
Case report

A Stepwise Diagnosis of Sarcoidosis Presenting with Renal Impairment and Hypercalcemia

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Abstract

Sarcoidosis is a multisystem, immune-mediated, granulomatous disease. Clinical presentation of this disease may vary; in majority of cases (~90%) thoracic involvement is the leading sign. Although renal involvement is thought to be uncommon in sarcoidosis this entity may not be so rare. Hypercalcemia seems to be the most likely cause of sarcoidosis-associated renal disease, it can even cause acute renal failure in 1-2% of sarcoidosis patients. Immediate treatment is appropriate whenever organ function is threatened or when symptoms are severe. We present a case of sarcoidosis with hypercalcemia excluding other clinical conditions, which may potentially confuse the diagnosis.

Key words: sarcoidosis, hypercalcemia, renal failure, primary biliary cirrhosis, biopsy

Introduction

Sarcoidosis is a multisystem, idiopathic, inflammatory granulomatous disease. The diagnosis is usually based on an appropriate clinical presentation, involvement of at least two organ systems, histologic evidence of non-caseating granuloma from at least one organ and exclusion of other granulomatous diseases [1]. Sarcoidosis can involve any organ system and the clinical course may be highly variable. Difficulties in diagnosis of the disease is caused by the varying forms and presentations, the lack of a single diagnostic test and high-quality randomized controlled trials. Renal involvement, especially hypercalcemia is the clinically severe presentation of sarcoidosis. Neurological, ocular, renal, cardiac, pulmonary hypertension and depression are the treated features

of sarcoidosis [2]. We should suspect sarcoidosis in a patient with renal failure associated with hypercalcaemia.

Case report

A 54-year-old woman had a 9-year history of primary biliary cirrhosis (the diagnosis was made on the basis of high levels of alkaline phosphatase and γ -glutamyl transpeptidase, positive antimitochondrial antibody-titer 1:20-and MRCP findings) and 4 months of depression, with a chronic use of daily ursodeoxycholic acid of 750 mg and sertraline of 50 mg. She was admitted to our hospital for further examination of renal impairment and hypercalcemia detected at a routine control. A week ago she was given an intramuscular injection of vitamin D. She was complaining of fatigue and loss of appetite. Family history of the patient was unremarkable. The patient did not have any history of cough, joint pains, dysuria, hematuria or any other symptoms. There was no history of tuberculosis or other granulomatous disorders. A physical examination upon admission revealed a poor general condition, body temperature of 36.8°C, blood pressure 135/80 mmHg and a regular pulse of 24 beats/min. No superficial lymph adenopathy was evident. Heart auscultation was normal. Bibasilar crackles were heard in her lungs. Abdominal examination revealed no hepatomegaly or splenomegaly. Skin examination revealed no changes. Laboratory investigations showed ESR of 34 mm/first hour, fasting blood sugar: 96 mg/dl, urea: 98 mg/dl, creatinine: 2.91 mg/dl, uric acid: 4.4 mg/dl, calcium: 13.6 mg/dl, potassium: 4.1 mmol/l, sodium: 136 mmol/L, phosphorus: 5.1 mg/dl, total protein: 7 gr/dl, albumin: 3.4 gr/dl, globulin: 3.6 gr/dl, WBC 7830, hemoglobin: 11.6 gr/dl, hematocrit: 35.2%, platelets: 339000, CRP: 4.2 mg/dl and ALP: 110 U/L. Urinalysis revealed density 1010, pH 5.5, protein ++, leukocytes none, eryth-

