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CASE REPORT

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# Glomerulonephritis induced by methicillin-sensitive *Staphylococcus aureus* infection

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**Abstract**
A 57-year-old woman developed exacerbation of atopic dermatitis, fever, and nephrotic syndrome with microscopic hematuria. By bacteriological study, methicillin-sensitive *Staphylococcus aureus* (MSSA) was detected from each culture of pharyngeal mucus, stool, and blood samples. Renal biopsy specimens showed endocapillary proliferative glomerulonephritis with massive IgA deposition in the mesangium and along the capillary loops. After antistaphylococcal therapy with antibiotics, MSSA was negative for each culture and urinary protein decreased. Nine months after the first renal biopsy, a re-biopsy was performed, which revealed apparent disappearance of both endocapillary cell proliferation and IgA deposition. It is known that methicillin-resistant *S. aureus* (MRSA) infection causes glomerulonephritis through T-cell stimulation by superantigen presented by MRSA. The present results suggest that not only MRSA but also MSSA can cause this type of glomerulonephritis.

**Key words** MSSA nephritis · MRSA nephritis · Superantigen · *Staphylococcus aureus*

## Introduction

Since 1995 when Koyama et al.[1] reported glomerulonephritis associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infection and named it MRSA nephritis, several cases have been reported as MRSA nephritis.[1–4] The pathogenesis is thought to be associated with superantigen, and the condition is also termed superantigen-related nephritis. We have observed a case of glomerulonephritis which was induced by methicillin-sensitive *S. aureus* (MSSA), and at renal biopsy, the microscopic findings closely resembled those of MRSA nephritis as previously reported. Compared with MRSA nephritis, MSSA nephritis may be uncommon. We discuss the similarity of MRSA and MSSA nephritides and the possibility that MSSA also presents a superantigen to cause nephritis.

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## Case report

A 57-year-old Japanese woman with a prior history of atopic dermatitis from the age of 20 years was referred to our hospital with exacerbation of dermatitis, fever, proteinuria, hematuria, hypoalbuminemia, and edema. Three years before the admission, the atopic dermatitis had deteriorated, and 3 months before the admission, leg edema developed. When she was hospitalized with dyspnea at another hospital a week before admission to our hospital, laboratory findings showed serum protein, 4.8 g/dl; albumin, 2.3 g/dl; urinary protein, (3+); and urinary occult blood, (3+), and she was diagnosed as having nephrotic syndrome and transported to our hospital for further examination. On admission, she was febrile, with a temperature of up to 40°C, with erythroderm-like skin and leg edema. Chest ausculation revealed systolic murmur at the apex and weakening of the breath sound in the bilateral lower lungs. Furthermore, bilateral axillary and inguinal lymphadenopathy was observed. Chest X-ray showed bilateral pleural effusion. Laboratory data were as follows: white blood cell count, $8.0 \times 10^9$/l; eosinophils, 10.8%; red blood cell count, $3.69 \times 10^{12}$/l; hemoglobin, 10.8 g/dl; platelet count, $244 \times 10^9$/l; C-reactive protein, 1.0 mg/dl; D-dimer, 3.4 μg/ml; aspartate transaminase, 56 IU/l; alanine transaminase, 47 IU/l; lactate dehydrogenase, 687 IU/l; serum total protein, 6.1 g/dl; serum albumin, 2.7 g/dl; total cholesterol, 230 mg/dl; blood urea nitrogen, 27 mg/dl; serum creatinine, 1.2 mg/dl;

