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【 CASE REPORT 】

Streptococcal Infection-related Glomerulonephritis in an Elderly Diabetic Patient Complicated by Hemophagocytic Syndrome and Cytomegalovirus Nephritis

Yoshikuni Nagayama[1], Mio Edamoto[1], Yuna Komine[1], Hiroki Nakai[1], Ayana Ichikura-Iida[1], Takashi Inoue[1], Kyoko Ono[2], Masako Otani[3] and Shigeki Iwasaki[1]

Abstract:
There has been a significant shift in epidemiology and renal outcomes of infection-related glomerulonephritis (IRGN) in recent years. The renal prognosis of IRGN is often poor in adults, especially in the elderly and diabetics. We herein report an elderly diabetic patient with IRGN due to streptococcal infection complicated by hemophagocytic syndrome and cytomegalovirus nephritis, which is uncommon among non-transplant patients. Infection control and steroids did not recover the patient's renal function. For elderly IRGN patients with diabetes, a further investigation of the most effective treatment for related renal outcomes is needed.

Key words: crescents, cytomegalovirus, diabetes, end-stage kidney disease, hemophagocytic syndrome, infection-related glomerulonephritis

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Introduction

In the past, infection-related glomerulonephritis (IRGN) mainly occurred in childhood. Over the past three decades, however, a large proportion of IRGN patients have been adults, especially the elderly and immunocompromised. The causative pathogens, sites, and duration of infection are different in adults and children. In adult IRGN, non-streptococcal infections, particularly staphylococcal infections, are more common, and the sites of infection are more heterogenous, including the upper respiratory tract, skin, teeth and oral mucosa, lungs, heart, urinary tract, and bones. Furthermore, the infection is usually ongoing at the time of the GN diagnosis (1). In contrast to favorable renal outcomes in children, the renal prognosis of IRGN in adults is often poor, especially in the elderly and diabetics (1). In addition, the efficacy of immunosuppressive therapy against IRGN in adults is unclear.

We herein report an elderly diabetic patient with IRGN due to streptococcal infection complicated by hemophagocytic syndrome (HPS) and cytomegalovirus (CMV) nephritis.

Case Report

Medical history and initial laboratory data

A 67-year-old man was referred to our department for severe renal dysfunction. He had been an outpatient in our hospital for diabetes and idiopathic interstitial pneumonia since the previous year. His diabetic history was unknown; however, fundoscopy revealed simple diabetic retinopathy. One month prior to admission, his laboratory findings showed renal dysfunction (serum creatinine of 1.03 mg/dL) and a high HbA1c level (9.2%). A few weeks before admission, his right big toe was wounded.

His clinical findings on admission were as follows: blood pressure, 166/83 mmHg; pulse rate, 97/min; body temperature, 36.9°C; height, 168 cm; and weight, 76 kg. He was

[1]Department of Nephrology, Yokohama Municipal Citizen's Hospital, Japan, [2]Department of Diagnostic Pathology, Yokohama Municipal Citizen's Hospital, Japan and [3]Division of Diagnostic Pathology, Yokohama City University Medical Center, Japan
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Correspondence to Dr. Yoshikuni Nagayama, ynaga1147@yahoo.co.jp

Table. Laboratory Findings on Admission.

Parameter	Value (reference range)	Parameter	Value (reference range)
Hematology		**Immunology**	
WBC count, /μL	20,690 (3,300-8,600)	IgG, mg/dL	2,185 (861-1,747)
Hemoglobin, g/dL	10.1 (13.7-16.8)	IgA, mg/dL	1,040 (93-393)
Platelet count, 10^4/μL	42.1 (15.8-34.8)	IgM, mg/dL	45 (33-183)
PT, %	67 (80-120)	IgE, IU/mL	99.1 (<170)
APTT, s	35.2 (24-39)	M protein	Negative
FDP, μg/mL	44.1 (<5)	FLC ratio	1.49 (0.26-1.65)
Blood chemistry		C3, mg/dL	31 (73-138)
Cr, mg/dL	16.13 (0.65-1.0)	C4, mg/dL	23 (11.0-31.0)
eGFR, mL/min/1.73m^2	2.8	CH_{50}, U/mL	<12 (30-45)
SUN, mg/dL	137.3 (8.0-20.0)	ANA	Negative
Total protein, g/dL	7.3 (6.6-8.1)	MPO-ANCA	Negative
Albumin, g/dL	1.6 (4.1-5.1)	PR3-ANCA	Negative
AST, U/L	19 (13-30)	Anti-GBM Ab	Negative
ALT, U/L	17 (10-42)	RF	Negative
LDH, U/L	402 (124-222)	Cryoglobulin	Negative
ALP, U/L	488 (106-322)	sIL-2R, U/mL	17,405 (204-587)
γ-GTP, U/L	102 (13-64)	Ferritin, ng/mL	1,344 (21.81-27)
T-Cho, mg/dL	117 (<220)	Haptoglobin, mg/dL	133 (83-209)
TG, mg/dL	163 (<150)	ADAMTS13 activity, %	40
Glucose, mg/dL	113 (73-109)	ASK, titer	10,240 (<1,280)
HbA1c, %	9.1 (4.9-6.0)	ASO, IU/mL	1,414 (<240)
CRP, mg/dL	21.0 (<0.14)	HBV surface Ag	Negative
Urinalysis		HCV Ab	Negative
Urine dipstick protein	4+	HIV Ab	Negative
Urine occult blood	3+	EBV VCA-IgG, titer	80 (<9)
Urinary protein, g/gCr	39.29 (<0.15)	EBV VCA-IgM, titer	<10 (<9)
β2-MG, μg/L	31,800 (<250)	EBV EBNA Ab, titer	40 (<10)
NAG, IU/L	219.3 (<10)	SARS-CoV-2 PCR	Negative
M protein	Negative		

