□ CASE REPORT □

Glomerulonephritis after Methicillin-resistant *Staphylococcus aureus* Infection Resulting in End-stage Renal Failure

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Abstract

A 58-year-old man developed proteinuria and renal dysfunction following pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin was administered, and prednisolone pulse therapy and plasmapheresis were performed. Subsequently, serum creatinine was decreased. Eight months later, creatinine and CRP were again elevated, and MRSA was detected. Vancomycin was again administered and plasmapheresis was performed. However, renal function was not improved and continuous hemodialysis was initiated. This case indicates that complete eradication of MRSA is necessary to treat MRSA-associated glomerulonephritis, and if this is not attained, a permanent loss of renal function occurs.
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Key words: superantigen, vancomycin, prednisolone pulse therapy, plasmapheresis

Introduction

From 1995, cases of superantigen-related glomerulonephritis associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infection have been reported and it is speculated that the enterotoxins of *S. aureus* may serve as superantigens in its pathogenesis (1–4). We present here a patient who developed glomerulonephritis after MRSA infection which resulted in end-stage renal failure even though he received prednisolone pulse therapy and plasmapheresis in addition to administration of vancomycin.

For editorial comment, see p 365.

Case Report

A 58-year-old man underwent an operation for well differentiated squamous cell carcinoma of esophagus (T3N2M0 pStage III) on November 26, 1998. On admission, laboratory tests revealed the following: proteinuria, negative; serum protein, 7.0 g/dl; serum albumin, 4.0 g/dl; serum creatinine, 0.8 mg/dl; blood urea nitrogen, 15 mg/dl. The patient developed pneumonia after the operation (Fig. 1). The pneumonia was not improved on treatment (cefazolin sodium for 6 days and imipenem/cilastatin for 9 days). Eighteen days after the operation, MRSA was detected in the sputum and feces cultures. Vancomycin was administered and the serum concentration of C-reactive protein decreased from a peak of 30.1 mg/dl to 1.7 mg/dl. Six weeks after the onset of pneumonia, proteinuria was detected for the first time. The patient had not exhibited proteinuria in the past. The serum creatinine level was also increased. On March 1, 1999, 3 months after the onset of pneumonia, laboratory tests revealed the following (Table 1): urinary protein, 1.1 g/day; occult blood in the urine, 3+; urinary β2-microglobulin, 1,099 μg/day; urinary NAG, 8.2 U/day; creatinine clearance, 8.9 ml/min.; serum protein, 7.4 g/dl; serum albumin, 3.1 g/dl; serum creatinine, 5.8 mg/dl; blood urea nitrogen, 100 mg/dl; C-reactive protein, 1.8 mg/dl; IgG, 2,046 mg/dl; IgA, 1,115mg/dl; IgM, 68 mg/dl; C3, 92 mg/dl; C4, 26 mg/dl; CH50, 57 U/ml; C1q 10.5 mg/dl. Autoantibodies and cryoglobulins were not detected. Each ratio of CD4 positive-cells and CD8 positive-cells, and the level of cytokine IL-2 were within the normal range. The MRSA detected in the sputum and feces was positive for type II coagulase. Enterotoxin type was SE-C. Ultrasonography showed that the size of kidney was normal (rt 113 mm, lt 120 mm). Renal biopsy was performed on March 1, 1999. The specimens were processed for evaluation by light and immunofluorescence microscopy (Fig. 2). The specimens contained 12 glomeruli. Light microscopy showed mild mesangial proliferation. Four glomeruli had cellular crescent formation. Mononuclear cell infiltration and fibrosis in the interstitium was also observed. For immuno-

