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Case report

Purpura-free small intestinal IgA vasculitis complicated by cytomegalovirus reactivation

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SUMMARY

IgA vasculitis (Henoch-Schönlein purpura) affects various organs, including the skin, gastrointestinal (GI) tract, joints and kidneys. Its clinical course typically consists of two phases: initial appearance of purpura and delayed onset of arthralgia, GI symptoms and haematuria. We report the case of an adult patient with IgA vasculitis of the small bowel, without skin involvement, complicated by cytomegalovirus (CMV) enteritis following prednisolone administration. Single-balloon enteroscopy revealed mucosal oedema, redness, erosions and transverse ulcers of the duodenum and jejunum. Jejunal biopsy specimens showed IgA deposition in the capillary walls. CMV reactivation was confirmed by PCR and immunostaining using jejunal biopsy specimens. This case report strongly suggests that adult patients with IgA vasculitis can present with isolated GI involvement, without characteristic skin purpura. Furthermore, CMV reactivation needs to be considered in patients with IgA vasculitis showing poor response to glucocorticoids.

BACKGROUND

IgA vasculitis, formerly known as Henoch-Schönlein purpura, is characterised by the deposition of IgA-immune complexes within small-vessel walls.¹ This disease can develop at any age, but it commonly affects children.²⁻³ IgA vasculitis is the most common systemic vasculitis in childhood, with an annual incidence of 3–26 per 100 000 children.^{4,5} In contrast, adult IgA vasculitis is extremely rare, with an annual incidence of 0.1–14 per 100 000 individuals.⁶ IgA vasculitis affects multiple organs, including the skin, joints, gastrointestinal (GI) tract and kidneys.⁷ Reflecting a wide variety of affected organs, patients with IgA vasculitis show various clinical symptoms such as fever, purpura, arthralgia, abdominal pain and haematuria. Purpura is observed in almost all paediatric patients⁸ and is reportedly the initial symptom of IgA vasculitis in approximately three-quarters of affected children.⁹ Thus, typically, patients with IgA vasculitis initially present with purpura, followed by the development of arthralgia, haematuria and GI-related symptoms within the following few days. Both typical clinical signs and histopathological detection of leucocytoclastic vasculitis associated with IgA deposition are used to establish the diagnosis of IgA vasculitis.¹ Glucocorticoids ameliorate GI-related symptoms, arthralgia and purpura in most patients with IgA vasculitis.

Diagnosing IgA vasculitis is easy when paediatric patients exhibit characteristic purpura and joint-related, GI-related and renal symptoms. However, clinicians may need to consider a possibility of IgA vasculitis, even in the absence of purpura, if any of these symptoms are present. A lack of skin involvement may make it difficult to diagnose this disease. Considering that the delayed diagnosis of IgA vasculitis may sometimes lead to serious complications such as intestinal obstruction, intussusception, intestinal perforation and massive bleeding, a prompt diagnosis is necessary.⁶ Here, we report a case of an adult patient with IgA vasculitis of the small bowel, without concurrent skin involvement. Interestingly, this patient also developed cytomegalovirus (CMV) enteritis after receiving glucocorticoid therapy. To the best of our knowledge, this is the first reported case of purpura-free, small intestinal IgA vasculitis, complicated by CMV reactivation, in an adult.

CASE PRESENTATION

A 68-year-old man, with no significant prior medical history, was admitted to our hospital after presenting with a 3-day history of abdominal pain, vomiting, diarrhoea and high fever (38.7°C). The bouts of vomiting and diarrhoea occurred several times a day. Physical abdominal examination revealed severe distention and tenderness.

