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【 CASE REPORT 】

# Successful Treatment of IgA Vasculitis Complicated with Bowel Perforation and Crescentic Glomerulonephritis by Combination Therapy of Glucocorticoid, Cyclosporine and Factor XIII Replacement

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**Abstract:**
We report the findings of an 18-year-old boy with immunoglobulin A vasculitis (IgAV) complicated with bowel perforation and nephritis. He presented with abdominal pain, arthralgia and palpable purpura. Massive proteinuria developed during his clinical course. The patient was treated successfully using combination therapy of glucocorticoid (GC), cyclosporine (CYA) and factor XIII (F XIII) replacement. A standard treatment strategy for severe IgAV patients has not been established due to its rarity. Combination therapy using GC, CYA and F XIII replacement should be considered for severe IgAV patients.

**Key words:** IgA vasculitis, Henoch-Schönlein purpura, cyclosporine, coagulation factor XIII, bowel perforation

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## Introduction

Immunoglobulin A vasculitis (IgAV), previously known as Henoch-Schönlein purpura, is a systemic disease affecting small vessels with IgA deposits (1). The pathogenesis of the disease remains unknown. The estimated annual incidence of IgAV in children is 20.4 per 100,000, occurring most frequently between 4 and 6 years of age (2). Generally, IgAV is self-limiting, and common clinical manifestations include cutaneous purpura, arthralgia, abdominal pain and mild renal involvement. However, serious organ involvement, such as crescentic glomerulonephritis, intussusception and gastrointestinal perforation, can develop. Although the frequency of IgAV decreases with age (3), an older onset age (>10 years of age) has been identified as a factor associated with nephritis, significant proteinuria and relapse (4). Furthermore, adult patients require more aggressive therapy than children (4, 5). No treatment strategy for these severe cases has been established (6, 7).

We herein report an adolescent case of IgAV with focal crescentic glomerulonephritis and small bowel perforation successfully treated with nonsurgical management by combination therapy of glucocorticoid (GC), cyclosporine (CYA) and factor XIII (F XIII) replacement.

## Case Report

An 18-year-old boy with no remarkable medical history was referred to a private clinic with colicky abdominal pain. Approximately two weeks before the presentation, he noted a purpuric rash on his lower extremities and bilateral knee pain without a preceding infection. Abdominal computed tomography (CT) revealed extraluminal air, small bowel wall thickening and mild ascites (Fig. 1). The patient was diagnosed with inflammatory bowel disease and treated with intravenous methylprednisolone (IVMP) at a dose of 120 mg per day for 2 days. However, the abdominal pain persisted despite this treatment, and he was transferred to our hospital.

On admission to our hospital, his blood pressure was 131/67 mmHg, pulse rate was 84 beats per minute, and body

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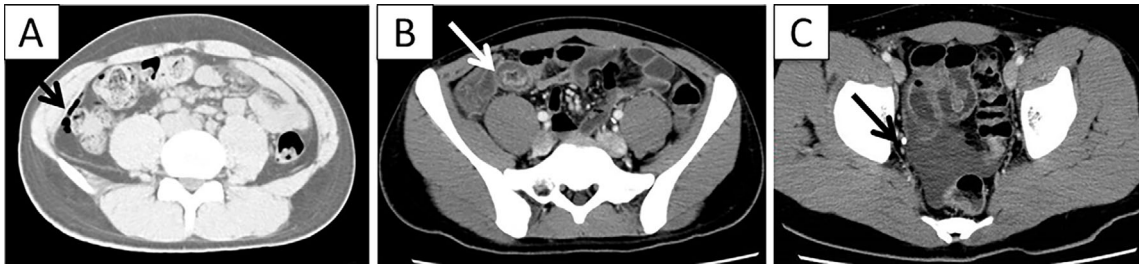


**Figure 1.** **Enhanced abdominal CT at the previous clinic. (A) extraluminal air (arrow), (B) small bowel wall thickening (arrow), (C) ascites (arrow).**