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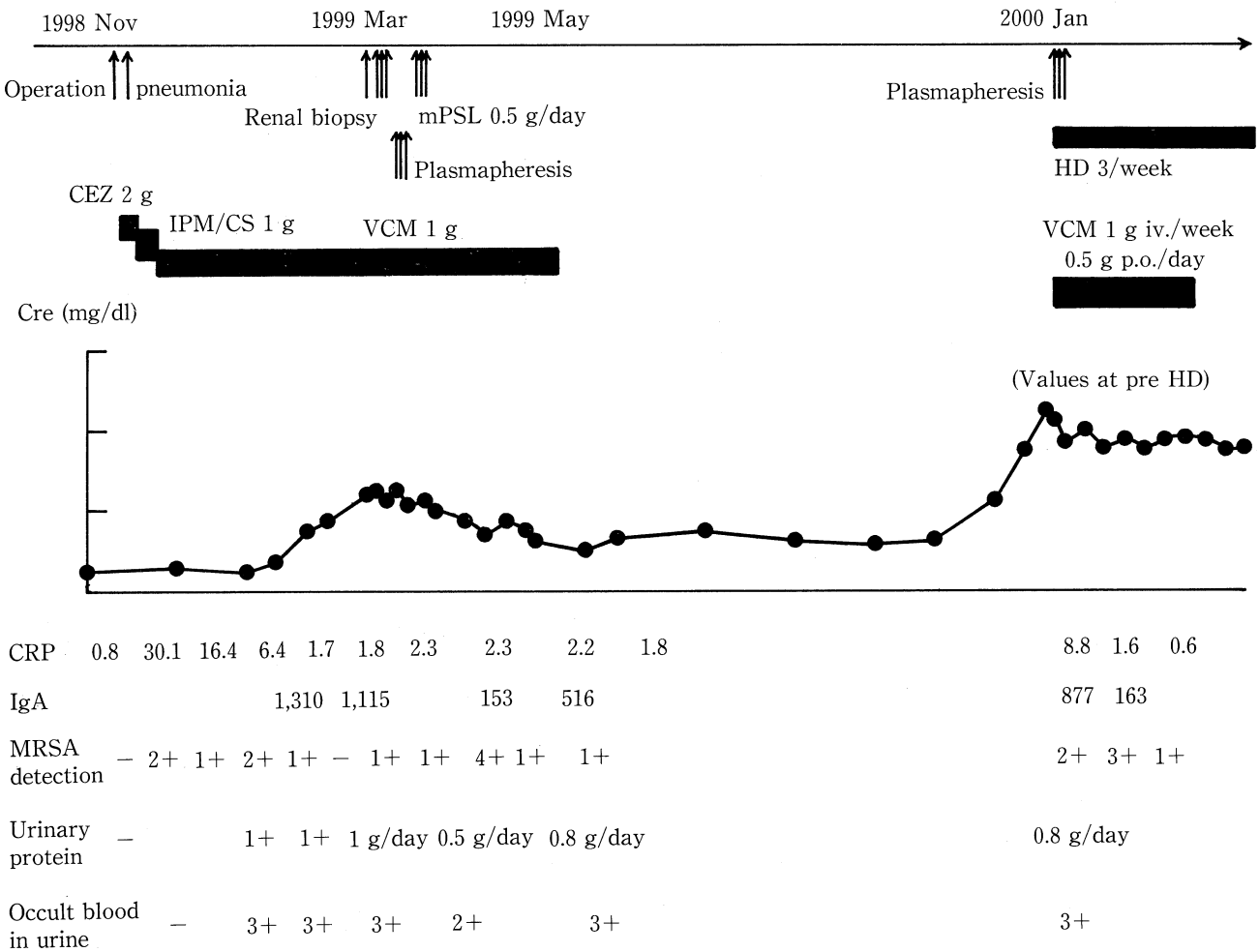


Figure 1. Clinical course of the present case. Cre: creatinine, CRP: C-reactive protein, CEZ: cefazolin, IPM/CS: imipenem/cilastatin, HD: hemodialysis, VCM: vancomycin.

fluorescence microscopy, frozen sections were stained with fluorescein-conjugated goat IgG fraction against human IgG, IgA, IgM, C3, C4, C1q and fibrinogen (Cappel, Ohio, USA). There was no significant staining for any of them.

These clinicopathological features were similar to those of superantigen-related glomerulonephritis after MRSA infection (MRSA-GN) (1, 4). Administration of vancomycin was continued. In addition, from March 2 to 4, and 17 to 19, 1999, methylprednisolone half pulse therapy was performed, and from March 11 to 13, plasmapheresis was performed. After these therapies, the serum creatinine was decreased from a peak of 6.0 mg/dl to 3.2 mg/dl. However, C-reactive protein was not normalized even after the partial improvement of renal function. He was discharged and followed infrequently in the outpatient clinic.