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rocytes 1/each field. Arterial blood gas analysis were as follows: pH 7.37, TCO_2 21.9, HCO_3 20.8, lactate 0.8. Daily urinary protein excretion was 844.6 mg/day, detected in the twenty-four hour urine sample. Serum antinuclear antibody, anti-double stranded-DNA, rheumatoid factor, hepatitis B surface antigen, HIV antibody, hepatitis C virus antibody, antineutrophil cytoplasmic antibody were all negative. Serum complement (C3,C4) and immunoglobulin levels were in normal ranges except for total IgE 114.7 IU/mL(N:1-100). Glo-

merular filtration rate was estimated as 17.9 ml/min/1.73 m² according to the short MDRD formula. Ultrasonography of the right kidney was reported as 100x49 mm and parenchymal thickness of 16 mm with a Grade 1 echogenicity. Ultrasonographic size, parenchymal thickness and echogenicity of the left kidney were 101x51 mm, 15 mm and Grade 1, respectively. There was no sign of stone or ectasia. The posterior anterior X-ray of the lungs showed bilateral reticulonodular infiltration in all lung zones (Figure 1).



Fig. 1. Chest X-ray. Stage III sarcoidosis. Bilateral reticulonodular infiltration in all lung zones. Regression of radiological findings after 3 weeks steroid therapy

12-lead ECG was in sinus rhythm. Transthoracic echocardiogram revealed ejection fraction of 60%, mitral regurgitation 1⁰, pulmonary arterial pressure 25 mmHg. Although the patient received a D vitamin injection (300.000/IU D3) 1 week ago that had been advised by her gastroenterologist due to the chronic liver disease, hypervitaminosis D was suspected at first. Serum level of PTH and 25-hydroxyvitamin D were 2.7 pg/ml (N: 16-88.3) and 6.9 ng/mL (N:88-963), respectively. With these findings, hypervitaminosis D and hyperparathyroidism were excluded. Tumor marker levels were not significantly high. Mammography and mammary ultrasonography were done to exclude malignant breast cancer and a 11x5 mm lobulated, solid, irregularly shaped hypoechoic nodule in the upper outer quadrant of the right breast was detected. Ultrasound guided needle biopsy of the breast was done and the biopsy result was a benign neoplasm. As she was found to have renal failure, hypercalcemia and additionally high serum

levels of globulins, serum and urine immunofixation electrophoresis, peripheral blood smear, X-ray of the bones was performed and they were not significant for multiple myeloma (A bone marrow aspiration and biopsy was suggested but she did not accept the procedure). Meanwhile, due to the chest X-ray findings (although not specific), renal failure and hypercalcemia sarcoidosis was suspected. Contrast-enhanced thoracoabdominal CT was performed and images showed mediastinal, bilateral hilar and right paratracheal nodal enlargement, bilateral reticulonodular infiltration and mosaic pattern of lung attenuation, hypodens areas within the spleen (Figure 2). Serum levels of angiotensin-converting enzyme (ACE) was elevated as 427 U/L (N:8-52). 24-hour urine level of calcium was 425 mg/day (N: 100-300). To investigate the lung involvement bronchoscopy was done. Bronchoscopy revealed diffuse mucosal nodularity and the biopsy specimen obtained from

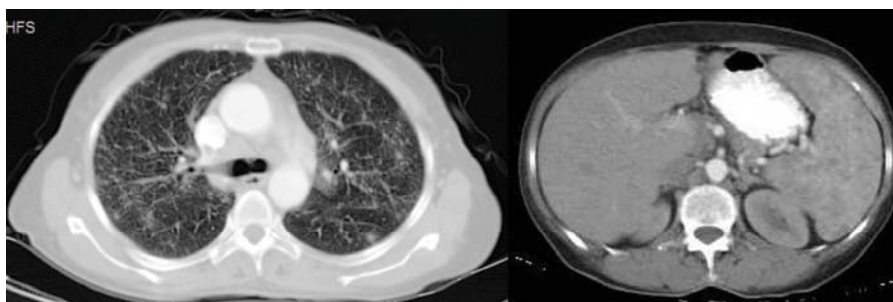


Fig. 2. Thoraco-abdominal CT. Bilateral reticulonodular infiltration and mosaic pattern of lung attenuation. Hypodens areas within the spleen

