CASE REPORT

Systemic Sarcoidosis Presenting with Renal Involvement Caused by Various Sarcoidosis-associated Pathophysiological Conditions

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Abstract:
A 61-year-old man was diagnosed with sarcoidosis involving the lungs, eyes, parotid gland and extrathoracic lymph nodes complicated by chronic kidney injury and hypercalcemia. Kidney biopsy showed non-specific interstitial nephritis and nephrosclerosis. However, immunohistochemical staining of cell surface markers revealed a multinucleated giant macrophage surrounded by T-cells, suggesting granulomatous interstitial nephritis. Corticosteroid improved the kidney function, and reduced the serum levels of calcium and angiotensin-converting enzyme. Sarcoid nephropathy may be caused by the combination of several sarcoidosis-associated pathophysiological conditions and a comprehensive kidney examination should be performed to assess the type of injury when determining a treatment strategy.

Key words: sarcoidosis, granulomatous interstitial nephritis, immunohistochemistry, hypercalcemia, nephrosclerosis

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Introduction
Sarcoidosis is a multisystem disorder that is pathologically characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and non-caseating granulomas in the involved organs (1). The lungs are the most commonly affected organ. Isolated extrapulmonary involvement of the skin, eyes, reticuloendothelial system, musculoskeletal system, nervous system, heart, exocrine glands or kidneys are rarely seen (2, 3). A diagnosis of sarcoidosis requires the demonstration of non-caseating granulomas in a biopsy specimen of one or more involved organs and the clinical exclusion of other causes of granulomatous inflammation (1). A characteristic pattern of renal involvement in sarcoidosis is granulomatous interstitial nephritis (GIN). GIN is a rare histological diagnosis that is detected in 0.5-0.9% of native kidney biopsies (4, 5). The frequency of GIN in sarcoidosis, which has been estimated from a postmortem series, ranges from 7% to 23% (6). Thus, it is usually difficult to determine whether or not nephropathy in sarcoidosis is due to GIN. We report a case of systemic sarcoidosis presenting with renal involvement resulting from various sarcoidosis-associated pathophysiological conditions wherein immunohistochemical staining of cell surface markers was useful for the diagnosis of GIN.

Case Report
A 61-year-old man presented to a community hospital be-
The patient was referred to our hospital due to suspected sarcoidosis with lymph node swelling and a pulmonary hilar lesion. The patient, a 62-year-old man, smoked 5 packs of cigarettes per day for approximately 40 years. Regarding visual loss, the patient was diagnosed with chronic kidney disease; however, he had never taken any medications for it. The patient had no history of tuberculosis, HTLV-1, or dengue fever. Despite his smoking history, we detected no evidence of lung cancer.

On admission, the patient’s blood pressure was 100/70 mmHg and his oxygen saturation by pulse oximetry was 95% with room air. A physical examination detected cervical and supraclavicular lymph node swelling. Late inspiratory crackles were heard from both dorsal surfaces. The laboratory results are summarized in Table, and indicate kidney failure with a creatinine level of 2.03 mg/dL and hypercalcemia with a serum corrected calcium level of 11.4 mg/dL. A laboratory analysis to determine the cause of hypercalcemia revealed the following findings: serum intact parathyroid hormone, 7 pg/mL (normal level, 10-65 pg/mL); serum 1,25-dihydroxyvitaminD (1,25(OH)2VitD), 111 pg/mL (normal level, 20-60 pg/mL); and urine calcium excretion, 423 mg/day (normal level, <200 mg/day). The results suggested that the patient’s hypercalcemia resulted from excess 1,25(OH)2VitD. The patient’s serum ACE and soluble interleukin-2 receptor (sIL-2R) levels increased to 47.9 IU/L. The patient’s serum free T3 and free T4 levels were 1.69 ng/dL (normal level, 0.85-1.72 ng/dL) and 1.52 ng/dL (normal level, 0.85-2.00 ng/dL), respectively. The patient’s serum anti-ds-DNA and anti-nuclear antibodies were negative. A renal biopsy specimen showed interstitial nephritis with a lymphoid interstitial infiltration. An unremarkable surgical specimen was retrieved from the right infrarenal aorta.