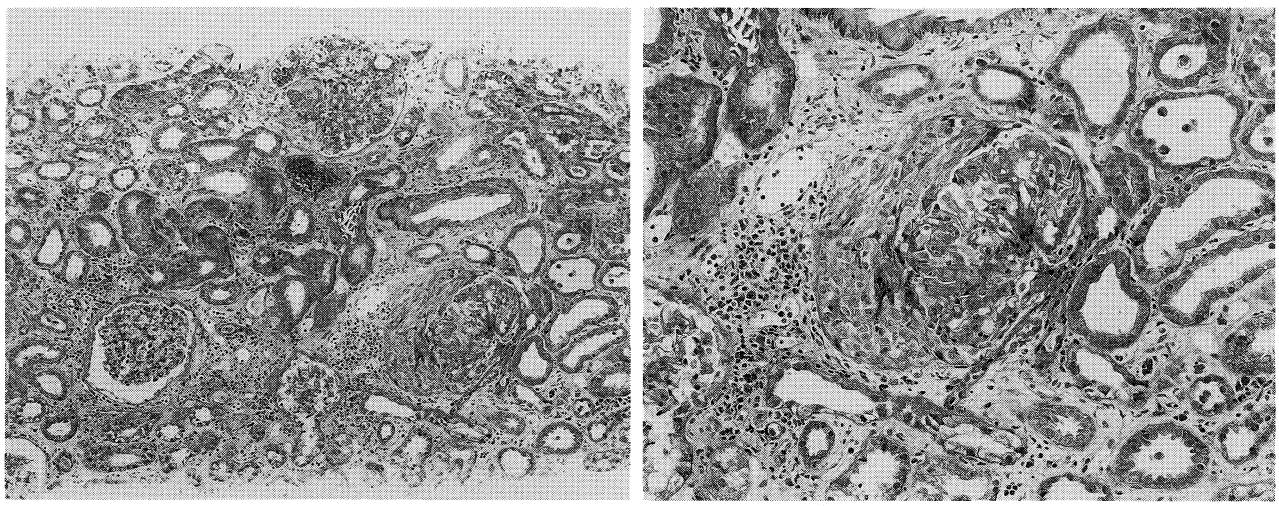
In December, 1999, the level of serum creatinine begun to elevate again. On January 11, 2000, laboratory tests revealed the following: serum creatinine, 11.2 mg/dl; blood urea nitrogen, 98 mg/dl; creatinine clearance, 2.2 ml/min; IgG, 1,478 mg/dl; IgA, 877 mg/dl; IgM, 112 mg/dl; C3, 76 mg/dl; C4, 25 mg/dl; CH50, 53 mg/dl; C-reactive protein, 8.8 mg/dl. MRSA was again detected in the sputum and feces cultures. Clinical features for dehydration were not observed. The elevation of serum creatinine level was accompanied by those of IgA and IgG, and C-reactive protein, indicating the relapse of MRSA-GN. Vancomycin was administered. From January 18 to 20, 2000, plasmapheresis was performed. In February, the level of C-reactive protein became normalized. However, renal function did not improve and therapy with continuous hemodialysis was ultimately required.

Discussion

Staphylococcal enterotoxins are known to act as superantigens (5). Superantigens can bind directly to major histocompatibility complex class II on antigen-presenting cells and are recognized by T cell receptor (TCR). They bind only to Vβ chain on the TCR, and cause massive activation of T cells and subsequent release of T cell-derived cytokines, such as IL-2, TNF and INF-γ. From 1995, cases of superantigen-related glom-

Table 1. Laboratory Data on March 1

Urinalysis		Blood chemistry		Serology		Immunoelectrophoresis of serum and urine	
Protein	1.1 g/day	TP	7.4 g/dl	IgG	2,046 mg/dl	M protein	–
Occult blood	3+	Alb	3.1 g/dl	IgM	68 mg/dl	Bence Jones protein	–
Glucose	–	BUN	100 mg/dl	IgA	1,115 mg/dl	IL-2	0.8 U/ml (<0.8)
Sediment	–	Cre	5.8 mg/dl	C_3	92 mg/dl	CD4	28.9% (25–56)
RBC	30–49/HPF	UA	10.8 mg/dl	C_4	26 mg/dl	CD8	44.2% (17–44)
WBC	50–99/HPF	Na	131 mEq/*l*	CH50	57 U/ml	Vβ positive T cells: increased	
Hyaline cast	+	K	4.8 mEq/*l*	Clq	10.5 mg/dl		
Epithelial cast	+	Cl	99 mEq/*l*	CRP	1.8 μg/dl	Blood gas analysis (room air)	
Ccr	8.9 ml/min	Ca	8.5 mg/dl	RA	4 IU/ml	pH	7.308
U-β2MG	1,099 μg/day	P	6.1 mg/dl	RAPA	40 IU/ml	$PaCO_2$	30.5 mmHg
U-NAG	8.2 U/day	LDH	186 U/*l*	ANA	–	PaO_2	106 mmHg
		GOT	14 U/*l*	anti DNA ab	–	BE	−10.1 mmol/*l*
Peripheral blood		GPT	15 U/*l*	anti ENA ab	–	HCO_3^-	14.8 mmol/*l*
WBC	9,000/μl	γ-GTP	56 U/*l*	anti Scl-70 ab	–		
(St 0%, Seg 79%, Ly 16%, Mo 3%, Eo 1%)		ALP	450 U/*l*	P-ANCA	–	MRSA strain separated from this case	
RBC	215×10⁴/μl	T-Bil	0.4 mg/dl	C-ANCA	–	coagulase; type II	
Hb	6.7 g/dl	D-Bil	0.1 mg/dl	Cryoglobulin	–	enterotoxin type; SE-C	
Ht	19.7%	T-Chol	127 mg/dl	ESR	140 mm/h		
Plt	17.2×10⁴/μl	Glu	106 mg/dl				
Ret	29.9 ‰	CK	49 U/*l*				



