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Case Report

A Case of Crescentic Glomerulonephritis Complicated with Hypocomplementemic Urticarial Vasculitis Syndrome and ANCA-Associated Vasculitis

Marenao Tanaka Norihito Moniwa Tomohiro Mita
Toshiyuki Tobisawa Tamaki Matsumoto Atsushi Mochizuki
Tomohisa Yamashita Toshiyuki Yano Masato Furuhashi Tetsuji Miura

Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

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Crescentic glomerulonephritis · Hypocomplementemic urticarial vasculitis · MPO-ANCA · ANCA-related nephritis

Abstract
Systemic urticaria in a 64-year-old woman was diagnosed as leukocytoclastic vasculitis by a punch biopsy of the skin. Her physical findings improved after prescription of prednisolone at a dose of 20 mg/day, but the skin rash relapsed with renal dysfunction, proteinuria, and hematuria when the dose of prednisolone was reduced over a period of 9 months to 1 mg/day. She was admitted to our institute for further examination, when urinary protein and plasma creatinine levels were 0.8 g/day and 1.7 mg/dL, respectively. Complement analysis showed that levels of total hemolytic component, component C3 fraction, and component

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Marenao Tanaka, MD, PhD
Department of Cardiovascular, Renal and Metabolic Medicine Internal Medicine
Sapporo Medical University School of Medicine
S-1, W-16, Chuo-ku, Sapporo 060-8543 (Japan)
E-Mail matanaka@sapmed.ac.jp

C4 fraction were 30~60% of normal values and the titer of anti-neutrophil cytoplasmic antibody for myeloperoxidase (MPO-ANCA) was 89 EU (normal range, <10 EU), though there were no immunologic disorders such as systemic lupus erythematosus. Cellular crescentic glomerulonephritis was observed by light microscopy, and immunofluorescent studies showed positive staining for IgG, IgM, C3, C4, and C1q. Electron microscopy showed mesangial and subendothelial deposits with circumferential mesangial interposition. She fulfilled the diagnostic criteria for hypocomplementemic urticarial vasculitis syndrome (HUV), and ANCA-associated vasculitis (AAV) was also indicated by small vessel vasculitis and positive MPO-ANCA. Steroid pulse therapy with methylprednisolone followed by oral prednisolone improved her general condition and hypocomplementemia, and MPO-ANCA became negative. HUV and AAV are distinct clinical disorders, though both affect small blood vessels. Here we report a case of AAV-complicated HUV with crescentic glomerulonephritis.

Introduction

Based on recent advances in the understanding of vasculitis, the classification and nomenclature of vasculitis were revised at the International Chapel Hill Consensus Conference (CHCC2012). In the revised definitions, small vessel vasculitis is classified into 2 subcategories: anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune complex vasculitis. The former is characterized by a paucity of vessel wall immunoglobulin, and the latter is characterized by a prominence of vessel wall immunoglobulin. These 2 subtypes of small vessel vasculitis are now recognized as 2 distinct clinical entities [1].

Hypocomplementemic urticarial vasculitis syndrome (HUV) is a rare systemic disease characterized by recurrent urticaria and hypocomplementemia [2–4]. To make a diagnosis of HUV, 2 major criteria (recurrent urticaria for >6 months and hypocomplementemia) and at least 2 of 6 minor criteria (venulitis on skin biopsy, arthralgias or arthritis, glomerulonephritis, ocular inflammation, abdominal pain, and positive C1q antibodies) must be fulfilled [3, 4]. Because C1q precipitins, composed of IgG bound to C1q, are thought to play a pathogenic role in the development of HUV, HUV was recently subcategorized into immune complex vasculitis. On the other hand, AAV is a form of necrotizing vasculitis associated with ANCA specific for myeloperoxidase (MPO) or proteinase 3 (PR3) with few or no immune deposits [1, 5].