| Blood cell test | Immunological test | Blood gas analysis |
|----------------|-------------------|--------------------|
| WBC 8.900 µL  | CRP 1.69 mg/dL    | pH 7.385           |
| Neutrophils 62.9 % | ANA 1.280 times | PCO2 42.3 mmHg     |
| Lymphocytes 20.2 % | IgG 2.613 mg/dL | PO2 89.3 mmHg      |
| Monocytes 8.2 % | IgG4 26.1 mg/dL  | HCO3 24.7 mEq/L    |
| Eosinophils 5.2 % | IgA 414 mg/dL    |                   |
| Basophil 1.0 % | IgM 163 mg/dL    |                   |
| RBC 474 ×10^12/L | C3 120 mg/dL  | Specific gravity 1.013 |
| Hemoglobin 14.3 g/dL | C4 27 mg/dL | pH 6.0             |
| Hct 42.8 % | CH50 64 U/mL | Protein (2+)       |
| MCV 90.2 fl | rheumatoid factor | <10 IU/mL Occult blood (1+) |
| Platelet 26.8 ×10^10/µL | Anti-ds-DNA | <2.0 IU/mL Glucose (±) |
| [Blood cell test] | Anti-RNP antibody negative | Red blood cell 1.5 /HPF |
| [Immunological test] | Anti-Sm antibody negative | White blood cell 1.5 /HPF |
| [Blood gas analysis] | Granulocast 0 /LPF | |
| Total bilirubin 0.4 mg/dL | sIL-2R 7.040 U/mL | Albumin 92 mg/day |
| Total protein 8.5 g/dL | T-SPOT negative | Calcium 423 mg/day |
| Albumin 3.4 g/dL | Creatinine 987 mg/day | |
| Total cholesterol 194 mg/dL | [Infection] | NAG 29.1 U/L |
| HDL cholesterol 28 mg/dL | HBs Ag negative | β2-microglobulin 173,080 µg/L |
| Triglyceride 149 mg/dL | HBe Ab negative | |
| Sodium 140 mEq/L | CMV Ag negative | |
| Potassium 3.1 mEq/L | HTLV-1 Ab negative | |
| Chloride 104 mEq/L | Corrected calcium 11.4 mg/dL | [Endocrine test] |
| Phosphorus 3.4 mg/dL | Intact-PTH 7 pg/mL | |
| Magnesium 2.4 mg/dL | 1,25-dihydroxyvitaminD 111 pg/mL | |
| Serum uric acid 4.4 mg/dL | ACE 47.9 IU/mL | |
| Blood urea nitrogen 24 mg/dL | Creatinine 2.03 mg/dL | |
| eGFR 27 mL/min/1.73m² | Blood sugar 88 g/dL | |
| KL-6 737 U/mL | | |

AST: aspartate transaminase, ALT: alanine aminotransferase, γ-GTP: γ glutamyl transpeptidase, LDH: lactate dehydrogenase, HDL: high density lipoprotein, eGFR: estimated glomerular filtration rate, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane, sIL-2R: soluble interleukin-2 receptor, HTLV-1: human T cell lymphotropic virus type 1, PTH: parathyroid hormone, ACE: angiotensin-converting enzyme, NAG: N-acetyl-beta-glucosaminidase.

Table. Laboratory Results on Admission.

cause of slowly progressive exertional dyspnea that had persisted for one year, anorexia, and visual loss. The patient's medical history included cataracts, uroterolithiasis, and chronic kidney disease; however, he had never taken any medications. His smoking history was significant; he had smoked 5 packs of cigarettes per day for approximately 40 years. Regarding visual loss, the patient was diagnosed with acute glaucoma and uveitis. A laboratory examination showed hypercalcemia and an elevated serum angiotensin-converting enzyme (ACE) level. Chest radiography revealed lymph node swelling with a pulmonary hilar lesion. The patient was referred to our hospital due to suspected sarcoidosis.