A B

Figure 2. Light microscopic findings of renal biopsy. A: Four glomeruli with mild mesangial proliferation were shown. Two of them had cellular crescent formation. There was mononuclear cell infiltration and fibrosis in the interstitium (Masson's trichrome staining; ×50). B: Marked cellular crescent formation with segmental necrosis was observed (Masson's trichrome staining; ×200).

erulonephritis after MRSA infection (MRSA-GN) have been reported (1–4). The pathogenesis of MRSA-GN is speculated as follows; long-term infection of MRSA leads to the production of Staphylococcal enterotoxins and these substances act as superantigens. That causes massive T cell activation and released cytokines induce kidney injuries including tubulointerstitial nephritis. The cytokines also cause polyclonal B cell activation that leads to the formation of immune complex, resulting in glomerulonephritis (1, 4, 5).

Most cases with MRSA-GN reveal rapidly progressive glomerulonephritis with various degrees of proteinuria and elevation of serum IgA and IgG (1, 4, 5). The present case also showed rapidly progressive glomerulonephritis and elevation of serum IgA and IgG. It is reported that the average duration

from MRSA infection to onset of glomerulonephritis is 5.4 weeks (4, 5). In the present case, the duration was 6 weeks. Autoantibodies were not detected in this case that was also consistent with the cases reported previously (1, 3–5).

In most cases with MRSA-GN reported previously, renal pathology showed mesangial and/or endocapillary proliferative glomerulonephritis with various degrees of crescent formation and tubulointerstitial nephritis (1–5). The present case also showed mesangial proliferative glomerulonephritis with cellular crescent formation and interstitial nephritis.

From these clinicopathological features, the deterioration of renal function was concluded to be due to MRSA-GN. Not only administration of vancomycin, but also prednisolone pulse therapy and plasmapheresis improved the renal function. However, 8 months after the partial improvement, the level of serum creatinine again became elevated paralleling the course of MRSA infection, and serum IgA was again increased. Thus, the deterioration of renal function was considered to be from the relapse of the superantigen-related glomerulonephritis induced by the continuous MRSA infection.

In addition to the superantigen-related glomerulonephritis, staphylococcal infections associated with glomerulonephritis have been reported: bacteremia associated with infected ventriculoatrial shunt (6), bacteremia associated with endocarditis (7), and glomerular lesion associated with visceral abcesses (8). In these cases, the level of complement is low, cryoglobulins are frequent, and the elevated immunoglobulin type is IgG but not IgA. These findings clearly differ from those of the present case. Futhermore, echocardiography revealed no abnormalities, and features associated with visceral abscesses were not observed in this case.

The clinical course in the present case also made the concept of drug-induced nephropathy unlikely: vancomycin was only administered at the time of onset and relapse of glomerulonephritis, but at the time of relapse, the deterioration of renal function occurred prior to the administration of vancomycin.

Previous studies of MRSA-GN have been shown an increase of cytokines including IL-2 and an increase of each ratio of CD4 positive and CD8 positive cells which were considered to be induced by superantigens. In the present case, the serum level of IL-2 and the ratios of CD4 positive and CD8 positive cells were within the normal range. The reason for the difference is not clear. Immunofluorescence study in most cases of MRSA-GN revealed glomerular deposition of IgA. In the present case, there was no significant staining for IgA. The cause of difference is also not clear. However, it may be possible that antibiotic therapy suppresses power of the infection and may hasten dissociation of immune complexes after the glomerulonephritis occurs. It is unlikely that these findings alone which differ from those in the previous studies can exclude that glomerulonephritis in this case was caused by superantigens. The clinical course of this case including association of serum IgA with development of glomerulonephritis is thought to indicate superantigen-related glomerulonephritis. The studies of MRSA-GN reported to date are few. The cases of MRSA-GN may have substantially more varied types of features.

It is reported that the prognosis of MRSA-GN is relatively good if the appropriate treatment is administered for the MRSA infection, and if the underlying disease does not worsen (1, 2, 5). In the present case, we speculate that we could prevent the second deterioration of renal function and subsequent requirement of contiuous HD therapy if we had completely eradicated MRSA. The present case emphasized the importance of the eradication of *Staphylococcus* infection in the treatment of MRSA-GN.

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