Churg-Strauss Syndrome Presenting with Acute Renal Insufficiency Accompanied by Eosinophilic Tubulointerstitial Nephritis

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Abstract

We encountered an unusual and rare case of 59-year-old woman with Churg-Strauss syndrome (CSS) showing myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-related acute renal insufficiency accompanied by eosinophilic tubulointerstitial nephritis. To date, reports in English of CSS presenting with rapidly progressive/acute renal insufficiency and biopsy-proven renal lesions have been uncommon. Here, we discuss this unusual case and review the previously reported CSS cases. The complication of eosinophilic tubulointerstitial nephritis in CSS cases with acute renal insufficiency might be higher than generally thought. Furthermore, the presence of eosinophilic infiltration and eosinophilic tubulointerstitial nephritis might be associated with the good renal outcome in CSS patients.

Key words: Churg-Strauss syndrome, acute renal insufficiency, eosinophilic tubulointerstitial nephritis, ANCA-associated vasculitis, MPO-ANCA

(Intern Med 51: 1555-1560, 2012)

(DOI: 10.2169/internalmedicine.51.6063)

Introduction

Churg-Strauss syndrome (CSS) is defined as an eosinophil-rich, granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and eosinophilia (1, 2). In Europe, the annual prevalence and incidence rate of CSS are 6.8 and 2.4 per million (3, 4), whereas the numbers of patients and new cases are lower (1,800 and 100 per year, respectively) in Japan (5). Pathological confirmation is based on the presence of extra-vascular granulomas in association with necrosis and predominant extra-vascular eosinophils, as well as necrotizing vasculitis (1, 2). All of these lesions however, are rarely found together in biopsy specimens (6-9). To date, CSS presenting with rapidly pro-

gressive/acute renal insufficiency and biopsy-proven renal lesions which were fully described in English-language literature have been rare. Moreover, these included some cases with eosinophilic tubulointerstitial nephritis. The gender distribution of CSS with rapidly progressive/acute renal insufficiency and eosinophilic tubulointerstitial nephritis is still unclear. Here, we report a rare case of a female CSS patient showing myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-related acute renal insufficiency accompanied by eosinophilic tubulointerstitial nephritis.

Case Report

A 59-year-old woman with a 2-year history of bronchial asthma (BA) presented with fever and fatigue for one month. In the past year, she had been exposed to no drugs

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Received for publication June 25, 2011; Accepted for publication February 27, 2012

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Figure 1. Light microscopic examination of the renal biopsy specimen showed a segmental necrotizing lesion with fibrin-rich material in the Bowman's space and tubulointerstitial nephritis with marked eosinophilic infiltration (a: Hematoxylin and Eosin staining; original magnification $\times 100$, b: periodic acid-Schiff staining; original magnification $\times 400$, c: Hematoxylin and Eosin staining; original magnification $\times 400$).

except for an inhaled corticosteroid (CS) for BA. A year before her admission, serum creatinine was 0.7 mg/dL, and eosinophilia was not found. A week before her admission, serum creatinine was 0.9 mg/dL.

On admission, her blood pressure and body temperature were 127/76 mmHg and 38.1°C, respectively. Cardiac and neurologic examinations showed normal findings. She had no extremity pitting edema, but reported the recent onset of purpura at both legs. Laboratory findings on admission were: white blood cell count, $14.5 \times 10^3/\mu\text{L}$; eosinophils, 17% (2,465 cells/ μL); hemoglobin, 10.5 g/dL; platelets, $343 \times 10^3/\mu\text{L}$; total protein, 6.7 g/dL; serum albumin, 2.4 g/dL; serum urea nitrogen, 21 mg/dL; serum creatinine, 1.4 mg/dL; serum uric acid, 3.6 mg/dL; sodium, 136 mEq/L; potassium, 4.2 mEq/L; chloride, 100 mEq/L; calcium, 8.0 mg/dL; phosphate, 3.5 mg/dL; IgG, 1,612 mg/dL; IgA, 159 mg/dL; IgM, 89 mg/dL; IgE, 296 IU/L; erythrocyte sedimentation rate, >110 mm/h; and C-reactive protein, 18.6 mg/dL. On serologic examination, her MPO-ANCA was elevated at 1,270 EU (normal <20 EU), proteinase 3-ANCA (PR3-ANCA) was negative at less than 10 EU. Anti-DNA antibody, anti-nuclear antibody, and anti-glomerular basement membrane antibody were not detected. Complement values were normal. Urinalysis showed many red blood cells and red blood

cell casts. Urinary protein excretion was 1.1 g/day. Creatinine clearance was 25.6 mL/min.