On admission, the patient’s blood pressure was 100/70 mmHg and his oxygen saturation by pulse oximetry was 95% with room air. A physical examination detected cervical and supraclavicular lymph node swelling. Late inspiratory crackles were heard from both dorsal surfaces. The laboratory results are summarized in Table, and indicate kidney failure with a creatinine level of 2.03 mg/dL and hypercalcemia with a serum corrected calcium level of 11.4 mg/dL. A laboratory analysis to determine the cause of hypercalcemia revealed the following findings: serum intact parathyroid hormone, 7 pg/mL (normal level, 10-65 pg/mL); serum 1,25-dihydroxyvitaminD (1,25(OH)2VitD), 111 pg/mL (normal level, 20-60 pg/mL); and urine calcium excretion, 423 mg/day (normal level, <200 mg/day). The results suggested that the patient’s hypercalcemia resulted from excess 1,25(OH)2VitD. The patient’s serum ACE and soluble interleukin-2 receptor (sIL-2R) levels increased to 47.9 IU/
mL and 7,040 U/mL, respectively. Computed tomography showed systemic lymphadenopathy, mainly in the pulmonary hilar lesion, mediastinum, retroperitoneum and para-aorta, interstitial changes of the basal lung, and a diffuse granuloreticular shadow. Spirometry showed a restrictive defect impairment and reduction in diffusing capacity of the lung. Gallium 67 scintigraphy showed an increased uptake in the right pulmonary hilar lymph nodes, abdominal lymph nodes, and parotid gland (Fig. 1). Transbronchial lung biopsy demonstrated epithelioid granulomas. Bronchoalveolar lavage showed an increase in lymphocytes accompanied by an elevated CD4+/ CD8+ T-cell ratio [4.02 (normal level, 1.5-3.2)]. These findings provided a definitive diagnosis of systemic sarcoidosis involving the lungs, eyes, parotid gland, and extrathoracic lymph nodes. A further examination was performed to evaluate the kidney injury. The patient’s urinary sediment showed no hematuria. Urine biochemical tests demonstrated overt proteinuria with a urinary protein level of 1.049 mg/day, and an elevated β2-microglobulin level of 173,080 μg/L, which suggested tubulointerstitial injury. The most likely diagnosis was sarcoid GIN; however, ultrasound revealed left kidney atrophy. Possible causes of kidney atrophy, including nephrolithiasis, hydrenephrosis and renovascular stenosis, were excluded based on the radiological findings. A renogram demonstrated laterality of the glomerular filtration rate (GFR): the right and left GFR were 16.8 mL/min and 5.3 mL/min, respectively. Gallium 67 scintigraphy did not show a significant uptake in the kidneys. Needle biopsy of the right kidney was performed with the consent of the patient and revealed left kidney GFR of 11.5 mL/min. These findings suggest that although prednisolone improved the reversible kidney injuries caused by GIN and hypercalcemia, the patient had developed irreversible tubulointerstitial fibrosis in the kidney before treatment.

Discussion

Sarcoidosis is an idiopathic multisystem disorder of unknown etiology (7). Renal involvement occurs in 30-50% of patients in association with a wide spectrum of mechanisms (8, 9). Common renal manifestations include hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis and renal tubular dysfunction; GIN is a classic renal lesion. Renal sarcoidosis is usually silent and in most cases remains undetected for many years, which leads to chronic damage. The present case developed both chronic kidney injury and acute reversible injury, which were thought to have been caused by a combination of GIN, abnormal calcium metabolism, and nephrocalcinosis. It is critical to differentiate the etiology of renal involvement because the treatment and prognosis depend on the pathophysiology.

The characteristic pathological finding of renal sarcoidosis

Figure 1. Gallium 67 scintigraphy. Gallium 67 scintigraphy showed an increased uptake in the pulmonary hilar lymph nodes (arrow 1), abdominal lymph nodes (arrow 2), and parotid gland (arrow 3).
is GIN (10). The formation of a sarcoid granuloma starts from the accumulation of mostly helper T-cells and monocyte/macrophages at sites of disease activity. The central core of granuloma consists of monocyte/macrophages, T cells and epithelioid cells. A number of chemokines that are released from involved cells eventually lead to fibrosis and hyalinization (11, 12). GIN, however, is rarely diagnosed. Shah et al. reported that 19% of patients with renal sarcoi-

Figure 2. The kidney pathology. (a) A kidney specimen subjected to Masson Trichrome staining (×100). Moderate focal interstitial fibrosis and tubular atrophy are observed. (b) Cellular infiltration is observed in the tubulointerstitium [Hematoxylin and Eosin (H&E) staining, ×200]. (c) A non-sclerotic glomerulus shows minor glomerular abnormality (Periodic acid-Schiff staining, ×400). (d) Intimal hyaline change of the afferent arteriole and fibrous intimal thickening of the interlobular artery are shown (Periodic acid silver methenamine and H&E staining, ×400). (e) An enlarged view of the square in (a). An isolated multinucleated giant cell (arrow) (×800).

Figure 3. Immunohistochemical staining for CD68/PGM-1, CD3 and CD20. A multinucleated giant macrophage surrounded by macrophages and T cells is observed (arrow). CD68/PGM-1, CD3 and CD20 are specific markers of macrophages, T-cells and B-cells, respectively (×400).
vated pulmonary macrophages often express 1
patients with granulomatous disease, granulomas and acti-
tional injuries or atypical granuloma.

