Sarcoidosis: a rheumatologist's perspective

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***Abstract*:** Sarcoidosis is a systemic disorder of unknown etiology, which may involve various tissues and organs and is characterized by a noncaseating granuloma reaction. While pathogenesis is not yet clear, cellular immune system activation and nonspecific inflammatory response occur secondarily to several genetic and environmental factors. T helper 1-cells and macrophage-derived pro-inflammatory cytokines stimulate the inflammatory cascade and formation of granuloma occurs as a result of tissue permeability, cell influx, and local cell proliferation. The different prevalence, clinical results, and disease course observed in different races and ethnic groups, is an indicator of the heterogeneous nature of the disease. Sarcoidosis may mimic and/or may occur concomitantly with numerous primary rheumatic diseases. This disease most commonly presents with bilateral hilar lymphadenopathy, pulmonary infiltrations, and skin and eye lesions. Locomotor system involvement is observed at a range of 15% and 25%. Two major joint involvements have been described: acute and chronic form. The most common form, the acute form, may be the first sign of sarcoidosis and present with arthralgia, arthritis, or periarthritis. Chronic sarcoid arthritis is usually associated with pulmonary parenchymal disease or other organ involvement and occurs rarely. While asymptomatic muscular involvement is reported between 25% and 75%, symptomatic muscular involvement is very rare. Symptomatic myopathy may present as three different types: chronic myopathy, palpable nodular myositis, or acute myositis. Even if rare, 2–5% of cases may exhibit osseous involvement and it is frequently associated with lupus pernio, chronic uveitis, and multisystemic disease. Sarcoidosis was reported together with different rheumatologic diseases. There are studies showing that sarcoidosis may mimic the clinical and laboratory findings of these disorders. Nonsteroidal anti-inflammatory drugs and corticosteroids are used for treating the symptoms of rheumatologic findings. In patients who are unresponsive to corticosteroids, immunosuppressive and anti-tumor necrosis factor alpha drugs may be used. In this review, the incidence of rheumatologic symptoms, the clinical findings, and the treatment of rheumatologic manifestations of sarcoidosis are discussed.

Keywords: rheumatologic manifestations, rheumatologist's perspective, sarcoidosis

Introduction

Sarcoidosis is a multisystemic inflammatory disorder of unknown etiology, characterized by T-lymphocyte infiltration, granuloma formation, and impairment of the normal micro-architecture [Iannuzzi *et al.* 2007]. It may involve all races and ethnic groups, and occurs with a different incidence in different countries worldwide [Hosoda *et al.* 1997]. The highest incidence was reported in the Scandinavian countries (15–53 cases/100,000) [Milman and Selroos, 1990]. In the incidence studies performed in the USA, a higher incidence was reported in black people compared with white (10.9 cases/100,000 compared with 35.5 cases/100.000, respectively) [Baughman *et al.* 2003]. The disease is observed more frequently in women, and the age of occurrence is between 20 years and 40 years with a second peak occurring above the age of 50 years [Newman *et al.* 1997]. In different ethnic groups, not only a different incidence, but also a different phenotype has been reported [Rybicki *et al.* 1997]. For example, while Löfgren syndrome frequently occurs in the northern European countries, it occurs very rarely among Africans and the Japanese. Uveitis and cardiac involvement are

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more common among Japanese patients with sarcoidosis. Erythema nodosum (EN), an indicator of acute-onset disease and a good prognosis, is more frequent in the white race while lupus pernio, an indicator of chronic disease, is more frequent among Afro-Americans [Bardinas *et al.* 1989]. The prevalence and activity of granulomatous process may differ among different organs; this is a major factor that determines the heterogeneity of the disease. The onset pattern also exhibits marked differences. The acute form, characterized by bilateral hilar lymphadenopathy, EN, and arthralgia, is known as the Löfgren syndrome and has a good prognosis [Statement on sarcoidosis, 1999]. Other onset patterns that exhibit an insidious start, a chronic course, or are incidentally detected have also been reported. The lungs are among the most commonly involved organs (90%), followed by the skin, eyes, heart, liver, and the locomotor system [Baughman and Iannuzzi, 2000]. Rheumatologic findings are among the important extrapulmonary involvement of sarcoidosis, and may occur prior to or simultaneously with the pulmonary involvement, thereby causing a potential delay in diagnosis [Chatham, 2010]. In this article, we investigated the rheumatologic findings of sarcoidosis (see Tables 1 and 2) based on data from recent literature from the perspective of a rheumatologist.

