

## Sarcoidosis: selected clinical cases

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### KEY WORDS

noncaseating  
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systemic connective  
tissue disease

### ABSTRACT

Two interesting cases of sarcoidosis and associated diagnostic challenges have been presented. Clinical similarities and disparities in the course of sarcoidosis and systemic connective tissue diseases, particularly Sjögren's syndrome, have been addressed. It has been highlighted that all organs, not only the lungs but also for example the liver, can be involved in sarcoidosis. Prompt diagnosis and a proper therapeutic approach are of vital importance.

**INTRODUCTION** Sarcoidosis is a systemic disease presenting with typical symptoms and characterized by the formation of noncaseating granulomas in multiple organs. This feature allows to distinguish between sarcoidosis and autoimmune or collagen vascular diseases.<sup>1</sup> Sarcoid granulomas are typically formed in the eye, nervous system, salivary glands, rarely in the liver and kidneys. Because of a wide range of signs and symptoms such as fatigue, arthralgia, fever, and skin lesions, patients with sarcoidosis are treated by various specialists. Therefore, sarcoidosis requires a multidisciplinary approach.

Sarcoidosis may coexist with connective tissue disease. Such cases are not common and the coincidence seems random rather than causal.<sup>2</sup> We describe two cases of sarcoidosis and diagnostic challenges resulting from heterogeneous clinical presentation.

**CASE REPORT I** A 56-year-old male was admitted to the Department of Connective Tissue Diseases of the Institute of Rheumatology in Warsaw in late February 2007, with the diagnosis of sarcoidosis and suspected Sjögren's syndrome. The patient has been under the care of laryngologists and rheumatologists since 2005, who suspected Sjögren's syndrome due to episodes of dry cough, xerophthalmia, xerostomia, submandibular and parotid gland dysfunction, and nasopharyngeal obstruction. Chest radiogram and computed tomography (CT) scans revealed a few enlarged right hilar and subcarinal lymph nodes. There were no nodules found in the lungs. Microscopic evaluation of the bronchial mucosa

specimen and bronchial lavage showed no atypical cells. The patient did not consent to lymph node biopsy. Subsequent hospital stays were due to nasopharyngeal obstruction, bronchospasm attacks with the subsequent loss of consciousness (he had fallen down and had his ribs broken). Repeated chest radiography and CT scans showed bilateral hilar and mediastinal lymphadenopathy, parenchymal lesions in the right lung and a considerable number of nodules. There was a purulent secretion in the bronchial lumen. At that time (February 2006), a provisional diagnosis of sarcoidosis was made and a differential diagnosis of either infectious or reactive changes was suggested. Video-assisted thoracoscopy with lung biopsy was scheduled. Microscopic evaluation of the specimens revealed non-necrotic granulomas. The differential diagnosis of infection, reactive changes and vascular collagen diseases was made because of eosinophilic parenchymal infiltrate. During the next hospital stay at the Institute of Tuberculosis and Lung Diseases in Warsaw (April 2008), vasculitis, including Wegener's granulomatosis and Churg-Strauss syndrome, was excluded. Microscopic examination of the salivary gland biopsy showed granulomas and lymphoid cells indicating either granulomatous disorder or Sjögren's syndrome. On bronchoscopy purulent airway secretion with the presence of *Staphylococcus aureus*, *Pseudomonas* and *Klebsiella pneumoniae* was observed. Pulmonary function tests demonstrated obstructive pattern and chest imaging revealed consolidations in both lungs. The patient was treated with antibiotics and prednisone 1 mg/kg b.w. titrated to 20 mg/day. His clinical condition

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improved but deteriorated when antibiotic discontinuation was attempted. Coexistence of sarcoidosis and Sjögren's syndrome was still being considered. At the Institute of Rheumatology serology for Sjögren's syndrome was performed. Anti-Ro/SSA and anti-La/SSB antibodies were negative and the salivary gland biopsy was reevaluated (focus score = 0). Methicillin-resistant *Staphylococcus aureus* was cultured from the nose and throat. Inflammation markers, i.e. erythrocyte sedimentation rate and serum C-reactive protein (CRP) level, were slightly elevated. Clarythromycin was administered together with 20 mg/day of prednisone, antifungal therapy, antiallergic drugs and moisturizers. The patient's condition improved. The diagnosis of sarcoidosis was confirmed with no coexistence of Sjögren's syndrome and the patient was referred to the Institute of Tuberculosis and Lung Diseases.