We experienced a patient with recurrent urticaria who developed rapidly progressive glomerulonephritis with positive MPO-ANCA, hypocomplementemia, and cellular crescentic glomerulonephritis with immune complex deposits in the mesangium and subendothelium. To our knowledge, this is the first case report of crescentic glomerulonephritis complicated with HUV and MPO-ANCA-associated vasculitis.

Case Report

History

A 64-year-old woman suffered from a systematic skin rash for 5 weeks and visited the Department of Dermatology in our institute. She was diagnosed with leukocytoclastic vasculitis by a punch biopsy of the skin (Fig. 1), and prednisolone at a dose of 20 mg/day was prescribed. Thereafter, physical findings improved, and the dose of prednisolone was tapered off. However, the skin rash relapsed when the dose of prednisolone was reduced over a period of 9 months to 1 mg/day. Then she also felt strong general malaise, abdominal pain, and appetite loss with a low-grade fever. Since the results of serum chemistry study and urinalysis showed renal dysfunction with proteinuria and hematuria, she was transferred to our department for further treatment.

Physical Findings

On admission to our department, her temperature was 36.8°C, her pulse was 72 beats per minute, and her blood pressure was 148/82 mm Hg. She had urticarial lesions all over her body and xerophthalmia.

Laboratory Data

Laboratory data on admission are shown in Table 1. Urinalysis showed more than 100 red blood cells/high-power field with red blood cell and epithelial casts. The urinary protein level was 0.8 g/day. Complete blood counts showed white blood cells of 4.9×10^6/L, red blood cells of 3.96×10^{12}/L, and platelets of 148×10^9/L. In serum chemistry, creatinine (Cr) was 1.7 mg/dL, estimated glomerular filtration rate (eGFR) was 22.2 mL/min/1.73m^2, blood urea nitrogen level was 21 mg/dL, uric acid level was 10 mg/dL, and C-reactive protein was 0.8 mg/dL. Complement analysis showed hypocomplementemia with a low total hemolytic component (CH50) of 18.5 U/mL (normal range, 31–66 U/mL), low component C3 fraction (C3) of 36 mg/dL (normal range, 86.3–184 mg/dL), and low component C4 fraction (C4) of less than 6 mg/dL (normal range, 19.7–57.0 mg/dL). The titer of immune complex, measured by C1q solid-phase enzyme immunoassay, was 16 μg/dL (normal range, <4.4 μg/dL). The titer of MPO-ANCA was high (89 EU [normal range, <10 EU]), but elevation of the titer was not observed for antinuclear antibody, anti-DNA (double-stranded) antibody, anti-Smith antibody, anti-SS-B, lupus anticoagulant, rheumatoid factor, antistreptolysin O, anti-glomerular basement membrane antibody, or PR3-ANCA. Levels of immunoglobulins were within normal ranges, and test results for cryoglobulins, hepatitis B, and hepatitis C were negative.

Kidney Biopsy

Kidney biopsy was performed 7 days after admission. Light microscopy showed 36 glomeruli, 4 of which were obsolete. A cellular or fibrocellular crescentic lesion was detected in 22 of the 36 glomeruli (Fig. 2a) and mild tubular atrophy with infiltration of inflammatory cells was confirmed in the tubulointerstitium. Positive staining for IgG, IgM, C3, C4, and C1q (Fig. 2b) was observed in immunofluorescent studies. Electron microscopy showed mesangial and subendothelial deposits with circumferential mesangial interposition (Fig. 2c).

Diagnosis and Treatment

The diagnosis of HUV was made on the basis of the presence of 2 major criteria (recurrent urticaria for 6 months and hypocomplementemia) and 3 minor criteria (abdominal pain, venulitis on skin biopsy, and glomerulonephritis) and the absence of exclusion criteria (i.e., systemic lupus erythematosus, mixed cryoglobulinemia, elevated antinuclear antibody titer, hereditary deficiency of a complement component, and presence of anti-native DNA or hepatitis B antigen). In addition, she was diagnosed as having AAV by positive MPO-ANCA.