Table 1. Rheumatologic manifestations of sarcoidosis.

Arthropathy
Arthralgia
Periarthritis
Tenosynovitis
Acute arthritis
Chronic arthritis
Sacroiliitis
Dactylitis
Enthesitis
Spondylitis
Myopathy
Acute myositis
Chronic myopathy
Nodular myopathy
Pseudohypertrophy
Bone sarcoidosis
Lytic/sclerotic lesions
Clubbing
Bone resorptions
Pathologic bone fractures
Other manifestations
Nonspecific symptoms (e.g. fatigue, myalgia)
Fibromyalgia/depression
Vasculitis
Sicca symptoms
Overlap syndrome (Sjögren syndrome, rheumatoid arthritis, scleroderma, ankylosing spondylitis)

Rheumatologic manifestations of sarcoidosis

Sarcoid arthropathy

Sarcoidosis may mimic and/or may occur concomitantly with numerous primary rheumatic diseases (e.g. connective tissue disorders, spondyloarthritis, vasculitis). Locomotor system involvement is observed at a range of 15% and 25% and commonly presents muscle and joint manifestations [Kobak *et al.* 2014c]. Arthritis findings are acute and chronic, and usually manifest as synovitis of the large joints in the lower extremities. Acute sarcoid arthritis is usually associated with bilateral hilar lymphadenopathy, fever, and EN, and a component of Löfgren syndrome [Pettersson, 2000]. It has a good prognosis and usually becomes self-limiting in 2 weeks to 4 months. It may sometimes involve prolonged musculoskeletal symptoms. The most common involves joints including the ankles, knees, wrists and the metacarpophalangeal joints. A study reported that the presence of three out of four criteria (e.g. symmetrical ankle arthritis, age < 40 years, EN, symptom onset > 2 months) was shown to have a 93% sensitivity and a 99% specificity for acute sarcoid arthritis [Visser *et al.* 2002]. A retrospective study detected acute sarcoid arthritis in 17 out of 186 patients (9%) who were investigated under the suspicion of reactive arthritis. Most of these patients presented in the spring time, and this was considered as potential evidence for a correlation between acute sarcoid arthritis and season [Glennas *et al.* 1995]. In patients presenting with ankle arthritis in the spring, the need to consider sarcoid arthritis was underlined. Among the clinical findings, it is important that redness, swelling and sensitivity in ankles are observed. Soft tissue ultrasonography shows periarticular soft tissue swelling rather than the typical arthritis findings. As for direct ankle graphy, soft tissue swelling is predominant with no changes in the bones and cartilage. Various publications reported the incidence of EN accompanying sarcoid arthritis [O'Neill, 1991]. A trial detected EN in two out of three patients with

Table 2. Characteristics of sarcoidosis and some primary rheumatic diseases.

