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Case Report

A Case Demonstrating the Pathological Relationship between Granulomatous Vasculitis and Glomerular Lesion in Renal Sarcoidosis

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Keywords
Renal sarcoidosis · Vasculitis · Focal segmental glomerulosclerosis · Perihilar variant

Abstract
We experienced a rare case of tubulointerstitial angiocentric granulomatous vasculitis with focal segmental glomerulosclerosis (FSGS) and associated sarcoidosis. Our patient was an 18-year-old man who presented with exertional cough and dyspnea. He also had overt proteinuria (3.0 g/24 h), normal renal function (eGFR 95 mL/min/1.73 m^2), heart failure, and hypertension. He had no previous episode of hypertension. These manifestations immediately improved after the administration of antihypertensive therapy that contained an angiotensin-converting enzyme inhibitor, calcium antagonists, beta antagonists, and diuretics. However, he, later on, developed renal dysfunction, with worsening of both proteinuria and hypertension. Renal biopsy was performed and showed epithelioid cells that were arranged concentrically around small blood vessels in tubulointerstitial granulomas. In the glomeruli, the segmental sclerotic lesions

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were classified as a perihilar variant of FSGS. There were no inflammatory changes, such as a mesangial lesion, inflammatory cell infiltration, fibrinoid necrosis, or crescent formation, and no glomerular granuloma. In the tubulointerstitial granulomas, the intimal elastic lamina of the interlobular arteries was reduplicated, and the intimal wall thickness of renal arterioles was remarkable. After receiving oral prednisolone therapy, the overt proteinuria resolved, the eGFR recovered from 39.4 to 60.6 mL/min/1.73 m^2, and hypertension was managed more easily. Thereafter, he did not experience any recurrence. The concurrent improvement of renal function and proteinuria by steroid treatment suggested a relationship between the glomerular lesions and the tubulointerstitial granulomatous vasculitis with associated sarcoidosis.

Introduction

Sarcoidosis, which is a systemic inflammatory granulomatous disease of unknown etiology, can be diagnosed by the following: typical multiple organ involvement related to sarcoidosis, presence of granulomatous lesions, and exclusion of other diagnoses, such as malignancy, infectious diseases, collagen diseases, and antineutrophil cytoplasmic antibody-associated vasculitis. The guidelines for the diagnosis of sarcoidosis have been proposed by the World Association for Sarcoidosis and Other Granulomatous Disorders [1]. The commonly affected organs include the lungs and peripheral lymph nodes, followed by the eyes, liver, and skin [2]. The reported incidence of renal sarcoidosis was lower compared with that of other organs [3], ranged from 3 to 19% among autopsy cases in postmortem studies [4, 5], and was extremely low among cases with renal biopsy [6]. The typical pathological finding of renal sarcoidosis comprises tubulointerstitial granulomatous nephritis, whereas renal parenchymal granulomatous vasculitis associated with sarcoidosis has been rarely reported. Although there have been sporadic case reports on sarcoidosis with glomerular disease, the causal relationship between sarcoidosis and concomitant glomerular disease has remained unclear. We report a very rare case of tubulointerstitial angiocentric granulomatous vasculitis with focal segmental glomerulosclerosis (FSGS) associated with sarcoidosis and discuss the pathophysiology of these findings.

Case Report

The patient was an 18-year-old man who had been complaining of exertional cough and dyspnea for 4 months. He had no medical and familial history. He graduated from junior high school but did not go to high school or work. He presented to our hospital after visiting a general practitioner for epigastric discomfort and nausea. At that time, urinalysis revealed massive proteinuria. On the next day, he was referred and admitted to our hospital for a thorough examination. He had no history of hypertension, human immunodeficiency virus (HIV) infection, drug abuse, ureteral reflux, premature birth, or any other diseases.

