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A case of acute kidney injury caused by granulomatous tubulointerstitial nephritis associated with sarcoidosis and concomitant presence of anti-glomerular basement membrane antibody

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Abstract. We encountered a case of granulomatous tubulointerstitial nephritis in a patient with sarcoidosis, who was also found to show an elevated serum titer of anti-glomerular basement membrane (GBM) antibody. The serum creatinine level had been documented to be within normal range 8 months before the first visit. Gallium scintigraphy revealed bilateral kidney uptake, but no uptake in the pulmonary hilum. No typical findings of sarcoidosis, e.g., bilateral hilar adenopathy, uveitis or elevated serum ACE level were recognized in the early stage. Echocardiography showed basal thinning of the interventricular septum, a specific feature of cardiac sarcoidosis, and hilar lymph node uptake on gallium scintigraphy and anterior uveitis appeared during the disease course. Active tuberculosis, fungal infection, vasculitis and malignancy were clinically excluded. We performed a renal biopsy. Light microscopy revealed non-caseating granulomatous tubulointerstitial nephritis with multinucleated giant cells and normal glomeruli. Inflammatory reaction was seen only within the interstitial tubules. The serum creatinine level had increased to 4.52 mg/dl. The patient was administered methylprednisolone pulse therapy, followed by administration of oral prednisolone. The renal function improved immediately in response to this therapy. Based on the above, we made the final diagnosis of granulomatous tubulointerstitial nephritis associated with sarcoidosis. While the serum titer of anti- GBM antibody was elevated, to our surprise, renal biopsy did not reveal linear anti-GBM antibody staining in this case. Furthermore, interestingly, the serum anti-GBM antibody titer in our patient decreased in parallel with the clinical improvement of sarcoidosis. Severe and progressive renal dysfunction was the most prominent clinical feature without other organ manifestations in our patient, which is a rare occurrence in sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 368-371)*

Key words: acute kidney injury, interstitial nephritis, anti-glomerular basement membrane antibody, renal sarcoidosis, autoantibody

Introduction

Sarcoidosis is a systemic inflammatory disease characterized by the formation of non-caseating granulomas, and the diagnosis is made by exclusion of other granulomatous diseases. Lung is the most frequently involved organ in sarcoidosis, followed in frequency by involvement of the eye and liver. Renal involvement is clinically rare while alive.

We encountered a case of granulomatous tubulointerstitial nephritis associated with sarcoidosis.

Steroid therapy was very effective and the renal function rapidly improved.

While the serum titer of anti-GBM antibody was elevated, light microscopic examination of a kidney biopsy specimen did not reveal any significant

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changes in the glomeruli. This is the first reported case of renal sarcoidosis with concomitant presence of anti-GBM antibody in the serum.

Case report

A 77-year-old female was referred to our hospital for generalized fatigue and body weight loss of about 4 kg over a period of a month in February 2013. She had undergone a cholecystectomy six years ago for cholecystitis. The serum creatinine (SCr) level had been documented to be 0.5 mg/dl eight months earlier.

On physical examination at admission, the temperature was 36.2 , the body weight was 41 kg and the height was 145 cm. Blood pressure was 122/51 mm Hg. There was no trunk or leg edema, no superficial lymphadenopathy, and no abnormal skin lesions. The laboratory findings were as follows: WBC 4480/μl RBC 343 × 10^4/μl, hemoglobin 9.4 g/dl, hematocrit 29.6%, platelets 250 × 10^3/μl, total protein 8.2 g/dl, alb 3.7 g/dl, SCr 3.19 mg/dl, blood urea nitrogen 43.6 mg/dl, and serum calcium 9.0 mg/dl, Urinalysis revealed a urinary protein excretion rate of 0.4 g/24h, microhematuria and leukocyturia. Urine culture was negative, including for fungi and mycobacteria. The serum IgG was elevated to 2427 mg/dl. The antinuclear antibody titer was 40-fold. The serum rheumatoid factor level was 22 U/l (0-20). Serum ACE was 19.5 IU/l (8.3-21.4). Serum titers of MPO-ANCA and PR3-ANCA were under the limits of measurement. However, the serum anti-GBM antibody titer was elevated to 35.4 EU (<3.0). The urinary α1 microglobulin (α1 mg) level was 62.5 mg/l (0.5-9.5). Chest x-ray and CT showed no hilarlymphadepathy. Gallium-67 scintigraphy showed uptake in both the kidneys, but no uptake in the pulmonary hilum. Uveitis was not found at the first examination by an ophthalmologist. Renal biopsy revealed the following: Prominent mononuclear cell infiltration and giant cell in the tubulointerstitum. Granuloma formation without caseous necrosis was noted (Figure 1a). Many of the cells showed positive immunostaining for CD68, marker of macrophage (Figure 1b). Immunofluorescence examination showed no significant deposits in the glomeruli (Figure 2) or tubules. Grocott's staining did not reveal evidence of fungal infection. The

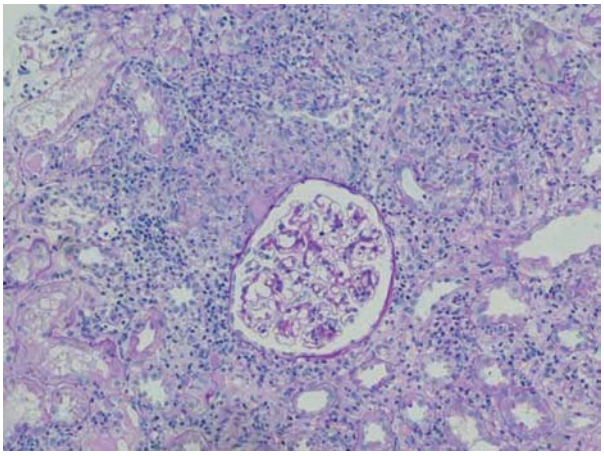

Fig. 1a. Periodic acid-Schiff stain at magnification 200×. Granulomatous interstitial nephritis with mononuclear and intact glomerulus

