Tubulointerstitial Nephritis Caused by Peritubular Capillaritis Accompanied by Cryoglobulinemia

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Abstract

A 73-year-old man with fever, renal insufficiency, and purpura was referred to our hospital to be evaluated for renal insufficiency. Renal biopsy revealed acute and chronic tubulointerstitial nephritis with no laboratory findings of sarcoidosis or connective tissue disease. Low C4 levels and elevation of rheumatoid factors suggested cryoglobulinemia, which was confirmed with quantitative analysis. CD34 staining of kidney tissue revealed peritubular capillaritis. Antineutrophil cytoplasmic antibodies were negative. The etiology of peritubular capillaritis was not clear in our patient; however, it might be associated with cryoglobulinemia because we cannot find any other diseases that could have induced the peritubular capillaritis.

Key words: peritubular capillaritis, tubulointerstitial nephritis, cryoglobulinemia

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Introduction

Cryoglobulinemic vasculitis is caused by the deposition of circulating cryoglobulins. It is well known that cryoglobulinemic vasculitis is often associated with hepatitis C virus (HCV) infection (1-3). Other viruses, connective tissue diseases, lymphoproliferative disorders, and liver diseases, such as autoimmune hepatitis and primary biliary cirrhosis, have also been implicated in this vasculitis (4-10). Renal involvement in patients with cryoglobulinemic vasculitis is not rare, as membranoproliferative glomerulonephritis (MPGN) has been reported to be associated with HCV infection (11) and cases of tubulointerstitial nephritis associated with cryoglobulinemic vasculitis have also been reported (12). However, there have been no reports of patients with cryoglobulinemic vasculitis who are complicated with an apparent peritubular capillaritis without glomerular lesions. We herein describe a case of tubulointerstitial nephritis caused by peritubular capillaritis, and consider that cryoglobulin might have been a contributing factor in the development of peritubular capillaritis.

Case Report

A 73-year-old man developed fever and purpura. A week later, he was admitted to a hospital because of rapidly progressing renal insufficiency; his serum creatinine concentration increased from 0.78 mg/dL (8 months before admission) to 1.26 mg/dL, and further increased to 1.58 mg/dL a few days later. On admission, purpura was found on his lower extremities and his laboratory findings showed inflammation, proteinuria, and hematuria; his serum C-reactive protein level (CRP) was 18.2 mg/dL, and urine protein and occult blood levels were 2+ and 3+, respectively, in qualitative tests. Antibiotic treatments were not effective, and oral prednisolone (0.5 mg·kg⁻¹·day⁻¹) was administered. A few days later, his renal insufficiency, inflammation, and urinary findings improved dramatically. His urinalysis in health check-ups consistently showed slightly positive urinary protein with hematuria for 3 years; in the qualitative analysis, urinary protein and occult blood were from negative to 2+. 

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Although paroxysmal atrial fibrillation was diagnosed and he was prescribed rivaroxaban 5 months ago, there have been no other medicines for ordinary use. He was transferred to our hospital to be evaluated for renal insufficiency and elevated inflammation 18 days after the initiation of steroid therapy.

Upon admission to our hospital, a physical examination revealed a blood pressure reading of 144/88 mmHg and a regular pulse rate of 84 beats/min. Purpura, lymphadenopathy, arthralgia, myalgias, and peripheral neuropathy were not found. Laboratory tests showed the following results (Table 1): blood urea nitrogen, 30.5 mg/dL; serum creatinine, 1.05 mg/dL; total protein, 7.1 g/dL; serum albumin, 3.3 g/dL; potassium, 4.6 mEq/L; calcium, 9.8 mg/dL; inorganic phosphate, 2.3 mg/dL; CRP, 0.31 mg/dL; anti-double-stranded DNA, anti-SSA, anti-SSB, and anti-STA were negative. Anti-streptolysin O was 30 IU/mL (reference, <239 IU/mL); hemoglobin, 13.0 g/dL; white blood cells, 24,360/μL; and platelets, 319,000/μL. Serological tests revealed anti-streptokinase titer 1/160 (reference, <1/2,560), and anti-streptolysin O 30 IU/mL (reference, <1/2,560), and an antinuclear antibody with a speckled pattern at a 1/40 titer. Anti-double-stranded DNA, anti-SSA, anti-SSB, and anti-STA were negative. Virological tests for the Epstein-Barr virus (EBV) showed a viral capsid antigen (VCA) IgG at 1/40 titer, a VCA IgM negative, and the EB nuclear antigen at 1/10 titer, indicating that chronic active EBV infection can be ruled out. Direct immunoperoxidase staining of leukocytes with peroxidase-labeled monoclonal antibody against cytomegalovirus was negative.

An arterial blood gas analysis showed a pH of 7.390, partial pressure of oxygen (PaO2) of 104 mmHg, partial pressure of carbon dioxide of (PaCO2) 36.1 mmHg, HCO3⁻ of 21.5 mmol/L, base excess of -2.4 mmol/L, and an anion gap of 8.5 mmol/L.

Urinalysis revealed proteinuria (protein level, 182 mg/day) with hematuria; in qualitative analysis, urinary protein and occult blood were 1+ and 2+, respectively. Creatinine clearance was 55.4 L/day. The urinary chemistry results were as follows: N-acetyl-β-D-glucosaminidase, 14.4 U/L; α1-microglobulin, 4.8 mg/L; and β2-microglobulin, <190 μg/L. Bence-Jones protein was not detected.

Chest radiography was normal, and abdominal echography showed that both kidneys are normal in size and shape. Computed tomography performed at a previous hospital showed a subpleural reticular pattern and patchy areas of consolidation, especially in the lower lung zone, which was undetectable upon admission to our hospital (data not shown). An ophthalmological examination did not reveal uveitis.

Renal biopsy was performed at 20 days after the initiation of steroid therapy. The tissue contained 27 glomeruli, which indicated a sufficient amount of material for the histopathological analysis. The light microscopy findings of the renal biopsy showed a mild increase in the mesangial matrix of some glomeruli (Fig. 1A), foci of mononuclear interstitial cell infiltration, and moderate interstitial fibrosis (Fig. 1B) with tubulitis (Fig. 1C). IgG4 staining was negative. Immunofluorescence findings showed positive staining for IgG,

### Table 1. Laboratory Findings on Admission.

| Hematology       | Serology               |
|------------------|------------------------|
| WBC 24,360/μL    | CRP 0.31 mg/dL         |
| Hb 13.0 g/dL     | ANA 1/40               |
| Pt 31.9×10⁹/μL   | HBs-Ag (-)             |
| IgG 1.536 mg/dL  | Anti-dsDNA Ab (-)      |
| IgA 381 mg/dL    | PR-3-ANCA (-)          |
| IgM 561 mg/dL    | MPO-ANCA (-)           |
| C3 83 mg/dL      | Anti-GBM Ab (-)        |
| C4 6 mg/dL       | cryoglobulin (+)       |
| CH50 25 U/mL     | Anti-SSA Ab (-)        |
| TP 7.1 g/dL      | ACE 4.6 IU/L           |
| Alb 3.3 g/dL     | Anti-CCP Ab (-)        |
| BUN 30.5 mg/dL   | RF < 92.9 IU/mL        |
| Cr 1.05 mg/dL    | Anti-mitochondrial M2 Ab (-) |
| Ca 9.8 mEq/L     | EBV VCA IgG1/40        |
| P 2.3 mEq/L      | EBV VCA IgM (-)        |
| ANA (normal)     | Anti-GBM Ab (-)        |
| C1q < 1.5 μg/mL  | Anti-GBM Ab (-)        |
| CH50 25 U/mL     | EBV VCA IgG1/40        |
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| BUN 30.5 mg/dL   | RF < 92.9 IU/mL        |
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IgA, IgM, C3, and fibrinogen mainly in the mesangium; however, C4 and C1q were negative in the glomerulus and tubule (Fig. 2). Acute and chronic tubulointerstitial nephritis was diagnosed; however, no obvious contributing factors such as recently prescribed new drugs, connective tissue diseases, or sarcoidosis were found.