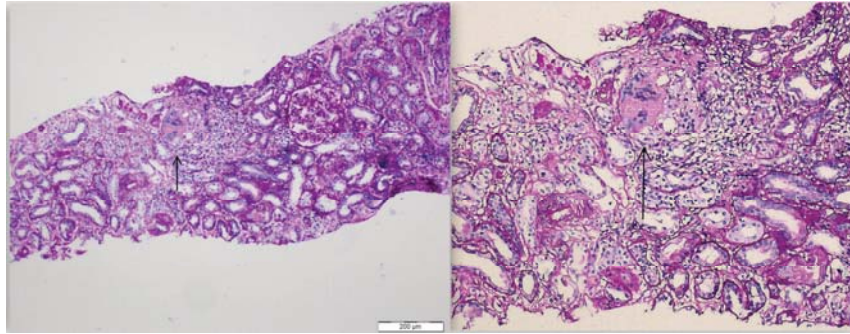


Fig. 3. Renal biopsy. Hematoxylin&Eosin and Periodic acid-Schiff stain. Diffuse interstitial inflammation, a noncaseating granuloma with a multinucleated giant cell (arrows)

these lesions later showed noncaseating granulomatous inflammation. No microorganisms were identified in specimens, visually or with special stains for fungi, mycobacteria, atypical mycobacteria and *Nocardia* spp. Cultures for fungi, bacteria, and acid-fast bacilli, as well as viral respiratory panel were all negative. A reduction in carbon monoxide diffusion capacity (DLCO) was detected (DLCO/VA:%53).

As soon as the possibility of urolithiasis-related renal failure was ruled out by ultrasonography and abdominal CT, ultrasound-guided renal biopsy was performed for better understanding the renal pathology. Light microscopy revealed 13 glomeruli, of which 2 had segmental glomerular sclerosis and others had an increase in the mesangial matrix. Diffuse interstitial inflammation, a noncaseating granuloma with a multinucleated giant cell, tubulitis and focal atrophy were apparent (Figure

3). Histochemically, periodic acid-Schiff, M. Silver, Masson's Trichrome staining was used. Congo red staining was negative. With direct immunofluorescence method, IgA, IgG, IgM, C3, C4, C1q, fibrinogen, kappa and lambda were applied and there was no specific deposition. The above findings indicated a diagnosis of sarcoidosis after clearly excluding other possible clinical entities potentially confusing the diagnosis. 18-FDG PET-CT (*Siemens, BiographTM mCT, 5mCi IV FDG*) was also performed due to the multiorgan involvement. During the follow-up the patient's calcium levels stayed constantly high although she was treated with continuous saline infusion and a loop diuretic, under calcium restricted diet. Oral prednisolone therapy of 1 mg/kg/day was started. The calcium concentration levels decreased with steroid therapy. Serum creatinine was also in normal ranges after 3 weeks of steroid therapy (Figure 4).

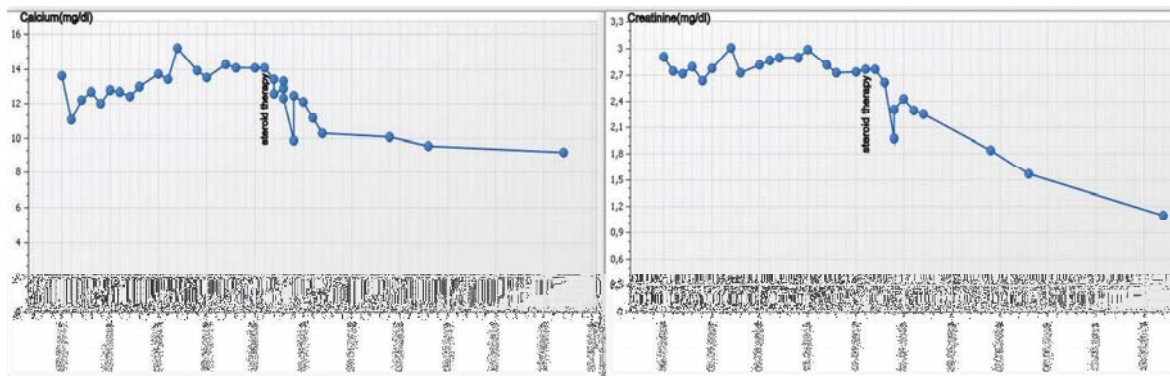


Fig. 4. Normalization of serum calcium&creatinine concentrations after steroid therapy