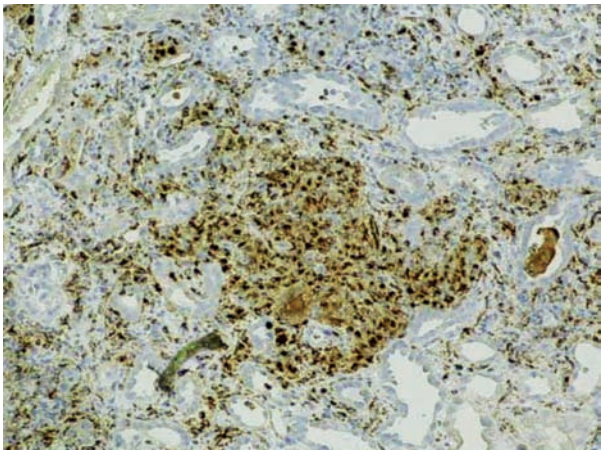

Fig. 1b. Immunostaining by CD68, marker of macrophage, at magnification 200× Most of granuloma cells are positive for CD68

histopathologic diagnosis was non-caseating granulomatous tubulointerstitial nephritis. Echocardiography showed normal cardiac function, but thinning of the base of the interventricular septum. The SCr had increased to 4.52 mg/dl by day 9 of hospitalization. Pulse therapy with 500 mg of methylpredonisolone was initiated, followed by oral prednisolone administration at 20 mg/day. With this treatment, the SCr decreased rapidly and was recorded to be 0.70 mg/dl at discharge. The serum anti-GBM antibody titer also decreased to 3.5 EU. Subsequently, at the second consultation, gallium scintigraphy revealed bilateral pulmonary hilar uptake and mutton fat precipitates.

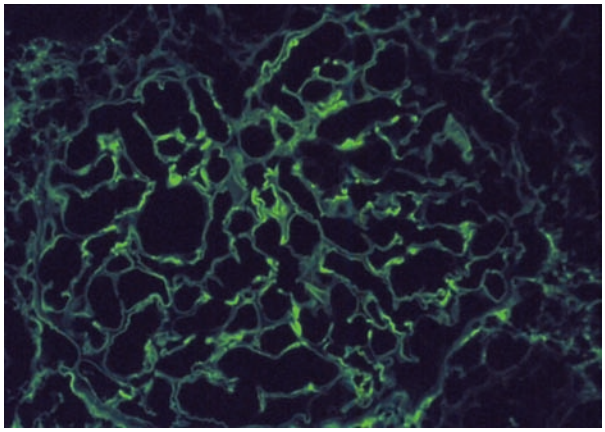

Fig. 2. Immunofluorecence at magnification 400×, It shows no significant deposition of IgG in glomerulus

Discussion

In our case, the only clinical manifestation at the first visit was deterioration of the renal function. Routine clinical examination failed to reveal the typical findings of sarcoidosis.

Renal biopsy showed granulomatous tubulointerstitial nephritis.

We finally confirmed this case as a case of sarcoidosis based on the subsequent appearance of hilar uptake on gallium scintigraphy and uveitis.

Postmortem studies have reported the existence of renal granulomas in 7 to 19% of cases (1, 2), however, clinical renal involvement is rare. A case-control etiologic study of sarcoidosis reported that the incidence of renal involvement was 0.7% (7).

However, later, Bergner reported that 15 of the 31 chronic sarcoidosis patients in his patient series had renal abnormalities (4). Thus, renal involvement may be more frequent than previously thought. In patients showing elevated urinary excretion of α1 mg and kidney uptake on gallium scintigraphy, as in our case, the diagnosis of granulomatous interstitial nephritis caused by sarcoidosis should be suspected and a renal biopsy should be considered.

There is non-specific immunological activation in sarcoidosis patients. Hyperglobulinemia and several autoantibodies are often found in such cases.

The serum anti-GBM antibody titer was also elevated in our patient and this could be associated with immunological abnormalities by sarcoidosis. However, renal biopsy revealed no glomerular abnormalities. Anti-GBM antibody is known to target non collagenous domain of a type IV collagen α3 (5, 6), which is distributed in the glomeruli, tubules and alveoli (7). Lerner et al. reported that anti-GBM antibody exerts pathogenicity in Goodpasture's syndrome (8). However, there are reports of the existence of anti-GBM antibody in the circulation in the absence of anti-GBM disease (9, 10); it would appear that in such cases, this antibody shows lower avidity as compared to that in patients with anti-GBM disease. The reason for the absence of glomerular changes associated with the presence of anti-GBM antibody in our case remains unclear.

Whether the elevated serum anti-GBM antibody titer was in any way related to the renal involvement of sarcoidosis in our patient is also unclear. But it is much of interest that the anti-GBM antibody titer decreased with clinical improvement of the sarcoidosis. Concomitant organ involvement of sarcoidosis and this organ associated autoantibody has occasionally been reported in endocrine organs, particularly the thyroid gland (11, 12). While the pathogenicity of thyroid autoantibody may be strongly suspected in such cases (13), the causal relationship remains unclear, and further study is needed.

Conclusion

We encountered a patient who was diagnosed as having non-caseating granulomatous interstitial nephritis associated with sarcoidosis. Acute kidney injury caused by granuloma formation as the main clinical manifestation and this manifestation serving as the basis for the clinical diagnosis of sarcoidosis is rare in the clinical setting. The cause of elevation of the anti-GBM antibody titer and the reason for the lack of pathogenicity of the antibody in our case warrants further discussion.

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