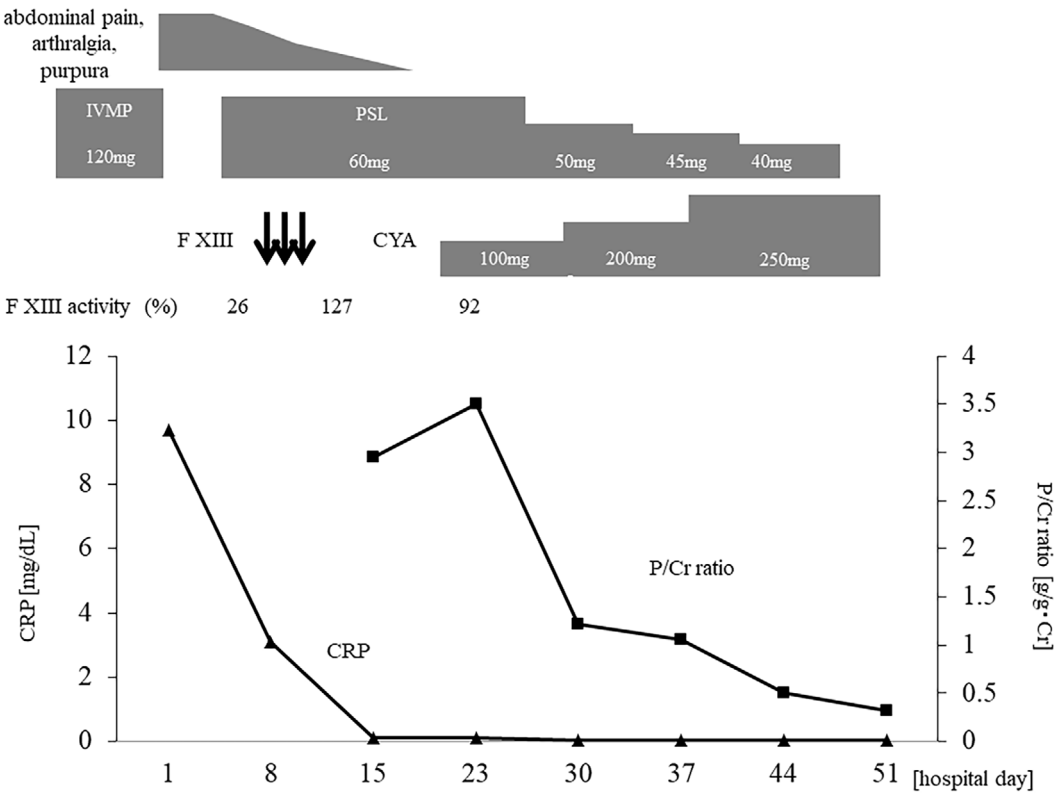


**Figure 2.** **The clinical course of the patient. CYA: cyclosporine, CRP: C-reactive protein, F XIII: factor XIII, IVMP: intravenous methylprednisolone, PSL: prednisolone, P/Cr ratio: protein/creatinine ratio**

temperature was 37.4℃. No abnormal respiratory sounds or heart murmurs were auscultated. An abdominal examination showed mild distension and moderate rebound tenderness at the umbilical region. The skin and joints were normal at the time of the examination. The laboratory results showed that the inflammatory responses were increased [C-reactive protein (CRP): 9.69 mg/dL and erythrocyte sedimentation rate: 17 mm/hr]. A complete blood cell count showed an increased white blood cell count of 11,800/μL (neutrophils: 91.9%, lymphocytes: 3.4% and monocytes: 3.0%). Serum albumin was decreased to 2.2 g/dL. His liver and renal functions were within normal ranges. Serum IgA was increased to 165 mg/dL, while no increases in other immunoglobulins were observed. The plasma level of coagulation F XIII activity was decreased to 26%. Antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibodies (ANCA) and cytoplasmic ANCA were negative. The qualitative measurement of urine revealed proteinuria (1+) without hematuria. Abdominal CT was immediately re-performed, but the findings were similar to these of the previous clinic, and chest CT showed normal findings. After consultation with a surgeon, we decided that there was no need for emergency surgery.

