al.* 2008]. Th1-related 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]. Determining noncaseating epithelioid cell granulomas is an essential pathologic

hallmark of sarcoidosis [Smith *et al.* 2008; Kataria and Holter, 1997]. Different prevalence, clinical signs and symptoms, and disease course determined in different races and ethnic groups is indicative of the heterogeneous nature of sarcoidosis [Rybicki *et al.* 1997]. Generally, it is more common among women and mostly occurs between 20–40 years of age, although a second peak has been reported in women over 50 years old. The incidence of sarcoidosis is 10.9 per 100,000 in the white population in the USA, and this ratio increases to 35.5 per 100,000 with a more severe disease course in African-Americans [Milman and Selroos, 1990]. Sarcoidosis is a chronic granulomatous disease which can present with various clinical manifestations. It can mimic many primary rheumatologic diseases and it can co-exist with them [Pettersson, 1998]. The disease presents most often with bilateral hilar lymphadenopathy, pulmonary infiltrates, and skin and eye lesions. Sarcoid arthropathy is seen at a rate of 15–25% [Gumpel *et al.* 1967]. Two major patterns of joint involvement have been defined: acute and chronic forms. The most common is the acute form and it can be the first symptom of sarcoidosis and may present with arthralgia, arthritis or periarthritis. Chronic sarcoid arthritis is usually associated with parenchymal lung disease or other organ involvements and is relatively rare. Although rare, muscle and bone involvements are also seen [Spilberg *et al.* 1969]. The prevalence of spondyloarthritis and sacroiliitis was shown to increase in patients with sarcoidosis [Erb *et al.* 2005; Kobak *et al.* 2014]. Many studies on the clinical characteristics of sarcoid arthropathy are from referral centers [Visser *et al.* 2002; Gran and Bøhmer, 1996; Glennas *et al.* 1995]. These may not reflect the disease as it occurs in the community. This study aimed to use the data from a well-defined cohort population which shows the clinical characteristics of sarcoid arthropathy.

Materials and methods

All our patients were prospectively evaluated in our single rheumatology outpatient center from 2011 to 2015. A cohort of 114 patients diagnosed with sarcoidosis were included in the study. Thorough rheumatology history was taken from all the patients, and the findings of systemic examination and musculoskeletal system examinations were recorded. All patients' data were collected and well documented using our computer system. Biochemical, serological, laboratory tests and imaging techniques were used for diagnosis. Biopsy specimens taken from different tissues (lymph nodes, skin, parotid gland, penis) were used for histological verification of sarcoidosis, and diagnosis was confirmed as the pathologists showed the noncaseating granulomas. All our sarcoidosis patients (except those with Löfgren syndrome in which biopsy was not performed) were diagnosed according to clinical, radiological and histopathological (noncaseating granuloma) findings. If the patients had typical Löfgren syndrome they were not required to have a pathological verification of sarcoidosis. Clinical, demographical, laboratory, radiological and histological data of these patients obtained during this 4-year follow-up and treatment period were compiled and analyzed. Ethics committee approval was obtained and informed consent forms were taken from all patients

Statistical analysis

Data was analyzed by the Statistical Package for the Social Sciences (SPSS) version 20.0, software for Windows (SPSS, Chicago, Illinois, USA). Cross tables were used in analysis of data and Chi-square and Fisher's exact test analyses were performed where appropriate. The data are given as frequency and percentages. The statistical significance threshold was taken as 0.05.

Results

In this study, 114 (32 male) patients were included. The mean patient age was 48.1 years (range, 20–82 years), and the mean disease duration was 40.5 months (range, 1–300 months). Joint pain occurred in 106 (92.9%) patients, and 71 (62.3%) patients had sarcoid arthritis. Out of the 71 patients with arthritis, 61 (85.9%) had ankle involvement, 7 (9.8%) had knee involvement, 2 (2.8%) had involvement of wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, and 1 (1.4%) had shoulder periarthritis (Table 1). Of the 71 cases with objective evidence of synovitis, oligoarthritis (two to four joints) was the most common pattern followed by monoarthritis and polyarthritis. Radiographic investigations were obtained in all patients. None of the radiographs obtained at diagnosis demonstrated any narrowing at joint space or bony erosion. Classic sarcoidal bone lesions such as bone cyst or lytic appearance were observed in one patient. In the majority of patients (78.9%), the arthritis resolved within

Table 1. Frequency of the rheumatic manifestations in patients with sarcoidosis.