She received steroid pulse therapy with methylprednisolone as a dose of 1,000 mg for 3 days followed by oral prednisolone at a dose of 50 mg/day. After the commencement of steroid therapy, urticarial lesions disappeared and her general condition improved. The dose of oral prednisolone was tapered by 10 mg every 2–4 weeks. MPO-ANCA was negative and C3 and C4 were increased to 47 mg/dL and 20 mg/dL, respectively, after 12 weeks of therapy. The patient was discharged when the dose of prednisolone was 30 mg/day. Eighteen months after discharge, she remained asymptomatic on 5 mg of prednisolone every other day with no hypocomplementemia, and eGFR was increased to 64.2 mL/min/1.73 m^2 (Fig. 3).

Discussion

HUV is a vasculitis affecting small vessels including capillaries, venules, and arterioles and is typically manifested as urticaria, arthralgia, arthritis, obstructive pulmonary disease, ocular inflammation, and/or glomerulonephritis. In 2 earlier studies, 16 (20%) of 78 HUV cases had abnormal urinalysis [6] and 9 (50%) of 18 HUV cases had renal involvement [4], indicating that glomerulonephritis is often complicated with HUV. Histopathological findings of the kidney in HUV are generally related to a membranoproliferative or a mesangial proliferative glomerulonephritis, though the factor that determines the onset of glomerulonephritis in HUV has not been determined [4, 6]. On the other hand, AAV is the most common cause of crescentic glomerulonephritis, and the prevalence of MPO-ANCA-associated glomerulonephritis is higher in Japan than in Europe [7, 8].

In this case, light microscopy showed cellular or fibrocellular crescentic lesion and mesangial and subendothelial deposits with IgG, IgM, C3, C4, and C1q positive were observed by immunofluorescence and electron microscopy. Therefore, we speculate that 2 pathological mechanisms, i.e., ANCA-associated and immune-complex-associated vasculitis, were related to the onset of glomerulonephritis in this case. To demonstrate the involvement of ANCA in the pathogenesis of HUV, we conducted a search in the PubMed database (January 1960 to January 2017) (Table 2) [9–13]. Five cases of HUV with crescentic glomerulonephritis were reported, but ANCA was positive in only 1 case [10]. In that case, "P-ANCA" was detected by the indirect immunofluorescence technique as a perinuclear pattern, which might indicate an antigen specific for MPO [5]. Therefore, that P-ANCA-positive case might be similar to our case. Hence, although AAV and immune complex disease such as HUV were classified into 2 distinct categories in CHCC2012, both pathological processes can coexist in patients. Further observations will be needed to clarify whether the prognosis of HUV with renal involvement is modified by concurrent AAV.

To make a diagnosis of HUV, disorders that mimic clinical features of HUV need to be excluded. It is known that clinical and pathological features of glomerulonephritis in HUV are very similar to those of lupus nephritis. In addition to hypocomplementemia, a C1q-positive pattern shown by immunofluorescence is typically observed in lupus nephritis. The kidney in the present case showed a condition like lupus nephritis partially, but all serological markers of lupus, including antinuclear antibody, anti-double-stranded DNA antibody, anti-Smith antibody, and anti-phospholipid antibody were negative. Therefore, it is unlikely that glomerulonephritis in HUV is a variant form of lupus nephritis.

C1q precipitins, composed of IgG bound to C1q, were detected in many cases of HUV, suggesting that an immune complex including anti-C1q autoantibodies is involved in the pathogenesis of HUV [6, 9]. The immune complex of C1q and anti-C1q autoantibody induces immune complex deposition in various tissue and results in full activation of the classical pathway of the complement system, leading to tissue injury mediated by membrane attack complex and influx of inflammatory cells [9]. In fact, our patient had low titers of C4 and CH50, indicating activation of the classical pathway. Additionally, increase in the titer of the immune complex in this case possibly suggests upregulation of anti-C1q autoantibody because C1q solid-phase enzyme immunoassay for the immune complex detects IgG reacted with C1q. The direct approach to establish the involvement of anti-C1q autoantibody is a C1q precipitin test by immunodiffusion, which is a gold standard method for detecting anti-C1q autoantibody. Unfortunately, we could not perform a C1q precipitin test for the present case in our laboratory.

