



Case report

A case of bone marrow involvement in sarcoidosis with crescentic glomerular lesions

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ABSTRACT

Renal and bone marrow involvements in sarcoidosis are rare. We experienced the case of a 67-year-old man with systemic sarcoidosis, with bone marrow involvement, hepatic involvement and a unique constellation of renal lesion with cellular crescent formation. Immunosuppressive therapy was helpful for maintaining the stability of his pancytopenia, hepatic function and renal function. To the best of our knowledge, the association between sarcoidosis, bone marrow involvement and crescentic glomerulonephritis has been reported in only few cases in literature.

1. Introduction

Sarcoidosis is a systemic, granulomatous inflammation distributed to multiple organ. Although lung involvement and chest lymphadenopathy are the most common morbidities, extrapulmonary manifestations including ocular involvement and cardiac disorders are often observed [1,2]. These involvements induce overt symptoms and need immediate treatment [1]. Although hepatic involvement is thought to occur in 50–90% of sarcoidosis patients [3], renal involvement is only observed in approximately 4–22% of cases [4]. Bone marrow involvement in sarcoidosis is also rare [5,6] (see Table 1).

We report on a 63-year-old Japanese man who presented with general fatigue, weight loss, pancytopenia, liver dysfunction and renal impairment.

2. Case report

The patient was a 63-year-old Japanese man. He smoked 14 cigarettes a day from the age of 22–45, and alcohol daily. He complained of fatigue and weight loss, and had lost 5 kg in weight over the previous 2 months. His condition had gradually deteriorated over the 2 months. It had difficult for him to move as usual, but he had no obvious neurological disorder. On initial consultation he was suspected to have a

serious underlying disease, and was referred to our hospital.

He was admitted to the department of hematology in our hospital and he had severe pancytopenia was detected. He had no respiratory symptoms and his X-ray showed no abnormal shadows. He had mild fever and reported appetite loss. He weighed 60 kg, height was 175 cm tall, the patient looked pale, and did not have congestion or butterfly shaped erythema. Blood pressure was 92/59 mmHg, heart rate was 78/min, and temperature was 37.5 °C. Physical examination showed no rales, no abnormal cardiac sound. There was no lymphadenopathy. He had no clubbing and no edema of his extremities.

Bone marrow biopsy revealed non-caseating epithelioid granulomas in the bone marrow structure. Malignant tumor, tuberculosis and fungal infections were excluded by histological findings and mycobacterial examinations. High levels of angiotensin-converting enzyme (ACE) and lysozyme suggested sarcoidosis and he was transferred to our respiratory department. His medical history included cerebral infarction, aortic valve stenosis, internal carotid artery stenosis, overactive bladder, and hyperlipidemia. However, these had been well controlled with his receiving medication including lansoprazole (15 mg, daily), carvedilol (2.5 mg, daily), mirabegron (50 mg, daily), and cilostazol (100 mg, daily).

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Table 1
Laboratory test results and reference range.

Test	Result	Reference range
Leukocyte	1530/ μ L	(3300–8600/ μ L)
Hemoglobin	8.6 g/dL	(13.7–16.8 g/dL)
Platelet	7.5×10^4 / μ L	(15.8 – 34.8×10^4 / μ L)
Reticulocyte	7.3×10^4 / μ L	(0.8 – 11×10^4 / μ L)
Albumin	2.8 g/dL	(4.1–5.1 g/dL)
Sodium	134 mEq/L	(138–145 mEq/L)
Potassium	4.3 mEq/L	(3.6–4.8 mEq/L)
Chloride	101 mEq/L	(101–108 mEq/L)
Calcemia	8.5 mg/dL	(8.8–10.1 mg/dL)
Urea	36.8 mg/dL	(8–20 mg/dL)
Creatinine	1.6 mg/dL	(0.65–1.07 mg/dL)
Aspartate transaminase	65 IU/L	(13–30 IU/L)
Alanine transaminase	57 IU/L	(10–42 IU/L)
Lactate dehydrogenase	517 IU/L	(124–222 IU/L)
Gamma glutamate transpeptidase	106 IU/L	(13–64 IU/L)
Alkaline phosphatase	1673 IU/L	(106–322 IU/L)
Total bilirubin	1.0 mg/dL	(0.4–1.5 mg/dL)
Ferrum	35 μ g/dL	(50–160 μ g/dL)
UIBC	142 μ g/dL	(104–259 μ g/dL)
TIBC	177 μ g/dL	(253–365 μ g/dL)
Ferritin	913.5 ng/mL	(39.4–340 ng/mL)
C-reactive protein	1.97 mg/dL	(0–0.14 mg/dL)
Angiotensin-converting enzyme	34.1 U/L	(8.3–21.4 U/L)
Lysozyme	29.8 μ g/mL	(5–10.2 μ g/mL)
Soluble interleukin-2 receptor	7835 U/mL	(145–519 U/mL)
Antinuclear antibody	negative	
Anti-neutrophil cytoplasmic antibodies	negative	
Rheumatoid factor	negative	
Interferon-gamma release assays	negative	
Viral hepatitis serology	negative	
Beta-glucan	0.8 pg/mL	(0–20 pg/mL)