Ab: antibody, ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13, Ag: antigen, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, APTT: activated partial thromboplastin time, ASK: anti-streptokinase antibody, ASO: anti-streptolysin O antibody, AST: aspartate aminotransferase, β2-MG: beta-2 microglobulin, Cr: creatinine, CRP: C-reactive protein, EBNA: EBV nuclear antigen, EBV: Epstein-Barr virus, eGFR: estimated glomerular filtration rate, FDP: fibrin degradation products, FLC: free light chain, GBM: glomerular basement membrane, γ-GTP: gamma-glutamyl transpeptidase, HbA1c: hemoglobin A1c, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, IgA: immunoglobulin A, IgE: immunoglobulin E, IgG: immunoglobulin G, IgM: immunoglobulin M, LDH: lactate dehydrogenase, MPO: myeloperoxidase, NAG: N-acetyl-β-D-glucosaminidase, PCR: polymerase chain reaction, PR3: proteinase 3, PT: prothrombin time, RF: rheumatoid factor, SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2, sIL-2R: soluble interleukin-2 receptor, SUN: serum urea nitrogen, T-Cho: total cholesterol, TG: triglyceride, VCA: viral capsid antigen, WBC: white blood cell

alert. He had no superficial lymphadenopathy, joint pain, neurological deficit, or edema, and an examination of his heart, lungs, and abdomen was unremarkable. The wound in his toe showed a partial ulcer and necrosis. Laboratory findings on admission are shown in Table. A urinalysis revealed a pH of 7.0, specific gravity of 1.032, protein 4+, blood 3+, sediment of white blood cells (30 to 49/high-power field), red blood cells (over 100/high-power field), many hyaline casts, elevated beta-2 microglobulin, and elevated N-acetyl-β-D-glucosaminidase. Blood tests revealed hyperleukocytosis (83% neutrophils, 8.1% lymphocytes, 7.6% monocytes, 0.7% eosinophils, and 0.6% basophils), anemia, abnormal coagulation, hypoalbuminemia, renal dysfunction [serum creatinine of 16.13 mg/dL and an estimated glomerular filtration rate (eGFR) of 2.8 mL/min/1.73 m^2], elevated lactate dehydrogenase, elevated alkaline phosphatase, elevated γ-glutamyl transpeptidase, elevated HbA1c, and elevated C-reactive protein (CRP). The eGFR was calculated using the Japanese eGFR equation (eGFR=194×serum creatinine$^{-1.094}$×age$^{-0.287}$) (2). Serum IgG and IgA were high without M protein. Serum ferritin and soluble interleukin-2 receptor were elevated. Serum C3 and CH_{50} were low with normal serum C4. The patient was negative for various autoantibodies, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and severe acute respiratory syndrome-coronavirus-2 infections. Anti-streptokinase antibody and anti-streptolysin O antibody were elevated. Group A β-hemolytic streptococcus was detected in cultures of the skin