The clinical course of the patient is shown in Fig. 2. On the day of admission, IVMP was discontinued. On hospital day 2, he developed arthralgia and bilateral edema, followed by palpable purpura on the upper and lower extremities (Fig. 3). Although a histopathological examination was not performed, the patient was diagnosed with IgAV accompanied by purpura, abdominal pain and arthralgia, according to the 2010 revised EULAR/PRINTO/PRES criteria (8). On hospital day 5, prednisolone (PSL) was administered at a

dose of 60 mg with F XIII substitution at a dose of 20 mL for 3 days. On hospital day 9, the abdominal pain, arthralgia and palpable purpura were resolved. On hospital day 12, the F XIII activity was increased to 127%. On hospital day 15, CRP also decreased to within normal levels. After the treatment, colonoscopy showed normal findings. However, a urine analysis indicated proteinuria (3.76 g/day). A renal biopsy revealed proliferative glomerulonephritis with crescent formation in 53% (19/36) of glomeruli (Fig. 4A). Immunofluorescence microscopy showed mesangial IgA deposits and trace deposition of IgG, IgM and C3, which was consistent with IgAV (Fig. 4B).

On hospital day 23, CYA was given at a dose of 100 mg. The proteinuria decreased to less than 0.5 g/day on hospital day 43, and he was discharged without any clinical symp-

