A Case of IgA-related Enteropathy Complicated with Gastrointestinal Bleeding and Progressive IgA Nephropathy: A Possible Variant Henoch-Schönlein Purpura?

Shoko Nakamura¹, Tadakazu Hisamatsu¹, Jun Kikuchi¹, Masayuki Adachi¹, Yoshiyuki Yamagishi¹, Hiroyuki Imaeda², Naoki Hosoe¹, Makoto Naganuma¹, Hirotoshi Ebinuma¹, Susumu Okamoto¹, Takanori Kanai¹, Haruhiko Ogata³, Hironari Hanaoka³, Yoshiaki Furuya¹, Yoshinaga Kawano⁴, Kanako Bokuda⁴, Hiroyuki Sasamura⁴, Hiroshi Uchida⁵, Takashi Endo⁵, Akinori Hashiguchi⁶, Kaori Kameyama⁶, Makio Mukai⁶ and Toshifumi Hibi¹

Abstract

Here, we report an adult patient with IgA-related enteropathy complicated with massive intestinal bleeding and acute renal failure, but without skin lesions. Surgical resection of the small intestine and steroid pulse therapy was performed. Histopathology revealed significant deposition of IgA and C3 in the small vessels of the intestine and the kidney mesangium. Although skin purpura was absent, the histopathology and clinical manifestations suggested that the pathophysiology was similar to Henoch-Schönlein purpura (HSP), implying IgA-related enteropathy as a subclass of HSP. Retrospective analysis indicates that terminal ileum lesions may be a poor prognostic indicator.

Key words: IgA related enteropathy, gastrointestinal bleeding, crescentic glomerulonephritis, Henoch-Schönlein purpura, steroid pulse therapy

(Inter Med 49: 1755-1761, 2010)
(DOI: 10.2169/internalmedicine.49.3678)

Introduction

Henoch-Schönlein purpura (HSP) is characterized as a systemic leukocytoclastic vasculitis of the small vessels with the deposition of IgA. The clinical manifestations usually include palpable purpura, arthralgia, nephritis and abdominal pain. In particular, renal lesions characterized by IgA nephropathy are the main cause of a poor prognosis and mortality in these patients (1). HSP usually affects children between 3 and 15 years old, while it is less common in adults. In adult cases, HSP typically represents more severe clinical manifestations, such as a severe renal dysfunction. Therefore, adult patients with HSP often require more aggressive therapy, such as steroid pulse therapy and cytotoxic agents (2). In addition, gastrointestinal lesions are frequently observed. Guaiac-positive stools are found in up to 56 percent of HSP patients, however massive gastrointestinal hemorrhaging is rare (3).

We report here an adult patient with IgA enteropathy accompanied by a severe renal lesion and massive gastrointestinal hemorrhaging who underwent small intestinal resection.

¹The Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo. ²The Center for Diagnostic and Therapeutic Endoscopy, School of Medicine, Keio University, Tokyo. ³The Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo. ⁴The Division of Nephrology and Endocrinology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo. ⁵The Department of Surgery, School of Medicine, Keio University, Tokyo and ⁶Division of Diagnostic Pathology, School of Medicine, Keio University, Tokyo

Received for publication March 19, 2010; Accepted for publication April 26, 2010
Correspondence to Dr. Toshifumi Hibi, thibi@sc.itc.keio.ac.jp
and methylprednisolone pulse therapy. Immunohistochemistry clearly demonstrated the deposition of IgA in the small vessels of the intestinal mucosa and kidney mesangium. There are few cases identified with IgA deposition in gastrointestinal mucosa. Therefore, the present case is important as it suggests that IgA-related enteropathy is involved in HSP.

### Case Report

A 61-year-old Japanese man was admitted to hospital because of high grade fever and intermittent abdominal pain. The computer tomography (CT) scan showed thickening of diarrheagenic Escherichia coli was positive. So, the patient was diagnosed with infectious colitis and was treated with antibiotics. However, there was no significant improvement of the abdominal symptoms and bloody diarrhea was observed. He also showed gross hematuria, proteinuria and arthralgias after admission. Three weeks later, since the clinical findings and blood examination revealed acute renal failure, he was transferred to our hospital.

He had no past history of diabetes mellitus or coronary artery disease, but smoked twenty cigarettes per day. In his family history, his mother had diabetes mellitus and coronary artery disease, and his brother had acute myocardial infarction.