Findings	Patients, $N = 114$ (%)
Arthralgia	106 (92.9%)
Arthritis	71 (62.3%)
Ankle joint involvement	61 (85.9%)
Knee joint involvement	7 (9.8%)
Wrist, MCP and PIP joint involvement	2 (2.8%)
Periarthritis	1 (1.4%)
Löfgren syndrome	20 (17.5%)
Erythema nodosum	53 (46.5%)
Raynaud's phenomenon	1 (0.87%)
Osseous lesions	1 (0.87%)
Lytic lesions	0 (0%)
Sclerotic lesions	1 (0.87%)
Reticular pattern	0 (0%)
Myopathy	1 (0.87%)
Overlap syndromes	11 (9.6%)

MCP, metacarpophalangeal; PIP, proximal interphalangeal.

Table 2. Demographic, clinical and laboratory features in patients with sarcoidosis.

Features	Patients, $N = 114$ (%)
Age, mean, year	48.1 years (20–82 years)
Disease duration, mean, months	40.5 months (1–300 months)
Sex (women/men)	82/32
Uveitis	12 (10.5%)
Myositis	1 (0.87%)
Neurosarcoidosis	1 (0.87%)
Penile mass	1 (0.87%)
Parotid involvement	1 (0.87%)
Elevated serum ACE level	72 (63.1%)
Elevated serum calcium level	15 (13.1%)
Elevated serum D3 level	4 (3.5%)
Increased CRP	45 (39.5%)
Increased ESR	59 (51.7%)
Stage 0	5 (4.3%)
Stage 1	57 (50%)
Stage 2	35 (30.4%)
Stage 3	7 (6.1%)
Stage 4	10 (8.7%)

ACE, angiotensin-converting enzyme; CRP, C-reactive protein; ESR erythrocyte sedimentation rate

6 weeks. Most patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) or oral glucocorticoids for a short period (61% with NSAID monotherapy, 26.3% with oral glucocorticoid monotherapy, 14% with no therapy). Chronic sarcoid arthritis (more than 6 weeks) occurred in 24 (21.1%) patients. These patients received courses of disease-modifying anti-rheumatic drugs (DMARDs) including hydroxychloroquine, methotrexate, azathioprine, sulfasalazine and colchicine. As for system and organ involvement; erythema nodosum was seen in 53 (46.5%) patients, uveitis in 12 (10.5%) patients, myositis in 1 (0.87%) patient, and neurosarcoidosis in 1 (0.87%) patient. Chest X-rays and thorax computerized tomography (CT) results showed stage 0 (extrapulmonary) disease in 5 (4.3%) patients, stage 1 (bilateral hilar lymphadenopathy) in 57 (50%) patients, stage 2 (bilateral hilar lymphadenopathy + pulmonary infiltrate) in 35 (30.4%) patients, stage 3 (only pulmonary infiltrate without hilar lymphadenopathy) in 7 (6.1%) patients, and stage 4 (pulmonary fibrosis) in 10 (8.7%) patients with sarcoidosis (Table 2). Histopathological verification of sarcoidosis was done by endobronchial ultrasound (EBUS) and mediastinoscopy and also by demonstrating noncaseating granulomas through biopsies of the skin, axillary lymphadenopathy, penile mass and parotid gland. Biopsy was not taken in 20 (17.5%) patients because they presented typical clinical features of Löfgren syndrome (fever, bilateral hilar lymphadenopathy, erythema nodosum, ankle arthralgia/arthritis). In laboratory tests, increased serum levels of angiotensin-converting enzyme (ACE) were detected in 72 (63.1%) patients, calcium in 15 (13.1%) patients, and vitamin D3 in 4 (3.5%) patients. As for the acute phase response reactants, increased C-reactive protein (CRP) level was detected in 45 (39.5%) patients and increased erythrocyte sedimentation rate (ESR) in 59 (51.7%) patients. A total of 11 patients, however, had another rheumatic pathology that coexisted with sarcoidosis (1 Sjögren's syndrome, 3 rheumatoid arthritis, 1 Still's disease, 1 scleroderma, 4 ankylosing spondylitis, 1 familial Mediterranean fever). When the correlation between clinical findings was considered, arthritis and erythema nodosum and arthritis and female sex were correlated ($p = 0.03$, and $p = 0.001$). Again, in patients with arthritis, even higher levels of CRP/ESR as well as antinuclear antibody (ANA) and rheumatoid factor (RF) positivity

were observed ($p = 0.03$, $p = 0.01$, $p = 0.01$ and $p = 0.02$, respectively).

