

[CASE REPORT]

Clinical Implications of Steroid Therapy for Crescentic Glomerulonephritis and *Gemella morbillorum*-associated Infective Endocarditis

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Abstract:

A 54-year-old man was admitted to our institute with a diagnosis of infective endocarditis (IE) with vegetation on the mitral valve and severe regurgitation due to *Gemella morbillorum* infection together with renal dysfunction, which was eventually diagnosed as infection-related pauci-immune necrotizing crescentic glomerulonephritis. Given the refractoriness to antibiotics, the persistent activity of nephritis, and repeated cerebral hemorrhaging, we prioritized steroid therapy over early surgical mitral valve replacement. Following steroid therapy, the glomerulonephritis completely improved. Although the administration of steroid therapy in the active phase of IE remains controversial, it might be indicated if comorbid glomerulonephritis is critical.

Key words: purpura, *Gemella morbillorum*, hypocomplementemia

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Introduction

Infective endocarditis (IE) often accompanies glomerulonephritis via an autoimmune response, showing necrotizing glomerulonephritis or endocapillary proliferative glomerulonephritis (1). The clinical outcome of IE accompanied by renal dysfunction is poor, and renal dysfunction is an independent risk factor of mortality (2).

The therapeutic strategy for glomerulonephritis in patients with IE remains controversial. Antibiotic therapy is often insufficient, whereas surgical intervention to the infectious valve is not applicable due to poor systemic conditions and comorbidities (3). Furthermore, immunosuppressants to manage the glomerulonephritis might actually worsen the infection.

We herein report a patient with IE and crescentic necrotizing glomerulonephritis who received successful steroid therapy in addition to antibiotics, followed by surgical valve replacement.

Case Report

On admission

A 54-year-old man with an 18-year history of mild mitral regurgitation was admitted to our institute with a high fever, bilateral leg edema, and dyspnea on effort for the past 2 months. Given the echocardiographic findings of a 10-mm vegetation on the mitral valve with severe mitral regurgitation (Fig. 1A, B) and systemic bacteremia with *Gemella morbillorum*, he was diagnosed with IE.

His body temperature was 38.0 °C, blood pressure 108/56 mmHg, and pulse rate 80 beats per minute. He had Roth spots on his fundus, Osler nodules on his fingers, Janeway lesions on his palms, and purpura on his lower legs (Fig. 2).

Laboratory data showed a white blood cell count of 10,710/ μ L, hemoglobin 7.7 g/dL, serum albumin 2.3 g/dL, and C-reactive protein 3.0 mg/dL (Table 1). Urinary data showed proteinuria (1.16 g/g of creatinine) and >100 red blood cells/high-power field (HPF). Immunological tests

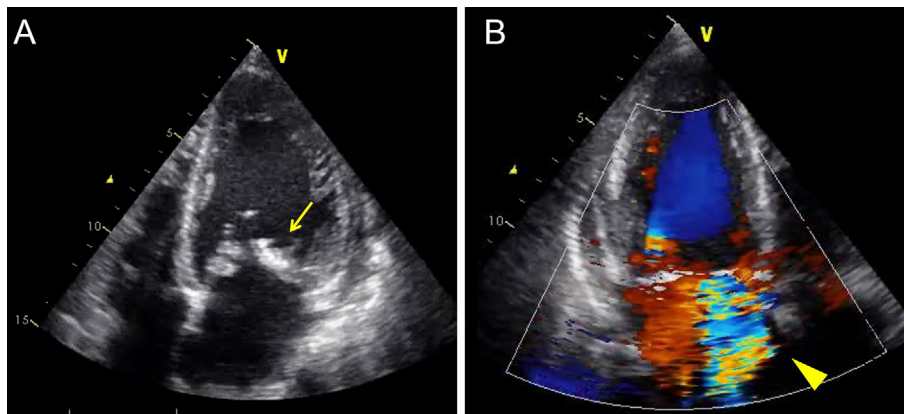


Figure 1. Transthoracic echocardiography showing the vegetation on the mitral valve (arrow; A) and severe mitral regurgitation (arrowhead; B)

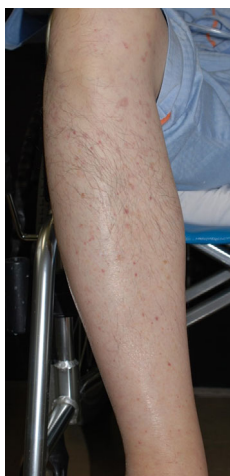


Figure 2. Lower leg purpura.