When he was admitted to our hospital, he had a normal temperature of 36.8°C, a pulse of 95/min and a blood pressure of 160/90 mmHg. Physical examination revealed abdominal tenderness at the umbilical region without rebound tenderness. The respiratory sounds were weak at the lower area of the bilateral lungs. He had peripheral edema on the lower extremities, but had no palpable purpura or skin rash. There were also aphthoid lesions in the mouth.

The laboratory findings are shown in Table 1. His urinary analysis showed massive proteinuria (3.49 g daily) and hematuria with a granular cast. Creatinine clearance was 13.2 mL/min and the serum creatinine level was 3.1 mg/dL, which led to a diagnosis of nephrotic syndrome. Other laboratory findings showed that the white blood cell count was 26,000/mm³ (92.0% neutrophils), total serum protein was 4.7 g/dL, serum CRP at 10.22 mg/dL, elevation of D-dimer and fibrin degradation products (FDP), decreased coagulation factor XIII activity, liver dysfunction and the absence of MPO-ANCA and PR3-ANCA.

After admission, the serum creatinine level rose rapidly and the abdominal pain and hematochezia became more serious. A CT scan performed in our hospital revealed a massive pleural effusion and ascites (Fig. 1A) and swelling of the terminal ileum (Fig. 1B), but no lung lesions. A lower intestinal endoscopy showed various forms of multiple ulcers in the terminal ileum (Fig. 2). Since we considered this as a case of systemic vasculitis complicated with rapidly
Figure 1. Computed tomography (CT) on the first day after admission. CT showed pleural effusion and ascites (A) and swelling of the terminal ileum (arrow, B).

Figure 2. Total colonoscopy showed mucosal edema and multiple ulcers exhibiting various forms in the terminal ileum.

progressive glomerulonephritis (RPGN) and small intestinal lesions, we performed a percutaneous renal biopsy to evaluate the renal lesions on day 10 of hospitalization. Histology by hematoxylin and eosin staining indicated mesangial proliferation and severe crescentic glomerulonephritis (Fig. 3A). Masson trichrome and PAM staining clearly showed the deposition of the immune complexes (Fig. 3B and C). Immunofluorescence studies revealed the intense granular deposition of IgA and C3 predominantly in the glomerular mesangium (Fig. 3D and E). Thus, the histopathology of the renal biopsy revealed the IgA-associated nephropathy, resulting in rapidly progressive renal failure. High-dose methylprednisolone therapy (1,000 mg/day for 3 days) was started, followed by prednisolone (PSL) at an initial dose of 60 mg/day.

Although the renal function and epigastralgia were gradually improving with steroid therapy, the hematochezia continued. We performed a capsule endoscopy and upper gastrointestinal endoscopy to evaluate the bleeding sites and revealed active bleeding from the ulcers of the terminal ileum (Fig. 4A and B). On day 21 of hospitalization, we performed an anal approach small intestinal endoscopy due to sudden bleeding from the intestine. This revealed massive bleeding at the terminal ileum, but the bleeding site was not identified. Accordingly, an angiography was performed, identifying extravasation at the ileum branch of the superior mesenteric artery marked by the coils (Fig. 5A and B). According to the information obtained from the angiography, a laparoscopic ileal resection was immediately performed. The histological findings of the resected ileum indicated a mucosal ulceration with a fibrinoid deposit on the wall of the small artery (Fig. 6A and B). Immunostaining studies revealed the intense deposition of IgA, C3 and C4, predominantly in the submucosal vascular wall (Fig. 6C, D and E).

Through the histological findings of the kidney and ileum, we made a diagnosis of IgA-related enteropathy and nephropathy. The hematochezia was improving and the serum creatinine was also preserved at a level of 2.0 mg/dL after the operation. The oral prednisolone was tapered gradually to 15 mg/day and he was discharged after 56 days (Fig. 7).

Discussion

HSP is a systemic vasculitis disease of the small vessels associated with the deposition of immune complexes containing IgA. HSP is characterized as a childhood onset disease. According to the American College of Rheumatology, there are four main criteria for the diagnosis of HSP, including an age of less than or equal to 20 years at disease onset, palpable purpura, acute abdominal pain and a biopsy showing granulocytes in the walls of small arterioles or venules, known as “leukoclastic vasculitis”. In these criteria, the existence of palpable purpura is not a mandatory clinical finding (4). On the other hand, the pediatric consensus criteria, established by the European League against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PReS) in 2005, included palpable purpura as an essential clinical finding and one or more of the following clinical findings: diffuse abdominal pain, arthritis or arthralgia, and any biopsy with predominant IgA deposition (5).