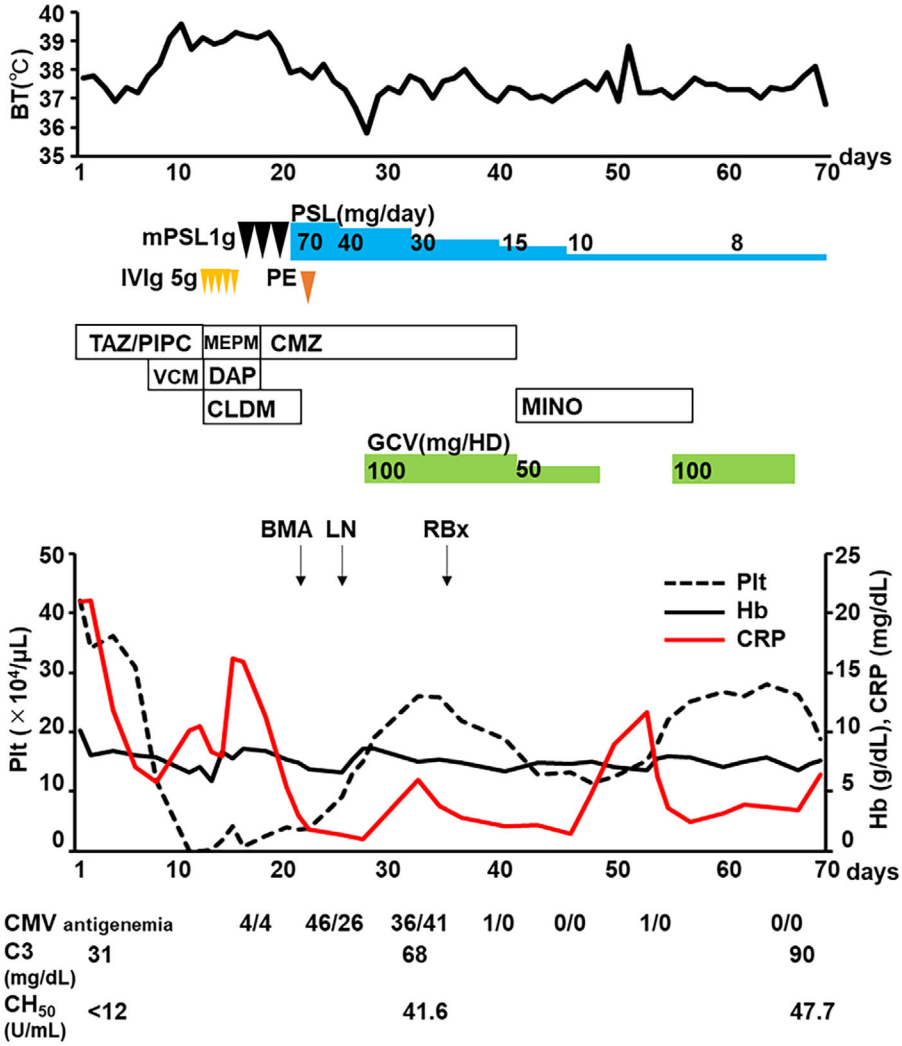

Figure 1. Clinical course of the patient. Anuria persisted during the course. Multiple combination therapy, including antimicrobial agents, intravenous immunoglobulin, local debridement for streptococcal infection, steroids, and plasmapheresis, failed to recover his renal function. BMA: bone marrow aspiration, BT: body temperature, CLDM: clindamycin, CMV: cytomegalovirus, CMZ: cefmetazole, CRP: C-reactive protein, DAP: daptomycin, GCV: ganciclovir, Hb: hemoglobin, HD: hemodialysis, IVIg: intravenous immunoglobulin, LN: lymph node biopsy, MEPM: meropenem, MINO: minocycline, mPSL: methylprednisolone, PE: plasma exchange, Plt: platelets, PSL: prednisolone, RBx: renal biopsy, TAZ/PIPC: tazobactam/piperacillin, VCM: vancomycin

abscess of the toe. There were no abnormalities on chest radiography or an electrocardiogram. Abdominal computed tomography (CT) revealed swelling of both kidneys.

Clinical Course

The clinical course is illustrated in Fig. 1. The patient became anuric and dialysis-dependent. He was hemodynamically stable during the clinical course. Therefore, we performed hemodialysis for renal replacement therapy. We considered the main cause of acute kidney injury (AKI) to be streptococcal IRGN. He therefore received antimicrobial therapy, intravenous immunoglobulin (5 g/day for five days), and local debridement of the toe; however, his high fever, high CRP, and anuria persisted.