**CASE REPORT II** In 2005, a 46-year-old female presented with fatigue, recurrent bacterial and fungal infections with moderate fever, ankle arthritis and nodal fever (erythema nodosum). Laboratory investigations showed elevated levels of serum CRP – 2 × upper limit of normal (ULN), alkaline phosphatase (ALP) – 2 × ULN and bilirubine – 1.5 × ULN. Chest radiogram was normal. Infectious arthritis was diagnosed. Amoxicillin-clavulanate 1.0 g 2 × daily, intravenous metronidazol 500 mg 3 × daily, enoxaparin 60 mg daily, Detralex 1 tab. 2 × daily, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors were used; however, the patient did not improve. The CRP level increased to 4 × ULN, erythrocyte sedimentation rate was 80 mm/h, D-dimer level exceeded 4 × ULN, neutrophil count increased and ALP level remained elevated to 3 × ULN. Ultrasound examination of the abdomen was normal. A CT scan of the chest revealed “slightly enlarged (10–15 mm) right and left paratracheal lymph nodes, discreetly (10–12 mm) enlarged bilateral hilar nodes; the largest bundle of subcarinal lymph nodes (45 × 20 mm)”, that “probably indicates sarcoidosis phase I”. There was no endoscopy performed and no lymph node biopsy for microscopic evaluation was taken. Three months after the onset of disease, arthritis and nodal fever resolved, and inflammatory markers returned to normal. Liver tests remained elevated: γ-glutamyltransferase (GGT) 4 × ULN, ALP 2 × ULN. Hypercalcemia occurred with serum calcium level of 2.9 mmol/l (limits of normal: 2.1–2.6 mmol/l). Serological tests, including antibodies to hepatitis B virus surface antigen (anti-HBs), antibodies to hepatitis C virus, antinuclear autoantibodies, antineutrophil cytoplasmic autoantibody (ANCA), antimitochondrial autoantibody were negative. Percutaneous core needle liver biopsy was performed. The microscopic evaluation of the specimens showed granulomatous hepatitis suggesting sarcoidosis. After a year since the onset of disease, the patient improved and laboratory abnormalities resolved,

excluding increased GGT and, occasionally, CRP levels. Repeated chest radiogram revealed resolution of lymphadenopathy.

**DISCUSSION** Sjögren's syndrome may develop as a primary disease or it may be secondary to other clinical conditions. In about half of the cases it accompanies other collagen vascular diseases. The diagnosis is based on clinical features, i.e. xerostomia, xerophthalmia with coexistence of either histopathological changes (lymphocytic infiltration of the salivary glands – the foci consisted of 50 T lymphocytes per 4 mm<sup>2</sup>) or typical serological disorders. The number of lymphocytic foci is described as a “focus score”. The presence of the foci is required to establish the diagnosis of Sjögren's syndrome. If there is no histopathological confirmation, it is necessary to detect lymphocyte reactivity against SSA or SSB antigens. Additionally, HLA-DR positive epithelial cells are able to present antigens and autoantigens to CD4(+) lymphocytes that stimulate B lymphocytes, and may result in lymphomas. Granulomas are not associated with Sjögren's syndrome.<sup>3</sup> In the current case noncaseating granulomas were observed in the lung parenchyma.

Immunological disorders in sarcoidosis are mainly caused by peripheral cell disorders, granuloma formation caused by hyperactivity of T lymphocytes and macrophages and inflammation cascade, i.e. interleukin-2 and interferon-γ production.

In our case dryness symptoms were present because of sarcoid involvement of the salivary glands and eyes, including the cornea. Moreover, the salivary glands were completely damaged during the disease, which increased xerostomia. Sarcoid granulomas may be found in salivary glands.<sup>5</sup> Both sarcoidosis and Sjögren's syndrome may predispose to bacterial infections of the respiratory tract. Bacterial etiology has been proven in sarcoidosis, while in Sjögren's syndrome bacterial infection is secondary to viral infection.

