


Widespread involvement of purpura related to gastrointestinal involvements in adults with immunoglobulin A vasculitis

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Abstract

Immunoglobulin A vasculitis (IgAV) is a type of vasculitis affecting small vessels with deposition of immune complexes consisting of IgA and complement component 3. IgAV involves the skin, gastrointestinal (GI) tract, joints, and kidneys. Adult patients have higher risks of gastrointestinal tract involvement than children. To investigate the risk factors of the GI tract involvements in adult IgAV patients, we enrolled 29 adult (aged ≥ 20 years) Japanese patients recently (from 2013 to 2019) histopathologically diagnosed with IgAV and classified them into the GI lesion (+) group and the GI lesion (-) group. All patients presented with purpura on the lower extremities; moreover, GI lesion (+) patients presented significantly more with extensive purpura on the upper extremities, and low levels of factor XIII activity ($\leq 70\%$) than gastrointestinal lesion (-) patients (87.5% vs 28.6% [$P = .004$]; odds ratio [OR], 17.5; 95% confidence interval [CI], 2.4 to 366], and 57.1% vs 14.3% [$P = .04$]; OR, 8; 95% CI, 1.06 to 83.9, respectively). There was no significant difference between the two groups in the populations with extensive purpura on the trunk, arthralgia, hematuria, proteinuria, or elevated serum levels of C-reactive protein or IgA. Widespread purpura on the upper extremities accompanied by a low factor XIII activity is a suggestive factor for severe GI lesions in adult IgAV patients.

KEYWORDS

adult, factor XIII activity, gastrointestinal involvement, immunoglobulin A vasculitis, palpable purpura

1 | INTRODUCTION

Immunoglobulin A vasculitis (IgAV), previously called “Henoch-Schönlein purpura,” is a type of vasculitis affecting small vessels with deposition of immune complexes consisting of IgA and complement component 3. IgAV generally involves the skin, gastrointestinal (GI)

tract, joints, and kidneys and develops occasionally after infectious triggers.¹ All patients with IgAV present with palpable purpura, located on the lower extremities commonly and on the trunk and upper extremities in one-third of the cases.² Renal disease is most likely to result in long-term morbidity; moreover, arthralgia and GI symptoms are frequently observed. The incidence of IgAV among

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adults is about one-tenth less than that among children.³ However, adult patients with IgAV have higher risks of GI tract involvement,³ the most common endoscopic finding of which is erythema/pepetechiae, followed by erosion/ulceration.⁴ Adult patients with GI involvements occasionally need to be treated with intensive therapies, such as prednisolone and cyclophosphamide; moreover, some of them develop serious conditions requiring transfusion or surgery or leading to death. In the present study, we retrospectively investigated what factors were associated with GI involvements in adult IgAV patients.

2 | METHODS

2.1 | Patients

We retrospectively studied 11 male and 18 female adult (aged ≥ 20 years) Japanese patients, who were recently (from 2013 to 2019) diagnosed with IgAV in University of Tsukuba Hospital (Table 1). According to EULAR/PRINTO/PRES criteria (2010),⁵ the diagnosis was based on a mandatory criterion, palpable purpura, and histopathologic examination revealing leukocytoclastic vasculitis with IgA deposition in skin biopsy samples. Further, we classified them into the GI lesion (+) group, presenting with bleeding erosive/ulcerative GI (stomach, duodenum, small intestine, and/or colon) involvements diagnosed with a fecal occult blood test and/or an examination using endoscopies, and the GI lesion (-) group, presenting with no GI involvement proved objectively. The study was approved by the medical ethics review committee of the University of Tsukuba Hospital (H30-089).

2.2 | Statistical methods

Significant differences and odds ratio (OR) with 95% confidence interval (CI) were basically estimated by the chi-square test and the logistic regression analysis, respectively, using GraphPad Prism 8 (GraphPad software, San Diego, CA). A *P*-value $< .05$ was considered statistically significant.

3 | RESULTS

3.1 | Symptoms of GI involvements

Eight patients (27.6%) were classified into the GI lesion (+) group, all of whom presented with abdominal pain and diarrhea, six of whom were positive in fecal occult blood tests, and seven of whom had erosive/ulcerative GI lesions confirmed using endoscopy examinations (esophagogastroduodenoscopy and/or colonoscopy; Table 1). Bowel thickening with mucosal hyperenhancement was observed in two patients in the GI lesion (+) group on computed tomography. On the other hand, only one patient in the GI lesion (-) group presented

with abdominal pain, and no GI lesions were observed even using endoscopies, which were performed for four patients in the GI lesion (-) group (Table 1).

3.2 | Clinical symptoms

GI lesion (+) patients tended to be younger than GI lesion (-) patients (40.75 ± 17.1 vs 50.86 ± 16.2 years, Table 2). The difference was not significant ($P = .213$ by the Mann-Whitney *U* test), and an additional statistical analysis revealed that the ratio of elderly patients (aged ≥ 65 years) in the GI lesion (+) group was not significantly different compared to that in the GI lesion (-) group (12.5% vs 28.6%, $P = .366$ by the chi-square test).