On admission, physical examination revealed a body temperature of 36.7°C, a body weight of 62 kg, and a height of 168 cm. Blood pressure was 157/85 mm Hg. There were evident leg edema, bilateral inguinal lymphadenopathy, and no skin lesions. The laboratory findings revealed decreased serum total protein (5.9 g/dL) and albumin (2.6 g/dL); normal serum creatinine (SCr, 0.9 mg/dL) and eGFR (95 mL/min/1.73 m^2); elevated LDL cholesterol (224 mg/dL); and slightly elevated serum calcium (10.6 mg/dL). BNP level was remarkably

elevated (1,850 pg/mL). Urinalysis revealed a subnephrotic level of urinary protein (3.0 g/day), microhematuria (5–9/HPF), no leukocyturia, and no bacteria. The soluble interleukin 2 receptor level was elevated (2,905 U/mL); serum angiotensin-converting enzyme (ACE) level was normal (14.2 U/L); renin activity was remarkably elevated (39 ng/mL/h); plasma aldosterone level was within normal limits (184 pg/mL). The urinary N-acetyl-glucosaminidase level was remarkably elevated (85.6 IU/L). Hepatitis B virus surface antigen, hepatitis C virus antibody, and HIV antigen and antibody were all negative. Immunoglobulins, complements, rheumatoid factor, antinuclear antibody, and antineutrophil cytoplasmic antibodies were all negative. Tuberculin test was negative.

The chest X-ray showed enhanced pulmonary congestion and no detectable hilar lymphadenopathy. In contrast, chest computed tomography (CT) revealed hilar lymphadenopathy without fibrosis in any lung field. Furthermore, abdominal CT revealed bilateral normal-sized kidneys and bilateral inguinal lymphadenopathy. Gallium-67 scintigraphy revealed uptakes in the pulmonary hilum, mediastinum, bilateral submaxillary glands, bilateral parotid glands, and bilateral inguinal regions. Echocardiography detected severe cardiac dysfunction (ejection fraction 25%), diffuse akinesis of the ventricular wall, and atrial septal defect, but it did not detect thinning of the interventricular septum base. However, electrocardiogram-gated cardiac CT revealed thinning of the interventricular septum base, and this finding was supported by a cine magnetic resonance imaging. Cardiac dysfunction and thinning of the ventricular septum base were supportive findings of cardiac sarcoidosis.

On the first admission, the patient received treatment for heart failure and hypertension, including temocapril hydrochloride, calcium channel antagonist, carvedilol, spironolactone, and carperitide. Thereafter, the urinary protein level decreased to <1 g/day, and the heart failure and hypertension improved. On the 30th hospital day, the patient was discharged. The inguinal biopsy that was performed as outpatient procedure detected granulomas; therefore, the diagnosis was sarcoidosis. On the 69th day, the SCr level gradually increased to 2.00 mg/dL (eGFR 39.4 mL/min/1.73 m^2) and the urinary protein-to-creatinine ratio increased to 3.2 g/gCr. At this time, the serum albumin and LDL cholesterol levels were 3.7 g/dL and 134 mg/dL, respectively. Therefore, he was readmitted for renal investigation.

Subsequent renal biopsy revealed the presence of 32 glomeruli, 8 of which showed global sclerosis. Mesangial proliferation, crescent formation, or epithelial change was not observed. In 4 glomeruli, segmental sclerotic lesions were found near the vascular pole and were classified as the perihilar variant of FSGS [7] (Fig. 1). The diameter of the Bowman's space of the FSGS lesions was maintained at approximately 200–230 μm. Conversely, several ischemic glomerular changes were found, including atrophic Bowman's capsule, glomerular tuft shrinking, and global sclerosis (Fig. 2a, b). Tubulointerstitial fibrosis and inflammatory cell infiltration accounted for 70% of the renal parenchyma. Mononuclear cell infiltration, giant cells, and non-caseous granulomas in the tubulointerstitium were noted. The majority of the granulomas involved small arteries and/or arterioles, many of which had intimal wall thickness, reduplicated internal elastic lamina, and narrow lumen (Fig. 2a). Many of the epithelioid cells of these granulomas were arranged concentrically around the artery/arteriole and formed a multilayer structure.

Immunostaining by an enzyme-labeled antibody method revealed focal and segmental deposits of IgM (1+) in the glomerular lesions. In the tubulointerstitium, no significant deposits of IgG, IgA, IgM, C1q, and C3 were found. Immunohistochemistry revealed CD68-positive macrophage accumulation in the tubulointerstitial granulomas but not in the glomeruli. Electron microscopy did not detect any glomeruli. Based on these findings, the pathological diagnosis was tubulointerstitial granulomatous angiocentric vasculitis with FSGS.