Repeat blood cultures showed no microbes, and echocardiography revealed no vegetation. Subsequently, chest CT showed bilateral extensive lung consolidations on the 18th day of hospitalization. Acute respiratory distress syndrome (ARDS) was suspected, so steroid pulse therapy (1 g/day of intravenous methylprednisolone) was initiated for 3 days. His fever and CRP level reduced considerably. Thereafter, 70 mg/day of intravenous prednisolone was administered. At the same time, severe thrombocytopenia developed. Thrombotic microangiopathy (TMA) was suspected; therefore, plasma exchange (4.8 L of freshly frozen plasma as replacement fluid) was performed. Subsequently, the diagnosis of TMA, including thrombotic thrombocytopenic purpura, was excluded due to the normal range of serum haptoglobin and a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity, and

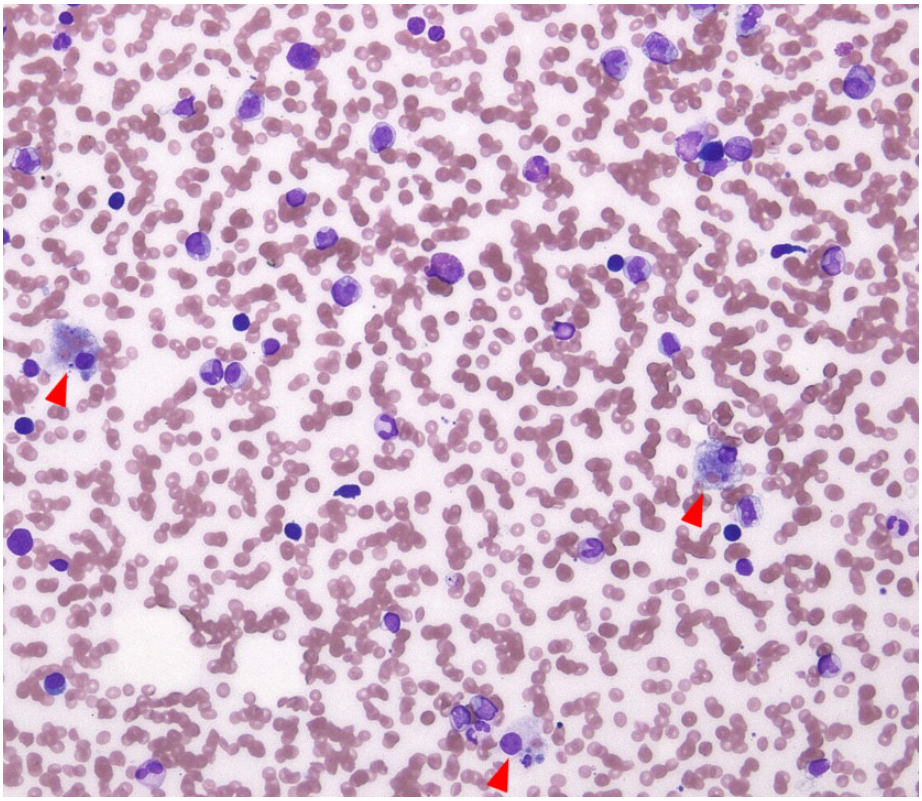

Figure 2. **Wright-Giemsa staining of bone marrow aspirate. There are three macrophages phagocytosing erythrocytes (arrowheads) (original magnification, ×200).**

plasma exchange was stopped.

On the 21st day of hospitalization, a bone marrow biopsy revealed reactive hypercellular marrow with hemophagocytosis (Fig. 2). Based on the criteria (3), he was diagnosed with HPS. Investigation for Epstein-Barr virus showed a previously infected pattern. At the same time, CMV PP65 antigenemia was detected. An ophthalmological examination revealed no CMV retinopathy, and there were no abdominal symptoms suggestive of CMV enteritis. Considering the patient's condition, intravenous ganciclovir was started. A biopsy of the inguinal lymph node was performed on the 25th day. There was no evidence of malignant lymphoma. Additional immunohistochemistry for CMV of the bone marrow and the inguinal lymph node was positive and negative, respectively. There was gradual improvement in his general condition, and serum C3 and CH_{50} levels returned to normal (Fig. 1). However, anuria persisted. Therefore, a kidney biopsy was performed on the 33rd day.

Kidney biopsy findings

Light microscopy revealed the presence of 23 glomeruli, of which 3 were globally sclerosed. The remaining glomeruli showed fibrocellular crescents with diffuse proliferative glomerulonephritis and some mesangial nodules (Fig. 3). The interstitium showed remarkable inflammatory cell infiltrates (including lymphocytes, neutrophils, and plasma cells), severe tubular atrophy, and fibrosis (Fig. 3A). The arterioles had remarkable hyalinosis. Immunofluorescence revealed strong C3 expression in the mesangium, and only trace IgG, IgA, IgM, and C1q were found (Fig. 4). Electron microscopy revealed mesangial electron-dense deposits, hump-like deposits on moderately thickened basement membranes, and diffuse foot process effacement (Fig. 5). Immunohistochemistry for CMV was positive in both the glomerulus and interstitium (Fig. 6).