Features	Sarcoidosis	Rheumatoid arthritis	Sjögren syndrome	Systemic lupus erythematosus	Systemic sclerosis	Dermatomyositis and polymyositis	Spondyloarthropathy
Age (year)	20–40	30–50	30–50	15–35	35–50	45–55	25–45
Gender (W/M)	2/1	3/1	20/1	10/1	3–7/1	3/1	1/2
Type	Insidious acute	Insidious	Insidious	Insidious	Insidious	Insidious	Insidious
Pathogenesis	Th1/Th17 CD4/CD8⇧	Th1/Th17 B cells	Th1/Th17 B cells	Th2 B cells	Th1 B cells	Th1/Th2 B cells	Th1/Th17
Genetic	*HLA-DRB1* *HLA-DQB1* *TNF-308A* *Butyrophilin-like 2 gene* Annexin A11	HLA-DR4 HLA-DR1 PTPN22 PADI4 TRAF1/C5 STAT4	*HLA-DRB1* *HLA-DQA1* IRF5 STAT4	HLA-DR2 HLA-DR3 C1q insufficiency FCGR2A IRF5 PTPN22	*HLA-DRB1* *HLA-DQA1* *HLA-DQB1* PTPN22 NLRP1 IRF5	*HLA-DRB1* *HLA-DQA1*, B8, HLA-DR3 HLA-DR52	HLA-B27 Endoplasmic reticulum amino peptidase 1 Interleukin 23 receptor Interleukin I receptor type II Anthrax toxin receptor
Prevalence	4–65/100,000	0.5–1%	0.1–4.6%	10–50/100,000	7–24/100,000	2.1–10/1,000,000/year	0.75–2%
Locomotor system involvement	Arthritis Myositis Dactylitis Sacroiliitis Enthesitis	Arthritis Myositis	Arthritis Myositis	Arthritis Tenosynovitis Myositis Avascular necrosis	Arthritis Tendonitis Myositis	Myositis Arthritis	Sacroiliitis Spondilitis Asymmetric oligoarthritis enthesitis
Pulmonary involvement	Hilar lymphadenopathy ILD PAH	ILD Pleuritis Rheumatoid nodule PAH SAD	SAD Nonspecific interstitial pneumonia ILD PAH	Pleuritis ILD Lupus pneumonia Alveolar hemorrhagia PAH	ILD PAH	ILD PAH	Apical lobe fibrosis
Neurologic involvement	Meningitis MNM İntracranial Tumor Multiple sclerosis-like features Peripheral neuropathy Multiple cranial neuritis	CTS PNP MNM	CNS Vasculitis PNS ANS MNM	Cognitive Lupus headache Vasculitis Hemorrhagia Transverse myelitis MNM	Neuropathy ANS	Neuropathy	Cauda equina syndrome
Gastrointestinal system involvement	Rare (1–2%)	Rare	Esophagus AIH Painful bladder syndrome Vasculitis	AIH Pancreatitis Vasculitis	Esophagus Stomach Intestine	Esophagus Stomach Intestine Vasculitis	Inflammatory bowel disease
Cardiac involvement	Arrhythmias Cardiomyopathy/congestive heart failure Pericarditis Valvulopathy PAH	Pericarditis Valvulopathy Atrioventricular block Myocarditis Coronary vasculitis	Valvulopathy Arrhythmias AHD PAH	Pericarditis Myocarditis Endocarditis AHD	Pericarditis Myocarditis	Myocarditis Arrhythmias	Aortitis Aortic valvulopathy AHD

(Continued)

Table 2. (Continued)

