Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1558-18
Intern Med 58: 679-684, 2019
http://internmed.jp

【 CASE REPORT 】

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

Sayo Ueda[1], Taichi Murakami[1], Hirokazu Ogino[2], Motokazu Matsuura[3], Masanori Tamaki[1], Seiji Kishi[1], Mike Hann[4], Yuko Toyoda[2], Kojiro Nagai[1], Yoshimi Bando[5], Hideharu Abe[1], Yasuhiko Nishioka[2] and Toshio Doi[1]

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 nonspecific 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

(Intern Med 58: 679-684, 2019)
(DOI: 10.2169/internalmedicine.1558-18)

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-

[1]Department of Nephrology, Graduate School of Biomedical Sciences, Tokushima University, Japan, [2]Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Japan, [3]Department of Nephrology, Tokushima Red Cross Hospital, Japan, [4]Department of the Directorate for Medical Services, US Navy Hospital, Japan and [5]Division of Pathology, Tokushima University Hospital, Japan
Received: May 17, 2018; Accepted: July 12, 2018; Advance Publication by J-STAGE: November 19, 2018
Correspondence to Dr. Taichi Murakami, murakami.taichi@tokushima-u.ac.jp

Table. Laboratory Results on Admission.

[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	PCO_2	42.3 mmHg
Lymphocytes	20.2 %	IgG	2,613 mg/dL	PO_2	89.3 mmHg
Monocytes	8.2 %	IgG4	26.1 mg/dL	HCO_3^-	24.7 mEq/L
Eosinophils	5.2 %	IgA	414 mg/dL		
Basophil	1.0 %	IgM	163 mg/dL	[Urinalysis]	
RBC	474 $\times10^4$/μL	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 $\times10^4$/μL	Anti-ds-DNA	<2.0 IU/mL	Glucose	(±)
		Anti-RNP antibody	negative		
[Biochemical test]		Anti-Sm antibody	negative	Red blood cell	1-5 /HPF
AST	24 U/L	Anti-SS-A antibody	negative	White blood cell	1-5 /HPF
ALT	18 U/L	PR3-ANCA	<1.0 U/mL	Granular cast	0 /LPF
γ-GTP	36 U/L	MPO-ANCA	<1.0 U/mL		
LDH	169 U/L	Anti-GBM antibody	<2.0 U/mL	Protein	1,049 mg/day
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	HBc 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/1.73m^2				
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

cause of slowly progressive exertional dyspnea that had persisted for one year, anorexia, and visual loss. The patient's medical history included cataracts, ureterolithiasis, 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 ($1,25(OH)_2$VitD), 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 $1,25(OH)_2$VitD. The patient's serum ACE and soluble interleukin-2 receptor (sIL-2R) levels increased to 47.9 IU/

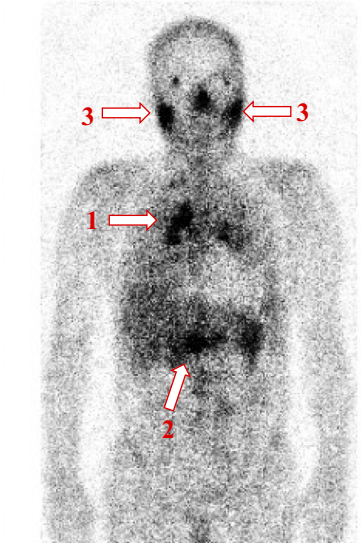


Figure 1. Gallium 67 scintigraphy. Gallium 67 scintigraphy showed an increased uptake in the pulmonary hilar lymph nodes (arrow 1), abdominal lymph nodes (arrow 2), and parotid gland (arrow 3).