showed C3 52 mg/dL, the expression of rheumatoid factor and cryoglobulin, and immunocomplex-C1q 32 μ g/mL as well as the absence of hepatitis C virus (HCV) antibody, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibody. The lower leg purpura was diagnosed as leukocytoclastic vasculitis given the skin biopsy findings of perivascular bleeding and infiltration of neutrophil in the superficial dermis (Fig. 3). Immunofluorescence showed no deposition of immunoglobulin or complement in the vessel walls.

Before the kidney biopsy

Following the intravenous administration of penicillin G and gentamicin, the bacteremia immediately improved, but the high fever and inflammatory reaction remained, and renal dysfunction again progressed from day 9 (Fig. 4). Despite the conversion of antibiotics from gentamicin to ceftriaxone, daptomycin, and vancomycin, the serum creatinine level increased to 3.6 mg/dL, lower leg purpura and proteinuria progressed gradually, and hypocomplementemia remained, which was eventually diagnosed as rapidly progressive glomerulonephritis (RPGN).

The kidney biopsy

A renal biopsy was performed on day 18. Cellular crescent formation was found in 6/16 glomeruli (Fig. 5). There was no deposition of immunoglobulins or complements on immunofluorescence staining. There were also no electron-dense deposits on electron microscopy. We eventually pathologically diagnosed him with pauci-immune necrotizing crescentic glomerulonephritis. Given the lack of deposition of immune complex in the kidney against the positive immunological test of cryoglobulin, we excluded cryoglobulinemia as a cause of nephritis.

Post-diagnosis course

Given the persistent inflammation despite the inversion of bacteremia, we highly suspected vasculitis. On day 22, under careful monitoring of recurrent bacteremia, we decided to perform 3-day steroid pulse therapy with the intravenous administration of methylprednisolone 500 mg/day, followed by oral prednisolone 40 mg/day, which immediately improved the high fever and lower leg purpura. Given the re-increase in the serum creatinine level as well as persistent proteinuria and mild hypocomplementemia, a second round of steroid pulse therapy was performed on day 50, which gradually improved all of these signs. The trough level of vancomycin was 15 μ g/mL. The daily dose of vancomycin was between 400 and 700 mg.

As extra-renal comorbidities, on days 30 and 81, he suffered repeated subarachnoid hemorrhaging. Given the risk of perioperative cerebral hemorrhaging, we wanted to avoid early surgical mitral valve replacement, which was eventually performed on day 113 without any perioperative comorbidities and enabled us to terminate steroid therapy. After two years without steroid therapy, the serum creatinine level had normalized to 1.0 mg/dL, and all urine abnormalities, including hematuria and proteinuria, remained absent.

Table 1. Laboratory Data on Admission.

Laboratory test	Result
White blood cells, mm ³	10,710
Hemoglobin, g/dL	7.7
Platelets, mm ³	196,000
Albumin, g/dL	2.3
Blood urea nitrogen, mg/dL	14
Creatinine, mg/dL	0.8
Sodium, mEq/L	135
Potassium, mEq/L	4
C-reactive protein, mg/dL	3
Immunoglobulin G, mg/dL	1,814
Immunoglobulin A, mg/dL	194
Immunoglobulin M, mg/dL	115
Complement 3, mg/dL	52
Complement 4, mg/dL	15.1
CH50, U/mL	14
Immuno-complex-C1q, µg/mL	32
Rheumatoid factor, U/mL	25
Antinuclear antibody	negative
MPO-ANCA	negative
PR3-ANCA	negative
Anti-GBM antibody	negative
Cryoglobulin	positive

CH50: 50% hemolytic complement activity, PR3: anti-proteinase 3, MPO: anti-myeloperoxidase, ANCA: anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane

Discussion

IE and renal dysfunction

One-third of patients with IE have renal dysfunction due to vegetation embolism, adverse effects of antibiotics, hemodynamics-related pre-renal dysfunction, and glomerulonephritis, which often progress as RPGN. In the analyses of 49 renal biopsies, 53% showed necrotizing crescentic glomerulonephritis, and 37% showed endocapillary proliferative glomerulonephritis (4). An immune response to the infection has been proposed as a mechanism underlying glomerulonephritis, given the presence of comorbid hypocomplementemia, rheumatoid factor, and antineutrophil cyto-