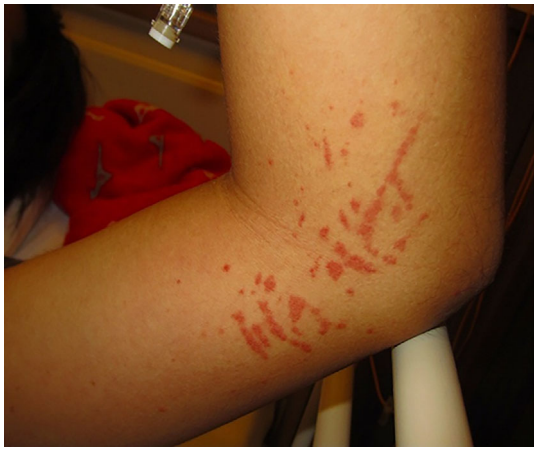

**Figure 3.** **Palpable purpura on the left brachium.**

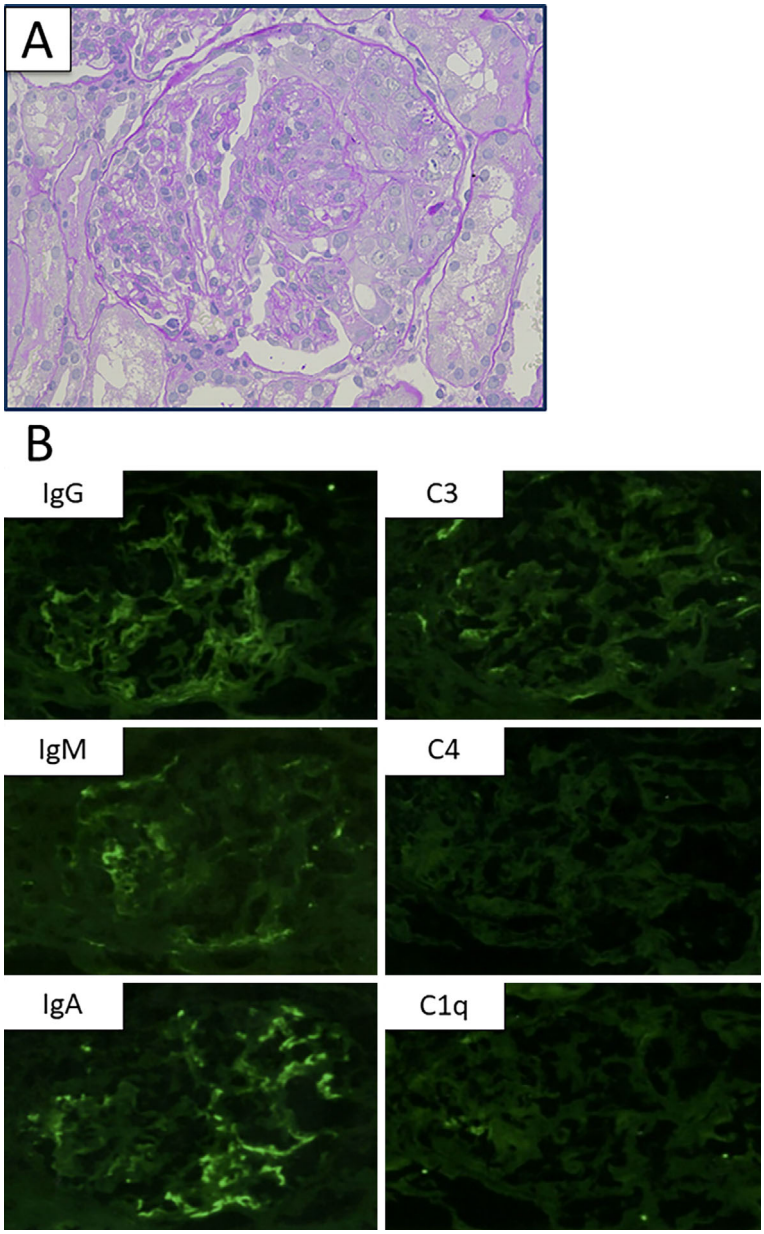


**Figure 4.** **The pathological findings of the renal biopsy. (A) Proliferative glomerulonephritis with crescent formation (periodic acid-Schiff's reagent stain, ×400). (B) Mesangial IgA deposition and trace deposition of IgG, IgM, and C3 (immunofluorescent staining) (×400).**

**Table.** **The Characteristics of Cases of IgA Vasculitis Complicated with Bowel Perforation.**

| Case No. | Ref. No. | Age | Sex | Location | Other clinical manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 11 | 43 | F | ileum, cecum and ascending colon | purpura, arthralgia, renal involvement | surgery, GC, CPA | alive |
| 2 | 12 | 4.5 | M | ileum | unknown | surgery | dead |
| 3 | 13 | 60 | M | ileum | purpura, arthralgia, renal involvement | surgery, GC | dead |
| 4 | 14 | 60 | M | jejunum | purpura, arthralgia | surgery, GC | alive |
| 5 | 14 | 60 | M | small intestine | purpura, arthralgia | surgery | dead |
| 6 | 15 | 7 | M | appendix | purpura, arthralgia, renal involvement | surgery, GC | alive |
| 7 | 16 | 12 | M | jejunum and ileum | purpura, arthralgia, renal involvement, cardiac tamponade, neurological symptom | surgery, GC, F XIII | alive |
| 8 | 17 | 42 | F | ileum | purpura, myalgia, renal involvement | surgery, GC, CPA | alive |
| 9 | 18 | 52 | M | jejunum and ileum | purpura, arthralgia, renal involvement | surgery, GC | dead |
| 10 | 19 | 65 | M | small intestine | purpura, renal involvement | surgery, GC, CPA | alive |
| 11 | 20 | 5 | F | ileum | purpura, renal involvement, cerebral hemorrhage | surgery, γ-globulin | dead |
| 12 | 21 | 4 | M | ileum | purpura | surgery, GC, γ-globulin | alive |
| 13 | 22 | 5 | M | ileum | purpura | surgery, GC | alive |
| 14 | 23 | 39 | M | ileum | purpura, arthralgia | surgery, GC | alive |
| 15 | 24 | 5 | M | ileum | purpura, arthralgia, intussusception | surgery, GC, F XIII | alive |
| 16 | 25 | 13 | M | jejunum, ileum and cecum | purpura, renal involvement | surgery, GC, CPA | dead |
| 17 | 26 | 7 | M | ileum | purpura, arthralgia, renal involvement | surgery, GC | alive |
| 18 | 26 | 11 | M | jejunum and ileum | purpura, brain hemorrhage | surgery, GC | dead |
| 19 | 27 | 78 | M | rectosigmoid colon | purpura, arthralgia, renal involvement | surgery, GC, CPA | dead |
| 20 | 28 | 5 | M | ileum | purpura, intussusception | surgery, GC | alive |
| 21 | 29 | 5 | M | ileum | purpura, arthralgia, intussusception | surgery, GC | alive |
| 22 | Our case | 18 | M | jejunum | purpura, arthralgia, renal involvement | GC, CYA, F XIII | alive |

M: male, F: female, GC: glucocorticoid, F XIII: factor XIII, CPA: cyclophosphamide, CYA: cyclosporine

toms. Seven months after presentation, he was treated with PSL 10 mg and CYA 200 mg.