In the present case, there were two main clinical findings, namely gastrointestinal bleeding and RPGN. However, we could not find any palpable purpura during his clinical...
course. Differential diagnoses were systemic vasculitis, like Wegener granulomatosis and MPO-ANCA-related vasculitis in addition to HSP. Histopathological analysis of the renal biopsy and surgically resected ileum identified IgA deposition in both organs, leading us to the conclusion that he suffered from HSP-like vasculitis even though he did not show any palpable purpura.

Pillebout et al described in a retrospective review that the clinical findings of adult HSP include a high prevalence of palpable purpura (96%) and gastrointestinal symptoms (48%) (6). On the other hand, there was a case report of HSP in a 6-year-old girl with severe gastrointestinal lesions without purpura, similar to our case (7). Considering the pathophysiology, IgA deposition may involve several organs as well as skin lesions. On this issue, we propose the clinical entity of systemic vasculitis caused by IgA deposition and that HSP may be a part of this clinical entity with skin lesions. Consistent with our proposal, Kato et al proposed a new syndrome characterized as IgA enteropathy including abdominal pain and multiple endoscopic lesions, predominantly in the descending duodenum without palpable purpura (8). They examined the gastroduodenal biopsy samples of nine patients without any purpura and found IgA deposition in the capillary wall of the intestinal mucosa in six pa-
Angiography showed the extravasation in the ileum branch of the superior mesenteric artery (arrow, A) and it was marked by the coil (arrow, B).

The histological findings of the resected ileum indicated a mucosal ulceration with a fibrinoid deposit on the wall of the submucosal small artery (arrows, A and B). Both figures were stained by Hematoxylin and Eosin staining; original magnification was ×10 and ×100. Immunostaining studies revealed the intense deposition of complement 3 (C3) (C, ×40), complement 4 (C4) (D, ×40) and immunoglobulin A (IgA) (E, ×40), predominantly in the submucosal vascular wall.

The present patient suffered from life-threatening gastrointestinal bleeding due to multiple ulcers of the terminal ileum. In patients with HSP, morbidity in the early stage is the result of gastrointestinal problems, such as intussusception and bowel bleeding. The gastrointestinal lesions occur in about half of the adult patients. Serious bleeding, requiring transfusion or surgery or leading to death, was shown in 11% of the patients, in a retrospective review of 250 French adult patients. They concluded that further studies are needed to determine whether such patients are in fact a variant of HSP or IgA-related enteropathy.

They concluded that further studies are needed to determine whether such patients are in fact a variant of HSP or IgA-related enteropathy.

The present patient suffered from life-threatening gastrointestinal bleeding due to multiple ulcers of the terminal ileum. In patients with HSP, morbidity in the early stage is the result of gastrointestinal problems, such as intussusception and bowel bleeding. The gastrointestinal lesions occur in about half of the adult patients. Serious bleeding, requiring transfusion or surgery or leading to death, was shown in 11% of the patients, in a retrospective review of 250 French adult patients. They concluded that further studies are needed to determine whether such patients are in fact a variant of HSP or IgA-related enteropathy.

We summarized our case and fifteen other cases of adult onset HSP with gastrointestinal lesions in Japan between 2004 and 2009 (Table 2). Almost all of the cases had symptoms of renal insufficiency, gastrointestinal bleeding or arthralgia with skin rash. Four cases (25%), including the present case,
needed surgical resection of the small intestine due to life-threatening bleeding, fourteen cases (87.5%) were treated with PSL and two patients (12.5%) died. They were all of advanced age, indicating age as a risk factor for poor prog-
nosis in HSP. Moreover, it was characteristic that the four cases in need of surgery showed gastrointestinal lesions at the ileum or terminal ileum. These findings suggest the possibility that the gastrointestinal lesions in the terminal ileum or ileum may become the prognostic factor indicating the need for more intensive therapy including steroid therapy and surgical resection in adult onset HSP.

Regarding the prognosis of this patient, we have to mention the possibility of recurrence and the progression of renal dysfunction. Recurrence of HSP is reported in about one-third of cases in children (28). In adults, the outcome is relatively worse. With the long-term prognosis of adult onset HSP often prescribed by renal function. It has been reported that adult patients with HSP are at increased risk of progression from significant renal involvement to end-stage renal failure. Eleven % of adult patients reached end-stage renal failure, and 13% showed severe renal failure (CCR <30mL/min) at a median follow-up of 14.8 years (6).

Here, we report a case of adult onset IgA-related enteropathy with severe renal lesions, but not skin lesions. This case may raise doubts about the clinical entity of IgA-related vasculitis including HSP.

References