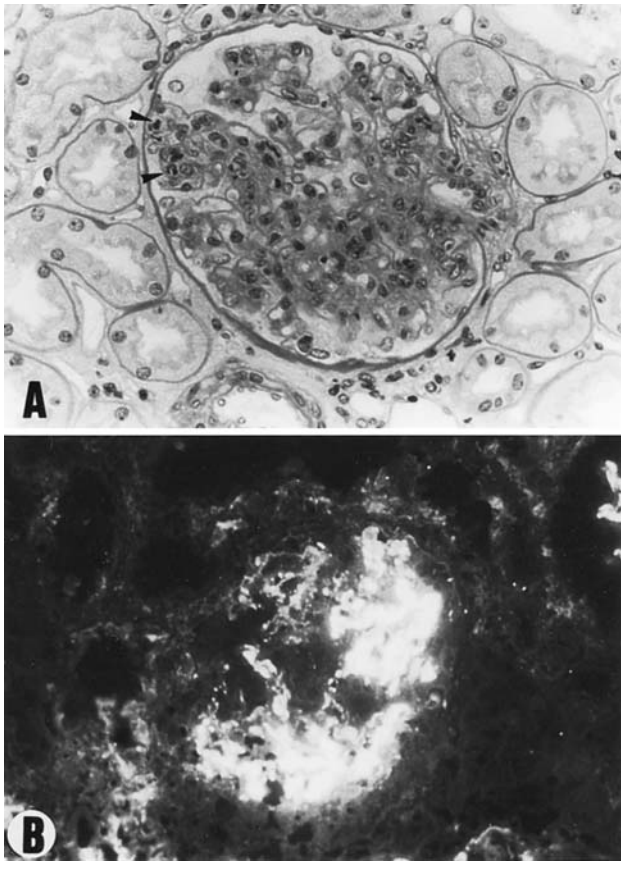


**Fig. 1A,B.** Renal biopsy findings. **A** Light microscopy. Endothelial cell proliferation, mild mesangial cell proliferation, and invasion of neutrophils (arrowheads) with mononuclear cells are observed. **B** Immunofluorescence staining of IgA. Massive predominant IgA deposition in the mesangium and along capillary loops is observed. **A** Periodic acid schiff (PAS), ×310; **B** ×310

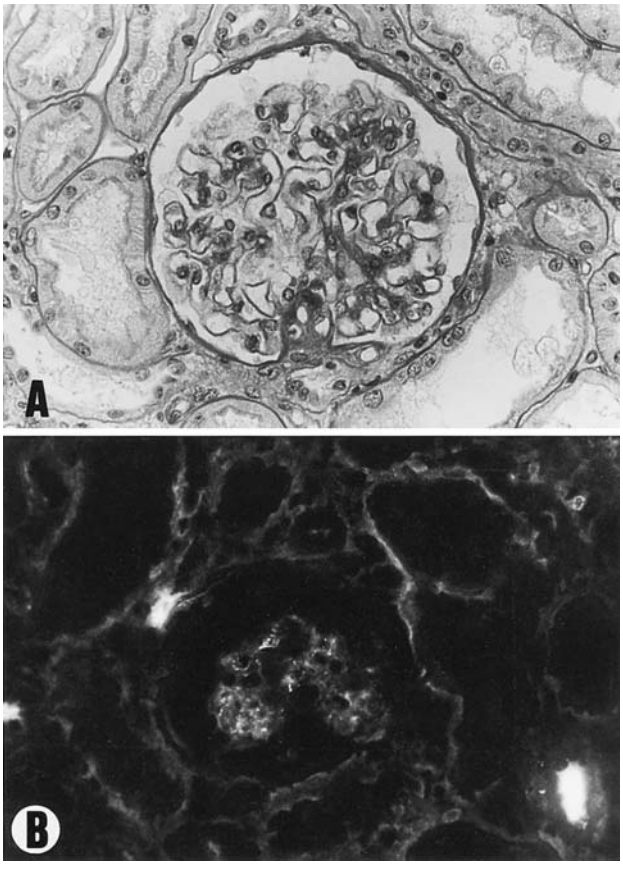


**Fig. 2A,B.** Renal re-biopsy findings. **A** Endocapillary cell proliferation has disappeared in the glomeruli, showing mild mesangial cell proliferation. **B** IgA deposition is scarce in contrast with that in the first biopsy findings, as shown in *Fig. 1B*. **A** PAS, ×310; **B** ×310

creatinine clearance, 34 ml/min; urinary occult blood, (3+); and daily urinary protein, 5.8 g. Other blood chemistry data were almost within the normal ranges. Serological study demonstrated marked elevation of serum IgA, at 520 mg/dl, in spite of massive urinary loss. Antinuclear antibody (ANA) negativity and antineutrophil cytoplasmic autoantibodies (ANCA) negativity were shown, and serum IgG (1459 mg/dl) and complement levels (C3, 88.6 mg/dl; C4, 29.0 mg/dl; CH50, 39.3 U/ml) were within the normal ranges.