Most patients with HUV respond to glucocorticoid therapy, though a combination with other immunosuppressive agents, especially cyclophosphamide, is necessary for some serious or recurrent cases [6]. The 5 reported cases of HUV with crescentic glomerulonephritis were treated with a combination of immunosuppressive therapy. One case showed good recovery of renal function [10], and another case recovered to mild renal insufficiency [11]. However, the other 3 cases ultimately required hemodialysis for end-stage renal failure [9, 12, 13]. Thus, the response of crescentic glomerulonephritis in HUV cases to a combination of immunosuppressive therapy does not seem to be favorable. In contrast, complete remission was achieved by steroid monotherapy in the present case. In terms of AAV, it was recently reported that the renal survival rate depends on the type of histological change in glomeruli. Berden et al. [14] classified AAV-related glomerulonephritis into 4 categories (focal, crescentic, mixed, and sclerotic), and renal survival rates at 5 years in these 4 categories were 93, 76, 61, and 50%, respectively. According to this classification, our case is categorized into the crescentic class. Thus, the favorable outcome in our case might be explained by the commencement of treatment at the acute stage of the disease. Further investigation is needed to reveal the prognostic determinant of HUV with crescentic glomerulonephritis. Because the accumulation of immune complex is a hallmark of glomerulonephritis in HUV, the possible role of plasmapheresis in the treatment of HUV with crescentic glomerulonephritis has been discussed [9]. Further accumulation of cases and further analyses are clearly necessary to clarify the prognostic determinants of HUV with crescentic glomerulonephritis and its optimal treatment.

In summary, we reported here a case that represents AAV-complicated HUV with crescentic glomerulonephritis. HUV is a rare disease, and the further accumulation of cases is necessary to understand the pathogenesis of the disease.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors declare no conflict of interest.

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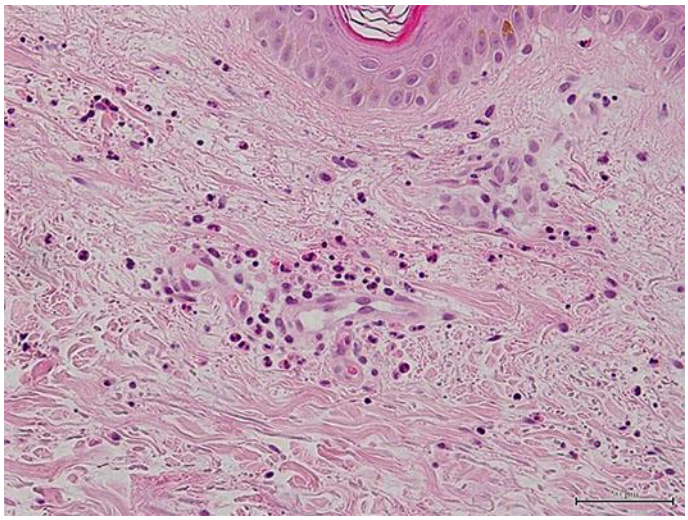

Fig. 1. Punch biopsy specimen of the skin. Light microscopy showed venulitis of the dermis. Polymorphonuclear leukocytes, eosinophilic leukocytes, and lymphocytes had infiltrated the perivascular capillary and venous wall in the dermis. Magnification: ×100.