3. Investigations

Laboratory finding showed pancytopenia, mild elevation of liver and biliary enzymes and renal dysfunction. Elevation of ACE, lysozyme, and soluble IL-2 receptor were suggestive of sarcoidosis (Table). Urinalysis revealed mild proteinuria, hematuria, and granular casts.

Chest radiographs revealed no significant findings, including bilateral hilar lymphadenopathy. Even chest computer tomography (CT) did not show hilar and mediastinal lymphadenopathy, or other significant findings in the lungs and mediastinum. Abdominal CT showed hepatosplenomegaly and renal enlargement (Figs. 1 and 2). Bone marrow biopsy revealed a large number of noncaseating epithelioid granulomas

within the hematopoietic area (Fig. 3). Liver biopsy was performed because of hepatosplenomegaly and mild liver dysfunction, and showed non-necrotizing small epithelioid granulomas (Fig. 4). Histological examination of renal biopsy sample showed tubulointerstitial nephritis and focal crescentic glomerulonephritis (Fig. 5). There were no epithelioid cell granulomas in the renal tissue. Immunofluorescence studies were negative for IgG, IgA, IgM, C3, and C1q. Electron microscopy revealed no electron dense deposits.

Based on these serial findings we made a diagnosis of sarcoidosis. The patient was started on prednisolone 20 mg daily (0.5 mg/body), after which an improvement in pancytopenia was noted. However, creatinine rose from 1.1 mg/dL to 1.76 mg/dL and hematuria worsened. Elevation of CRP and lysozyme were considered to indicate continued activity of sarcoidosis. We increased prednisolone to 50 mg daily, after which renal dysfunction and laboratory data including CRP and lysozyme were improved (Fig. 6).

4. Discussion

Sarcoidosis is a systemic granulomatous disease involving almost all organs and tissues [1]. Over 90% of patients with sarcoidosis develop lung lesions. The eyes, lymph nodes, and skin are the next most common sites, but any organ can be affected by sarcoidosis [2]. In the ACCESS study, in 50% of 736 sarcoidosis patients it was just localized to the lungs and total 95% of patients had pulmonary lesions. Only 14 (2%) patients had extrapulmonary lesions without pulmonary lesions. The remaining patients had involvement of multiple organs. In addition, the prevalence of extrapulmonary lesions was higher in African Americans than in whites [7]. In a cohort study of 1686 patients with sarcoidosis, the skin was the organ most commonly affected for extrapulmonary sarcoidosis. There was no significant difference in other affected organs between pulmonary sarcoidosis and extrapulmonary sarcoidosis [4]. In Japan, ocular involvement is the most frequent lesion as extrapulmonary sarcoidosis. In general, sarcoidosis in Japan is reported to have higher incidences of ocular and cardiac lesions compared to in western countries. Main cause of death is cardiac involvements in Japan compared to pulmonary involvements in the Western [8]. The nationwide survey in Japan showed incidences of pulmonary lesions (86.0%), ocular lesions (54.8%), skin lesions (35.4%), and cardiac lesions (23.0%). Kidney lesions were seen in only 3.7% and bone marrow lesions were not reported [9]. Only 3 Japanese cases of bone marrow lesions have been reported as far as we are aware. Renal and bone marrow involvement are too rare to compare among races and nations.