Magnetic resonance imaging brain scans showed mucosal thickening of nasal sinuses, which was compatible with bilateral sinusitis. A computed tomographic chest scan showed no evidence of pulmonary vasculitis. A skin biopsy specimen taken from purpura of her right lateral lower thigh revealed perivascular dermatitis with eosinophilic infiltration. Renal ultrasound identified 2 normal-sized kidneys. CSS was considered, and renal biopsy was performed in order to establish a pathological diagnosis.

The renal biopsy specimen showed 19 glomeruli. In 2 of 19 glomeruli, segmental necrotizing lesions with fibrin-rich material in the Bowman's space were observed, and there were intraluminal eosinophils and neutrophils in the glomeruli (Fig. 1-a, b). There were slight degrees of fibrosis and marked infiltration of eosinophils in the interstitium (Fig. 1-c), but no granulomas were observed. Arteries and arterioles were slightly hyalinized but fibrinoid necrosis was not found. Immunofluorescence showed no immune deposits. We diagnosed it as an eosinophilic tubulointerstitial nephritis, rather than a pauci-immune type crescentic and necrotizing glomerulonephritis with severe eosinophilic interstitial infiltration, because the percentage of crescentic for-

Figure 2. Clinical course after first visit. After treatment with pulses of intravenous methylprednisolone, oral prednisolone, and a high dose of intravenous cyclophosphamide, her clinical condition improved markedly. ANCA: antineutrophil cytoplasmic antibodies, β2 MG: Beta-2 microglobulin, CRP: C-reactive protein, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, PSL: prednisolone, sCr: serum creatinine

mation in Bowman's capsule was far less than 50%, the number of affected glomeruli was less than 10%, and the degree of eosinophilic infiltration was much more severe in the interstitium than in glomeruli. CSS was comprehensively diagnosed based on the presence of asthma, eosinophilia, sinusitis, and histological findings showing infiltration of many eosinophils to glomeruli and tubulointerstitium.

Treatment included pulses of intravenous methylprednisolone, oral prednisolone, and a high dose of intravenous cyclophosphamide. After immunosuppressive therapy, her clinical condition improved markedly. At outpatient review after 9 months in August 2010, her serum creatinine had decreased to 1.0 mg/dL without any hematuria, proteinuria, nor MPO-ANCA titers. She is now on a daily maintenance dose of 5 mg prednisolone, and remains in good condition (Fig. 2).

Discussion

CSS is known as an allergic granulomatosis and angiitis, characterized by classic histopathological findings of vasculitis, and necrotizing extra-vascular granulomas with eosinophilic infiltration (1). However, these three histopathological findings rarely coexist, particularly in tissue biopsy specimens. Microscopic polyangiitis, Wegener's granulomatosis and CSS also share pathologically identical pauci-immune systemic vasculitis (10). Moreover, since approximately 75% of patients with pauci-immune crescentic glomerulonephritis have overt evidence for systemic vasculitis, patients with

pauci-immune crescentic glomerulonephritis with and without systemic vasculitis are indistinguishable (10).

Renal disease is often an overlooked feature of CSS. Although less frequent and less severe than in other forms of ANCA-associated vasculitis, nonetheless renal manifestations occur in 25-45% of CSS patients (11, 12). The most typical picture is pauci-immune focal and segmental necrotizing glomerulonephritis, with or without crescents, which usually involve <50% of the glomeruli (11). In addition, since eosinophilic tubulointerstitial nephritis is not specific to CSS, clinicians always need to carefully carry out a comprehensive diagnosis.