INVESTIGATIONS

Laboratory findings revealed an elevated C-reactive protein level, along with leucocytosis (table 1). Biochemical tests revealed elevated levels of serum transaminases (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and creatine kinase). Abdominal CT showed thickening of the descending duodenal and jejunal walls, a finding that was consistent with the diagnosis of infectious gastroenteritis. Based on these data, we initially suspected infectious enteritis, and the patient was treated with antibiotics. However, he did not respond to bowel rest and antibiotic treatment. Thus, we considered the possibility of other diseases such as vasculitis, malignant lymphoma and malignant tumour since stool and blood cultures were negative for pathogenic microorganisms. To explore this possibility, we measured the serum concentrations of interleukin 2 receptor, carcinoembryonic antigen, carbohydrate antigen 19-9 and factor XIII activity levels. The soluble interleukin 2 receptor level was also elevated



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Table 1 Laboratory findings

Biochemistry		CBC		Others	
CRP	16.4 mg/dL	WBC	4080/ μ L	IgG	690 mg/dL
Na	133 mEq/L	RBC	404×10^4 / μ L	IgA	175 mg/dL
K	3.7 mEq/L	Hb	13.4 g/dL	IgM	24 mg/dL
Cl	100 mEq/L	Ht	37.70%	IgE	295 IU/mL
AST	131 IU/L	Plt	17.6×10^4 / μ L	RF	4 U/mL
ALT	69 IU/L	Neut	73.60%	C3	124 mg/dL
LDH	429 IU/L	Lymph	17.60%	C4	28 mg/dL
CK	2922 U/L	Mono	8.80%	CH50	82 U/mL
CKMB	11 U/L	Eosin	0.00%	sIL-2R	1988 U/mL
T-Bil	0.8 mg/dL	Baso	0.00%	CEA	1.6 ng/mL
TP	5.8 g/dL			CA19-9	3 U/mL
Alb	3.2 g/dL			ANA	Negative
BUN	43 mg/dL			MPO-ANCA	295 IU/mL
Cr	1.38 mg/dL			PR3-ANCA	24 IU/mL
				Blood coagulation factor XIII activity	37.00%

Alb, albumin; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; Baso, basophils; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; CA19-9, carbohydrate antigen 19–9; CBC, complete blood count; CEA, carcinoembryonic antigen; CH50, total hemolytic complement; CK, creatine kinase; CKMB, creatine kinase-myoglobin; Cl, chlorine; Cr, creatinine; CRP, C-reactive protein; Eosin, eosinophils; Hb, haemoglobin; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; Lymph, lymphocytes; MB, myoglobin; Mono, monocytes; MPO-ANCA, myeloperoxidase–antineutrophil cytoplasmic antibody; Na, sodium; Neut, neutrophils; Plt, platelets; PR3-ANCA, proteinase 3–antineutrophil cytoplasmic antibody; RBC, red blood cells; RF, rheumatoid factor; sIL-2R, soluble interleukin 2 receptor; T-Bil, total bilirubin; TP, total protein; WBC, white blood cells.

(1988 U/mL, normal range: 121–613 U/mL), whereas those of tumour markers were within the normal range. Serum factor XIII activity decreased to 37%. Contrast-enhanced abdominal CT imaging after antibiotic treatment revealed marked thickening of the small bowel wall originating from the duodenum to the proximal portion of the jejunum (figure 1A). Persistent high fever and abdominal pain, despite administration the antibiotic treatment, prompted us to examine the mucosa of the upper GI tract, including the jejunum, by balloon enteroscopy on the 11th day of hospitalisation. Mucosal oedema, redness, erosion and transverse ulcers were observed from the descending

