Use of Immunosuppressive Therapy in the Treatment of IgA-dominant Infection-related Glomerulonephritis

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Abstract:
A 51-year-old Japanese man who experienced colon cancer recurrence following primary and metastatic lesion resection was hospitalized due to facial cellulitis with febrile neutropenia and purpura on his lower extremities after chemotherapy. It was complicated by rapidly progressive glomerulonephritis. He was diagnosed with immunoglobulin A (IgA)-dominant endocapillary proliferative glomerulonephritis based on kidney histology. His glomeruli were positive for the nephritis-associated plasmin receptor, plasmin activity and galactose-deficient IgA1 (Gd-IgA1). A skin biopsy immunofluorescence study revealed IgA deposition within perivascular regions but no Gd-IgA1 deposition. The final diagnosis was IgA-dominant infection-related glomerulonephritis (IRGN). The patient’s renal function returned to normal after receiving immunosuppressive therapy that consisted of a glucocorticoid and a cyclophosphamide. Immunosuppressive therapy should be considered in cases of IRGN if the patient’s infection is completely under control.

Key words: galactose-deficient IgA1, infection-related glomerulonephritis, immunosuppressive therapy, nephritis-associated plasmin receptor (NAPlr)

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Introduction
Immunoglobulin A nephropathy (IgAN) is the most common type of glomerulonephritis globally (1). In adults, the treatment for IgAN, particularly acute kidney injury and massive proteinuria, is glucocorticoid therapy (2). Some cases of IgAN have been associated with infectious triggers, such as tonsillitis. Infection-related glomerulonephritis (IRGN) treatment typically addresses the infection, but the use of immunosuppressive therapy is controversial (3). Some cases of IgA-dominant IRGN have been associated with staphylococcal infection (4). However, the optimal treatment for IgA-dominant IRGN remains unclear.

We herein report a case of severe IgA-dominant IRGN diagnosed based on positive staining for the nephritis-associated plasmin receptor (NAPlr) and the presence of plasmin activity within a frozen kidney biopsy section. The patient recovered after immunosuppressive therapy with glucocorticoid and cyclophosphamide.

Case Report
A 51-year-old Japanese man who experienced colon cancer recurrence following resection of the primary and metastatic lesions was hospitalized due to febrile neutropenia (FN) after undergoing 27-course chemotherapy (fluorouracil, irinotecan, calcium levofofinate). The patient had experienced hypertension, hyperuricemia, and asthma, but not kidney disease.
On a physical examination, the cause of FN in the patient was determined to be a bacterial infection, which manifested as an acne-like rash that was aggravated by sunburn (Fig. 1a). A total of seven blood cultures were negative. The patient’s general condition recovered after treatment with antibiotics (piperacillin-tazobactam for seven days and vancomycin for three days). However, he rapidly developed renal dysfunction (serum creatinine level: 2.43 mg/dL), hematuria (>100/high-power field), and proteinuria (6.4 g/day), and the patient had decreased serum complement 3 levels (C3: 59 mg/dL) on the ninth day post-admission. Furthermore, his serum IgA level (423 mg/dL) was high. Other serum complement and immunoglobulin levels were within the normal ranges (IgG: 880 mg/dL, IgM: 24 mg/dL, and C4: 26.8 mg/dL).

A kidney biopsy was performed on day 13 post-admission. Light microscopy revealed diffuse endocapillary hypercellularity within glomeruli and focal infiltration of inflammatory cells in both tubules and the interstitium (Fig. 2a, b). Immunofluorescence (IF) revealed strongly positive C3 and IgA staining in the mesangial and capillary areas. Furthermore, C3 staining produced a star-like pattern. Similar to IgA staining, galactose-deficient IgA1 (Gd-IgA1) staining using formalin-fixed paraffin-embedded section was

![Figure 1. Photographs of the patient. Images of the patient’s face and left legs are shown in a and b, respectively.](image)

![Figure 2. Kidney biopsy findings. Periodic acid-Schiff staining viewed via light microscopy (a, b). Glomerulus revealed endocapillary proliferation. (a) Interstitium and tubules showed inflammatory cells. (b) Electron microscopy showing electron-dense deposits mainly in the mesangial and subendothelial areas as well as the subepithelial area are shown (c, d).](image)
positive (Fig. 3a-c). Tests for IgG, IgM, and C1q were negative. Electron microscopy revealed electron-dense deposits mainly within subendothelial and mesangial lesions. In addition, some hump-shaped subepithelial deposits were also observed (Fig. 2c-d).

A further investigation revealed the presence of NAPIr and plasmin activity in the glomeruli of a frozen section (Fig. 3d, e). Accordingly, a histological diagnosis of IgA-dominant IRGN was made. On day 16, the patient again developed a fever, and his laboratory data were indicative of a high-level inflammatory response. Simultaneously, palpable purpura appeared on both of his lower legs (Fig. 1b). A skin biopsy was performed, which revealed no inflammatory cell infiltration suggesting vasculitis on light microscopy. IF revealed IgA and C3, but not Gd-IgA1, deposition within perivascular regions (Fig. 4). Skin histological findings indicated that IgA cutaneous vasculopathy was present, secondary to his infection.