## Discussion

Gastrointestinal involvement occurs in approximately two-thirds of children with IgAV and usually is not severe. However, some patients develop serious complications, such as intestinal intussusception (3.5%) and massive hemorrhaging (5%) (9). Bowel perforation is a particularly rare complication. Of the 261 patients with IgAV, 151 (58%) had abdominal pain, and only 1 case of bowel perforation was reported (10). Bissonnette et al. (11) found colonic IgA deposits and fibrinoid necrosis of the vessel in a patient with colonic perforation as a complication of IgAV. It is suggested that bowel perforation results from vasculitis leading to ischemic necrosis.

A review of the literature on PubMed concerning IgAV-related bowel perforation in English or Japanese is shown in Table (11-29). A total of 22 cases, including the present case, were identified. The mean age of patients was 27.3 years, and most of the patients were men. Patients with an older age at the onset (4) and men (30) reportedly exhibited the most severe cases. The most common site of perforation was the ileum followed by the jejunum. Eight patients (36.4%) died. Those that died tended to be older than those who survived (mean ± standard deviation age 35.4±30.0 vs. 22.6±22.3 years) and tended to have more renal involvement (62.5% vs. 50%) than those that survived. Regarding treatment, surgery was performed in all cases except for our case. All three patients treated without GC died; in contrast, all three patients treated with F XIII survived. Three out of five patients treated with cyclophosphamide (CPA) survived. The present case was the only one treated with CYA.

CPA is widely used to treat various types of vasculitis. However, the efficacy of CPA for IgAV is controversial. A non-randomized study showed that none of the 17 patients treated with CPA and GC, compared to 4 of 20 treated with GC alone, had persistent nephropathy (31). However, other randomized control trials reported that neither CPA alone (32) nor its concomitant use with GC (33) showed any benefit for patients with IgAV with nephritis. In con-

trast, several case studies have shown the efficacy of CYA in steroid-refractory patients (34-37). In addition, CYA and GC in combination ameliorated the histological progression in severe IgAV patients with nephritis (38). Jauhola et al. (39) conducted a randomized study comparing the efficacy of CYA alone with that of methylprednisolone in IgAV patients with severe nephritis. The results showed that CYA-treated patients achieved resolution of proteinuria faster than GC-treated patients, and all CYA-treated patients responded to the treatment with no need for additional therapy. In addition, CPA carries an increased risk of malignancy and gonadal toxicity and is associated with severe enteritis (40). Therefore, CYA may be another choice for treating severe IgAV. In the present patient, combination therapy using GC, CYA and factor XIII replacement was effective for resolving IgAV with bowel perforation and nephritis. This is the first reported case successfully treated with this combination for IgAV.

F XIII catalyzes the cross-linking of fibrin and plays an important role in clot formation and wound healing. Decreases in the F XIII level were correlated with an increased severity of complications, such as nephritis and gastrointestinal involvement, and an increase in the F XIII level was associated with recovery (41). It has been suggested that F XIII may be degraded by proteases of leukocytes or consumed around affected vessels, leading to the decreased F XIII activity in IgAV patients (42). A comparative controlled study confirmed the efficacy of F XIII substitution for IgAV patients (42). There have also been several reports of treating severe gastrointestinal involvement using F XIII replacement (43, 44). Table shows that all three patients treated with F XIII survived.

In conclusion, we encountered a rare case of IgAV with bowel perforation and glomerulonephritis. We were able to achieve a successful outcome with the use of combination therapy including GC, CYA and F XIII replacement. Although a standard treatment strategy has not been established due to the rarity of this condition, this combination therapy may be an effective option for treating severe manifestations in IgAV.

**Author's disclosure of potential Conflicts of Interest (COI).**
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