By bacteriological study, MSSA was detected from each culture of pharyngeal mucus, stool, and blood samples. After admission, her general condition further deteriorated, and prednisolone, 40 mg daily, was administered to alleviate the dermal symptoms. For the MSSA infection, oral cefdinir followed by intravenous cefazolin was given. Renal biopsy was performed soon after the initiation of this therapy. Renal biopsy specimens showed glomerular swelling with endothelial cell proliferation and multiple polymorphonuclear and mononuclear leukocyte invasion into the glomerular capillary lumina (Fig. 1A). These findings were compatible with endocapillary proliferative glomerulonephritis, as categorized in the WHO *Atlas of glomerular diseases* by Churg et al.[5] Cellular crescent formation was observed in 2 of 32 glomeruli. In the interstitium, mild mononuclear cell infiltration was observed. In an immunofluorescence study, massive IgA deposition in the mesangium and along the capillary loops was predominant (Fig. 1B), and IgM, IgG, and C3 depositions were also observed.

After 1 week of antistaphylococcal therapy with antibiotics, MSSA was negative in each culture, and urinary protein decreased to 0.2 g/day, although recovery from the microscopic hematuria was delayed. The dermatitis was alleviated and prednisolone was tapered carefully to maintain an inactive dermatological condition. Nine months after the first renal biopsy, her creatinine clearance had mildly recovered to 48 ml/min, and mild microscopic hematuria without proteinuria persisted. A re-biopsy revealed almost total disappearance of both endocapillary cell proliferation and IgA deposition (Fig. 2).

## Discussion

According to the analysis of MRSA glomerulonephritis first reported by Koyama et al.,[1] most patients presented either with rapidly progressive glomerulonephritis and/or with

nephrotic syndrome with various degrees of proteinuria after an episode of severe MRSA infection. The abnormal immunological findings were polyclonal increases of serum IgA and IgG, normal complement levels without elevation of autoantibodies such as ANA or ANCA, and a marked increase in several specific T-cell receptor V (TCRV)β-positive cells in peripheral blood by MRSA-derived superantigens. The characteristic histologic features were various types of mesangial and/or endocapillary proliferative glomerulonephritis with varying degrees of crescent formation and tubulointerstitial nephritis. Immunofluorescence revealed glomerular deposits, especially of IgA, with IgG and C3.[2] Yoh et al.[4] observed that the frequency of T cells expressing several TCRVβs among peripheral lymphocytes was high in MRSA-associated nephritis. Staphylococcal enterotoxins are known to stimulate the proliferation of resting T cells and are called superantigens,[6] and they markedly activate T cells and the release of T-cell-derived cytokines.[7,8] The relationship between atopic dermatitis and superantigen was also reported by Strickland et al.,[9] who pointed out that superantigen from *S. aureus* can contribute to atopic dermatitis by increasing the frequency of memory T cells.

In the present patient, the clinical, histological, and laboratory findings closely resembled the features of MRSA nephritis as reported by Koyama et al.[1] Therefore, in our patient with severe atopic dermatitis, T cells, stimulated by superantigen presented by MSSA, could have induced the glomerulonephritis. Previously, T-cell receptor usage in Henoch-Schönlein purpura nephritis associated with *S. aureus* infection was reported by Hirayama et al.,[10] including five cases of MRSA and one case of MSSA. Therefore, to our knowledge, the present case may be the second report of MSSA nephritis. Compared with MRSA nephritis, MSSA nephritis may be rare. One of the possible reasons for this is the relatively higher sensitivity of MSSA to antibiotics compared with MRSA infection. Akiyama et al.[11] reported the efficacy of cefdinir in treating erythema in atopic dermatitis infected by MSSA. In accordance with these clinical finding, the erythroderm-like disorder in the present patient was rapidly ameliorated after the use of cefdinir followed by cefazolin. Marked histological amelioration was observed in the re-biopsy specimen. Other types of glomerular lesions with staphylococcal infections such as nephritis due to ventriculoatrial shunt infection (shunt nephritis) and glomerulonephritis in infective endocarditis are well known.[12] Histologically, shunt nephritis often presents as mesangiocapillary glomerulonephritis with granular depositions of IgM and sometimes also IgG and C3 along capillary loops. Glomerulonephritis in infective endocarditis presents as focal glomerulonephritis with fibrinoid necrosis, thrombosis, and cellular proliferation, together with granular deposits of IgG and C3. Because the histopathological features in the present patient were endocapillary proliferation and massive IgA deposition in the mesangium and along capillary loops, differential diagnosis was possible. Concerning the treatment of MSSA nephritis, antibiotic therapy should be considered, with or without steroid, and steroid therapy alone needs to be avoided. In conclusion, our results suggest that not only MRSA but also MSSA can cause glomerulonephritis, and the pathogenesis may include the association of superantigen.

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