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 granular-reticular 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 levels 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, hydronephrosis 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 to identify the cause of kidney failure. On light microscopy, there were 20 glomeruli including 4 with global sclerosis and 4 collapsed glomeruli. Non-sclerotic glomeruli showed minor glomerular abnormality without deposition of immunoglobulin or complement (Fig. 2c). Intimal hyalinosis of the afferent arteriole and fibrous intimal thickening of the interlobular artery was also detected (Fig. 2d). There were no findings of evident non-caseating granuloma or nephrolithiasis (characterized by calcium deposits); however, the tubulointerstitium showed moderate focal interstitial fibrosis, tubular atrophy, and cellular infiltration (Fig. 2a and b). An isolated multinucleated cell was observed (Fig. 2e). We considered that this multinucleated cell might have been a macrophage; thus immunostaining of cell surface markers was performed to characterize this cell. The multinucleated cell was positive for CD68/PGM-1, a specific macrophage marker (Fig. 3a). CD68-positive cells and CD3-positive T cells surrounded the multinucleated giant macrophage (Fig. 3b). CD20, a specific B-cell marker, was not detected (Fig. 3c). The other causes of GIN, including tuberculosis, granulomatosis with polyangiitis (Wegener's), drug use and Sjögren's syndrome, were excluded according to the patient's medical history, laboratory results and imaging findings. Thus, we finally made a diagnosis of sarcoid GIN.

The clinical course is shown in Fig. 4. Treatment with oral prednisolone (30 mg/day) was initiated. Within a few days of treatment, the patient's respiratory symptoms disappeared. This was followed by a decrease in the serum levels of corrected calcium, ACE and sIL-2R. The patient's kidney function rapidly improved, which was accompanied by a decrease in the serum calcium level. Thereafter, steroid treatment resulted in a gradual increase in the GFR and a decrease in the urinary markers of tubulointerstitial injury. However, the urine β2-microglobulin level did not completely normalize. At six months after the initiation of prednisolone, a renogram demonstrated the improvement of the bilateral kidney function with a right kidney GFR of 23.6 mL/min and a 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 nephrosclerosis. 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