Clinical Follow-up

Given the renal pathological damage and CMV infection, the recovery of his renal function could not be expected, and steroids were promptly tapered (Fig. 1). After three weeks of intravenous ganciclovir, CMV PP65 antigenemia resolved. Thereafter, CMV PP65 antigenemia was detected again, requiring an additional two weeks of intravenous ganciclovir for the negative conversion (Fig. 1). Finally, prednisolone was tapered to 5 mg/day, and he was transferred to a dialysis facility on the 93rd day of hospitalization.

Discussion

In the present case, AKI on admission may have been related to IRGN superimposed on diabetic nephropathy. For the diagnosis of IRGN, Nasr et al. (1) proposed that at least three of the following criteria be met: (i) clinical or laboratory evidence of infection preceding or at the onset of glomerulonephritis; (ii) reduced serum complement; (iii) endocapillary proliferative and exudative glomerulonephritis; (iv) C3-dominant or co-dominant glomerular immunofluorescence staining; and (v) hump-shaped subepithelial depos-

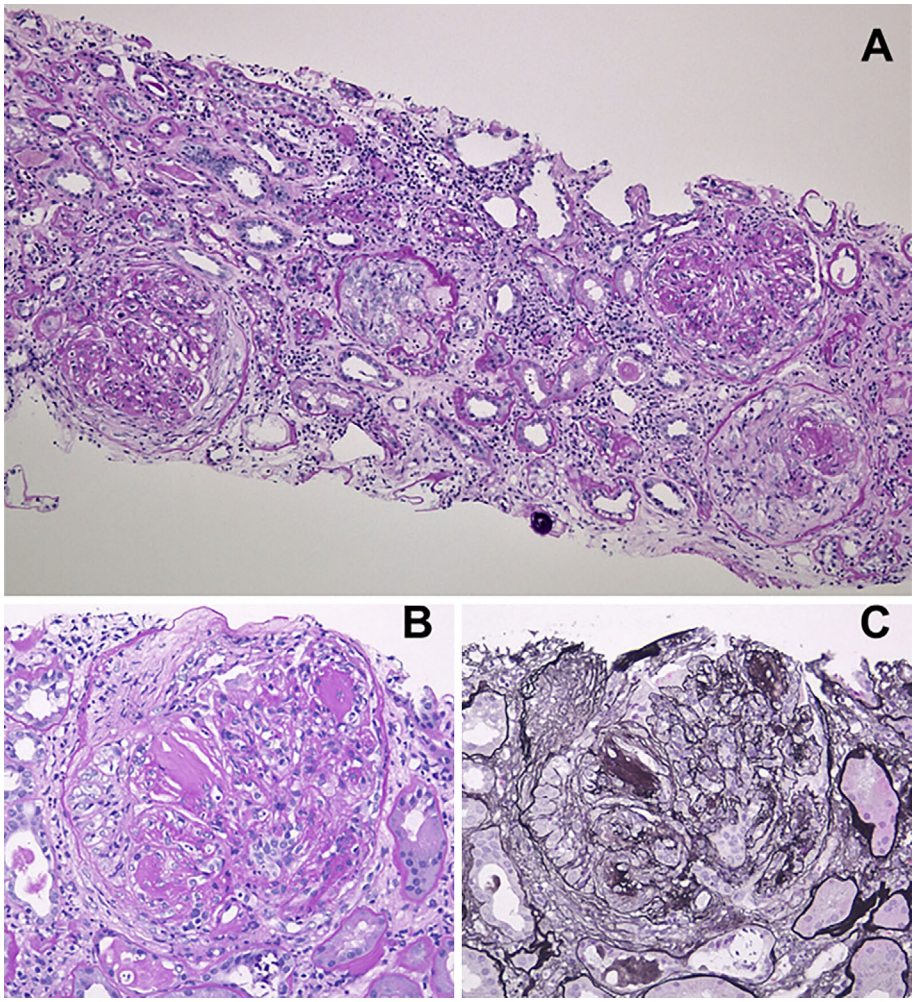

Figure 3. **Kidney biopsy light microscopy findings. Periodic-acid-Schiff staining section. (A) shows some glomeruli with diffuse proliferative fibrocellular crescentic glomerulonephritis and mesangial nodules, remarkable interstitial inflammatory cell infiltrates, severe tubular atrophy, and interstitial fibrosis. A periodic-acid-Schiff staining section (B) and periodic-acid-silver-methenamine staining section (C) show fibrocellular crescentic glomerulonephritis with some mesangial nodules (original magnification, ×100, ×200, and ×200 for A-C, respectively).**

its on electron microscopy. Our patient met four of the five stated criteria.