Discussion

Sarcoidosis is a multisystem, inflammatory granulomatous disease of undetermined etiology. Histopathology of the disease is characterized by T-lymphocyte infiltration, presence of noncaseating granulomas as pathologic hallmark and deformation of normal microarchitecture. It has a variable clinical presentation; in majority of cases (~90%) there is thoracic involvement whereas other commonly affected organs are the liver, skin, and eye. In our case multiorgan involvement was also present.

Extrathoracic involvement can be an initial manifestation in one-half of symptomatic patients. The involvement of two or more organs for a specific diagnosis is needed. Skin lesions, lymph node enlargement, renal stone, bundle branch block can be the initial signs of sarcoidosis and these entities may stay unrecognized for a long time. Almost 30% of patients have a persistent disease, which may lead to significant organ impairment. It can occur at all ages, but it usually develops before the age of 40-50 years; incidence peak occurs at 20 to 40 years and it seems to affect women more frequently [3].

Constitutional symptoms such as fatigue, fever, night sweats, and weight loss may be seen frequently. In our patient these symptoms could partially or strongly be related to depression, malignancy, infections or primary biliary cirrhosis; therefore, the initial presentation of sarcoidosis can mimic various clinical situations. It is well-documented that the main presentation of sarcoidosis is pulmonary with a chest X-ray carried out by chance. Although our patient had no respiratory complaints, lung involvement was present and even showed regression after steroid therapy. Lung and lymphatic systems are the principal localizations [4]. Hilar lymphadenopathy in sarcoidosis is typically bilateral and symmetric, being the most common radiological finding. Overall mortality from sarcoidosis is reported to be about 1-5% (respiratory, cardiac or central nervous system disease) [5]. Some environmental/occupational exposures and microbial origins are speculated to be associated with the risk for sarcoidosis (musty odors, pesticides, propionibacter acnes, mycobacterial KatG protein, beryllium, IFN α/β , employment in the aerospace, automotive, ceramic or computer industries) [1]. The exact inciting stimulus/cause of sarcoidosis is unknown. HLA-DQB1*0201 and HLA-DRB1*0301 alleles are associated with acute disease and good prognosis. HLADRB1*1501/DQB1*0602 haplotype predicts a chronic course and severe pulmonary sarcoidosis. We could not find a relationship between the disease and any of the exposures mentioned above.

Noncaseating epithelioid granulomas are the most important and the basic pathologic abnormality in sarcoidosis [6]. Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma follicle and often have cytoplasmic inclusions, such as asteroid bodies, Schaumann bodies, and birefringent crystalline particles [7]. There was granuloma in our renal biopsy specimen. Sarcoidal granulomas produce angiotensin-converting enzyme (ACE). Elevated levels of ACE are reported in 60-75% of patients with acute/

untreated disease [8]. In our patient the level of ACE was significantly high, supporting our diagnosis.

Symmetrical hilar adenopathy with or without parenchymal lung involvement is the most common thoracic manifestation. Dyspnea, persistent/mild/dry cough and wheezing can be the symptoms. A decreased diffusion capacity and a restrictive ventilatory defect, obstructive airways disease, pulmonary arterial hypertension, chest pain are the clinical features of sarcoidosis with lung involvement. Examination of the chest can often show nothing [1]. The CD4/CD8 ratio may be increased in bronchoalveolar lavage in about 50% of patients with sarcoidosis, but bronchoalveolar lavage findings are nonspecific and should not be used to diagnose sarcoidosis alone. Bronchoalveolar lavage findings also cannot predict prognosis or responsiveness to corticosteroid therapy. The diffusion of carbon monoxide (DLCO) is the most sensitive test for an interstitial lung disease and it was decreased in our case, too.