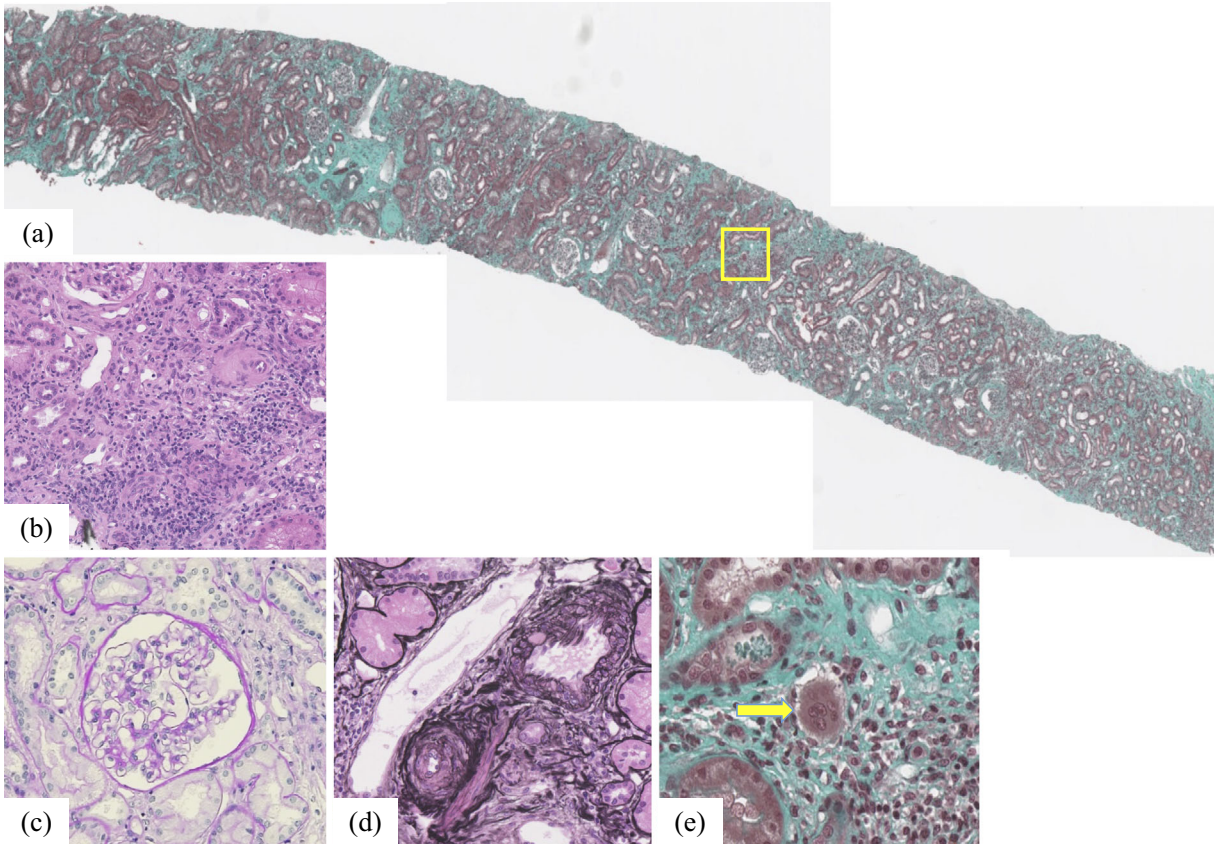


Figure 2. **The kidney pathology. (a) A kidney specimen subjected to Masson Trichrome staining (×100). Moderate focal interstitial fibrosis and tubular atrophy are observed. (b) Cellular infiltration is observed in the tubulointerstitium [Hematoxylin and Eosin (H&E) staining, ×200]. (c) A non-sclerotic 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).**

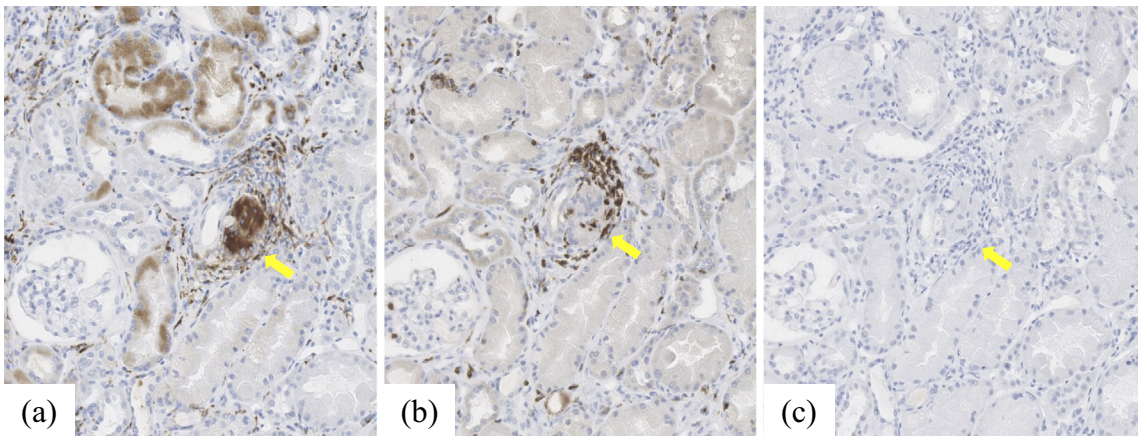
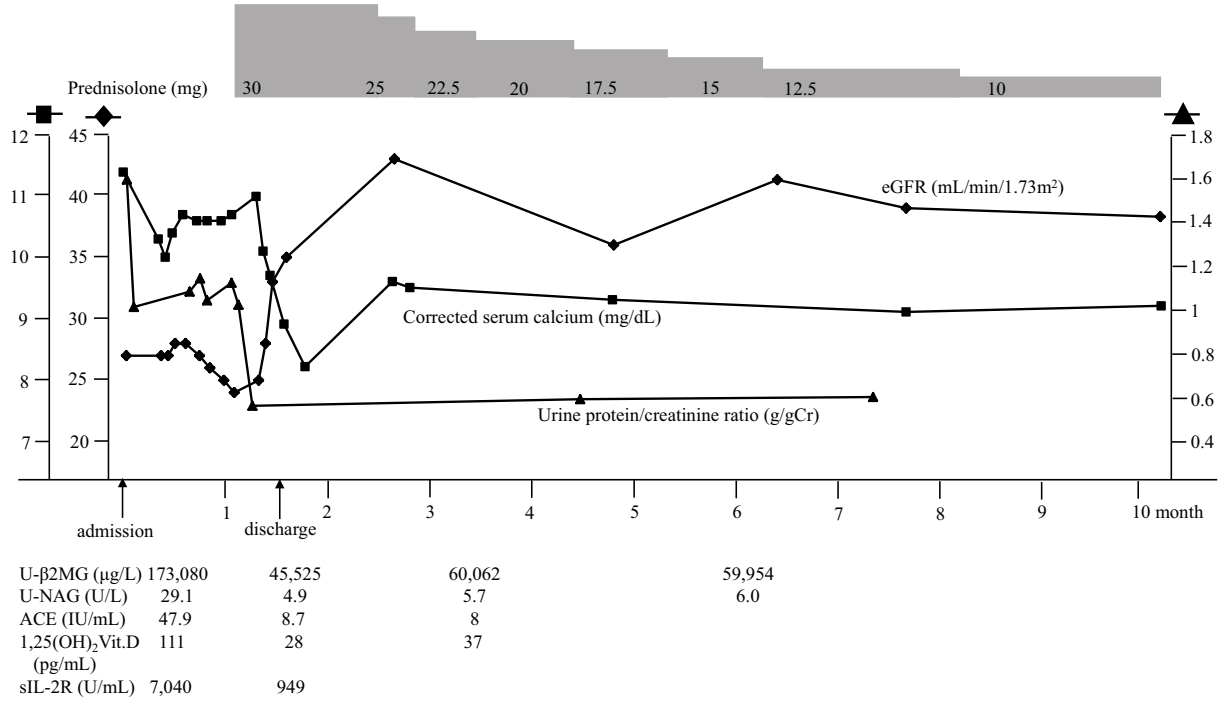