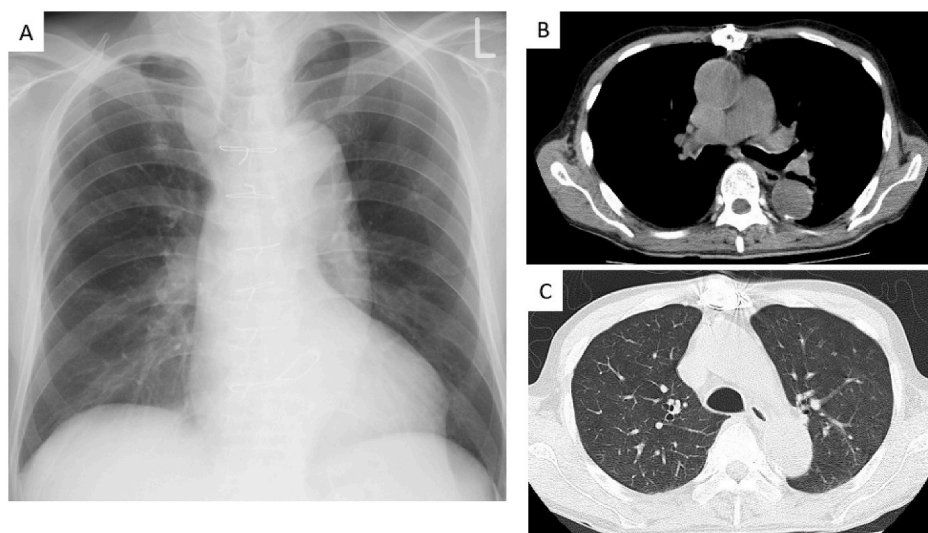


Fig. 1. Chest radiographs did not show bilateral hilar lymphadenopathy (A). Computer tomography (CT) did not show hilar and mediastinal lymphadenopathy or reveal other significant findings in the lung area (B and C).

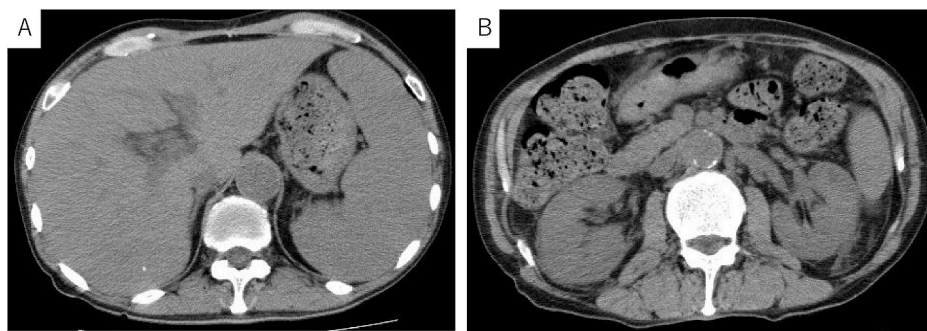


Fig. 2. CT of the abdomen showing hepatosplenomegaly (A) and renal enlargement(B).

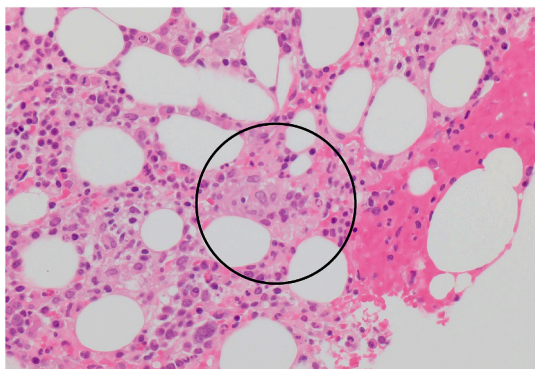


Fig. 3. Bone marrow biopsy showing noncaseating epithelioid granulomas(circle).