Noncaseating granulomas in the lungs at focus score of 0 and the lack of serum autoantibodies indicate sarcoidosis as the single disease. Given the common involvement of the salivary and/or lacrimal glands in sarcoidosis, this entity should be always taken into consideration while Sjögren's syndrome is suspected. The diseases differ in pathogenesis, complications and prognosis (vasculitis and possibility of lymphomas in Sjögren's syndrome; progressive organ – mainly lung – destruction resulting in organ failure in sarcoidosis).<sup>2,6</sup> Out of 200 patients with sarcoidosis examined by James, Sjögren's syndrome coexisted only in 4 cases.<sup>7</sup>

To confirm the diagnosis of sarcoidosis, histological evaluation is required with simultaneous exclusion of other conditions presenting with noncaseating granulomas.

Granulomas are present in the liver not only in sarcoidosis, but also in other clinical disorders, including infections, drug-induced lesions

(e.g. after the use of quinidine, sulfonamides, allopurinol, phenylbutazone), collagen vascular diseases (e.g. vasculitis, systemic lupus erythematosus), malignancies (e.g. lymphomas). Infectious agents causing formation of granulomas include bacteria (e.g. *Mycobacterium tuberculosis*, *Brucella*, *Francisella tularensis*), fungi (e.g. *Histoplasma*, *Cryptococcus*), parasites (e.g. *Schistosoma*, *Toxoplasma*) and viruses (Epstein-Barr virus, Cytomegalovirus). Granulomas may resolve without treatment or they may remain stable for many years, without altering liver function. Nevertheless, in some cases progressive fibrosis, portal hypertension and liver cirrhosis are observed.<sup>8</sup>

The treatment of the sarcoid hepatitis depends on clinical presentation. In the case of abdominal pain and general symptoms, low-dose oral prednisolone (10–15 mg/day) is recommended, typically for many years. Higher doses (30–60 mg/day) are used in patients with cholestatic liver disease, hyperbilirubinemia and pruritus. Improved liver function tests after corticosteroids are not always associated with microscopic resolution. It is possible to reduce the dose of corticosteroids using drugs such as methotrexate, chlorambucil, chloroquine, cyclosporine A, and ursodeoxycholic acid. In the case of isolated histopathological or both histopathological and laboratory abnormalities, the disease often resolves without treatment.<sup>8</sup> Hepatitis is a common extrapulmonary manifestation of sarcoidosis that it is observed in over 70% of liver biopsies. In most cases it is asymptomatic; abnormal liver function tests are observed in 20–40% of patients. It is believed that systemic signs and symptoms including weight loss, night sweats and fever are associated with liver involvement.<sup>9</sup>

In conclusion, sarcoidosis involving other organs than the lungs may present diagnostic challenges and delay in the initiation of treatment. Reported cases illustrate how important early histological evaluation is to provide the most effective and least harmful treatment.

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# Sarkoidoza – wybrane przypadki kliniczne

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### SŁOWA KLUCZOWE

sarkoidoza, układowa  
choroba tkanki  
łącznej, ziarniniak  
nieserowaciejący

### STRESZCZENIE

W pracy przedstawiono dwa interesujące przypadki sarkoidozy oraz związane z nimi problemy diagnostyczne. Szczególną uwagę zwrócono nie tylko na podobieństwo kliniczne, ale także na różnice w przebiegu sarkoidozy oraz układowych chorób tkanki łącznej, głównie zespołu Sjögrena. Przypomniano o możliwości zajęcia przez proces chorobowy każdego narządu, nie tylko płuc, ale także np. wątroby. Podkreślono znaczenie szybkiego ustalenia rozpoznania i prawidłowego postępowania terapeutycznego.

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#### **Erratum**

Bowman AW, Kantor B, Gerber TC. Coronary computed tomographic angiography: current role in the diagnosis and management of coronary artery disease. *Pol Arch Med Wewn.* 2009; 119 (6): 381-390.

On page 382, paragraph 1 under What are our current approaches for the assessment of coronary artery disease? should read "Therefore, a large body of literature has examined the predictive value of "novel" cardiac risk factors such as *lipoprotein(a)*, *homocysteine*, highly sensitive C-reactive protein (CRP), or biomarkers of atherosclerosis and inflammation, such as CRP, interleukin 6, or matrix metalloproteinase."