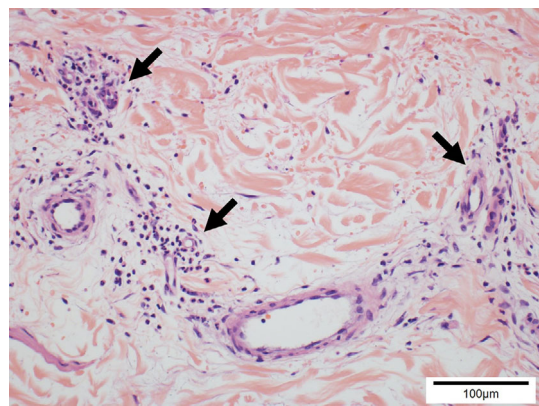


Figure 3. Pathological findings of his skin biopsy, showing perivascular infiltration of neutrophil and nuclear dust in the dermis (arrows) (×100).

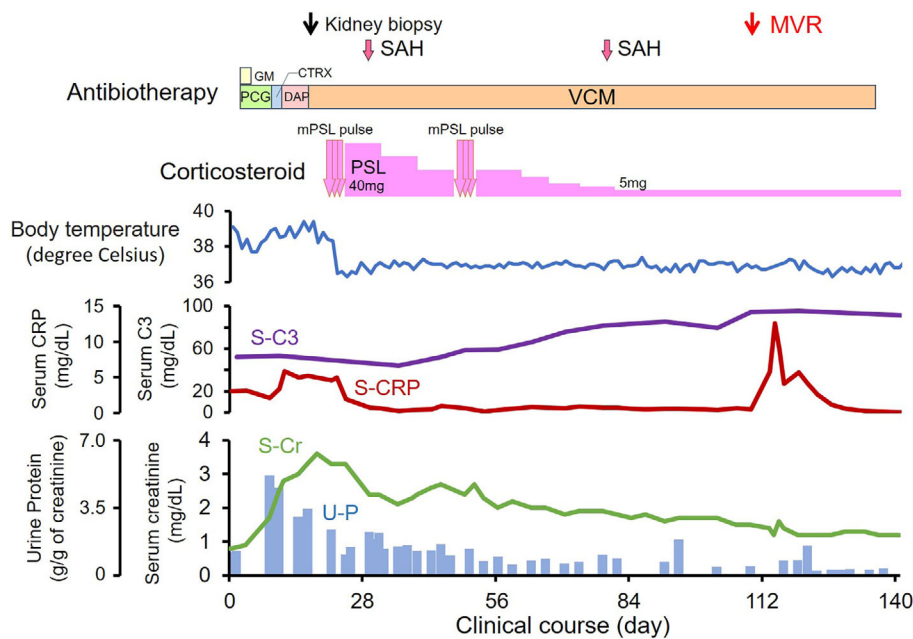


Figure 4. Clinical course. CTRX: ceftriaxone, DAP: daptomycin, GM: gentamicin, mPSL: methylprednisolone, MVR: mitral valve replacement, PCG: penicillin G, PSL: prednisolone, SAH: subarachnoid hemorrhaging, VCM: vancomycin

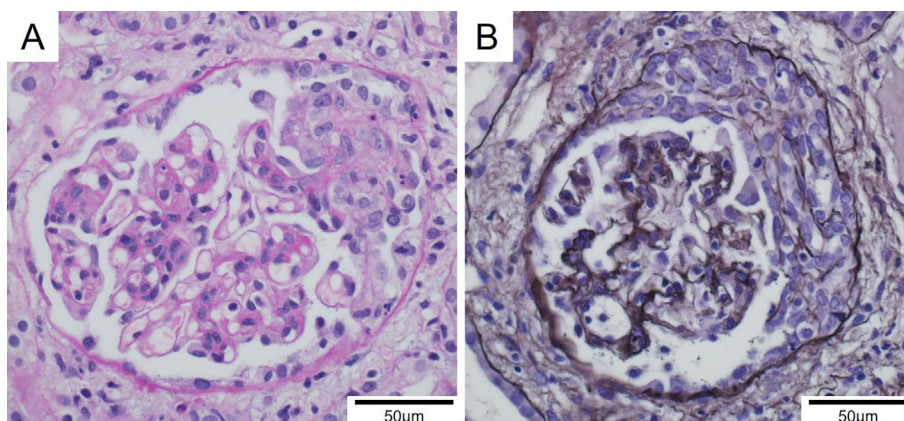


Figure 5. Pathological findings of his kidney biopsy. A: Necrotizing and extracapillary proliferative lesion (periodic acid-Schiff stain, $\times 200$). B: Cellular crescent formation in another glomerulus (Periodic acid-methenamine-silver stain, $\times 200$).

