Renal-limited Cryoglobulinemic Vasculitis: Two Case Reports

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Abstract:
Cryoglobulinemic vasculitis (CV) presents with systemic manifestations, including renal disease, arthritis, peripheral neuropathy, and muscle weakness. We encountered two patients who developed severe nephrotic range proteinuria; however, extrarenal manifestations were not noted during the clinical course. A renal biopsy revealed typical membranoproliferative glomerulonephritis (MPGN) with huge thrombus-like endothelial deposits and predominant IgM positivity, but electron microscopy did not reveal any definite microtubules. Immunosuppressive therapy and plasmapheresis were only partially effective, and the improvement was not durable. Biological therapy with rituximab (RTX) had no effect. Renal-limited CV should be recognized as a subset of essential CV.

Key words: cryoglobulinemic vasculitis, nephrotic syndrome

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Introduction

Cryoglobulinemia (CG) is a systemic disease caused by cryoglobulins that usually presents with various clinical manifestations, including purpura, muscle weakness, and arthralgia. Type II cryoglobulins are a mixture of monoclonal IgM and polyclonal IgG with rheumatoid factor activity, and disease caused by such cryoglobulins is referred to as mixed CG. The majority of essential CG has been confirmed to be related to hepatitis C virus (HCV) infection. Other infectious causes include hepatitis B virus (HBV) and human immunodeficiency virus (HIV), and autoimmune diseases, including primary Sjögren’s syndrome have also been reported to cause CG (1, 2). The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides defined cryoglobulinemic vasculitis (CV) as one category of small vessel vasculitis (SVV). CV is a vasculitis in which immune deposits of cryoglobulins affect small vessels (predominantly capillaries, venules, and/or arterioles), and which is associated with cryoglobulins circulating in the blood. The skin, glomeruli, and peripheral nerves are often involved in patients with CV. The term “idiopathic” or “essential” may be used as a prefix when the etiology of CV is unknown (3).

We report two cases of “essential” cryoglobulinemic vasculitis in which the patients presented with renal manifestations alone, and discuss the diagnosis and characteristics of essential (idiopathic) CG in these patients.

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Table. The Clinical Courses of Both Cases.

|                | 2015 (May) | 2015 (Dec) | 2017 (Jan) | 2004 (Feb) | 2004 (Oct) | 2015 (Feb) | normal range |
|----------------|------------|------------|------------|------------|------------|------------|--------------|
| White blood cell (g/L) onset | 5.100 | 8.800 | 4.100 | n/a | 7.300 | 6.400 | 3.400 - 9.200 |
| Red blood cell (10^6/µL) onset | 3.75 | 2.73 | 2.77 | 4.26 | 3.78 | 5.00 | 4.0 - 5.7 |
| Platelet (×10^9/µL) onset | 30.7 | 25.7 | 34.1 | n/a | 22.2 | 27.4 | 14.1 - 32.7 |
| Total protein (g/dL) onset | 5.6 | 5.5 | 4.1 | n/a | 6.3 | 7.0 | 6.9 - 8.4 |
| Albumin (g/dL) onset | 3.2 | 3.3 | 2.2 | n/a | 3.4 | 3.0 | 3.9 - 5.2 |
| Urea nitrogen (mg/dL) onset | 43 | 17 | 24 | 19 | 22 | 27 | 8 - 21 |
| Creatinine (mg/dL) onset | 1.2 | 1.19 | 1.26 | 0.97 | 1.1 | 1.72 | 0.6 - 1.1 |
| eGFR (mL/min/1.73 m²) onset | 47.6 | 47.4 | 44.3 | 64 | 56 | 32.3 | ≥ 90 |
| IgG (mg/dL) onset | n/a | 177 | 191 | 1,183 | 980 | 1,512 | 870 - 1,700 |
| IgM (mg/dL) onset | n/a | 185.3 | 97.1 | 142 | 113 | 144 | 35 - 220 |
| IgA (mg/dL) onset | n/a | 86.3 | 141.6 | 135 | 110 | 88.3 | 110 - 470 |
| CH50 (U/mL) onset | n/a | 30 | 37 | 27.6 | 38 | 48 | 30 - 50 |
| C3 (mg/dL) onset | 67.6 | 72 | 80 | 111 | 111 | 119 | 86 - 160 |
| C4 (mg/dL) onset | 8.4 | 8 | 12 | 25 | 24 | 32 | 17 - 45 |
| Cryocrit onset | n/a | weakly positive (<1%) | weakly positive (<1%) | weakly positive (<1%) | weakly positive (<1%) | weakly positive (<1%) | negative |
| Antinuclear antibody (ANA) onset | n/a | <5.0 | n/a | n/a | 14.2 | n/a | <40 |
| Cyclic citrullinated peptide antibodies onset | n/a | negative | n/a | n/a | negative | negative | negative |
| Rheumatoid factor (RF) onset | n/a | 39 | n/a | n/a | 39 | n/a | 0 - 15 |
| Anti-double strand DNA (dsDNA) antibody onset | n/a | <10 | n/a | n/a | 0.3 | n/a | <12 |
| Anti-SS (Sjögren syndrome) - A antibody onset | n/a | negative | n/a | n/a | negative | n/a | negative |
| Myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) onset | negative | negative | n/a | n/a | negative | n/a | negative |
| Anti-proteinase-3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA) onset | negative | negative | n/a | n/a | negative | n/a | negative |
| Hepatitis B virus (HBV) DNA onset | negative | negative | n/a | n/a | negative | negative | negative |
| Anti-hepatitis C virus (HCV) antibody onset | negative | negative | n/a | n/a | negative | negative | negative |
| Anti-human immunodeficiency virus (HIV) antibody onset | n/a | negative | n/a | n/a | negative | negative | negative |
| Serum monoclonal protein onset | negative | negative | negative | n/a | negative | negative | negative |
| Urinary RBC sediment (HPF) onset | 10 - 19 | many | 11 - 30 | 1 - 4 | 6 - 10 | 1 - 4 | <1 |
| Urinary protein (g/day) onset | 9.1 | 7.0 | 5.4 | 3.4 | 1.4 | 2.8 | <0.1 |
| Urinary Bence Jones protein onset | negative | negative | n/a | n/a | negative | negative | negative |