The patient’s clinical course is shown in Fig. 5. His clinical symptoms, including his acne-like rash and fever, improved. To treat IRGN, antibiotics (cephazolin administered for ten days) were re-administered. However, despite treatment, the patient’s serum creatinine level increased to 5.12 mg/dL, and his C reactive protein (CRP) level did not decrease. Therefore, we administered immunosuppressive therapy, which included 3 days of 500 mg methylprednisolone administration daily via pulse IV, followed by oral prednisolone (0.6 mg per body weight) and cyclosporine (50 mg per day). The patient’s renal function did not improve based on the measured serum creatinine levels, which increased to 6.21 mg/dL. Therefore, the cyclosporine administration was terminated. Considering the patient’s worsening kidney function, we chose to administer intermittent intravenous cyclophosphamide (250 mg every 2-4 weeks). The patient’s CRP level then decreased, his renal function gradually improved, and his serum creatinine level reached 3.00 mg/dL after undergoing 2 courses of intravenous cyclophosphamide upon discharge. His serum creatinine level finally normalized at 1.21 mg/dL, which was similar to the level measured before hospitalization.

**Figure 3.** Immunofluorescence imaging. IgA (a), C3 (b), Gd-IgA1 (c) and merged images of NAPIr (green) and C3 (red) (d) in the glomerulus are shown. *In situ* zymography using a plasmin-sensitive synthetic substrate revealing plasmin activity in the segmental positive portion of the glomerulus is shown (e).

**Discussion**

We presented a case of IgA-dominant IRGN induced by an acne-causing skin infection that occurred while the patient was undergoing chemotherapy for colon cancer. His condition improved after aggressive immunosuppressive therapy was administered. The infectious etiology of the condition was confirmed clinically (low complement levels and facial images) as well as via a histological examination of the kidney biopsy specimen (positive NAPIr, plasmin activity, and Gd-IgA1 staining). The rate of skin infection in IRGN due to *Staphylococcus* has been reported to be as high as 20-30% (5). Both glomerular deposition of NAPIr and plasmin activity have been reported to occur due to *Staphylococcus*, *Streptococcus pneumoniae*, *Aggregatibacter actinomycetemcomitans*, and *Mycoplasma pneumoniae* infections (6-9). Therefore, NAPIr is an essential marker of IRGN.

Various IF patterns of IRGN were observed in the present
Figure 4. Skin biopsy findings. Hematoxylin and Eosin staining showing inconspicuous inflammatory cells. (a) Immunofluorescence staining images revealing IgA (b), perivascular C3 (c), and the absence of Gd-IgA1 (d) deposition are shown.

Figure 5. The clinical course of the patient. After prednisolone and cyclophosphamide initiation, serum creatinine level recovery and proteinuria were observed. CRP: C-reactive protein, mPSL: methylprednisolone, PSL: prednisolone, P/T: piperacillin-tazobactam, VCM: vancomycin

case. IgA-dominant glomerulonephritis has often been observed in *Staphylococcus*-associated IRGN (10, 11). The pathogenesis of IgAN has been associated with Gd-IgA1 (12). Furthermore, staining has revealed the presence of Gd-IgA1 in primary and secondary IgAN associated with *Staphylococcus* infection and IgA vasculitis with nephritis
(IgA-VN) (13, 14). Recently, we reported a case of IgA-dominant IRGN in which glomerular staining was positive for NAPlr and Gd-IgA1. The patient also had high titers of serum Gd-IgA1 (15). In addition, some patients with IgA-VN also were positive for NAPlr and plasmin activity via glomerular staining (16). In the unique and informative case presented here, the patient suffered from IgA-IRGN and was positive for NAPlr and Gd-IgA1 on histological staining.

For patients with IRGN, antibiotic administration and supportive therapy are standard treatments. In patients with endocarditis-related Staphylococcus IRGN, immunosuppressive therapy reportedly fails to improve the renal recovery and increases the mortality (6). However, IgA-dominant IRGN and infection-induced IgA-VN treatments remain controversial. IgA-dominant IRGN has a poor prognosis, with only about 20% of patients attaining a full recovery of their renal function (11). A previous patient with NAPlr-positive IgA-IRGN did not respond to high-dose glucocorticoid treatment, and required hemodialysis (15). Furthermore, NAPlr-positive IgA-VN has been shown to be improved by a combination treatment regimen that consists of prednisolone, cyclophosphamide, dipyridamole, and warfarin, as well as three sessions of plasma exchange (16). In the present case, the pathological findings revealed an infectious trigger of IgA-dominant IRGN. Antibiotic therapy was initially prescribed but was followed by a dramatic deterioration in the renal function. After confirming the absence of active infection, glucocorticoid and cyclophosphamide immunosuppressive therapy was administered, and the renal function of the patient normalized. Therefore, aggressive immunosuppressive therapy may be effective against IgA-dominant IRGN with NAPlr.

In conclusion, the patient described was determined to have IgA-dominant IRGN induced by a skin infection, which was accompanied by rapid renal dysfunction and decreased serum levels of C3. The patient was diagnosed with IgA-dominant IRGN due to a skin infection based on his clinical and pathological features, and positive NAPlr, plasmin activity and Gd-IgA1 staining. In cases involving renal function deterioration, immunosuppressive therapy should be considered, even in IRGN, while paying careful attention to infection control.

Informed consent was obtained from the patient.

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

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