He received oral prednisolone 30 mg/day after the renal biopsy revealed renal sarcoidosis. At 27 days after the initiation of steroid therapy, the SCr level decreased to 1.60 mg/dL (eGFR 50.2 mL/min/1.73 m^2), with a simultaneous decrease in the urinary protein-to-creatinine ratio to <0.5 g/gCr. Thereafter, oral prednisolone was tapered to 25 mg/day, and the patient was discharged on the 38th day of the second hospital stay (the 108th day).

After discharge, his blood pressure stabilized. Later in the clinical course, nifedipine could be reduced, and temocapril was discontinued. Echocardiography showed recovery of cardiac function (ejection fraction 55.4%). Oral prednisolone was gradually tapered to 2 mg/day after 8 years of steroid initiation, and the SCr level decreased to 1.22 mg/dL (eGFR 60.6 mL/min/1.73 m^2) after 8.8 years of the initial presentation. The urinary protein-to-creatinine ratio was maintained at <0.3 g/gCr. No other immunosuppressants were used. No relapse in the clinical course has occurred at the time of writing this manuscript.

Discussion/Conclusion

Our case had several characteristic renal pathological findings that included angiocentric granulomas and the concomitant perihilar variant of FSGS. Many of the epithelioid cells of the granulomas were arranged concentrically around the artery/arteriole, the majority of which had findings seen in hypertensive sclerotic changes. However, he had no previous episode of hypertension, and ophthalmologic examination revealed no hypertensive arterial changes. Therefore, his clinical course of hypertension had been unclear before the initial consultation. The narrow sclerotic arteries and arterioles may have caused microcirculatory disturbances and relevant ischemic glomerular changes such as the atrophy of Bowman's capsule and global sclerosis (Fig. 2a, b). These arterial changes could consequently stimulate renin secretion. Furthermore, these decreased functioning glomeruli may lead to an increase in other glomerular blood flow. The elevated renin secretion and redistribution of intrarenal blood flow could result in hypertension and hyperfiltration in other glomeruli that escaped ischemia; this potential mechanism may have led to the development of the perihilar variant of adaptive FSGS.

Thinning of the ventricular septum base is a typical finding of cardiac sarcoidosis. The normal recovery of cardiac function is consistent with the course of cardiac sarcoidosis. It is possible that cardiac dysfunction at presentation contributed to glomerular hypertension through the activation of the renin-angiotensin system.

Initially, the antihypertensive drugs, including ACE inhibitors, only had a temporary effect on overt proteinuria. Subsequently, the coadministration of steroid therapy was continuously effective in improving renal function and in reducing and maintaining urinary protein in the normal range. Moreover, after the initiation of steroid therapy, his hypertension became stable, and some of the antihypertensive agents could be reduced in the later clinical course. However, the perihilar variant of adaptive FSGS is generally treated by ACE inhibitors/angiotensin receptor blockers, so it is exceptional that steroid therapy was effective for FSGS lesions that caused proteinuria. Then, we supposed that steroid therapy had an indirect effect on the glomerular lesions by acting on the tubulointerstitial granulomas, including the sclerotic small arteries/arterioles. Sarcoidosis-related granulomatous tubulointerstitial nephritis was reported to be highly responsive to steroid therapy for improving renal function [8]. In our case, the improvement of renal function by steroid therapy synchronized with the decrease of proteinuria and improved the clinical course of hypertension (Fig. 3). According to previous reports, the granulomatous lesions might have had a detrimental circulatory effect on the

adjacent vessels [9, 10]. Hence, we consider the following: by steroid treatment on tubulointerstitial granulomas, the microcirculation of the relevant small arteries/arterioles was improved, which led to the amelioration of glomerular hypertension and hyperfiltration.

Two cases of angiocentric granulomatous vasculitis in renal sarcoidosis have been reported previously [11, 12]. However, unlike the previous reports, this case report showed various outstanding concomitant findings, such as epithelioid cell arrangement and glomerular and renal vascular lesions. The glomerular lesions associated with sarcoidosis include minimal change disease, IgA nephropathy, mesangial proliferative nephritis, membranous proliferative nephritis, and FSGS [13, 14]. So far, there have been some case reports on sarcoidosis with FSGS, which showed improved renal function and decreased proteinuria in response to steroid therapy. However, none of these cases had the typical pathological finding of renal granulomatous lesions in renal sarcoidosis, and those previous reports did not describe the classification of FSGS variants. Therefore, whether the occurrence of these FSGS lesions was associated with sarcoidosis or was accidental remains unclear.