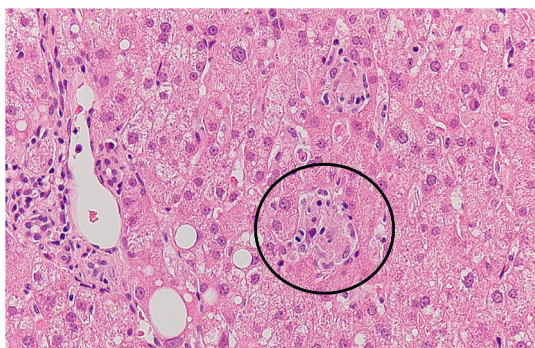


Fig. 4. Liver biopsy showing small epithelioid granulomas (circle).

Bone marrow lesions are very rare, occurring in less than 5% of cases of extrapulmonary sarcoidosis. A study of 9641 patients undergoing bone marrow biopsy, in which 21% of cases involved sarcoidosis, reported that the frequency of granulation species detection in bone marrow biopsy was 0.6% [5]. In a study of bone marrow biopsy in 50 sarcoidosis patients, granulomatous lesions were detected in 5 (10%) of 50 patients. Patients with those bone marrow lesions had a higher frequency of extrapulmonary lesions, leukopenia, and anemia than those without bone marrow lesions [10]. Bone marrow lesions are rarely diagnosed in sarcoidosis, and are frequently missed until abnormal findings appear in blood tests. This patient had no history of sarcoidosis, and complained of weight loss. Diagnosis was based on detection of pancytopenia. Among the differential diagnoses for forming granulomas in the bone marrow are malignant tumors including lymphoma, mycobacterial diseases including tuberculosis, infectious diseases including fungi, cytomegalovirus, EBV, AIDS, drugs and collagen disease. In this case, no malignant cells, fungi or tuberculosis were observed in any tissue. His blood test was negative for opportunistic infections and collagen disease, and he had received no oral medications reported to form granulomas [11]. Bone marrow granulomas and high levels of plasma ACE and lysozyme were consistent with the diagnosis of bone marrow sarcoidosis.

Renal lesions are occasionally reported in sarcoidosis, with a frequency of about 4–22% [12]. Hypercalciuria, causing glomerular and tubular damage, accounts for half of abnormal renal findings. Although lesions related to hypercalciuria are the most common in renal lesions in sarcoidosis, the next most frequent disease is granulomatous interstitial nephritis, with a prevalence of 7–27%. Glomerular lesions are uncommon and show patterns such as membranous nephropathy, focal glomerulosclerosis, proliferative glomerulonephritis, membranous proliferative nephritis, IgA nephropathy, and crescent formation [13]. Proteinuria, nephrotic syndrome, hematuria, and hypertension are common symptoms of glomerular lesions [14]. Diseases that cause crescentic glomerular lesions include anti-glomerular basement membrane antibody disease, lupus nephritis, IgA nephropathy, ANCA-associated vasculitis, and postinfectious glomerulonephritis [15].

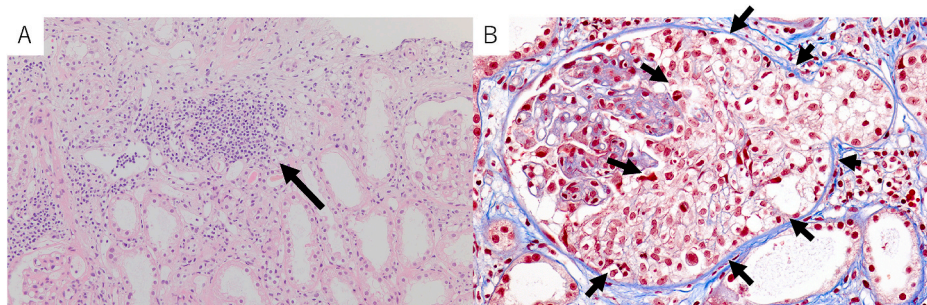


Fig. 5. Renal biopsy showing interstitial nephritis (A). The arrow indicates infiltration of lymphocytes in the interstitial site. High-magnification pictures show focal crescentic glomerulonephritis (B). Arrow heads indicate the crescent formation.