Case Reports

Case 1

In May 2015, a 70-year-old Japanese man was admitted to another hospital with leg edema and nephrotic range proteinuria (9.1 g/day). Treatment was initiated with intravenous steroid pulse therapy [methylprednisolone (mPSL), 500 mg/day for 3 days], followed by oral prednisolone (PSL, 40 mg/day). The dose of PSL was tapered after the patient’s proteinuria decreased to 1.5 g/day. However, patient’s proteinuria increased to 7 g/day again after 4 months. In September 2015, the patient was referred to our hospital to undergo further evaluation to determine the cause of his proteinuria.

On admission, he was 163 cm tall and weighed 54.5 kg, with a blood pressure of 116/69 mmHg and a body temperature of 36.7°C. Severe bilateral leg edema was noted, but there was no purpura, neuropathy, or arthritis. Laboratory tests revealed that the patient’s serum creatinine level was 1.19 mg/dL and his estimated glomerular filtration rate (eGFR) was 47 mL/min/1.73 m² (Table). The patient was positive for rheumatoid factor (RF) (39 U/mL; normal, <10), but negative for all autoantibodies, including antinuclear antibody (ANA). The serum C3 level was 72 mg/dL (normal: >86 mg/dL), the C4 level was 8 mg/dL (normal: >18 mg/dL), and the CH50 level was 30 U/mL (normal: >30 U/mL). The serum level of immunoglobulins were as follows: IgG, 177 mg/dL (normal: 870-1,700); IgA, 86.3 mg/dL (normal: 110-410); and IgM, 185.3 mg/dL (normal: 33-190). The patient was negative for anti-HCV, anti-HBV, and anti-HIV antibodies. A test for serum monoclonal protein was negative. His 24-hour urinary protein excretion was 7.0 g/day; the urine sediment contained numerous erythrocytes and 1-4
leukocytes per high-power field (HPF). A test for urinary Bence-Jones protein was negative. Bone marrow aspiration revealed no evidence of myeloma or monoclonal gammopathy of undetermined significance. Computed tomography (CT) revealed no evidence of hepatosplenomegaly or lymphadenopathy.

**Detection of cryoglobulins**

A venous blood sample was collected, promptly injected into a preheated glass test tube, and maintained at 37°C until the cells and serum separated. The serum was then allowed to stand at 4°C for at least 72 hours in a hematocrit tube. Since agglutination/gelation was detected and dissolution occurred on heating, the presence of cryoglobulin was confirmed. The precipitate/serum volume ratio was calculated to determine the cryocrit titer, which was weakly positive at < 1%. (normal: not detected) (2).