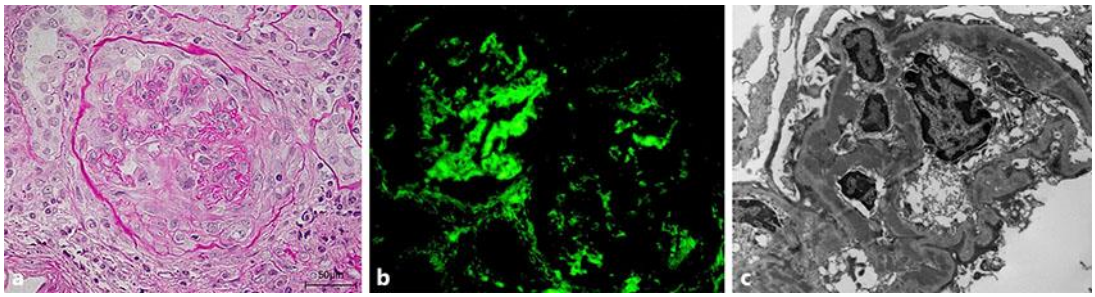

Fig. 2. Renal biopsy specimen. **a** Light microscopy showed cellular crescent glomerulonephritis. Periodic acid-Schiff stain. Magnification: ×400. **b** Immunofluorescence showed positive staining for C1q. Magnification: ×400. **c** Electron microscopy showed mesangial and subendothelial deposits with circumferential mesangial interposition. Magnification: ×6,000.

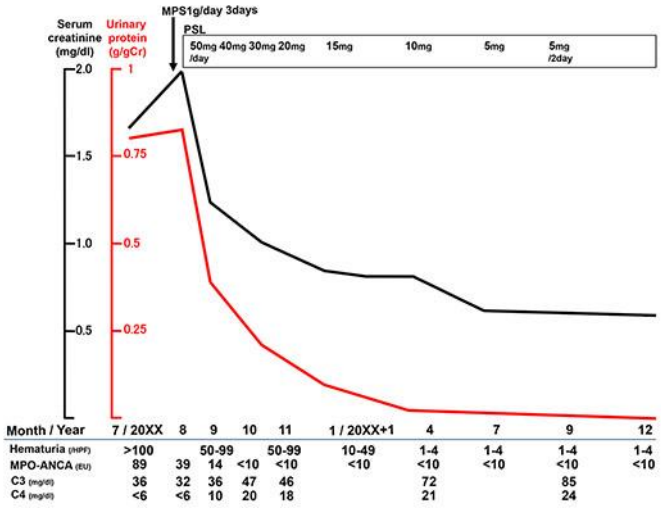

Fig. 3. Clinical course of the patient. MPS, methylprednisolone; PSL, prednisolone; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; HPF, high-power field; EU, ELISA units.

Table 1. Laboratory data on admission

Complete blood count		Serological test	
WBC	4.9×10^6/L	IgG	2,140 mg/dL
RBC	3.96×10^{12}/L	IgA	384 mg/dL
Hb	11.1 g/dL	IgM	138 mg/dL
Ht	34.1%	C3	36 mg/dL
Plt	148×10^9/L	C4	6 mg/dL
Blood chemistry		CH50	18.5 U/mL
TP	7.9 g/dL	ANCA	
Alb	4.3 g/dL	MPO	89 EU
T-Bil	0.6 mg/dL	PR3	<10 EU
AST	16 IU/dL	Anti-GBM	<10 EU
ALT	9 IU/dL	IC	16 μg/dL
LDH	179 IU/dL	Urinalysis	
T-Cho	173 mg/dL	Protein	(1+)
LDL-Cho	104 mg/dL	Blood	(3+)
TG	93 mg/dL	Glucose	(–)
UA	10 mg/dL	RBC	>100/HPF
BUN	21 mg/dL	WBC	0–4/HPF
Cr	1.7 mg/dL	Cast	
Na	138 mEq/dL	Hyaline	(+)
K	4.4 mEq/dL	Granular	(+)
Cl	105 mEq/dL	Epithelial	(+)
Ca	9.8 mEq/dL	NAG	12.4 U/L
P	2.6 mEq/dL	β2MG	3,826 μg/L
CRP	0.8 mg/dL	U-protein	0.8 g/day

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Cho, total cholesterol, LDL-Cho, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P, phosphorus; CRP, cross-reactive protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M, C3, complement C3; C4, complement C4; CH50, hemolytic complement; ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; GBM, glomerular basement membrane; IC, immunocomplex; NAG, N-acetyl-b-glucosaminidase; β2MG, β_2 microglobulin; U-protein, urinary protein.