Features	Sarcoidosis	Rheumatoid arthritis	Sjögren syndrome	Systemic lupus erythematosus	Systemic sclerosis	Dermatomyositis and polymyositis	Spondyloarthropathy
Ocular involvement	Uveitis Scleritis Sicca syndrome Orbital tumor Optic neuritis	Sicca syndrome Scleritis Episcleritis Scleromalacia perforans	Sicca syndrome Conjunctivitis Retinal vasculitis	Retinal vasculitis Orbital myositis Episcleritis Sicca syndrome	Sicca syndrome	Sicca syndrome	Anterior uveitis Conjunctivitis
Renal involvement	Calciuria Chronic renal failure	AA amyloidosis	Tubulointerstitial nephritis Renal tubular acidosis GN	GN	Scleroderma renal crisis	Rare	IgA nephropathy AA amyloidosis
Lymphadenopathy	Yes	Yes	Yes	Yes	Rare	Rare	No
Skin-mucosa involvement	Erythema nodosum Lupus pernio Maculopapular Subcutaneous nodule Psoriasis-like	Rheumatoid nodule Palmar erythema Rheumatoid vasculitis	Raynaud Palpable purpura Annular erythema Pernio	Malar rash Alopecia Discoid lupus Raynaud Livedo reticularis Paniculitis Oral lesion	Raynaud Localized Diffuse Calcinosis	Heliotropic rash Gottron papule V-erythema Machinist hand Raynaud Calcinosis	Oral lesion Psoriatic lesion Keratoderma Blenorragica Balanitis circinata
Serology tests	ANA RF Anti-CCP (overlap)	RF Anti-CCP ANA	ANA Ro La Aquaporin-4	ANA dsDNA Sm Ro La Anti-cardiolipin antibodies Ribosomal P	ANA Scl-70 Sentromer	ANA Signal recognition particle Mi-2 tRNA synthetase	None
Pathology	Noncaseating granuloma	Pannus	Autoimmune epithelitis	Complement Ig	Fibrosis Vasculopathy	Muscle inflammation/ necrosis	None
Treatment	CS, MTX, AZA, LEF, anti-TNF-alpha	CS, MTX, LEF, SSZ, anti-TNF-alpha RTX, abatacept, tocilizumab, tofacitinib	CS, HQ, MTX, RTX	CS, HQ, MTX, CyP, belimumab, RTX	HQ, MTX, CyP, AZA, CS, Ca blocker, apremilast endothelin receptor antagonist	CS, MTX, AZA, RTX, Iv İg, plasmapheresis	Nonsteroidal anti-inflammatory drug, SSZ, anti-TNF-alpha, anti-interleukin-17

AHD, atherosclerotic heart disease; AIH, autoimmune hepatitis; ANA, antinuclear antibody; ANS, autonomic nervous system; anti-CCP: anti-cyclic citrullinated peptide; anti-TNF-alpha, anti-tumor necrosis factor-alpha; AZA, azathioprine; CHF, congestive heart failure; CMP, cardiomyopathy; CNS, central nervous system; CS, corticosteroid; CTS, carpal tunnel syndrome; CyP, cyclophosphamide; FCGR2A, Fc gamma receptor IIa; GN, glomerulonephritis; HQ, hydroxychloroquine; Ig, immunoglobulin; ILD, interstitial lung disease; IRF5, interferon regulatory factor 5; LEF, leflunomide; MNM, mononeuritis multiplex; MTX, methotrexate; PADI4, peptidyl arginine deiminase; PAH, pulmonary arterial hypertension; PNP, polyneuropathy; PNS, peripheral nervous system; PTPN22, protein tyrosine phosphatase-22; RF, rheumatoid factor; RTX, rituximab; SAD, small airway disease; SRC, scleroderma renal crisis; STAT4, signal transducer and activator of transcription4; Th, T helper cell; TRAF1/C5, tumor necrosis factor-receptor associated factor 1/complement component 5.

acute sarcoid arthritis. However, the differential diagnosis of EN should be established carefully. In the presence of EN accompanying hilar lymphadenopathy, bacterial, viral, and fungal infections should be investigated (e.g. histoplasmosis, coccidioidomycosis). In addition, other factors that cause EN should also be ruled out (e.g. drugs, inflammatory bowel disease, Behçet's disease, malignancy). A mononuclear cell-predominant inflammatory cell population is observed in patients with acute sarcoid arthritis. The biopsy in patients with tenosynovitis also detected a noncaseating granulomatous reaction.