In contrast to favorable outcomes in children, many adults with IRGN do not recover their renal function; approximately 8-54% of patients develop persistent renal dysfunction, and 4-33% progress to end-stage kidney disease (ESKD) (1). The predictors of progression to ESKD in adult IRGN include diabetes (4), diabetic glomerulosclerosis (4), dialysis at biopsy (4), significant tubular atrophy, interstitial fibrosis (4, 5), older age (6), higher serum creatinine at a biopsy (4, 6), presence of underlying disease (7, 8), ongoing infection at the time of GN onset (5), and diffuse crescent formation (9). The present case had all of these predictors.

Treatment of IRGN in adults should include elimination of the responsible infection and supportive care for complications of nephritis; however, the role of immunosuppressive therapy remains controversial. The available data are based on retrospective observational studies without the beneficial effect of steroids for IRGN in adults (4-7, 9, 10). In addition, evidence supporting the use of immunosuppressive therapy in adult crescentic IRGN is very scarce. However, a small retrospective study in adult crescentic IRGN showed that the renal outcome could be improved with steroids (11). Nevertheless, given the risk of infection aggravation, especially in patients in an immunocompromised state, such as those with diabetes, the addition of steroids or immunosuppressants is challenging.

The present case was complicated by ARDS and HPS, which were likely clinical manifestations of cytokine storm due to the streptococcal infection. The general treatment strategy for cytokine storm includes supportive care for critical organs, control of the underlying diseases, and inhibition of abnormal immune system activation due to specific or non-specific immunosuppression (12). Therefore, we used steroids. The patient's fever and CRP level were considerably reduced, with a gradual improvement in his general condition noted as well. However, his renal function did not recover, and a CMV infection occurred. Regarding the treat-

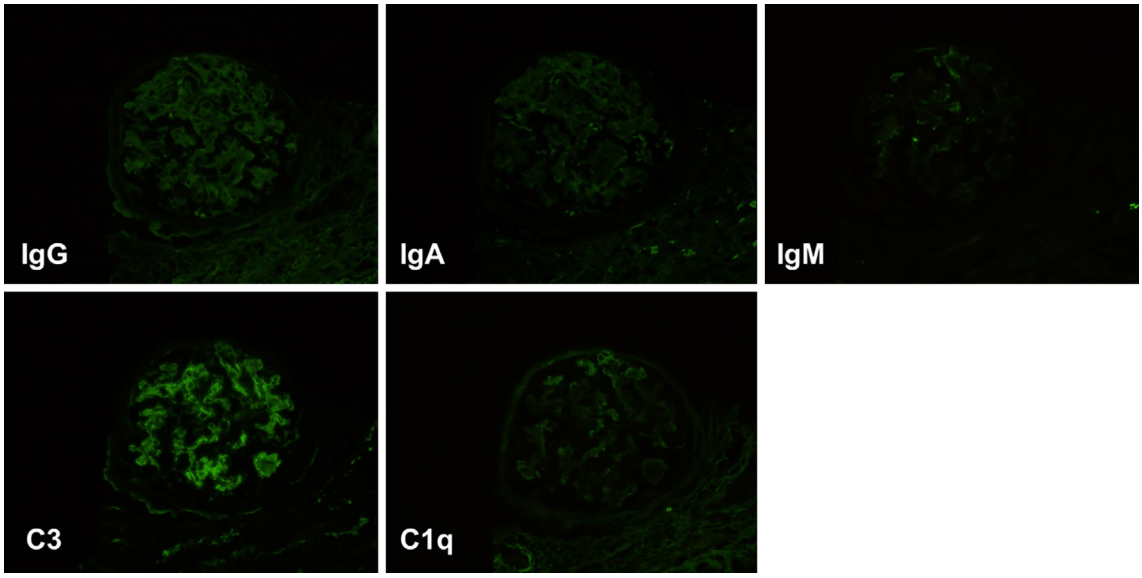

Figure 4. **Kidney biopsy immunofluorescence microscopy findings. Immunofluorescence reveals strong C3 expression in the mesangium, with only trace IgG, IgA, IgM, and C1q found (original magnification, ×40).**