Table 2. Summary of all reported cases of crescentic glomerulonephritis complicated with hypocomplementemic urticarial vasculitis syndrome

Authors [Ref.]	Age, years/ Sex	Clinical findings	Laboratory findings	Skin biopsy	Kidney biopsy	Prognosis
Martini et al. [13]	12/male	Urticaria, arthralgia, conjunctival hyperemia, glomerulonephritis	Cr: 3.5 mg/dL C3: 45.0 mg/dL C4: 14.0 mg/dL ANCA: not available	Not available	LM: mesangial proliferation with complete sclerosis and crescents in 50% glomeruli IF: C3, C1q, C4, IgG, IgM EM: not available	Maintenance hemodialysis initiated 5 months after diagnosis
Renard et al. [10]	13/male	Urticaria, angioedema, arthritis, conjunctivitis, abdominal pain, nephrotic syndrome	Cr: 1.3 mg/dL C4: 17.0 mg/dL P-ANCA: positive C-ANCA: negative	Not available	LM: extra- and intracapillary proliferation with mesangial hypercellularity and crescent IF: not available EM: not available	Recover of renal function with mild proteinuria
Messiaen et al. [12]	27/female	Urticaria, arthritis, episcleritis, hemoptysis, glomerulonephritis	Cr: 5.7 mg/dL C3: 52 mg/dL C4: 12.6 mg/dL CH50: 19 U/mL ANCA: not available	Leukocytoclastic vasculitis	LM: membranoproliferative with crescent IF: C3, C1q, IgM EM: subepithelial and subendothelial deposits	Maintenance hemodialysis initiated 3 years after diagnosis
Enriquez et al. [11]	39/female	Urticaria, arthralgia, xerophthalmia, nephrotic syndrome	Cr: 1.0 mg/dL C3: 46 mg/L C4: <5 mg/dL MPO-ANCA: negative PR3-ANCA: negative	Not available	LM: mesangial proliferation, membranoproliferative with crescents IF: C3, C4, C1q, IgG, IgM EM: not available	Mild renal insufficiency and nephrotic syndrome 42 months after diagnosis
Balsam et al. [9]	23/female	Urticaria, arthralgia, abdominal pain, glomerulonephritis	Cr: 1.0 mg/dL C3: 41.8 mg/dL C4: 10.4 mg/dL CH50: <10 U/mL MPO-ANCA: negative PR3-ANCA: negative	Acute venulitis, leukocytoclastic vasculitis	LM: crescent with extensive tubular loss and interstitial inflammation IF: C3, C4, C1q, IgG, IgA, IgM EM: subendothelial deposits	Maintenance hemodialysis initiated 3 weeks after diagnosis
Present case	64/female	Urticaria, abdominal pain, xerophthalmia, glomerulonephritis	Cr: 1.7 mg/dL C3: 36 mg/dL C4: <6 mg/dL CH50: 18.5 U/mL MPO-ANCA: 89 EU PR3-ANCA: <10 EU	Acute venulitis, leukocytoclastic vasculitis	LM: crescent with extensive dissolution of Bowman's capsule IF: C3, C4, C1q, IgG, IgM EM: mesangial and subendothelial deposits	Recover of renal function and proteinuria

Cr, creatinine; C3, complement C3; C4, complement C4; CH50, hemolytic complement; ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C1q, complement C1q; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy.