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Seiichi Kato
Kyoko Ebina
Hiroshi Naganuma
Shin-ichi Sato
Shun-ichi Maisawa
Hiroshi Nakagawa

Intestinal IgA deposition in Henoch-Schönlein purpura with severe gastro-intestinal manifestations

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S. Kato (✉) · K. Ebina · H. Nakagawa
Department of Paediatrics
Sendai City Hospital, 3-1 Shimizukoji,
Wakabayashi-ku, Sendai 980, Japan
Tel.: +81-22-266-7111
Fax: +81-22-211-8972

H. Naganuma · S. Sato
Department of Pathology,
Sendai City Hospital, Sendai, Japan

S. Maisawa
Department of Paediatrics,
Morioka Children's Hospital,
Morioka, Japan

Abstract In patients with Henoch-Schönlein purpura (HSP) presenting with severe gastro-intestinal (GI) symptoms, IgA deposition was studied in endoscopically obtained mucosal biopsies. A total number of 11 patients (male, 7; female, 4) were enrolled in this study; 7 patients underwent upper GI endoscopy and biopsy 1 underwent sigmoidoscopy and 3 underwent both. Upper GI endoscopy in each patient showed various mucosal changes including redness, petechiae, erosions, and ulcerations, most predominant in the second part of the duodenum. Sigmoidoscopy demonstrated no abnormality in two of four patients. Intestinal deposition of IgA was positive in 7 of 11 patients with HSP. Histological examination showed non-specific inflammation of varying degrees in each patient, but no small vessel vasculitis was observed. IgA deposits were seen in only 2 of 23 control subjects with various GI diseases. Positive rate of IgA deposition per patient was significantly higher in patients with HSP than in controls ($P < 0.005$).

Conclusion IgA deposition in the GI tract, as in the skin and kidneys, is characteristic of HSP. Intestinal IgA deposition complements the diagnostic criteria of HSP.

Key words Biopsy · Endoscopy · Henoch-Schönlein purpura · IgA · Intestinal mucosa

Abbreviations *GI* gastro-intestinal · *HSP* Henoch-Schönlein purpura

Introduction

Henoch-Schönlein purpura (HSP) is a systemic small vessel vasculitis involving the skin and all or some joints, gastro-intestinal (GI) tract, or kidneys. Because HSP vasculitis is IgA-mediated, HSP can be differentiated from other forms of vasculitis. Previous investigators have reported increased serum IgA levels [22], circulating IgA-containing immune complexes [16], increased peripheral IgA-bearing lymphocytes [6, 18], and other immunological abnormalities including dysregulation of IgA production [4, 5]. In a few sporadic cases of HSP, small vessel vasculitis with IgA deposits in the GI tract have been described [1, 19–21]. However, a direct association between IgA and GI injury in HSP has not been established. We suggested previously that GI endoscopy may be useful, although IgA deposition was examined in only three patients [15]. We have now studied endoscopically 11 new patients with HSP. The purpose of the present study was to investigate IgA deposition in the intestinal mucosa of HSP patients who presented severe GI symptoms.

Patients and methods

Patients

Eleven patients with HSP, aged 5–11 years, were enrolled in the present study (Table 1). The diagnosis of HSP was made on the basis of clinical manifestations including a characteristic skin rash, joint pain/swelling, GI symptoms, or nephritis. Three patients had a recent infection and/or medication. No patient had a bleeding

Table 1 Clinical data of the patients enrolled in this study

Patient	Age/sex	Major complaints	Time from onset to endoscopy	Treatment at endoscopy	Serum IgA (mg/dl)
1	5 years/M	Haematemesis/tarry stool	14 days	Prednisolone	228
2	7 years/M	Haematochezia	38 days	No treatment	Not done
3	7 years/M	Epigastric pain	13 days	No treatment	195
4	5 years/M	Haematemesis	6 days	Prednisolone	165
5	8 years/F	Epigastric pain	12 days	Factor XIII	180
6	9 years/M	Epigastric pain	14 days	Prednisolone	475
7	6 years/M	Haematemesis	7 days	Factor XIII	225
8	5 years/F	Haematemesis/haematochezia	5 days	Factor XIII	155
9	7 years/F	Haematemesis/haematochezia	10 days	Prednisolone	102
10	7 years/F	Epigastric pain	20 days	Prednisolone	Not done
11	11 years/M	Epigastric pain/haematochezia	15 days	Prednisolone	165

diathesis, including thrombocytopenia, nor any clinical or serological evidence of liver disease. Serum IgA levels were high in only 1 patient as compared to age-matched normal values. At the time of endoscopy, each patient had a purpuric rash, mainly of the lower extremities. Chief GI symptoms included haematemesis, tarry stools, severe epigastric pain/tenderness, and haematochezia. The average period between the onset of symptoms and endoscopy was 14.0 days (range, 5–38 days). Six patients were treated with prednisolone (dose ranging from 1.4 to 1.9 mg/kg/day) for 1–12 days (mean, 5 days) prior to endoscopy. Four patients (patients 6, 8, 9, and 11) were treated with intravenous hyperalimentation. Informed consent was obtained verbally from the parents of each patient.

Biopsies of 23 children without HSP or any renal symptom were taken as controls for IgA staining. The number of biopsies per control subject ranged between 1 and 6 (mean, 3.4). The diagnoses of the control patients who underwent a gastric biopsy (n = 9) were gastritis, eosinophilic gastro-enteritis, cow's milk allergy, and acute leukaemia in remission; diagnoses of those who underwent a duodenal biopsy (n = 8) included duodenitis, lymphoid hyperplasia of the duodenum, eosinophilic gastro-enteritis, cow's milk allergy, and Crohn disease; those who underwent rectal or colonic biopsies (n = 12) had proctitis, colitis, ulcerative colitis, Crohn disease, eosinophilic gastro-enteritis, cow's milk allergy, and lymphoid hyperplasia of the colon.

Endoscopic biopsy and IgA staining

Endoscopic techniques were performed as previously described [14]. In patients with HSP, the GI tract was inspected up to the second part of the duodenum and on colonoscopy, up to the sigmoid. Using an FB-21K biopsy forceps (Olympus, Japan), biopsy specimens were taken from the endoscopically affected mucosa.

Biopsy specimens were fixed overnight in 3% formalin solution and embedded in paraffin. Sections for light microscopy were stained routinely with haematoxylin and eosin. IgA deposits were detected by an immunohistochemical method described previously [15]. Briefly, sections were incubated with a rabbit IgG fraction against human IgA (1:400) as the primary antibody for 16 h at 4° C and then with a biotinylated goat IgG against rabbit IgG as the second antibody.

Statistical analysis

Positive rate of IgA deposition was compared between patients with HSP and controls by Fisher's exact probability test. A P value < 0.05 was considered statistically significant.

Results

Endoscopic findings

Upper GI endoscopy demonstrated some mucosal abnormalities in each of the ten patients studied (Table 2). Endoscopic findings included redness, swelling, petechiae, erosions, or ulcerations. Five of ten patients had mild to moderate redness of the oesophagus, especially in the lower portion. Many patients had more severe lesions such as multiple erosions or ulcerations in the second part of the duodenum as compared to the stomach or duodenal bulb. No abnormal finding could be demonstrated in two of four patients undergoing sigmoidoscopy.