portion of the duodenum to the proximal jejunum (figure 1B). Jejunal biopsy specimens obtained during the first single-balloon enteroscopy (SBE) procedure revealed destruction of the crypt architecture, massive infiltration of immune cells and mucosal haemorrhage (figure 2A). Moreover, IgA deposition in the capillary vessel walls and IgA-expressing plasma cells were visualised in the immunohistochemical analysis (figure 2B). IgA expression not only in the lamina propria immune cells but also in the capillary vessel walls (figure 2C) led us to consider the possibility of enteric IgA vasculitis as IgA deposition in capillary walls is a specific finding of this immune disorder.¹⁰ A significant decrease in serum factor XIII activity was also consistent with IgA vasculitis. Thus, this patient was diagnosed with solitary enteric IgA vasculitis and then treated with prednisolone (PSL). PCR using jejunal biopsy samples did not detect tuberculosis. A second SBE was performed 2 weeks after initiation of PSL treatment to re-examine the small intestinal mucosa. Persistent mucosal oedema, erosions and transverse ulcers were still present within the GI tract, extending from the descending duodenum to the proximal jejunum. In addition, large shallow ulcers had appeared in the jejunum (figure 3A). Histopathological examination of the jejunal biopsy specimens, obtained during the second SBE, showed massive infiltration of immune cells, IgA deposition within the capillary walls and accumulation of IgA-expressing plasma cells (figure 3B). In addition to these pathological findings, giant cells with inclusion bodies as well as CMV-positive cells, characteristic of IgA vasculitis, were also found in the jejunal biopsy specimens (figure 3C). We also detected blood leucocytes expressing CMV pp65 antigen (5/50 000; normal, 0). The response to PSL during the first 7 days was quite effective, similar to the response in most cases of IgA vasculitis; subsequently, the effect was lost. Such alterations in responses to PSL can be explained by the occurrence of CMV reactivation after PSL treatment. Thus, it is likely that CMV enteritis developed owing to immunosuppression by PSL. Simultaneous occurrence of IgA vasculitis and CMV enteritis was less likely, as the CMV immunostaining test performed on the first jejunum biopsy specimen had a negative result. These findings strongly suggest that

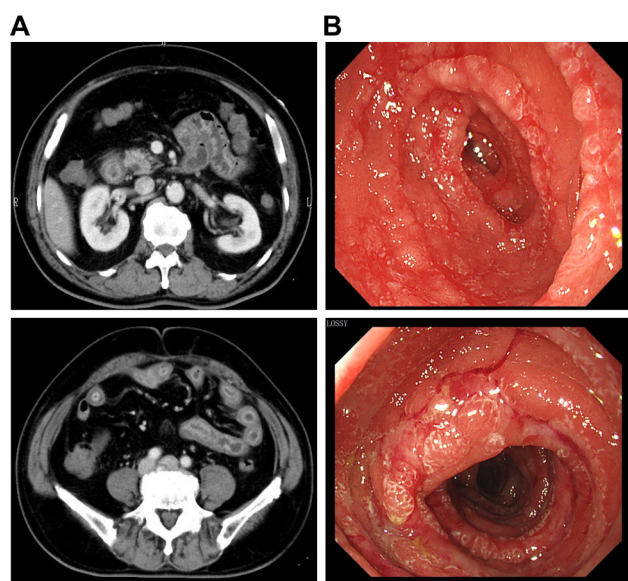


Figure 1 Endoscopic findings of the jejunal mucosa during single-balloon enteroscopy (SBE): (A) contrast-enhanced abdominal CT shows marked thickening of the descending duodenal (left) and proximal jejunal (right) walls. (B) SBE shows oedema, redness, erosions and transverse ulcers involving the duodenal (left) and jejunal (right) mucosae.

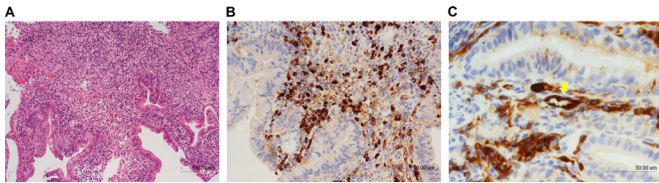


Figure 2 IgA deposition within the jejunal mucosal capillary walls: (A) histopathological examination of the jejunal mucosa shows destruction of crypt architecture, massive infiltration by immune cells and mucosal haemorrhage (H&E, 40× magnification); (B) immunohistochemical examination of a jejunal biopsy sample shows deposition of IgA within the capillary walls along with aggregated IgA-expressing plasma cells (IgA immunostaining, 40× magnification); (C) high-magnification image of immunohistochemical staining shows IgA deposition in the capillary vessel walls (yellow arrow) (IgA immunostaining, 80× magnification).

CMV reactivation had occurred after administration of high-dose PSL and that the abdominal symptoms had persisted owing to the development of CMV enteritis.

DIFFERENTIAL DIAGNOSIS

Considering the initial clinical presentation and investigation, the patient had been briefly considered to have infectious gastroenteritis, IgA vasculitis, eosinophilic gastroenteritis or CMV enteritis.

TREATMENT

The patient was initially treated with fluid replacement and antibiotics for suspected infectious gastroenteritis. After the histopathological diagnosis of IgA vasculitis following the first SBE, PSL (60 mg/kg) therapy was initiated. Ganciclovir (5 mg/kg two times per day) was added to the PSL treatment according to the findings of the subsequent (second) jejunal biopsy, which confirmed the occurrence of CMV enteritis. This led to symptom relief, and PSL was gradually tapered to a dose of 30 mg/day by discharge.

OUTCOME AND FOLLOW-UP

A marked improvement in abdominal symptoms was observed after initiation of ganciclovir. Blood leucocytes expressing CMV pp65 were no longer detected 2 weeks after initiation of antiviral therapy. The patient was discharged on the 53rd day of hospitalisation.

DISCUSSION

IgA vasculitis, formerly known as Henoch-Schönlein purpura, commonly affects children, and an adult onset is relatively rare.^{3,6} The typical clinical course of IgA vasculitis comprises two phases: ~75% of patients initially exhibit purpura and this is followed by arthralgia, GI symptoms and haematuria.⁹ Diagnosing IgA vasculitis is straightforward if a paediatric patient manifests sequential clinical signs. However, diagnosis of IgA vasculitis could be difficult in patients presenting only with GI symptoms. In this report, we describe the case of an adult with IgA vasculitis presenting with isolated involvement of the small intestine. We arrived at the diagnosis based on several investigative findings. First, mucosal oedema, redness, erosions and ulcers were found localised to the duodenal and proximal jejunal mucosae, both of which are GI regions known to be involved in this condition.¹¹ Second, serum factor XIII activity was found to be markedly decreased, which is considered indicative of IgA vasculitis.¹² Third, massive infiltration of immune cells and

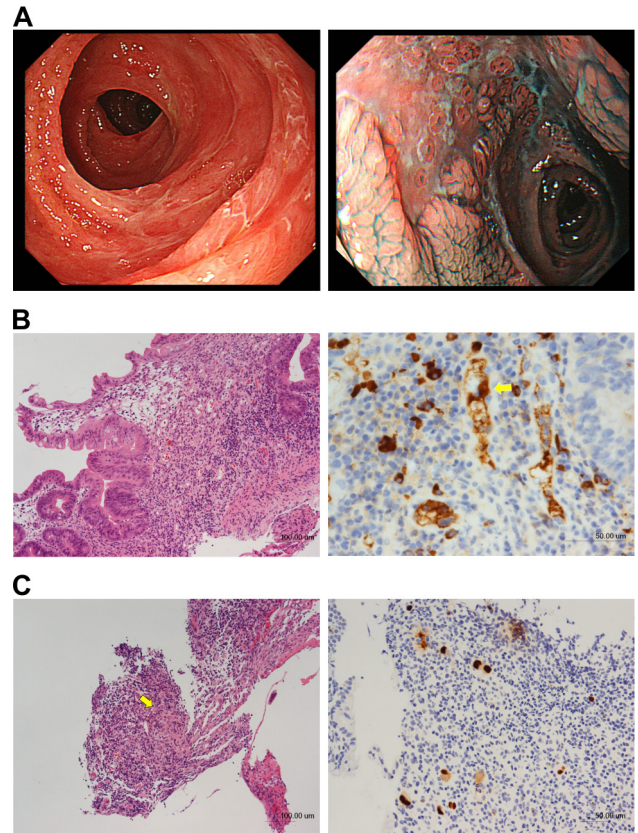


Figure 3 Jejunal mucosal findings indicating cytomegalovirus (CMV) reactivation: (A) single-balloon enteroscopy (SBE) shows mucosal oedema, redness, erosions and transverse ulcers involving the jejunal mucosa (left). Image taken after staining the jejunal mucosa with indigo carmine (right). (B) Jejunal biopsy samples obtained during the follow-up SBE show massive infiltration of immune cells within the jejunal mucosa (left) (H&E, 40× magnification) along with deposition of IgA in the capillary walls and high-magnification image of immunohistochemical staining shows accumulation of IgA-expressing plasma cells and IgA deposition in the capillary vessel walls (yellow arrow) (IgA immunostaining, 80× magnification) (right). (C) Histopathological examination of jejunal biopsy samples obtained during the follow-up SBE shows a giant cell with inclusion bodies (yellow arrow) (left) (H&E, 40× magnification) and positive immunoreactivity for CMV (right) (anti-CMV monoclonal immunostaining, 40× magnification).