Discussion

In this study of the prevalence of sarcoid arthropathy in a well-defined inception cohort population, joint pain was a most common clinical manifestation, seen in 92.9% of patients with sarcoidosis. Acute sarcoid arthritis was seen in 71 (62.3%) patients, while chronic arthritis occurred in 24 (21.1%) patients. Oligoarthritis was the most common pattern of joint involvement, and bilateral ankle arthritis was the prominent feature. The prognosis of sarcoid arthropathy was generally favorable, as the arthritis resolved within 6 weeks in the majority of patients. Cutaneous manifestations were observed in 46.5% of patients with sarcoid arthropathy. Erythema nodosum was the most common cutaneous finding. Other dermatologic manifestations of sarcoidosis including lupus pernio, maculopapular rashes, psoriasis-like lesions, scars or tattoos were not observed in this cohort. A relationship between sarcoid arthritis and the female sex and acute phase reactants was detected in our cohort.

Sarcoidosis is a Th1-mediated systemic granulomatous disease of unknown etiology involving many different organs. It primarily starts with pulmonary symptoms, but extrapulmonary involvement is also frequent. Sarcoidosis can mimic many rheumatologic diseases or co-exist with them. It may present most frequently with clinical symptoms resembling connective tissue diseases such as primary Sjögren's syndrome (SS), Systemic Lupus Erythematosus (SLE) and scleroderma, as well as vasculitis and spondyloarthritis [Hansen *et al.* 2008; Fernandes *et al.* 2000]. Overall, two different patterns of joint involvement (acute /chronic) can be seen in 15–25% of patients with sarcoidosis. Acute arthritis is more common and usually affects uni/bilateral ankle, knee and wrist joints. Generalized arthralgia may also occur, in addition to some constitutional symptoms such as fatigue and fever. The incidence of Löfgren syndrome in our patients (17.5%) was consistent with the results reported in the literature [Sharma *et al.* 2012]. The high prevalence of musculoskeletal involvement detected in our study may be caused by genetic and racial reasons. Again, similar to other studies, ankle, knee and wrist were the most common joints involved. Chronic sarcoid arthritis is less common and seen in diffuse disease and in the black race, and it involves joints such as knee, ankle, wrist, and MCP and PIP joints [Torralba and Quismorio, 2003]. It may cause Jaccoud's-type deformative arthropathy or joint destruction. An increase is detected in synovial fluid analysis in mononuclear or polymorphonuclear cells as well as noncaseating granulomas and sometimes nonspecific signs are detected in synovial biopsy. Erosive destructive changes are rare in direct radiography, albeit soft tissue swelling, periarticular osteoporosis, and joint space narrowing may be seen. In our series, 24 (21.1%) patients developed chronic sarcoid arthritis. Also a positive correlation was detected between arthritis and acute phase reactants, ANA and RF positivity. Sarcoidosis can mimic many rheumatologic diseases or accompany them. It may present most frequently with clinical symptoms resembling connective tissue diseases such as primary SS, SLE and scleroderma, as well as vasculitis or spondyloarthritis [Kobak *et al.* 2013; Iannuzzi *et al.* 2007]. In our series, 11 patients had another rheumatic pathology concurrent with sarcoidosis

Our study has some limitations. Restricted data from only one center and a relatively small number of patients would not allow us to generalize these rheumatologic manifestations of sarcoidosis. The clinical presentations of sarcoidosis vary with respect to ethnicity; the results of the current study might not be generalizable to other populations, particularly those with a higher proportion of African-Americans. Nevertheless, our findings were similar to those reported in the literature.