Although renal manifestations are considered not rare in CSS patients, CSS presenting with rapidly progressive/acute renal insufficiency and biopsy-proven renal lesions which were fully described in English have been rare. To the best of our knowledge, these included 18 men and 12 women with ages ranging from 23 to 86 years (Table 1). Compared to the CSS incidence or prevalence rate mentioned above, remarkably few CSS cases have presented with rapidly progressive/acute renal insufficiency. A necrotizing crescentic glomerulonephritis was present in 25 patients (83%). In described cases, extracapillary proliferation in more than 50% of glomeruli was present in 10 of 19 patients (53%). An eosinophil-rich interstitial infiltration was present in 18 of 31 patients (58%), 13 of them had eosinophilic tubulointerstitial nephritis (patients 5, 6, 7, 8, 15, 17, 20, 21, 22, 23, 24, 28 and the present patient), including 2 eosinophilic tubulointerstitial nephritis cases without glomerular involve-

Table 1. Churg-Strauss Syndrome Presenting with Rapidly Progressive/Acute Renal Insufficiency and Biopsy-proven Renal Lesions

Patient No.	First author ^{Ref}	Age/Sex	sCr (mg/dL)	Hematuria	Proteinuria (g/day)	ANCA	Histology	Crescent (%)	Eo	Vas	Therapy	Outcome (sCr, mg/dL)
1	Sinico ¹¹	45/F	6.2	+	1.3	P/MPO	NCGN	67	-	-	PSL + CY	0.8
2	Sinico ¹¹	29/F	1.8	+	4.0	P/MPO	NCGN	30	-	-	PSL + CY	0.9
3	Sinico ¹¹	66/F	2.8	+	1.0	P + C/MPO	NCGN	55	-	-	PSL + CY	2.5
4	Sinico ¹¹	86/M	5.0	+	1.8	C/PR3	NCGN	60	-	-	PSL	HD
5	Sinico ¹¹	51/M	5.7	+	2.5	P/MPO	NCGN + TIN	62	+	+	PSL	1.3
6	Sinico ¹¹	40/M	2.3	+	1.2	P/MPO	NCGN + TIN	30	+	+	PSL + CY	1.1
7	Sinico ¹¹	77/F	3.3	+	0.4	C/PR3	TIN	0	+	-	PSL + AZ	2.1
8	Davenport ¹³	37/M	11.5	+	+++	NA	TIN	NA	+	-	PSL	5.1
9	Clutterbuck ¹⁴	23/M	<2.3	-	-	NA	Mesangial prolif	NA	-	-	PSL	Normal
10	Clutterbuck ¹⁴	49/M	<2.3	+	+	NA	NCGN	NA	+	+	PSL	Normal
11	Clutterbuck ¹⁴	48/F	<2.3	+	+	NA	NCGN	NA	-	-	PSL	Normal
12	Clutterbuck ¹⁴	52/F	<2.3	+	-	NA	FSGN + Leiomyoma	NA	-	-	PSL + CY + AZ	Normal
13	Clutterbuck ¹⁴	55/M	<2.3	+	-	NA	Glomerulosclerosis	NA	-	-	PSL	Normal
14	Clutterbuck ¹⁴	42/F	<2.3	+	+	NA	NCGN	NA	+	+	PSL	Normal
15	Clutterbuck ¹⁴	49/M	<2.3	+	12	NA	NCGN + TIN	NA	+	-	PSL	Normal
16	Clutterbuck ¹⁴	39/M	2.3 - 5.6	+	3	NA	NCGN	NA	-	-	PSL → PSL + AZ	2.3 - 5.6
17	Clutterbuck ¹⁴	46/M	7.5	+	4	NA	NCGN + TIN	50	+	-	PSL → PSL + CY + AZ	2.8
18	Clutterbuck ¹⁴	62/M	7.7	+	4	NA	NCGN	45	-	-	PSL → PSL + CY + AZ + PEx	1.6
19	Clutterbuck ¹⁴	58/M	HD	+	+++	NA	NCGN	NA	-	-	PSL + CY + PEx	2.3 - 5.6
20	Clutterbuck ¹⁴	27/F	12.3	+	++	NA	NCGN + TIN	13	+	-	PSL + CY + AZ	PD
21	Antiga ¹⁵	51/M	5.7	NA	NA	Detected	NCGN + TIN	NA	+	+	PSL	1.3
22	Maeda ¹⁶	64/F	1.5	+	1.3	P + C	NCGN + TIN	88	+	+	PSL + CY	2.3
23	Minami ¹⁷	45/M	2.1	+	3.7	MPO	NCGN + TIN	61	+	-	PSL	0.9
24	Rychlik ¹⁸	56/M	NA*	NA	NA	P	NCGN + TIN	89	+	+	PSL + CY	<5.1
25	Yamashita ¹⁹	61/M	2.4	+	0.9	P	NCGN	20	+	-	PSL	0.8
26	Kikuchi ²⁰	66/F	0.9	+	1.0	MPO	NCGN	71	-	-	PSL	53**
27	Kikuchi ²⁰	45/F	1.3	+	1.7	MPO	NCGN	83	+	-	PSL + CY	46**
28	Kikuchi ²⁰	79/M	9.1	NA	NA	NA	NCGN + TIN	49	+	+	PSL	HD
29	Sugino ²¹	46/M	5.9	+	++	MPO	NCGN	NA	-	-	PSL + CY	1.9
30	Kanda ²²	77/F	1.5	+	0.6	MPO	NCGN	38	+	+	PSL	1.4
our patient		59/F	1.4	+	1.1	MPO	NCGN + TIN	0	+	-	PSL + CY	1.0