To further investigate the cause of the tubulointerstitial nephritis, we investigated whether peritubular capillaritis was found due to the patient’s history of purpura symptoms, acute renal failure with hematuria, and inflammation, which might suggest the existence of vasculitis. Immunohistochemical staining for CD34, an endothelial cell marker, revealed that some cells in the peritubular capillaries with blurred capillary walls were found within the lesion where interstitial cell infiltration was severe (Fig. 3A), indicating peritubular capillaritis. Reexamination of the renal section revealed mainly mononuclear cells in the peritubular capillaries (Fig. 1C). However, no malignant cells were detected. Additional examination using immunofluorescence showed no positive staining for any Ig or complement on the tubular basement membranes or peritubular capillaries (data not shown). Alternatively, when electron microscopy was used, lamination of the peritubular capillary basement membranes was detected (Fig. 3B); however, no electron-dense deposits were detected in the glomeruli, tubular basement membranes, or peritubular capillaries (data not shown).

The patient’s clinical symptoms, inflammation, and renal function did not become aggravated after his admission (Fig. 4). The level of RF, IgM, and the urinalysis findings all improved, but the C4 and CH50 levels remained unchanged (Table 2). He was discharged from our hospital 2 months after admission.
Discussion

It is well known that cryoglobulinemic vasculitis is often associated with infection (1-6). HCV infection is most commonly associated with cryoglobulinemic vasculitis infection and is detected in 80% of patients with cryoglobulinemic vasculitis (13). Renal involvement is often seen, and MPGN, a typical renal lesion in HCV infection, is sometimes found in patients with cryoglobulinemic vasculitis (11). Although relatively rare, other glomerular lesions such as crescent formation, fibrinoid necrosis, and intraluminal thrombi could also be found (14-16). In addition, tubulointerstitial nephritis with cryoglobulinemia has also been reported (12).

In our case, the tubulointerstitial nephritis was presumed to result from peritubular capillaritis because the kidney specimens showed almost completely normal glomeruli and no deposition of immunoglobulins or complements on the
tubular basement membrane. Moreover, there were no causes of tubulointerstitial nephritis such as any newly prescribed medication, sarcoidosis, or connective tissue diseases. Although the etiology of peritubular capillaritis was not clear in our case, it might be associated with cryoglobulin because the improvement in the urinary findings correlated with a decrease in the RF and IgM levels during electrophoresis. The vasculitis activity in HCV-associated cryoglobulinemic vasculitis has been reported to correlate with a decrease in the RF and cryoglobulin levels, but not an increase in C4 and CH50 (17). There has been only one case of biopsy-proven peritubular capillaritis with cryoglobulinemic vasculitis (18). However, the renal specimen in that case showed MPGN with interstitial inflammation. Therefore, this is the first report to show tubulointerstitial nephritis with peritubular capillaritis accompanied by cryoglobulinemia. Recently, cases of tubulointerstitial nephritis in ANCA-associated vasculitis have been reported (19-21), and peritubular capillaritis is thought to play a role in the pathogenesis of tubulointerstitial nephritis (22, 23). Although the reason why peritubular capillaries were mainly damaged in our case is unclear, we speculate that there are two possible mechanisms. First, decreased vascular flow speed and pressure in the peritubular capillaries, compared to the glomerular capillaries might be involved, leading to the trapping or deposition of cryoglobulin within the peritubular capillaries where inflammatory cells might be induced, as hypothesized in ANCA-associated vasculitis (22). Cryoglobulinemic vasculitis of the skin particularly occurs in postcapillary venules (24), indicating that vessels with slow flow and low pressure, such as peritubular capillaries, could be involved in cryoglobulinemic vasculitis. Second, peritubular capillaritis might represent an early event in the course of cryoglobulinemic vasculitis. Transformation from tubulointerstitial nephritis with peritubular capillaritis to crescentic glomerulonephritis in ANCA-associated vasculitis has been reported (25). On average, renal disease in cryoglobulinemic vasculitis is detected at approximately 2.5 years after the onset of disease (26). In our case, renal biopsy was performed at 1 month after the onset of purpura and inflammation. Early treatment with steroids might also be associated with the limited involvement of the peritubular capillaries.