**First renal biopsy**

Light microscopy of a renal biopsy specimen revealed global sclerosis in 5 of 50 glomeruli. Endocapillary glomerulonephritis was noted with a marked increase of mesangial matrix and the extensive proliferation of mesangial cells and leukocytes, including monocytes and macrophages, resulting in the lobular accentuation of the glomerular tufts. The capillary walls displayed circumferential mesangial interposition with double contours. Huge thrombus-like subendothelial deposits were also detected (Fig. 1a). Fibrosis and atrophy of the tubulointerstitial region occupied 30% of the cortex. The small arteries showed mild sclerotic changes, but there was no evidence of vasculitis. Immunofluorescence (IF) demonstrated the granular deposition of IgM, C3, and κ light chain in the mesangial region and along the capillary walls. C1q was weakly positive, but IgG, IgA, and λ light chain were negative (Fig. 1c). Electron microscopy (EM) revealed huge electron-dense deposits in the mesangial region and the subendothelial space, but microtubular structures were not identified (Fig. 1d). Partial effacement of the foot processes of podocytes. The patient was diagnosed with membranoproliferative glomerulonephritis (MPGN) based on these findings.

**Diagnosis**

According to the 2012 International Chapel Hill Consensus conference, the MPGN in this patient was consistent with CV due to the detection of cryoglobulins and rheumatoid factor in the serum along with the predominant deposition of IgM in the glomeruli (2, 3). However, systemic diseases that are considered to be the underlying cause of CV were excluded, including autoimmune diseases such as systemic lupus erythematosis and Sjögren’s syndrome or active infectious diseases such as hepatitis C and hepatitis B.

**Clinical course**

The patient received six cycles of intravenous cyclophosphamide (IVCY) pulse therapy (800 mg per cycle at monthly intervals), with PSL being tapered and discontinued because his proteinuria decreased to 1.27 g/day. However, his proteinuria relapsed to 6.24 g/day within one month after the completion of IVCY pulse therapy. Treatment with rituximab (580 mg weekly for 4 weeks) was initiated in August 2016, but his proteinuria persisted and his leg edema became more severe (Fig. 2). Renal biopsy was therefore reperformed to reassess the patient’s nephropathy.

**Second renal biopsy**

Light microscopy of the biopsy specimen revealed global sclerosis in 6 of 56 glomeruli. In comparison to the findings at the time of the first biopsy, the endocapillary glomerular lesions, which included thrombus-like deposits, was observed to have progressed on LM (Fig. 1b); however, IF and EM showed the same features as before (Fig. 1e). Fibrosis and atrophy of the tubulointerstitial region still occupied 30% of the renal cortex, and the small arteries did not show any evidence of vasculitis.

**Clinical course**

In February 2004, a 53-year-old Japanese man was admitted to another hospital with leg edema and proteinuria (3.4 g/day). Treatment was initiated with three courses of intravenous steroid pulse therapy (mPSL at 500 mg daily for 3 days) followed by oral PSL (20 mg on alternate days). In addition, double-filtration plasmapheresis was performed three times. PSL was tapered when the patient’s proteinuria subsided to 0.8 g/day; however, proteinuria subsequently persisted at around 1 g/day.

In October 2005, the patient was admitted to our hospital to undergo an evaluation to determine the source of his proteinuria. On admission, he was 173 cm tall and weighed 68.5 kg, with a blood pressure of 161/101 mmHg and a body temperature of 36.8°C. There was no evidence of purpura, muscle weakness, neuropathy, or arthralgia. Laboratory revealed the following findings (Table): serum creatinine, 1.1 mg/dL; eGFR, 56 mL/min/1.73 m²; proteinuria, 0.94 g/day, and the urine sediment contained 6-10 erythrocytes per HPF and 1-5 leukocytes per HPF. The patient was positive for RF (39 U/mL; normal, <10), but negative for all autoantibodies (including ANA). The serum C3 level was 111 mg/dL (normal: >86 mg/dL), the C4 level was 24 mg/dL (normal: >18 mg/dL), and the CH50 level was 38 U/mL (normal: >30 U/mL). The serum immunoglobulin levels were as follows: IgG, 980 mg/dL (normal: 870-1,700); IgA, 110 mg/dL (normal: 110-410); and IgM, 113 mg/dL (normal: 33-190). Tests for HCV, HBV, and HIV were all negative. Tests for serum monoclonal protein and urinary Bence Jones protein were negative. When measured by the same method as
Figure 1. The renal biopsy findings in Case 1. a: Light microscopy of the first renal biopsy specimen revealed endocapillary glomerulonephritis (large arrow) and thrombi in the glomerular capillaries (small arrow). Inset: On immunohistochemistry, leukocytes in the glomerular tufts were positive for CD68, which was expressed by tissue monocytes and macrophages (arrow). b: Light microscopy of the second renal biopsy specimen. c: Immunofluorescence microscopy demonstrated granular deposits of IgM along the glomerular basement membrane (GBM) and in the mesangium (arrow). d: Electron microscopy of first renal biopsy showed massive electron-dense deposits in the subendothelial region. e: Electron microscopy of the second renal biopsy.
was used for Case 1, the cryocrit titer was weakly positive, at <1% (normal: not detected). CT scans showed no evidence of hepatosplenomegaly or lymphadenopathy.