F; female, M; male, NA; not available, HD; hemodialysis, sCr; serum creatinine, PSL; prednisolone, CY; cyclophosphamide, AZ; azathioprine, PEx; plasma exchange, ANCA; antineutrophil cytoplasmic antibodies, P; perinuclear-ANCA, MPO; myeloperoxidase-ANCA, C; cytoplasmic ANCA, PR-3; proteinase-3 ANCA, NCGN; necrotizing crescentic glomerulonephritis, TIN; tubulointerstitial nephritis, FSGN; focal segmental glomerulonephritis, Eo; eosinophil-rich interstitial infiltrate, Vas; vasculitis, PD; peritoneal dialysis, * Dialysis-dependent renal failure, ** glomerular filtration rate (mL/min/1.73m²)

Table 2. The Renal Outcome of CSS Cases with or without Eosinophilic Tubulointerstitial Nephritis

		Recovery of renal function		Total
		Yes	No	
Eosinophilic tubulointerstitial nephritis	Yes	10	3	13
	No	14	1	15
Total		24	4	28

Fisher's exact test, p = 0.31

ment (patients 7 and 8). Necrotizing vasculitis was present in 9 of 31 patients (29%) (patients 5, 6, 10, 14, 21, 22, 24, 28 and 30). All patients were treated with corticosteroids, in association with immunosuppressive drugs. All renal biopsies were performed at the time of diagnosis of CSS.

Guillevin et al. (7) reported 4 renal biopsy-performed CSS cases with segmental proliferative glomerulonephritis. Of these, 3 had crescentic lesions and 2 had renal insufficiency. However, none of them had vascular inflammation or extra-vascular eosinophil granulomas.

Concerning the renal outcome, 28 cases in which association between pre- and post-renal function was clearly referred, were available (excluding patients 16, 26 and 27). In this paper, recovery of renal function is defined as a decrease of serum creatinine. The renal outcome of CSS cases with rapidly progressive/acute renal insufficiency is generally good because only 3 of 28 patients (11%) progressed to end-stage renal disease (patients 4, 20 and 28), and only 1