Figure 3. **Immunohistochemical staining for CD68/PGM-1, CD3 and CD20. A multinucleated giant macrophage surrounded by macrophages and T cells is observed (arrow). CD68/PGM-1, CD3 and CD20 are specific markers of macrophages, T-cells and B-cells, respectively (×400).**

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-



U-β2MG (μg/L)	173,080	45,525	60,062	59,954
U-NAG (U/L)	29.1	4.9	5.7	6.0
ACE (IU/mL)	47.9	8.7	8	
$1,25(OH)_2$Vit.D (pg/mL)	111	28	37	
sIL-2R (U/mL)	7,040	949		

Figure 4. The clinical course. eGFR: estimated glomerular filtration rate, U-β2MG: urine β2 microglobulin, U-NAG: urine N-acetyl-beta-glucosaminidase, ACE: angiotensin-converting enzyme, sIL-2R: soluble interleukin-2 receptor

dosis showed GIN and that more than half of these cases showed non-specific findings (13). Granuloma may be missed 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 sarcoidosis 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 immunostaining of cell surface markers. Careful observation of kidney tissue and immunohistochemistry may lead to a correct diagnosis of GIN in patients with non-specific interstitial 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 activated pulmonary macrophages often express 1α hydroxylase, a cytochrome P-450 enzyme, and the expression is resistant to normal negative feedback (17). Elevated enzymatic activity increases the conversion of 25(OH)VitD into biologically active calcitriol, $1,25(OH)_2$VitD. Excess calcitriol increases the intestinal absorption of dietary calcium, osteoclast activity and bony reabsorption, and suppresses the excretion of parathyroid hormone, thus predisposing the patient to hypercalciuria and hypercalcemia. The abnormal calcium metabolism can cause nephrocalcinosis, nephrolithiasis, afferent arteriolar vasoconstriction or polyuria due to decreased responsiveness to antidiuretic hormone. Moreover, longstanding hypercalcemia and hypercalciuria may lead to the degeneration of the tubular cells, resulting in tubular atrophy and interstitial fibrosis. Thus, calcium metabolic abnormalities 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 abnormal serum calcium concentration, which suggested reversible hemodynamic insult from hypercalcemia. The abnormal calcium metabolism was thought to contribute to the impaired kidney function through several mechanisms.