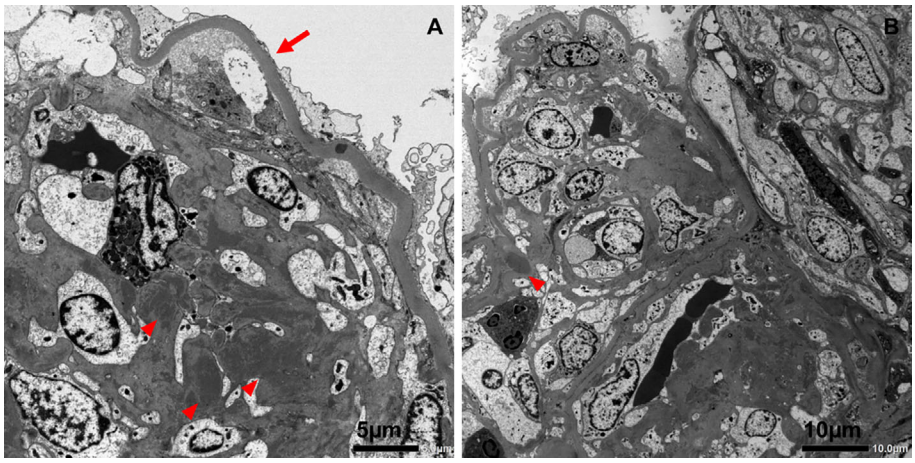

Figure 5. **Kidney biopsy electron microscopy findings. (A) Diffuse moderately thickened glomerular basement membranes, diffuse foot process effacement (arrow) and mesangial electron-dense deposits (arrowheads) (original magnification, ×1,000). (B) Hump-like deposits at the glomerular basement membrane (arrowhead) (original magnification, ×500).**

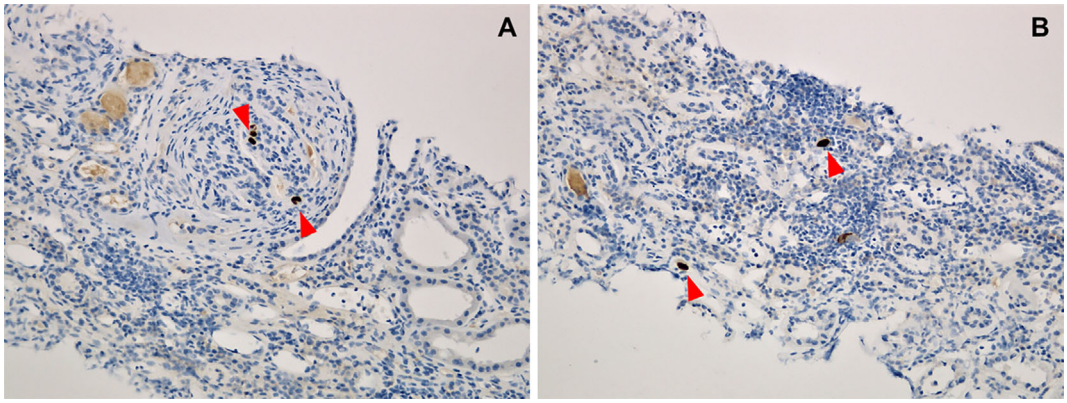

Figure 6. **Kidney biopsy immunohistochemistry findings for cytomegalovirus (CMV). (A) CMV-positive cells in the glomerulus (arrowheads). (B) CMV-positive cells in the interstitium (arrowheads) (original magnification, ×200).**

ment of cytokine storm by means other than steroids or immunosuppressants, the clinical efficacy of cytokine removal therapy with continuous hemodiafiltration using a cytokine-adsorbing hemofilter with a membrane made of polymethylmethacrylate (PMMA-CHDF) and plasmapheresis have been reported for ARDS (13) and secondary HPS (14, 15), respectively. Cytokine removal therapy may thus be a viable treatment option for cytokine storm-related disease. PMMA-CHDF or repeated plasmapheresis might have been beneficial in the present case.

We suspect that HPS and CMV nephritis contributed to the patient's kidney impairment. AKI due to acute tubular necrosis with various degrees of interstitial inflammation is frequently observed in HPS (16). In our case, the interstitium mainly revealed not acute tubular necrosis but chronic changes, such as severe tubular atrophy and advanced fibrosis. In addition, glomerular disease, including minimal change disease, TMA, and collapsing glomerulopathy, are also reported in HPS (17); however, these glomerular diseases were absent in this case. Based on the renal pathological findings, it seemed that there was little involvement of HPS in kidney impairment.

CMV is a major viral pathogen complicating renal transplantation (18). Common manifestations of CMV infection are colitis, retinitis, hepatitis, pneumonitis, and pancreatitis; CMV nephritis is uncommon. In renal transplant patients, renal pathological findings of CMV infection are mainly tubulointerstitial nephritis (19, 20), although CMV glomerulopathy (21, 22) and CMV-induced crescentic glomerulonephritis (23) are also reported. However, in non-transplant patients, there are few reports of CMV nephritis. CMV-positive cells were detected in both the glomeruli and interstitium in the present case. To what extent CMV nephritis contributed to the patient's kidney impairment was unclear.