Microscopic polyangiitis and malignant diseases are diagnoses of exclusion. In our patient, the renal biopsy did not identify any fibrinoid necrosis in the vessel wall or crescent formation in the glomerulus. Polymorphonuclear cell infiltration was not evident in the granulomatous vascular lesions. In addition to those findings, a negative titer of the antineutrophil antibody supported the exclusion of microscopic polyangiitis in our patient. Moreover, we did not detect any malignancy on whole-body CT and gallium scintigraphy.

Corticosteroid is the standard treatment for renal sarcoidosis, similar to that for sarcoidosis in other organs. However, in many cases of renal sarcoidosis, renal function remains at a subnormal level [8]. Steroid therapy is effective in suppressing active inflammation in the granulomatous lesions, which can subsequently transform into nonfunctioning fibrotic scars. Therefore, the available antifibrotic agents for the treatment of idiopathic interstitial pneumoniae may also improve the prognosis of renal sarcoidosis [15].

In conclusion, we report a case of tubulointerstitial angiocentric granulomatous vasculitis associated with renal sarcoidosis and a perihilar variant of FSGS. The characteristic finding was the arrangement of the epithelioid cells around the sclerotic and narrow arteries/arterioles, which might have affected the glomerular hemodynamics and triggered renin secretion. Steroid treatment led to improved renal function, significantly decreased overt proteinuria to normal range, and led to easy control of blood pressure. The clinical course demonstrated the pathophysiologic relationship among tubulointerstitial granulomas, vascular lesions, and possibly adaptive FSGS. The detailed relationship between each of the pathological findings needs further study.

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Statement of Ethics

This case report has been approved by the ethics committee of Kitamurayama Hospital (approval number does not exist) and Tohoku University (approval number 2017-1-37). Informed written consent for publication of the case report and accompanying images was

obtained from the patient. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest directly relevant to the content of this article.

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Author Contributions

Y. Kamata picked up the data, reviewed the literature, and wrote the manuscript. H. Sato offered several suggestions, reviewed the literature, and revised it in terms of nephrology and pathology. A. Azuma offered many suggestions and revised it in terms of respiratory medicine. A. Sugiura and M. Miyata followed up the patient in the hospital and as an outpatient. K. Kisu prepared the specimens for optic and electric microscopic observation.

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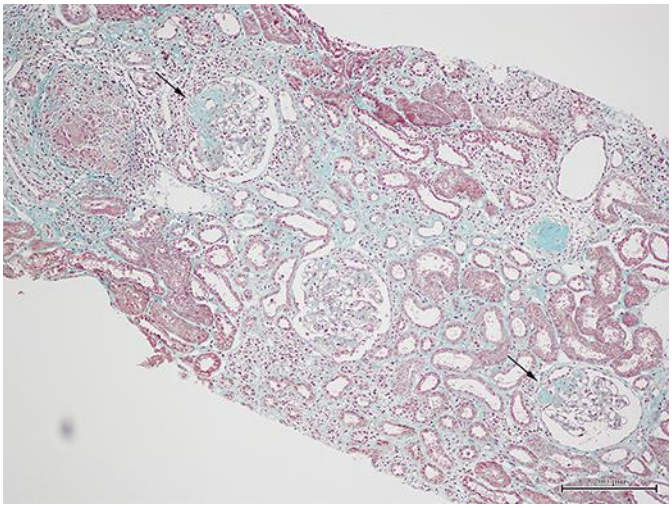

Fig. 1. There is a granulomatous lesion in the tubulointerstitium and segmental sclerosis at the vascular pole (black arrow) of the glomeruli (Masson's trichrome stain, ×100).