**First renal biopsy**

Light microscopy of a renal biopsy specimen revealed global sclerosis in 3 of 22 glomeruli. Endocapillary glomerulonephritis with proliferation of the mesangial matrix and circumferential mesangial interposition with double contours were observed. Huge thrombus-like subendothelial deposits were also detected in the glomerular capillaries (Fib. 3a). Fibrosis and atrophy of the tubulointerstitial region occupied 10% of the renal cortex. Small arteries showed minor sclerotic changes, but there was no evidence of vasculitis. IF demonstrated granular deposits of IgM, κ light chain, and λ light chain in the mesangial region and along the capillary walls. C3 and C1q were also weakly positive, but IgG and IgA were not detected (Fig. 3c). EM revealed huge electron-dense deposits in the mesangial region and subendothelial space, but microtubular structures were not confirmed (Fig. 3d). The patient was diagnosed with MPGN based on these findings.

**Diagnosis**

In this patient, MPGN was also consistent with essential CV and showed the same overall pattern as Case 1. However, the equivalent deposition of κ and λ light chains was observed, which was different from Case 1.

**Clinical course**

The patient’s proteinuria persisted and increased to 3.97 g/day. Accordingly, PSL was discontinued in May 2007 and cyclosporine (CyA) was started at a dose of 100 mg/day. Thereafter, his proteinuria decreased to 0.94 g/day. His proteinuria increased again to 3.18 g/day in December 2008, and three courses of intravenous steroid pulse therapy (mPSL, 500 mg/day for 3 days), followed by oral PSL (30 mg on alternate days) were administered. His proteinuria subsequently decreased to 0.64 g/day, and PSL was tapered. In January 2011, his proteinuria increased again to 2.34 g/day. Six cycles of IVCY pulse therapy were delivered (500 mg per cycle at monthly intervals), and tacrolimus (3 mg/day) was initiated. Thereafter, his proteinuria decreased to 0.3 g/day and tacrolimus was tapered to 2 mg/day because of hypertension and renal dysfunction. In May 2015, his proteinuria increased again to 2.86 g/day and a second renal biopsy was performed to reevaluate his renal histology.

**Second renal biopsy**

Light microscopy of the biopsy specimen revealed global sclerosis in 4 of 19 glomeruli. The sclerotic changes of the small arteries were moderate to severe. The huge thrombus-like subendothelial deposits that were noted in the first biopsy specimen were seen in the second renal biopsy specimen (Fig. 3b). The IF and EM findings were largely the same as those at the first biopsy (Fig. 3c). Tubulointerstitial fibrosis and atrophy had increased to occupy 30% of the renal cortex, while the small arteries showed moderate sclerosis with no evidence of vasculitis.

**Clinical course**

Treatment with rituximab (500 mg weekly for 3 weeks) was initiated, and was repeated 3 times at 6-month intervals. However, his proteinuria persisted and increased to 6.37 g/day. In April 2017, a third course of intravenous steroid pulse therapy was administered (mPSL, 500 mg/day for 3 days), followed by oral PSL (40 mg/day). His proteinuria decreased to 3.2 g/day, but his renal function showed deterioration (Fig. 4).
Figure 3. The renal biopsy findings in Case 2. a: Light microscopy of the first renal biopsy specimen showed the proliferation of mesangial matrix and thrombi in the glomerular capillaries (arrow). The inset shows CD68. b: Light microscopy of the second renal biopsy specimen. c: Immunofluorescence microscopy displayed granular deposits of IgM along the GBM and in the mesangium (arrow). The arteriolar deposition of C3 seems apparent (arrow), which may show microscopic findings of vasculitis. d: Electron microscopy of the first renal biopsy specimen revealed massive subendothelial electron-dense deposits. e: Electron microscopy of the second renal biopsy specimen.
Figure 4. The clinical course of Case 2.

Discussion

We encountered two patients with CV who presented with pure renal manifestations. In both patients, the condition was refractory to both immunosuppressive therapy and biological therapy.