of 28 patients (4%) showed no recovery of renal function (patient 22). On the other hand, 24 of 28 (86%) CSS cases showed partial or complete recovery of renal function even if they had necrotizing crescentic glomerulonephritis (Table 1). Moreover, though it is rare (11), the renal outcome of CSS cases with eosinophilic tubulointerstitial nephritis might be worse than in cases without eosinophilic tubulointerstitial nephritis. In cases with or without eosinophilic tubulointerstitial nephritis, 10 of 13 (77 %) or 14 of 15 (93%) cases showed partial or complete recovery of renal function, respectively (Fisher's exact test, p=0.31) (Table 2). The complication of eosinophilic tubulointerstitial nephritis in CSS cases with acute renal insufficiency might be higher than generally thought. The presence of eosinophilic infiltration and eosinophilic tubulointerstitial nephritis might be associated with the good renal outcome. Eosinophils may cause tissue damage by releasing cytotoxic granule proteins (for example, eosinophil cationic and major basic protein) or by inducing apoptosis of target cells (23). Previously reported CSS cases with eosinophilic tubulointerstitial nephritis in which renal function did not recover were in end-stage renal disease at the time of diagnosis. Meanwhile in CSS cases as in the present case, in which eosinophilic tubulointerstitial nephritis was found at an early stage of renal insufficiency, the renal outcome might be better. The difference between eosinophilic tubulointerstitial nephritis with or without glomerular involvement in CSS remains unclear. Although most of the renal involvement of CSS is mild and not rare (45%) (10), the number of reported CSS patients with acute renal insufficiency is small. Hence, it is reason-

able to assume that CSS patients with glomerular involvement tend to have severe interstitial nephritis, and, as a result, have a worse renal outcome.

In any event, the clinical condition in CSS cases with rapidly progressive or acute renal insufficiency can most likely be improved by immunosuppressive therapy. Thus, it is important for detection and treatment to be carried out at an early stage.

In a previous study of 82 CSS patients (and 260 polyarteritis nodosa) (24), the French Vasculitis Study Group (FVSG) identified 5 factors that were significantly associated with a poor outcome (Five-Factors Score, FFS): elevated serum creatinine levels ($>140 \mu\text{mol/L}$, or 1.58 mg/dL), proteinuria ($>1 \text{ g/day}$), severe gastrointestinal tract involvement, cardiomyopathy, and/or central nervous system involvement. According to that analysis, when one factor was present at disease onset, as in the present case, the 5-year mortality rate was 25.9%. Current views indicate that the treatment of CSS should be tailored on the basis of patient prognosis. Patients with $\text{FFS}=0$ should receive CS alone, whereas those with $\text{FFS}>0$ should also receive cytotoxic agents (for example, cyclophosphamide, CY) as first-line therapy (4, 25-27). High CS doses (usually 1 mg/kg/day of prednisone, PSL) are used as initial therapy, with CS pulses before oral treatment in severe cases. CY is also added to CS in cases of steroid-resistant, steroid-dependent, or frequently relapsing diseases (25, 26). As for the duration of induction therapy, it has been shown that patients given CY for 4-6 months have higher relapse rates than those treated for 1 year (26). According to the European Vasculitis Study Group, following the induction of remission, intermittent high-dose intravenous CY achieves similar or better outcomes than oral CY, and is associated with lower recurrence rates (28). In the present case, the decision was made to administer CS pulses, followed by oral PSL at 40 mg (0.8 mg/kg/day). Furthermore, intermittent high-dose intravenous CY was administered in addition to CS pulse therapy, as her FFS was 1.

In this report, we could not perform immunostaining using the renal biopsy specimen. This was a limitation, however, our pathological findings suggest the proportion of infiltrating cells other than eosinophils is rare. In conclusion, the complication of eosinophilic tubulointerstitial nephritis in CSS cases with acute renal insufficiency might be higher than generally thought. Furthermore, the presence of eosinophilic infiltration and eosinophilic tubulointerstitial nephritis might be associated with the good renal outcome in CSS patients. Although CSS often responds to CS and immunosuppressants, more selective therapeutic approaches are needed to reduce exposure to immunosuppression and for refractory cases. Future studies are warranted to elucidate the genetic and immune-mediated pathogenetic mechanisms.

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

Acknowledgement

This study was funded by the Okinaka Memorial Institute for Medical Research.

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