Another distinct lesion in the present case was atherosclerosis 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, suggesting kidney injury caused by vascular lesions. There is accumulating 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 hypercholesterolemia, whereas his long-term heavy smoking habit and sarcoidosis, itself, might have been responsible for atherogenesis. Tuleta et al. reported that sarcoidosis is associated with an increased pulse wave index, which may indi-

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).

References

1. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee. Statement on sarcoidosis. February 1999. Am J Respir Crit Care Med **160**: 736-755, 1999.
2. Ricker W, Clark M. Sarcoidosis; a clinicopathologic review of 300 cases, including 22 autopsies. Am J Clin Pathol **19**: 725-749, 1949.
3. Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. Medicine (Baltimore) **31**: 1-132, 1952.
4. O'Riordan E, Willert RP, Reeve R, et al. Isolated sarcoid granulomatous interstitial nephritis: review of five cases at one center. Clin Nephrol **55**: 297-302, 2001.
5. Mignon F, Mery JP, Mougenot B, Ronco P, Roland J, Morel-Maroger L. Granulomatous interstitial nephritis. Adv Nephrol Necker Hosp **13**: 219-245, 1984.
6. Robson MG, Banerjee D, Hopster D, Cairns HS. Seven cases of granulomatous interstitial nephritis in the absence of extrarenal sarcoid. Nephrol Dial Transplant **18**: 280-284, 2003.
7. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet **361**: 1111-1118, 2003.
8. MacSearraigh ET, Doyle CT, Twomey M, O'Sullivan DJ. Sarcoidosis with renal involvement. Postgrad Med J **54**: 528-532, 1978.
9. Bergner R, Hoffmann M, Waldherr R, Uppenkamp M. Frequency of kidney disease in chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis **20**: 126-132, 2003.
10. Berger KW, Relman AS. Renal impairment due to sarcoid infiltration of the kidney; report of a case proved by renal biopsies before and after treatment with cortisone. N Engl J Med **252**: 44-49, 1955.
11. Agostini C, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma. Curr Opin Rheumatol **12**: 71-76, 2000.
12. Gobel U, Kettritz R, Schneider W, Luft F. The protean face of renal sarcoidosis. J Am Soc Nephrol **12**: 616-623, 2001.
13. Shah R, Shidham G, Agarwal A, Albawardi A, Nadasdy T. Diagnostic utility of kidney biopsy in patients with sarcoidosis and acute kidney injury. Int J Nephrol Renovasc Dis **4**: 131-136, 2011.
14. Ito Y, Suzuki T, Mizuno M, et al. A case of renal sarcoidosis showing central necrosis and abnormal expression of angiotensin converting enzyme in the granuloma. Clin Nephrol **42**: 331-336, 1994.
15. Sharma OP. Vitamin D, calcium, and sarcoidosis. Chest **109**: 535-539, 1996.
16. Adams JS. Vitamin D metabolite-mediated hypercalcemia. Endocrinol Metab Clin North Am **18**: 765-778, 1989.
17. Reichel H, Koeffler HP, Barbers R, Norman AW. Regulation of 1,25-dihydroxyvitamin D3 production by cultured alveolar macrophages from normal human donors and from patients with pulmonary sarcoidosis. J Clin Endocrinol Metab **65**: 1201-1209, 1987.
18. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. Hypertension **45**: 1042-1049, 2005.
19. Drueke TB, Massy ZA. Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol **6**: 723-735, 2010.
20. Tuleta I, Pingel S, Biener L, et al. Atherosclerotic vessel changes in sarcoidosis. Adv Exp Med Biol **910**: 23-30, 2016.
21. van Leuven SI, Kastelein JJ, D'Cruz DP, Hughes GR, Stroes ES. Atherogenesis in rheumatology. Lupus **15**: 117-121, 2006.
22. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest **124**: 186-195, 2003.
23. Harel-Meir M, Sherer Y, Shoenfeld Y. Tobacco smoking and autoimmune rheumatic diseases. Nat Clin Pract Rheumatol **3**: 707-715, 2007.