It is important to note some of the limitations associated with our study. First, we detected neither electron dense deposits nor deposition of cryoglobulin within peritubular capillaries and glomeruli. Methodologically, one of the disadvantages of electron microscopy is that only a limited area can be observed; thus, electron dense deposits and cryoglobulin might not be included in the sample that was examined randomly. In addition, to the best of our knowledge, there have been no reports about the detection of cryoglobulin surrounding the tubular basement membrane or within the peritubular capillaries, indicating the difficulty of detecting cryoglobulin deposition at these sites. Although cryoglobulin was not certified by electron microscopy, a previous report showing 2 cases of tubulointerstitial nephritis

Figure 3. Photographs of peritubular capillaritis in the kidney. (A) Immunohistochemistry for CD34 showed mononuclear cell infiltration in the peritubular capillary with blurred capillary walls (arrows). Mouse monoclonal anti-human CD34 antibody (Dako, Glostrup, Denmark) was used. Original magnification, 1,000×. (B) Electron micrograph showing lamination of peritubular capillary basement membranes (arrowhead). Original magnification, 20,000×.

Figure 4. Clinical course. The solid red line indicates changes in serum creatinine concentrations. The dotted blue line indicates changes in serum C-reactive protein concentrations. CRP: C-reactive protein, Cr: creatinine, U-PRO: urinary protein, U-OB: urinary occult blood
with cryoglobulinemia demonstrated that deposits of Ig and C3 were present along the tubular basement membrane, and a proliferative glomerulonephritis was also found (12). In addition, renal specimens from a patient showed deposits of Ig and C3 in walls of arteries as well (12). Meanwhile, a report showing peritubular capillaritis with cryoglobulinemic vasculitis demonstrated that focal interstitial deposits of IgG, IgM, and C3 were present, and granular deposits of C3 were also found along the tubular basement membrane (18). Because renal biopsy was performed at 3 weeks after the initiation of steroid therapy, when the renal function and the urine analysis findings had already improved, the steroid treatment might have masked the detection of cryoglobulin in our case. It was described that cryoglobulin precipitates or disappears rapidly (27). Second, because IgA deposition was found mainly in the mesangium, we cannot discount IgA nephropathy or IgA vasculitis. However, we could not explain the clinical course of this case as IgA nephropathy because of the lack of active glomerular lesions such as crescent formation. In general, serum C3 and C4 levels are normal in most patients with IgA vasculitis. Although it has been reported that <10% of patients with IgA vasculitis showed a low level of complements (28), its etiology is thought to be an alternative pathway activation (29). Therefore, C3 rather than C4 should decrease in IgA vasculitis. In addition, cryoglobulin rarely contains IgA (30). Third, cryoglobulin in our case was not classified using the Brouet classification, the conventional classification (31). It has been reported that the sensitivity of immunoelectrophoresis on detecting cryoglobulin was only 30% because of the umbrella effect of polyclonal immunoglobulin, which masks other immunoglobulins (32). Unfortunately, we did not perform more sensitive methods, such as immunoblotting or immunofixation to identify the cryoglobulin components. However, we detected polyclonal IgM, thus indicating not type I but type II or III cryoglobulinemia. Therefore, mixed cryoglobulinemia, which involves other immunoglobulins, was suspected. Therefore, the staining of IgG and IgA could be explained only by the precipitation of cryoglobulin.

A case of tubulointerstitial nephritis caused by peritubular capillaritis accompanied by cryoglobulinemia was herein described. Peritubular capillaritis might have contributed to the onset of tubulointerstitial nephritis, and cryoglobulin is therefore suggested to play a role in the potential etiology of peritubular capillaritis. Detecting peritubular capillaritis is difficult because of the destruction of the interstitial architecture. Therefore, it is likely that peritubular capillaritis has often been overlooked in some patients, and their condition might have been misdiagnosed as idiopathic tubulointerstitial nephritis. As a result, increased attention should be paid to the existence of peritubular capillaritis in patients presenting with idiopathic tubulointerstitial nephritis, especially in those associated with cryoglobulinemia.

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

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