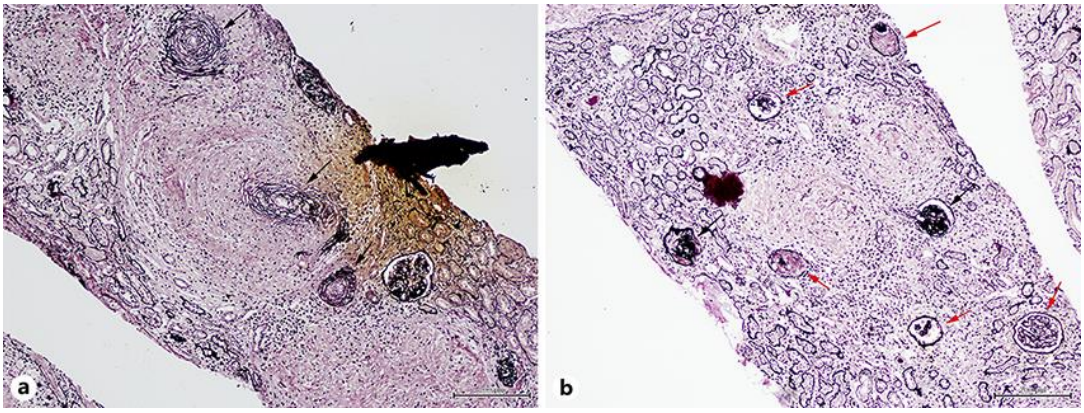

Fig. 2. **a** Tubulointerstitial granulomatous vasculitis and the sclerotic glomeruli. The granulomas involve small arteries, which have reduplicated internal elastic lamina, narrow lumens (black allows), and epithelioid cells that are concentrically arranged around these arteries (Periodic acid-Schiff stain, ×100). **b** Tubulointerstitial granulomatous vasculitis and the glomerular global sclerosis. There are global sclerosis (black arrows) and ischemic glomeruli (red arrows) around angiocentric granulomas (Periodic acid-Schiff stain, ×100).

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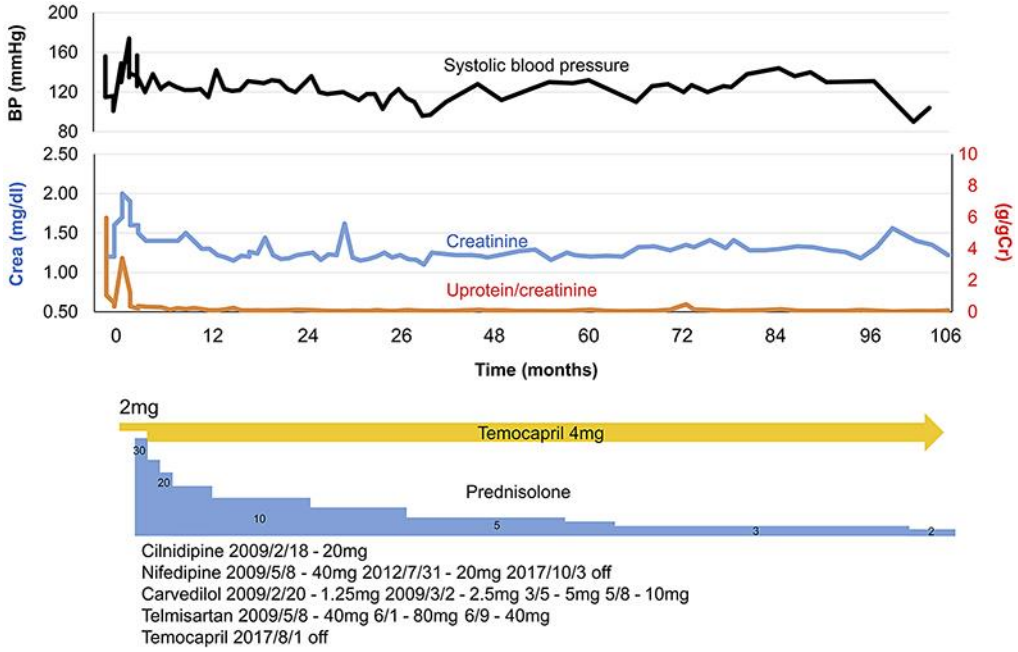

Fig. 3. Clinical course of treatment. After the initiation of prednisolone therapy, there is a remarkable decrease in the massive proteinuria at presentation and improvement of the deteriorated renal function, allowing the reduction or discontinuation of some antihypertensive agents.