CV causes vasculitis that involves the small to medium-sized vessels in the skin, joints, nerves, and/or kidneys (1, 3). The clinical triad of purpura, weakness, and arthralgia (“Meltzer’s triad”) is found early in the course of this disease in almost 80% of patients (4). According to the French multicenter Cryo-Vas survey, the early manifestations of CV included purpura (75%), peripheral neuropathy (52%), arthralgia or arthritis (44%), glomerulonephritis (35%), cutaneous ulcers (16%), and cutaneous necrosis (14%) (5). A study of 265 CV patients with low cryoglobulin levels showed that their clinical manifestations were related to involvement of the skin (39.3%), joints (27.9%), kidneys (13.3%: proteinuria in 11.4%, microscopic hematuria in 6.0%, and GFR <60 mL/min in 7.9%), and nerves (8.3%) (6). In another study of 242 CV patients who had low cryoglobulin levels showed that their clinical manifestations were related to involvement of the skin (39.3%), joints (27.9%), kidneys (13.3%: proteinuria in 11.4%, microscopic hematuria in 6.0%, and GFR <60 mL/min in 7.9%), and nerves (8.3%) (6). In another study of 242 patients who had mixed cryoglobulinemia (MC) without HCV infection, the clinical manifestations included purpura (75%), necrosis (16%), joint involvement (40%), peripheral neuropathy (52%), and kidney involvement (35%) (7). However, there have not been any previous reports of CV presenting with renal manifestations alone.

Ramos-Casals suggested four treatment strategies for CV: conventional immunosuppression, plasmapheresis, antiviral therapy, and biological therapy (1). Conventional immunosuppressive therapy is used to treat systemic vasculitis, but the response is not satisfactory, especially in patients with severe CV (8). While plasmapheresis can rapidly remove circulating cryoglobulins, it does not address the underlying disease and the cryoglobulin level can rise rapidly again. Biological therapy with rituximab is superior to steroid treatment alone (5). Ferri treated 87 MC patients with rituximab and reported that glomerulonephritis improved in 95% of them (24-hour proteinuria decreased from 2.2±2.1SD to 0.9±1.7SD g/24 hours, p<0.0001), with complete remission achieved in 50% of the patients (9). Antiviral therapy is the key treatment for CV patients with HCV infection, since CV can improve or resolve when sustained clearance of HCV is achieved (10). Gragnani et al. treated 44 patients who had HCV-associated CV with direct antiviral agents and two patients with severe vasculitis received rituximab. All patients were negative for HCV viremia after 12 and 24 weeks, at which time a clinical response was observed in the vasculitis of all patients (11).

Hasegawa et al. reported the case of a 63-year-old Japanese woman Sjögren’s syndrome-associated CV. She showed no response to high-dose steroid therapy and plasmapheresis, but IVCY pulse therapy was effective for 4 years. Thereafter, rituximab was effective for treating her skin lesions and nephropathy; however, relapse occurred within 2 years and increased doses of this agent were required (12).

The quantification of the cryocrit titer is important because the amount of serum cryoglobulin (cryocrit) may be correlated with the severity of symptoms and is useful in monitoring the response to treatment. The severity of this disease is correlated with the cryocrit titer. This characteristic fits CV patients with systemic manifestations (1). On the other hand, the cryocrit titer of the two patients in this
study were consistently very low (<1%). The precipitation of cryoglobulin in low temperature might be related to peripheral organ injuries; especially skin lesions with thrombus formation exposed to low temperatures; in contrast, renal lesions are highly influenced by immune-complex formation. The renal pathology of our cases revealed relatively small but apparent intraluminal thrombus in comparison to the immune deposition along the capillary walls and the mesangium. In the present cases, these findings might be related to the low cryocrit titer without systemic (especially skin) lesions.

Our two cases with renal-limited CV were refractory to aggressive immunosuppressive therapy, which—in combination with antiviral therapy—has been reported to be effective in the treatment of systemic CV (1, 8, 11, 12).

In conclusion, we evaluated two patients with renal-limited CV who never displayed systemic manifestations such as skin lesions (purpura, cutaneous ulcers, and necrosis), peripheral neuropathy, or arthralgia. Although the serum cryocrit titers of the patients were very low (<0.1%), renal biopsy revealed typical MPGN that featured huge thrombus-like endothelial deposits without a definite microtubular structure. Immunosuppressive therapy (including steroids and IVCY) and plasmapheresis were only partially effective, and the improvement was not sustained. Biological therapy (including rituximab) was also ineffective. Renal-limited disease may occur in some patients with idiopathic or essential CV, but not in those with secondary CV.

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