mucosal haemorrhage were found in the jejunal biopsy specimens obtained during SBE. Finally, immunohistochemical analysis of the jejunal samples revealed deposition of IgA within the capillary walls. These histopathological findings supported the diagnosis of IgA vasculitis with isolated involvement of the small intestine, despite the absence of skin involvement. However, leucocytoclastic vasculitis was not detected in this case. Failure to detect leucocytoclastic vasculitis can be explained by the limited available extent of submucosal tissue that is suitable for detection of vasculitis in jejunal biopsy specimens. In line with this, the detection rate of vasculitis in biopsy specimens is very low (5.4%).¹¹

IgA vasculitis lesions can occur anywhere throughout the length of the GI tract, but most patients have small intestinal lesions, including those affecting the duodenum.⁹ Endoscopic findings in this disorder include redness, erosions, mucosal oedema, punctate bleeding, ulcers and purpura-like lesions

affecting the intestinal mucosa,^{13–15} most of which were seen in the second SBE in our case. Considering that GI symptoms precede skin manifestations in 15%–35% of IgA vasculitis patients and that a significant proportion of patients are known to develop severe intestinal complications, such as ischaemia, obstruction, intussusception and perforation,⁹ recognition of the above-mentioned endoscopic findings is important for early diagnosis.^{13–15} In this case, the laboratory tests showed a markedly high creatine kinase level, which suggested the presence of small bowel ischaemia due to severe inflammation. In such severe cases, a prompt diagnosis, mainly based on endoscopic findings, is necessary even in the absence of typical skin purpura to avoid the development of complications requiring emergency surgery.

CMV is a viral pathogen that causes opportunistic infections, leading to a severe and fatal disease in immunocompromised hosts.¹⁶ The prevalence of CMV infection in inflammatory bowel diseases has been examined, and the proportion of ulcerative colitis (UC) patients with CMV infection has been reported to be 6.3%.¹⁷ Such a high incidence of CMV reactivation in UC is related to the use of immunosuppressive agents, including PSL.¹⁸ As in the cases of UC with CMV reactivation, virus reactivation delayed mucosal healing in this patient with enteric IgA vasculitis after PSL treatment. To the best of our knowledge, this is the first case of small intestinal IgA vasculitis complicated by CMV enteritis. It is worth noting that mucosal oedema, erosions and transverse ulcers were seen in the small intestinal mucosa in this case, both before and after CMV reactivation. Therefore, in such cases, it might be challenging to diagnose CMV enteritis based only on endoscopic findings. Detection of CMV by PCR and immunostaining of intestinal biopsy specimens are required for diagnosing CMV enteritis after PSL administration for IgA vasculitis. Although the prognosis of IgA vasculitis is generally excellent owing to its high sensitivity to glucocorticoid therapy,⁵ this case report strongly suggests that CMV enteritis should be considered in patients with IgA vasculitis showing a poor response to glucocorticoids.

Learning points

- ▶ Adult patients with IgA vasculitis can present with isolated gastrointestinal involvement, without characteristic skin manifestations.
- ▶ An early diagnosis of this condition can be made on the basis of enteroscopic and histopathological findings to avoid emergence of surgical complications.
- ▶ The possibility of cytomegalovirus (CMV) enteritis should be considered in IgA vasculitis patients showing a poor response to glucocorticoids.
- ▶ Detection of CMV on PCR and immunostaining of intestinal biopsy specimens are required for the diagnosis of CMV enteritis after administration of prednisolone for IgA vasculitis.

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