Depression is not seldom reported; its incidence was nearly between 13% and 66% in a large multicenter study [9]. Our patient was also under sertraline therapy for 4 months and it was important to differentiate chronic complaints of depression from another serious clinical entity. Clinical manifestations of sarcoidosis include heart failure (restrictive cardiomyopathy), conduction abnormalities (atrioventricular blocks), atrial and ventricular arrhythmias (monomorphic VT), pericardial effusion, valvular dysfunction and sudden cardiac death. These entities may be induced by sarcoidal granulomas and patchy myocardial fibrosis. Although clinical cardiac involvement occurs in less than 10% of patients, in postmortem studies this rate may range up to 25%. Thus, cardiac monitoring and evaluation in these patients should seriously be done. In our patient, 18-FDG PET-CT (*Siemens, BiographTM mCT, 5mCi IV FDG*) was performed for investigating the cardiac involvement and high myocardial uptake was detected (SUV max 5.1). The patient was called for frequent follow-up and cardiac monitoring although she did not have any cardiac symptoms (Figure 5).

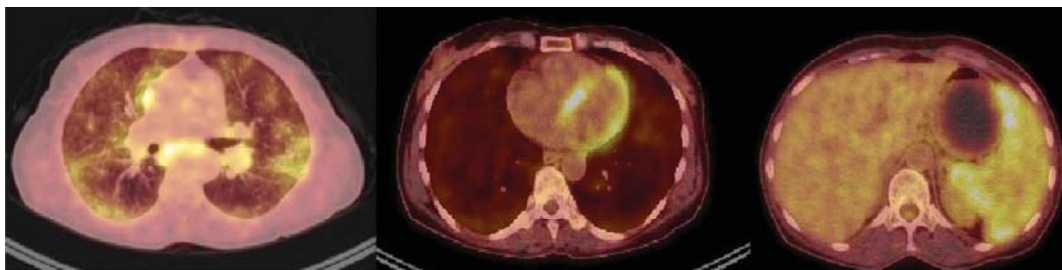


Fig. 5. 18-FDG PET/CT. High thoracic, myocardial, splenic uptake (SUV max 3.4, 5.1, 4.9, respectively)

Bone lesions are rare in sarcoidosis. The reported incidence of radiographically evident osseous involvement is between 1% and 13%, with an average of 5% [10]. We excluded the skeletal involvement by 18FDG-PET/CT in our patient showing high levels of calcium concentrations. Gallium scanning has a historical role in the diag-

nosis of sarcoidosis but its sensitivity is limited [11]. Recently 18FDG-PET/CT has been used more frequently with a high sensitivity among sarcoidosis patients [12-14]. The abdomen is the commonest extrapulmonary site of involvement with a frequency of 50-70% [15]. Autopsy studies have revealed splenic involvement in 38-77% of

patients with this disease [6]. The mean serum ACE levels were found to be higher in patients with splenic nodules than in cases without splenic nodules [6]. Our patient had similar presentation showing both splenic involvement and high levels of ACE. Association of primary biliary cirrhosis and sarcoidosis was reported before but the relationship between these two entities is still not clear. Kishor, *et al.* recently reviewed 17 patients with sarcoidosis and PBC and suggested that a common pathway contributes to granuloma formation in both disorders [16]. On the other hand, no significant association has been identified in a large database in the United Kingdom [17].