Chronic arthritis is observed more commonly in patients with diffuse organ involvement (e.g. pulmonary, lupus pernio, chronic uveitis, etc.), and has a poorer prognosis [Torralba and Quismorio, 2003]. Black race and chronic skin lesions (lupus pernio) represent a predisposing factor for chronic sarcoid arthritis. Usually, more than one joint is involved (i.e. knees, ankles, wrists, and the small joints of hand and feet). Erosive changes and Jaccoud-type arthropathy may occur in advanced cases. Dactylitis involving the bones and soft tissue manifests with soft tissue swelling, sensitivity, and limited motion. Severe cases may also involve bone destruction and marked deformities. The articular fluid investigation of chronic sarcoid arthritis shows mononuclear and polymorphonuclear cells predominant while synovial biopsy shows noncaseating granulomas. Since similar findings may also be detected in tuberculosis, berylliosis, fungal infections, and foreign matter reactions, care should be exercised. Direct graphy shows swollen soft tissue, periarticular osteoporosis, cystic changes, and sometimes rheumatoid arthritis-like erosive cartilage and bone lesions.

Sacroiliac joint involvement is rare in patients with sarcoidosis [Erb *et al.* 2005]. The literature data are limited. While sacroiliitis is usually unilateral, it may be difficult to differentiate from tuberculosis or sacroiliitis secondary to another infection without conducting a biopsy. Investigation of other clinical findings and HLA-B27 is recommended to differentiate from patients with ankylosing spondylitis. A study reported the rate of sacroiliac joint involvement as 14.3% in patients with sarcoidosis [Kobak *et al.* 2014a]. The patient characteristics included female gender, negative HLA-B27, and bilateral sacroiliitis presence.

Sarcoid arthropathy treatment. Spontaneous remission is observed in more than 90% of patients with acute sarcoid arthritis. There are no randomized controlled trials and no drugs specifically approved for rheumatologic manifestations of sarcoidosis. In some cases, nonsteroidal anti-inflammatory drugs, local corticosteroid injection, or short-term, low-dose oral corticosteroids may be required. Colchicine and hydroxychloroquine (HQ) may be used in some patients with Löfgren syndrome and EN. In patients with corticosteroid-resistant progressive chronic sarcoid arthritis immunosuppressive drugs, for example, methotrexate (MTX), azathioprine (AZA), leflunomide, may be considered [Baughman and Lower, 1997]. The efficacy and safety of anti-tumor necrosis factor alpha (anti-TNF-alpha) agents in sarcoidosis patients have been discussed [Baughman and Lower, 2001]. Regarding the important role of TNF-alpha in granuloma formation anti-TNF-alpha drugs seem to be a reasonable treatment option. The efficacy of anti-TNF-alpha drugs in refractory sarcoidosis patients has been shown in some studies, but sarcoidosis developments due to the anti-TNF-alpha drugs used have also been reported. This paradoxical effect, which could not be explained, but must be known from clinicians. However, in patients with sarcoidosis with pulmonary involvement and arthropathy, B-cell depletion has been shown to be an effective treatment option [Sweiss *et al.* 2014]. Recently it has been reported that golimumab and ustekinumab do not have any advantage compared with placebo in patients with pulmonary sarcoidosis and skin involvement [Judson *et al.* 2014].

Sarcoid myopathy

Sarcoid myopathy was described for the first time in a 17-year old female patient who presented with lupus pernio, splenomegaly, and multiple muscle nodules. Asymptomatic involvement of the muscles is seen in 25–75% of patients, while symptomatic involvement occurs in only 0.5–5%. Symptomatic myopathy may present with three different types: acute myositis, palpable nodules, or chronic myopathy [Fayad *et al.* 2006]. Acute myositis may be the first symptom of sarcoidosis and/or be a part of the progressive form [Matsui *et al.* 2007]. Clinical signs such as fever, myalgia, and muscle weakness may mimic acute polymyositis. Proximal muscle weakness with fever and fatigue is one of the key findings. Depending on the bulbar and respiratory muscle involvement