In conclusion, sarcoidosis is an important disease. Occasionally, diagnosis of sarcoidosis may be delayed or mistaken because it can mimic various rheumatologic diseases. Therefore, it must be considered within the context of differential diagnosis for the patients admitted to the rheumatology physician with complaints of the musculoskeletal system. Sarcoidosis is not just a great mimicker but it should also be considered as a Th1-mediated, primary rheumatologic pathology. Further trials are needed to be performed on this subject.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Chen, E. and Moller, D. (2008) Etiology of sarcoidosis. *Clin Chest Med* 29: 365–377.

Erb, N., Cushley, M., Kassimos, D., Shave, R. and Kitas, G. (2005) An assessment of back pain and the prevalence of sacroiliitis in sarcoidosis. *Chest* 127: 192–196.

Fernandes, S., Singsen, B. and Hoffman, G. (2000) Sarcoidosis and systemic vasculitis. *Semin Arthritis Rheum* 30: 33–46.

Glennas, A., Kvien, T., Melby, K., Refvem, O., Andrup, O., Karstensen, B. *et al.* (1995) Acute sarcoid arthritis: occurrence, seasonal onset, clinical features and outcome. *Br J Rheumatol* 34: 45–50.

Gran, J. and Bøhmer, E. (1996) Acute sarcoid arthritis: a favourable outcome? A retrospective survey of 49 patients with review of the literature. *Scand J Rheumatol* 25: 70–73.

Gumpel, J., Johns, C. and Shulman, L. (1967) The joint disease in sarcoidosis. *Ann Rheum Dis* 26: 194–205.

Hansen, S., Hetta, A. and Omdal, R. (2008) Primary Sjögren's syndrome and sarcoidosis: coexistence more than by chance? *Scand J Rheumatol* 37: 485–486.

Hofmann, S., Franke, A., Fischer, A., Jacobs, G., Nothnagel, M., Gaede, K. *et al.* (2008) Genome-wide association study identifies ANXA11 as a new susceptibility locus for sarcoidosis. *Nat Genet* 40: 1103–1106.

Iannuzzi, M., Rybicki, B. and Teirstein, A. (2007) Sarcoidosis. *N Engl J Med* 357: 2153–2165.

Kataria, Y. and Holter, J. (1997) Immunology of sarcoidosis. *Clin Chest Med* 18: 719–739.

Kobak, S., Sever, F., Ince, O. and Orman, M. (2014) The prevalence of sacroiliitis and spondyloarthritis in patients with sarcoidosis. *Int J Rheumatol* 2014: 289454. DOI: 10.1155/2014/289454 [Epub ahead of print 12 May 2014].

Kobak, S., Sever, F., Sivrikoz, O. and Karaarslan, A. (2013) Coexistence of sarcoidosis and systemic sclerosis. *Case Rep Rheumatol* 2013: 684216. DOI: 10.1155/2013/684216 [Epub ahead of print 5 December 2013].

Milman, N. and Selroos, O. (1990) Pulmonary sarcoidosis in the Nordic countries 1950–1982: epidemiology and clinical picture. *Sarcoidosis* 7: 50–57.

Newman, L., Rose, C. and Maier, L. (1997) Sarcoidosis. *N Engl J Med* 336: 1224–1234.

Pettersson, T. (1998) Rheumatic features of sarcoidosis. *Curr Opin Rheumatol* 10: 73–78.

Rybicki, B., Major, M., Popovich, J., Maliarik, M. and Iannuzzi, M. (1997) Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 145: 234–241.

Sharma, S., Soneja, M., Sharma, A., Sharma, M. and Hari, S. (2012) Rare manifestations of sarcoidosis in modern era of new diagnostic tools. *Ind J Med Res* 135: 621–629.

Smith, G., Brownell, I., Sanchez, M. and Prystowsky, S. (2008) Advances in the genetics of sarcoidosis. *Clin Genet* 73: 401–412.

Spilberg, I., Siltzbach, L. and McEwen, C. (1969) The arthritis of sarcoidosis. *Arthritis Rheum* 12: 126–137.

Torralba, K. and Quismorio, F. (2003) Sarcoid arthritis: a review of clinical features, pathology, and therapy. *Sarc Vasc Diff Lung Dis* 20: 95–103.

Visser, H., Vos, K., Zanelli, E., Verduyn, W., Schreuder, G., Speyer, I. *et al.* (2002) Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* 61: 499–504.