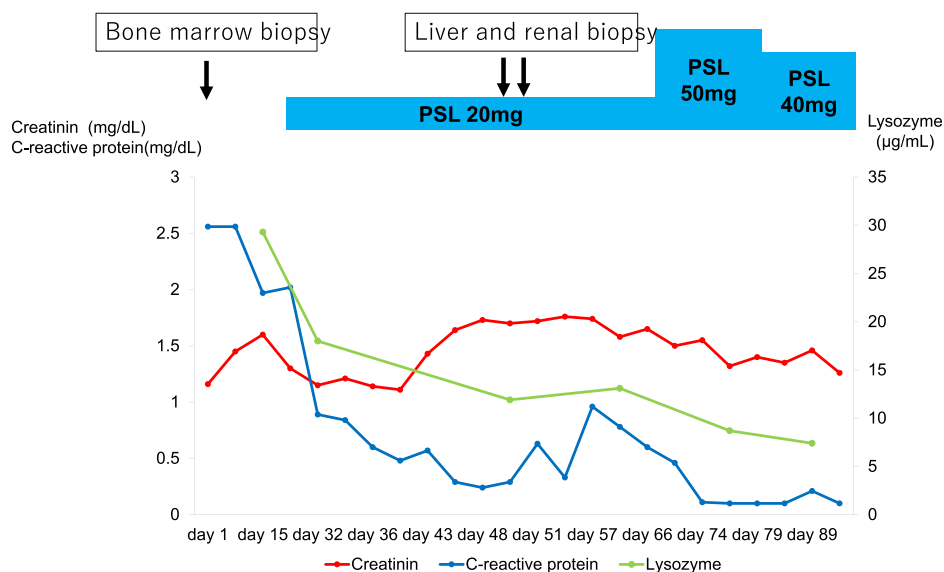


Fig. 6. Follow-up of laboratory data.

In this case, the glomerular staining pattern of the fluorescent antibody technique was of the pauci-immune type, and glomerular lesions due to ANCA-associated vasculitis were considered as a potential diagnosis. However, ANCA-associated vasculitis was ruled out because of the normal levels of plasma ANCA and the absence of findings of either renal or systemic vasculitis. Besides, there was no history of infectious diseases such as tonsillitis, and the findings are not compatible with the diagnostic criteria of anti-glomerular basement membrane antibody disease and lupus nephritis. IgA nephropathy was excluded from the differential diagnoses because no IgA deposition was seen with the fluorescent antibody technique. In this case, granulomatous lesions were confirmed in several organs other than the kidneys, and infectious disease, drug-induced disease, and collagen disease were ruled out. Therefore, it is considered most likely that the interstitial nephritis and glomerular lesions are associated with sarcoidosis. The failure to detect granulomas by renal biopsy might be also related to the fact that the biopsy was performed after a month of daily administration of Prednisolone 20 mg [16].

The clinical course of sarcoidosis varies from spontaneous improvement in a very short period to chronic persistence with or without treatment, and sarcoidosis is sometimes refractory to treatment, with severe QOL decline [1]. Cases of renal disease progressing to chronic kidney disease have been reported [13], and treatment intervention at an appropriate time is warranted. Regardless of the location of the lesion, the standard treatment for sarcoidosis is systemic steroid administration [1]. In bone marrow lesions, a systemic administration of steroids has been reported to improve pancytopenia [15]. Prednisolone is indicated at a dose of 20–40 mg/day, and gradually reduced to a maintenance dose of less than 10 mg/day. Immunosuppressants are also considered for intractable cases [17].

Regarding bone marrow sarcoidosis, three types of cases have been reported. The first case was that of a patient with pulmonary sarcoidosis who had lesions in the bone and bone marrow lasting a long time [18]. The second was a case of granulomatous lesions in the bone marrow, spleen, and abdominal lymph nodes without lung lesions [7]. The last was a case of granulomatous lesions in the lungs and bone marrow following development of cutaneous sarcoidosis [6]. On the other hand, although there has been a case report of renal dysfunction resulting in hypercalcemia due to bone marrow sarcoidosis [19], there have been no reports of cases of simultaneous glomerulonephritis and bone marrow sarcoidosis. Therefore, we consider that this case to be extremely rare.

5. Conclusion

We encountered a rare case of bone marrow involvement in renal sarcoidosis. The patient's condition improved with steroid treatment. It is important to keep in mind that sarcoidosis involves various organs including the bone marrow and kidneys.

Declaration of competing interest

The authors declare that they have no Conflicts of Interest (COI).

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