may cause dyspnea and respiratory distress. Serum muscle enzymes may be elevated, and electromyography (EMG) may show nonspecific myositis findings. The nodular form, which is very rare, is characterized by tumor-like lesions in the muscles [Nemoto *et al.* 2007]. Two large series including 1300 patients with sarcoidosis reported only three patients with nodular muscle involvement. So far, only 60 cases with the nodular form have been reported in the literature. Chronic myopathy, which is characterized by proximal muscle weakness, is the most common form [Silverstein and Siltzbach, 1969]. Muscle atrophy, contractures, or pseudohypertrophy may be seen. Muscle pain may begin before muscle weakness. Although rare, distal muscle involvement may also occur with peripheral neuropathy. Muscle enzyme elevation, imaging (e.g. muscle magnetic resonance imaging [MRI], gallium-67 scintigraphy, positron emission tomography [PET]), EMG, and/or muscle biopsy are methods that lead to diagnosis. Noncaseating granulomas infiltrating perimisial connective tissue, which cause muscle atrophy and fibrosis, are the main muscle biopsy findings. However, as we reported earlier in a case, it is not always the occurrence of noncaseating granulomas requirement for diagnosis of muscle involvement. In sarcoid myopathy, the presence of different clinical and pathological findings in different cases suggest a complex and complicated pathophysiology. In some cases, widespread destruction of muscle fibers from granuloma formation was observed, while in other cases only myopathic changes were determined. In immunohistochemical studies, high CD4 T lymphocytes and CD4/CD8 ratio were detected in sarcoid myopathy, while CD8 T-lymphocyte predominance was observed in patients with inclusion body myositis and polymyositis [Vattemi *et al.* 2008]. Cellular immune mechanisms play a key role in the pathogenesis of polymyositis. *In vitro* studies have demonstrated that they are toxic to peripheral blood lymphocytes of myoblasts and fibroblasts. Lymphocytes, indirectly through cytokines or directly by cytolysis of the muscle fibers, are able to damage the muscles. Myopathy in sarcoidosis may apply similar mechanisms seen in polymyositis. The presence of an inflammatory process without granuloma formation in the muscles suggests that myositis may occur with secreted cytokines. In fact, increased serum interleukin (IL)-1 and IL-2 in patients with sarcoidosis was determined in some studies [Authier *et al.* 1997].

Sarcoid myopathy treatment. Corticosteroids are used in the treatment of sarcoid myopathy. Controversial findings were reported on the response to treatment. Response was achieved in 12 out of 21 patients with sarcoid myopathy in a trial [Baughman *et al.* 2008a]. In another study, a complete response was achieved in only 7 out of 26 patients, while 6 patients were considered stable and the other 13 patients were nonresponsive. In patients who do not respond to steroids, or a combination therapy, immunosuppressive drugs such as MTX, HQ, and AZA may also be used [Baughman and Lower, 1997]. There are also case reports on the use of thalidomide and anti-TNF drugs [Baughman *et al.* 2008b].

Bone sarcoidosis

The first case of bone sarcoidosis was reported by Besnier in 1898 in a patient with lupus pernio. In 1949, direct graphy results of 279 patients with sarcoidosis were investigated and bone lesions were detected in 42 (15%) patients [Wilcox *et al.* 2000]. In another study, 160 patients with sarcoidosis were investigated and typical cystic bone lesions were detected in 19 patients [Shorr *et al.* 1998]. Neville and colleagues evaluated 29 patients with bone sarcoidosis and detected lupus pernio and ocular sarcoidosis in 48% of the patients [Neville *et al.* 1977]. Due to the absence of prospective trials, based on the retrospective data, bone involvement was detected in 1–15% of the patients with sarcoidosis. Patients with bone sarcoidosis have other organ involvement, most commonly pulmonary 80–90%, lupus pernio 48–70%, and uveitis 30–50%. In a study of 818 patients with sarcoidosis, 35 were detected to have lupus pernio while 3 had bone cysts [Shorr *et al.* 2000]. Based on these findings, the risk of bone sarcoidosis was shown to be 21-fold higher in patients with lupus pernio. On the other hand, EN was observed in only 3% of the patients with bone sarcoidosis. While the pathogenesis is not clear, direct and indirect effects of granuloma formation are considered to potentially cause bone resorption and osteopenia. Firstly, granuloma formation directly activates the osteoclasts. In a case report, the bone biopsy performed in a sarcoidosis patient with abnormal bone densitometry showed peritrabecular granuloma and osteoclast resorption. Secondly, granuloma formation secretes the osteoclast-activating factor. Based on this evidence, it is obvious that the pathogenesis of sarcoidosis is multifactorial. Bone