Kidney tissue and immunohistochemistry may lead to a cor-
munostaining of cell surface markers. Careful observation of
case in which sarcoid GIN was diagnosed based on im-
and CD3 was used to detect sarcoid granuloma that showed
our case, immunohistochemical staining of CD68/ PGM-1
sarcoidosis patients without systemic manifestations (14). In
the differentiation of granuloma with central necrosis in sar-
et al. reported that immunostaining of ACE was useful for
may be useful for characterizing or detecting granuloma. Ito
sarcoidosis showed GIN and that more than half of these cases
showed non-specific findings (13). Granuloma may be
moss in a kidney biopsy specimen, and sometimes only
represents the interstitial infiltration of mononuclear cells;
thus, patients with renal sarcoidosis often present non-
specific tubulointerstitial injuries. Immunohistochemistry
may be useful for characterizing or detecting granuloma. Ito
et al. reported that immunostaining of ACE was useful for
the differentiation of granuloma with central necrosis in sar-
coidosis patients without systemic manifestations (14).
In our case, immunohistochemical staining of CD68/ PGM-1
and CD3 was used to detect sarcoid granuloma that showed
an atypical morphology. To our knowledge, this is the first
case in which sarcoid GIN was diagnosed based on im-
umnostaining of cell surface markers. Careful observation of
kidney tissue and immunohistochemistry may lead to a cor-
rect diagnosis of GIN in patients with non-specific intersti-
tial injuries or atypical granuloma.

Approximately 30-50% of patients with sarcoidosis have
hypercalciuria, and 10-20% have hypercalcemia (15, 16). In
patients with granulomatous disease, granulomas and acti-
vated pulmonary macrophages often express 1α hydroxy-
lase, a cytochrome P-450 enzyme, and the expression is re-
sistant to normal negative feedback (17). Elevated enzymatic
activity increases the conversion of 25(OH)VitD into bio-
logically active calcitriol, 1,25(OH)2VitD. Excess calcitriol
increases the intestinal absorption of dietary calcium, osteo-
clast activity and bony reabsorption, and suppresses the ex-
cretion of parathyroid hormone, thus predisposing the pa-
tient to hypercalciuria and hypercalcemia. The abnormal cal-
cium metabolism can cause nephrocalcinosis, nephrolithias-
sis, afferent arteriolar vasoconstriction or polyuria due to de-
creased responsiveness to antidiuretic hormone. Moreover,
longstanding hypercalcemia and hypercalciuria may lead to
the degeneration of the tubular cells, resulting in tubular at-
rophy and interstitial fibrosis. Thus, calcium metabolic ab-
normalities are often responsible for the significant reduction
in the kidney function of patients with renal sarcoidosis. In
our case, neither nephrocalcinosis nor nephrolithiasis, which
occasionally present resistance to steroid therapy in renal
sarcoidosis, were observed. However, steroid therapy rapidly
ameliorated both the decreased kidney function and the ab-
normal serum calcium concentration, which suggested re-
versible hemodynamic insult from hypercalcemia. The ab-
normal calcium metabolism was thought to contribute to the
impaired kidney function through several mechanisms.

Another distinct lesion in the present case was atheroscle-
rosis and arteriosclerosis of the renal vessels, which could
eventually cause tubulointerstitial fibrosis. A kidney biopsy
demonstrated fibrous intimal thickening of the interlobular
artery and hyalinosis of the afferent arteriole in addition to
collapsed glomeruli and global glomerular sclerosis, suggest-
ing kidney injury caused by vascular lesions. There is accu-
mulating evidence on the risk factors for arteriosclerosis in
patients with kidney disease (18, 19). The present patient
had no history of hypertension, diabetes mellitus, and hyper-
cholesterolemia, whereas his long-term heavy smoking habit
and sarcoidosis, itself, might have been responsible for
atherogenesis. Tuleta et al. reported that sarcoidosis is asso-
ciated with an increased pulse wave index, which may indi-

![Figure 4. The clinical course. eGFR: estimated glomerular filtration rate, U-β2MG: urine β2 mi-
croglobulin, U-NAG: urine N-acetyl-beta-glucosaminidase, ACE: angiotensin-converting enzyme,
sIL-2R: soluble interleukin-2 receptor](image-url)
cate an early stage of atherosclerosis (20). In rheumatology, inflammation mediated by activated T cells and cytokines is known to be a predisposing factor for atherosclerosis (21). Serum sIL-2R reflects the degree of activated T cell-derived inflammation in sarcoidosis (22). This patient presented with several involved organs and his serum level of sIL-2R was highly elevated. Furthermore, smoking, a classic risk factor of atherosclerosis, is reported to affect both the course and outcome of rheumatic diseases (23). Sarcoidosis and smoking might have cooperatively promoted the atherogenic process of this case.

We reported a case of systemic sarcoidosis in a patient presenting renal involvement that resulting from various sarcoidosis-associated pathophysiological factors. The differential diagnosis of renal sarcoidosis is occasionally difficult, particularly in cases complicated by more than one mechanism. A comprehensive examination of the kidney should be performed to assess the type and prognosis of kidney disease when determining the treatment strategy for sarcoidosis.

The authors state that they have no Conflict of Interest (COI).

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