Although renal involvement is thought to be uncommon in sarcoidosis, this entity may not be so rare-about 10% of cases [18,19]. In another study, comparing clinical series of sarcoidosis, the incidence of renal involvement was between 9.8-18% [20]. Renal disease may include hypercalciuria (30-50% of cases), granulomatous interstitial nephritis, glomerular disease (membranous nephropathy, proliferative or crescentic glomerulonephritis, focal glomerulosclerosis), renal tubular dysfunction, polyuria (due to nephrogenic and/or central diabetes insipidus), hypertension, nephrocalcinosis-lithiasis (10-14% of cases), hypergammaglobulinemia-related disease, renal vascular disease and obstructive uropathy [21]. The occurrence of hypercalcemia (10-20% of cases) is correlated with disseminated sarcoidosis. Our patient also had multisystem involvement, supporting this finding. Hypercalcemia seems to be the most likely cause of sarcoidosis-associated renal disease, it can even cause acute renal failure in 1-2% of sarcoidosis patients. The effects of hypercalcemia on the kidney are more common than direct granulomatous involvement or interstitial sarcoid inflammation [22]. Direct kidney involvement-granulomas in the kidney-occurs in <5% of sarcoidosis patients and this can lead to nephritis [23]. The prevalence of tubulointerstitial nephritis ranges from 7% to 27%, although chronic renal failure develops in less than 1% of cases [24]. In our case, renal failure was attributed to hypercalciuria and granulomatous interstitial nephritis (seen histopathologically).

Increased 1- α hydroxylase activity in macrophages within granulomas and the alveoli converts 25-hydroxyvitamin D to the biologically active form 1,25-dihydroxyvitamin D (calcitriol), therefore resulting in increased intestinal absorption of calcium leading to hypercalcemia with a suppressed parathyroid hormone (PTH) level. An increased exogenous vitamin D from diet or sunlight (during the summer months) exposure may exacerbate this problem. Patients with sarcoidosis may be sensitive to vitamin D therapy and even in small doses hypercalcemia can be apparent [25]. One dose of vitamin D injection seems to clarify our clinical vignette.

A breast lesion in a patient with sarcoidosis is generally more likely to be a granuloma than breast cancer. However, in a trial comprising 629-women with sarcoidosis

it was shown that mammographic and physical findings could not distinguish between sarcoidosis in the breast and breast cancer [26]. Thus, it is recommended that routine screening including mammography be performed along with other imaging studies (ultrasound, MRI) or biopsy as clinically indicated. We also performed an ultrasound-guided needle biopsy from the hypoechoic nodule of the right breast. The biopsy confirmed the presence of dense fibrous (connective) tissue and granulomas were not seen. Therefore, we excluded malignant breast cancer in this patient.

Corticosteroids remain the principal treatment and may improve renal function by correcting hypercalcemia and/or hypercalciuria and by decreasing granuloma formation in the renal interstitium, along with the associated interstitial nephritis [27,28]. Immediate treatment is appropriate whenever organ function is threatened or when symptoms are severe. Oral prednisone at a dose of 20 to 40 mg per day for 3 months is usually the initial recommended therapy. Patients should be followed closely for 1-2 years after discontinuing treatment because of the risk of recurrence. Failure of serum calcium to normalize within 2 weeks should alert the clinician to an alternative diagnosis such as underlying malignancy. The granulomatous response of sarcoidosis can resolve with or without therapy. Initiating treatment, most patients with granulomatous interstitial nephritis regain renal function. However, in at least 20% of patients with sarcoidosis, a chronic form of the disease develops. Certain risk factors at presentation for a possible chronicity are fibrosis on chest X-ray, presence of lupus pernio, bone cysts, cardiac or neurologic disease (except isolated seventh nerve paralysis), and presence of renal calculi due to hypercalciuria. Hydroxychloroquine, methotrexate, azathioprin, anti-CD20 antibodies, statins, phosphodiesterase inhibitors, infliximab are the other potential therapies highlighted in the literature [2]. Our patient had serious organ involvement and hence we started oral steroid therapy of 40 mg prednisolone. During the close follow-up after starting the treatment, high levels of calcium and creatinine showed regression (Figure 4).

Conclusions

There are often delays in the diagnosis of the disease and care because there is no criterion diagnostic test. Therefore, being suspicious for sarcoidosis should be the first step of the diagnosis in our clinical practice. Novel algorithms and modern tools such as 18-FDG PET/CT can broaden the vision in diagnosis of sarcoidosis from "a disease of exclusion" to a more frequently seen entity.

Conflict of interest statement. None declared.

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