sarcoidosis is particularly more common in the black race and patients with infiltrative skin lesions, and its course is usually asymptomatic. In some patients, it exhibits a sausage-like involvement in two or three fingers and needs to be differentiated from spondyloarthropathies. Bone lesions may be cystic or sclerotic. In the presence of multiple lesions, it is known as the lacy pattern and is an indicator of the typical bone involvement of sarcoidosis. The cystic lesions of the hand and feet bones are known as Perthes–Jungling disease. Acro-osteolysis may also occur. There are three types of sarcoid bone disease on direct graphy; type 1 involves a large cystic lesion that is rarely observed and causes pathological stress fracture; type 2 involves multiple small cysts; and type 3 is a form that forms tunnels in the cortex of the finger bones. Vertebral sarcoidosis may frequently involve lower thoracic and upper lumbar vertebrae, and may manifest with lytic, sclerotic, or mixed lesions. It may mimic metastatic lesions; the MRI findings are not always conclusive and a biopsy may be necessary for definitive diagnosis. MRI imaging is a method that could be useful in the diagnosis of bone sarcoidosis. Bone sarcoidosis is observed to be a hypointense lesion on T1 images and a hyperintense lesion on T2 images. In a retrospective study in 52 patients, abnormal bone marrow findings were detected in seven patients (14%) on MRI of the vertebrae. In another study comparing direct graphy and MRI, lesions could not be detected in 60% of patients on direct graphy. In addition to MRI, PET-computed tomography is another method that could be used in diagnosing bone sarcoidosis [Rúa-Figueroa *et al.* 2002].

Bone sarcoidosis treatment. While asymptomatic patients do not need treatment, patients with uncontrolled pain, stiffness, and bone destruction should be treated. Low to moderate doses of corticosteroids are usually effective although no efficacy on radiologic findings could be demonstrated. As for patients who are nonresponsive to corticosteroid treatment, agents such as MTX, HQ, and anti-TNF-alpha may also be used [Garg *et al.* 2008]. There are a few case reports showing the efficacy of HQ in sarcoid-associated hypercalcemia and hypercalciuria, granulomatous infiltration of the talus, hypertrophic osteoarthopathy, and skin and bone sarcoidosis. In another case report, MTX was shown to be an effective treatment option in three patients with bone sarcoidosis. These drugs are considered to lead potentially to direct granuloma formation or inhibition of the extrarenal synthesis of 1,25-dihydroxycholecalciferol [O'Leary *et al.* 1986].