Table 2. Features of Reported Cases of *Gemella morbillorum*-associated Glomerulonephritis.

Case	[6]	[7]	Present report
Age (years)/sex	17/F	12/F	54/M
Infectious disease	VA shunt infection	endocarditis	endocarditis
C3/C4 levels	low/low	low/normal	low/normal
ANCA	PR3-ANCA	negative	negative
Light microscopy	MPGN	crescentic GN	crescentic GN
IF microscopy	IgG/IgM/C1q/C4	C3	pauci-immune
Therapy	removal of shunt, antibiotics, PSL, mPSL pulse	antibiotics, PSL, mPSL pulse, rituximab, plasmapheresis	valve replacement surgery, antibiotics, PSL, mPSL pulse
Renal outcome	improved	improved	improved
Clinical outcome	improved	improved	improved

IF: immunofluorescence, ANCA: antineutrophil cytoplasmic autoantibody, VA: ventricle-atrial, PR3: proteinase 3, MPGN: membranoproliferative glomerulonephritis, GN: glomerulonephritis, PSL: prednisolone, mPSL: methylprednisolone

plasmic antibodies.

In our patient, a renal histopathological assessment showed pauci-immune necrotizing crescentic glomerulonephritis without any electron-dense deposits on electron microscopy, despite hypocomplementemia and cryoglobulinemia. Our patient did not express any antineutrophil cytoplasmic antibodies, despite a renal histopathological assessment showing necrotizing crescentic glomerulonephritis. Of note, among those with IE-related glomerulonephritis, electron-dense deposits are negative in 10%, and antineutrophil cytoplasmic antibodies are negative in 72% (4).

Causative bacteria in this case

G. morbillorum, the Gram-positive streptococci with hypovirulence that we found in this case, rarely causes IE and associating glomerulonephritis (5). Kumar et al. reported a pediatric patient with IE-related crescentic glomerulonephritis due to *G. morbillorum* (6). Another team reported a patient with cerebral ventricle-atrial shunt-related nephritis due to *G. morbillorum* (Table 2) (7). The duration is associated with the severity of nephritis. A relatively long duration of infection due to the hypovirulence of *G. morbillorum* might actually cause an immune response and glomerulonephritis.

Therapeutic strategy of IE-related glomerulonephritis

The therapeutic strategy of IE-related glomerulonephritis remains controversial. Antibiotics therapy alone might not be sufficient to improve the renal function (3). In addition to applying steroid therapy as we did in the present case (8), plasma exchange is recommended (9). However, we should pay close attention, as these therapies can actually worsen the severity of infection. One study reported that immunosuppressant therapy increased the mortality (10), although another argued the safety of steroid therapy with appropriate concomitant antibiotics (11). Careful case-by-case discussion considering the risks and benefits and continuous monitoring of recurrent bacteremia are essential for steroid therapy in such situations.

Another option is surgical intervention to remove the pathogen causing nephritis, i.e. vegetation in the present case. However, there are no recommendations concerning early surgical intervention in cases of comorbid glomerulonephritis (12, 13). Surgical intervention is often challenging in patients with unstable hemodynamics or IE-related comorbidities, including renal dysfunction (14). However, successful early surgery might improve renal dysfunction.

tion (15).

In the present patient, given the repeated cerebral hemorrhaging, persistent vasculitis, and progressive renal dysfunction with crescentic formation, we prioritized steroid therapy over early surgery, which probably improved the systemic inflammation and hemodynamics and reduced the perioperative risk. In patients with IE and nephritis, multidisciplinary therapy including antibiotics, steroids, and surgical intervention should be considered at an appropriate timing based on the histopathological assessment of renal tissue.

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

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