Histochemical studies

In the control group, only 2 of 23 subjects demonstrated IgA deposition; one subject with acute leukaemia and one

Table 2 Endoscopic characteristics of patients with HSP (*N* normal, *ND* not done)

Patient	Stomach	Duodenal bulb	2nd part of the duodenum	Rectosigmoid colon
1	N	N	Redness	ND
2	ND	ND	ND	Ulceration
3	N	N	Redness	ND
4	N	Redness	Ulceration	ND
5	Redness	Redness	Petechiae	ND
6	Redness	Redness	Erosion	ND
7	Redness	Redness	Redness	ND
8	Redness	N	Ulceration	N
9	Petechiae	Erosion	Erosion	N
10	N	Petechiae	Petechiae	ND
11	Petechiae	Erosion	Ulceration	Petechiae

Table 3 Intestinal IgA deposition in biopsy specimens (*ND* not done)

Patient	Stomach	Duodenal bulb	2nd part of the duodenum	Rectosigmoid colon	No. of positive/ total biopsies
1	–	ND	+	ND	1/2
2	ND	ND	ND	–	0/5
3	ND	ND	–	ND	0/1
4	ND	+	+	ND	2/2
5	–	ND	–	ND	0/2
6	+	ND	–	ND	1/3
7	+	ND	–	ND	1/2
8	+	ND	–	+	4/6
9	–	–	–	+	2/6
10	ND	ND	–	ND	0/1
11	+	+	–	+	4/5
No. of positive/ total patients	4/7	2/3	2/10	3/4	

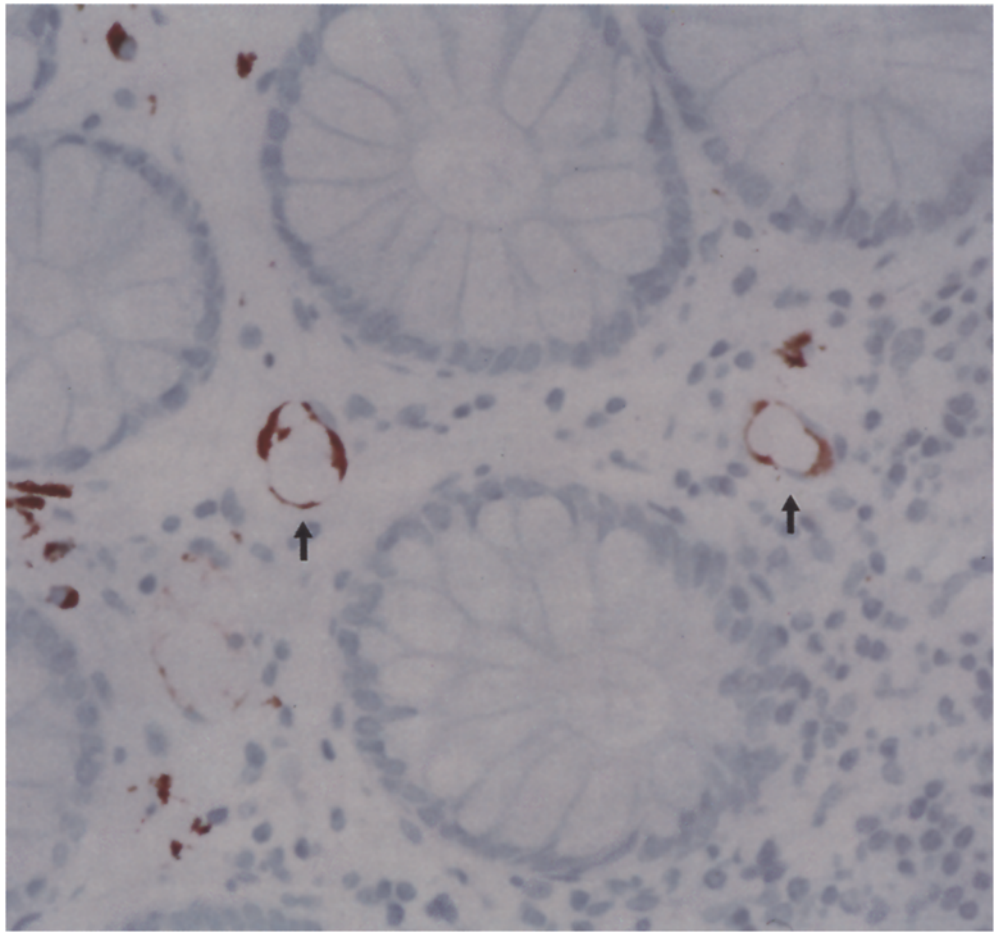

Fig. 1 Colonic biopsy specimen of patient 8 showing deposition of IgA in the superficial capillaries *(arrows)*, × 50. No vasculitis is found

with non-specific colitis had IgA deposits in the capillaries of the gastric and colonic mucosa, respectively.