Association of sarcoidosis and rheumatologic diseases

Sarcoidosis was reported together with different rheumatologic disorders (e.g Sjögren's syndrome, ankylosing spondylitis, scleroderma) [Kobak *et al.* 2013, 2014b]. There are studies showing that sarcoidosis may mimic their clinical and laboratory findings. Alopecia and discoid lupus erythematous-like lesions may occur in patients with sarcoidosis. Early sarcoidosis may mimic juvenile rheumatoid arthritis with the findings of rash, arthritis, and uveitis. Positive *rheumatoid factor* (RF) and antinuclear antibodies results were also reported in patients with sarcoidosis [Kobak *et al.* 2014e]. In a trial, the incidence of anti-cyclic citrullinated peptide antibodies was detected to be 4.7% among patients with sarcoidosis; however these same patients had also had a diagnosis of rheumatoid arthritis. Thus, the findings showed that these antibodies were not involved in the pathogenesis of sarcoidosis, however they could be important in the differential diagnosis of sarcoidosis-rheumatoid arthritis overlap syndrome [Kobak *et al.* 2014d]. There are many case reports showing the association of sarcoidosis and Sjögren syndrome [Hansen *et al.* 2008]. Sicca symptoms and parotid enlargement may also occur in patients with sarcoidosis. To differentiate between these two diseases, exocrine gland biopsy, serologic tests, and clinical findings should be considered. While the presence of uveitis supports sarcoidosis, positive serologic tests (anti-Ro and anti-La antibodies) support the presence of Sjögren syndrome. The clinical manifestations of these two disorders are interlocked to an extent that sarcoidosis should be ruled out based on the American–European classification criteria of Sjögren syndrome. Sarcoidosis is rarely associated with vasculitis and is reported with manifestations of skin lesions, pulmonary hypertension, or systemic vasculitis [Fernandes *et al.* 2000]. It may occasionally mimic or occur concomitantly with primary vasculitis (Takayasu's arteritis). It is a rare disorder that may present with diffuse pulmonary nodules without necrotizing sarcoid granulomatosis (NSG), mediastinal lymphadenopathy, and may mimic Wegener's granulomatosis or Churg–Strauss vasculitis and exhibit sarcoid-like granuloma, vasculitis, and necrosis on histopathological investigation. Since NSG is more common in families with sarcoidosis, it is

thought that it may be a subvariant of sarcoidosis. Sarcoid neuropathy may present as sensorineural neuropathy, mononeuritis multiplex, or chronic inflammatory demyelinating neuropathy [Vital *et al.* 2008]. Sarcoid vasculitis may affect vessels of all diameters and mimic primary vasculitis. Pulmonary arterial involvement is a significant and life-threatening vascular involvement of sarcoidosis. Aortitis is a rare complication of sarcoidosis and it should be differentiated from Takayasu's arteritis and the other forms of vasculitis. Anti-endothelial cell antibodies (AECA) are involved in the pathogenesis of connective tissue disorders such as systemic lupus erythematosus and primary vasculitis, and are associated with vascular damage. In a trial, a high titer of AECA was detected in the bronchoalveolar lavage fluids of patients with sarcoidosis; however the question as to whether it is secondary to the destruction of a single vessel or is pathogenic for the disease could not be answered [Inui *et al.* 2008]. Rare associations of sarcoidosis include gouty arthritis and psoriatic arthritis [Kaplan and Klatskin, 1960; Healy and Helliwell, 2006]. The association of gouty arthritis and sarcoidosis was reported by Hutchinson 120 years ago. Since both may manifest with hyperuricemia and similar clinical findings, demonstration of monosodium urate crystals phagocytozed by neutrophils is diagnostic. Trials have shown that 6% of patients with sarcoidosis develop psoriatic arthritis-like manifestations with the most common form being dactylitis causing 'sausage finger'.

In conclusion, the immunopathogenesis of sarcoidosis has not yet been elucidated. We can mention an immunologic process involving alveolar macrophage activation, antigen processing and presentation, acquired T-cell response, specific T-cell activation, granuloma formation, and occasional formation of fibrosis following exposure to a nondefined antigen. Sarcoidosis is a systemic granulomatous disease of unknown etiology, which progresses with multi-organ involvement and develops *via* T-helper 1 (Th1) cells. It starts with pulmonary findings; however extrapulmonary involvement is also frequent. Sarcoidosis may mimic or occur concomitantly with many rheumatologic diseases. In addition to the most common diseases of connective tissue disorders such as primary Sjögren syndrome, systemic lupus erythematosus, and scleroderma, it may also present with clinical findings that resemble vasculitis and/or spondyloarthritis. Due to the fact that it can mimic rheumatologic diseases, delayed diagnosis and/or misdiagnosis can occur. Therefore, in patients presenting to a rheumatologist with musculoskeletal system findings, it should definitely be considered in the differential diagnosis. Sarcoidosis should not be considered only as a mimicking but also a Th1-mediated, primary rheumatologic pathology. Further trials are needed to investigate this subject.

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