In conclusion, we reported an elderly diabetic patient with IRGN due to streptococcal infection complicated by HPS and CMV nephritis. Infection control and steroids did not recover his renal function. The number of elderly IRGN patients with diabetes will increase in the future. Further investigation of effective treatments for related renal outcomes is needed.

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

References

1. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. Kidney Int **83**: 792-803, 2013.
2. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.
3. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer **48**: 124-131, 2007.
4. Nasr SH, Fidler ME, Valeri AM, et al. Postinfectious glomerulonephritis in the elderly. J Am Soc Nephrol **22**: 187-195, 2011.
5. John EE, Thomas A, Eapen JJ, et al. Latency, anti-bacterial resistance pattern, and bacterial infection-related glomerulonephritis. Clin J Am Soc Nephrol **16**: 1210-1220, 2021.
6. Nasr SH, Markowitz GS, Stokes MB, Said SM, Valeri AM, D'Agati VD. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore) **87**: 21-32, 2008.
7. Moroni G, Pozzi C, Quaglini S, et al. Long-term prognosis of diffuse proliferative glomerulonephritis associated with infection in adults. Nephrol Dial Transplant **17**: 1204-1211, 2002.
8. Luo C, Tang Z, Chen D, Liu Z. Long-term prognosis for Chinese adult patients with acute postinfectious glomerulonephritis. Clin Nephrol **76**: 186-194, 2011.
9. Montseny JJ, Meyrier A, Kleinknecht D, Callard P. The current spectrum of infectious glomerulonephritis. Experience with 76 patients and review of the literature. Medicine (Baltimore) **74**: 63-73, 1995.
10. Ramineni S, Bandi VK. Clinicopathological profile and outcomes of infection-related glomerulonephritis in adults. Clin Nephrol **95**: 93-98, 2021.
11. Baikunje S, Vankalakunti M, Nikith A, Srivatsa A, Alva S, Kamath J. Post-infectious glomerulonephritis with crescents in adults: a retrospective study. Clin Kidney J **9**: 222-226, 2016.
12. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med **383**: 2255-2273, 2020.
13. Matsuda K, Moriguchi T, Oda S, Hirasawa H. Efficacy of continuous hemodiafiltration with a cytokine-adsorbing hemofilter in the treatment of acute respiratory distress syndrome. Contrib Nephrol **166**: 83-92, 2010.
14. Matsumoto Y, Naniwa D, Banno S, Sugiura Y. The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: two case reports. Ther Apher **2**: 300-304, 1998.
15. Satomi A, Nagai S, Nagai T, et al. Effect of plasma exchange on refractory hemophagocytic syndrome complicated with myelodysplastic syndrome. Ther Apher **3**: 317-319, 1999.
16. Karras A. What nephrologists need to know about hemophagocytic syndrome. Nat Rev Nephrol **5**: 329-336, 2009.
17. Thaunat O, Delahousse M, Fakhouri F, et al. Nephrotic syndrome associated with hemophagocytic syndrome. Kidney Int **69**: 1892-1898, 2006.
18. De Keyzer K, Van Laecke S, Peeters P, Vanholder R. Human cytomegalovirus and kidney transplantation: a clinician's update. Am J Kidney Dis **58**: 118-126, 2011.
19. Cameron J, Rigby RJ, van Deth AG, Petrie JJ. Severe tubulointerstitial disease in a renal allograft due to cytomegalovirus infection. Clin Nephrol **18**: 321-325, 1982.
20. Platt JL, Sibley RK, Michael AF. Interstitial nephritis associated with cytomegalovirus infection. Kidney Int **28**: 550-552, 1985.
21. Richardson WP, Colvin RB, Cheeseman SH, et al. Glomerulopathy associated with cytomegalovirus viremia in renal allografts. N Engl J Med **305**: 57-63, 1981.
22. Onuigbo M, Haririan A, Ramos E, Klassen D, Wali R, Drachenberg C. Cytomegalovirus-induced glomerular vasculopathy in renal allografts: a report of two cases. Am J Transplant **2**: 684-688, 2002.
23. Detwiler RK, Singh HK, Bolin P Jr, Jennette JC. Cytomegalovirus-induced necrotizing and crescentic glomerulonephritis in a renal transplant patient. Am J Kidney Dis **32**: 820-824, 1998.