In the HSP group, an average of 3.2 biopsy specimens (range, 1–6) were obtained from each patient (Table 3). Pathological examination showed non-specific mucosal inflammation of variable severity. In seven of 11 patients, IgA deposits were detected in one or more sites in the GI tract. A typical photomicrograph of IgA deposition is presented in Fig. 1. Positivity of IgA deposition was significantly higher in patients with HSP than in controls ($P < 0.005$). However, the second part of the duodenum stained for IgA in only 20% of the studied patients. One biopsy

specimen taken from an endoscopically normal rectum (patient 9) showed IgA deposits. In patient 8 with IgA deposition in the gastric and sigmoid mucosa, repeated upper GI endoscopy was performed 4 days after the first examination because of persistent tarry stool. No IgA deposits could be demonstrated in biopsy specimens of the stomach and the second part of the duodenum, while endoscopic abnormalities were still proven.

Two patients (patients 9, 11) underwent renal biopsy because of persistent proteinuria exceeding 1 g/day. The pathological diagnosis according to the renal biopsy in both patients was mesangial proliferative glomerulonephritis accompanied by deposition of predominantly IgA, IgG, IgM, and fibrinogen. Deposits of C1q and C3 were not detected.

Discussion

Dermal and mesangial deposition of predominantly IgA has been established as being characteristic of HSP [3, 9]. Since circulating IgA immune complexes have been observed in HSP [16], its deposition may precipitate the inflammatory process [17]. To date, studies of the dermal and mesangial deposition of IgA have focused mainly on the immunopathogenesis and diagnosis of HSP. The present data suggest that intestinal IgA deposition, as in the skin and kidneys, is characteristic in HSP. Moreover, this fact leads us to hypothesize that IgA deposition is responsible for the GI injury by an immunological process related to IgA. In the present study, however, IgA deposits were not accompanied by small vessel vasculitis. Therefore, this hypothesis remains to be confirmed.

It should be noted that positivity of IgA deposition was low in the second part of the duodenum, while being the most predominant site of involvement endoscopically. Moreover, IgA-associated vasculitis in GI biopsies has been reported [1, 19, 21]. However, intestinal IgA deposition is not necessarily accompanied by vasculitis [15, 20]. Furthermore, IgA deposits were demonstrated in clinically normal skin of patients with HSP [3, 23]. Pathologically, the most common abnormality in the GI tract is submucosal or intramural [10]. Because endoscopic biopsies are superficial, they are probably limited somehow in demonstrating vasculitis.

Complement components C3 and C4 are often co-deposited with IgA. Götze et al. [11] stated that though neither IgA subclass activates the classical complement pathway, both may activate the alternate pathway. However, activation of the complement system by human IgA immune complexes continues to be a subject of debate [12, 13]. In either case, concomitant deposition of immunoglobulins and complement components suggests an immunological role in the pathogenesis of HSP. Although IgA subclasses have been studied to determine whether the IgA in HSP originates from the systemic or mucosal immune system, previous studies have demonstrated conflicting results [2, 7, 8]. Further investigation is required to determine the precise role of IgA in HSP.

Endoscopic findings are not specific to HSP. However, the distribution of findings, such as the predominant changes in the second part of the duodenum are characteristic and consistent with our previous report [15]. We believe that the described endoscopic pattern and intestinal IgA deposition should play complementary roles in the diagnosis of HSP, especially, in patients in whom GI symptoms precede a pathognomonic skin rash or in patients whose episode of rash is obscure.

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