All patients presented with purpura on the lower extremities; moreover, GI lesion (+) patients presented with significantly more extensive purpura on the upper extremities than GI lesion (-) patients (87.5% vs 28.6%, $P = .004$ by the chi-square test; OR, 17.5; 95% CI, 2.4 to 366; Table 2). Extensive purpura on the trunk, arthralgia, and hematuria (red cells in the urine $\geq 20/\mu\text{L}$), but not proteinuria (urine protein excretion ≥ 30 mg/dL), tended to be frequent in the GI lesion (+) group compared to the GI lesion (-) group (Table 2). These differences were not significant.

3.3 | Laboratory tests

Patients with low levels of factor XIII activity ($\leq 70\%$) were significantly more common in the GI lesion (+) group than in the GI lesion (-) group (57.1% vs 14.3%, $P = .04$ by the chi-square test; OR, 8; 95% CI, 1.06 to 83.9). There was no significant difference between the two groups in the populations with elevated serum levels of C-reactive protein (≥ 0.2 mg/dL) and IgA (≥ 410 mg/dL).

4 | DISCUSSION

IgAV-related clinical manifestations including palpable purpura, abdominal pain and diarrhea, arthralgia, and glomerulonephritis develop over the course of days to weeks; moreover, the initial manifestations are usually with purpura and arthralgia.⁶ The rash usually begins with petechiae and palpable purpura. Some previous studies have shown an association between extensive distribution of purpura and systemic involvements. A multicenter cohort study involving 260 French patients showed that adult IgAV patients presenting with GI symptoms developed more extensive purpura on the abdomen and upper limbs than those without GI symptoms ($P = .02$ and $.07$, respectively, by the chi-square test).⁷ On the other hand, the presence of purpura limited only on the upper and lower extremities, but not above the waist, was trended to be related to long-term renal involvements in a cohort of adult American cases of IgAV (total 102 cases including 71 white patients [69.6%]), which also revealed that it was not related to the presence of GI involvement

TABLE 1 Gastrointestinal signs of immunoglobulin A vasculitis in patients with erosive/ulcerative gastrointestinal lesions compared to those without gastrointestinal lesions

Group	Case	Gender	Age	Abdominal pain and/or diarrhea	Fecal occult blood test	GI endoscopies (EGD and/or colonoscopy)	Computed tomography
GI lesion (+)	1	Male	20	+	+	Erythema on large bowel	N/A
	2	Female	22	+	+	N/A	Bowel wall thickening on small and large bowels
	3	Female	25	+	-	Erosion on duodenum and stomach	N/A
	4	Female	34	+	+	N/A	N/A
	5	Male	46	+	-	Erosion and ulcer on large bowel	Bowel wall thickening on large bowel
	6	Male	49	+	+	Erythema on stomach	N/A
	7	Female	64	+	+	Erosion on duodenum and large bowel	N/A
	8	Male	66	+	+	Erosion on large bowel	N/A
GI lesion (-)	9	Male	21	-	N/A	N/A	N/A
	10	Female	24	+	-	No finding (EGD)	N/A
	11	Male	24	-	N/A	N/A	N/A
	12	Female	39	-	N/A	No finding (colonoscopy)	N/A
	13	Female	40	-	N/A	N/A	N/A
	14	Female	44	-	N/A	N/A	N/A
	15	Female	45	-	-	N/A	N/A
	16	Female	45	-	N/A	N/A	N/A
	17	Female	45	-	N/A	N/A	N/A
	18	Male	47	-	N/A	N/A	N/A
	19	Female	47	-	N/A	N/A	N/A
	20	Female	52	-	N/A	N/A	N/A
	21	Female	52	-	N/A	N/A	N/A
	22	Male	54	-	N/A	N/A	N/A
	23	Female	61	-	N/A	N/A	N/A
	24	Female	65	-	-	N/A	N/A
	25	Male	69	-	N/A	N/A	N/A
	26	Male	69	-	-	No finding (EGD)	N/A
	27	Female	71	-	N/A	N/A	N/A
	28	Male	75	-	N/A	N/A	N/A
	29	Female	79	-	N/A	N/A	N/A

Abbreviation: EGD, esophagogastroduodenoscopy.

TABLE 2 Characteristics of immunoglobulin A vasculitis in patients with erosive/ulcerative gastrointestinal lesions compared to those without gastrointestinal lesions

Characteristics	GI lesion (+) n = 8	GI lesion (-) n = 21	P-value (chi-square test)	Odds ratio (95% CI)
Average age \pm SD	40.75 \pm 17.1	50.86 \pm 16.2	.213 ^a	
Purpura				
Lower extremities, n (%)	8 (100)	21 (100)	N/A	N/A
Upper extremities, n (%)	7 (87.5)	6 (28.6)	.004 [*]	17.5 (2.4, 366)
Trunk, n (%)	2 (25)	3 (14.3)	.495	2 (0.22, 15.2)
Arthralgia, n (%)	3 (37.5)	5 (23.8)	.461	1.92 (0.31, 11.2)
Proteinuria, n (%)	3 (37.5)	8 (38.1)	.976	0.98 (0.16, 5.16)
Hematuria, n (%)	5 (62.5)	12 (57.1)	.793	1.25 (0.24, 7.42)
Laboratory tests				
Elevated serum level of IgA, n (%)	2 (28.6)	8 (44.4)	.467	0.5 (0.06, 3.04)
Elevated serum level of C-reactive protein, n (%)	6 (75)	17 (81)	.724	0.71 (0.11, 6.03)
Low activity of factor XIII, n (%)	4 (57.1)	2 (14.3)	.04 [*]	8 (1.06, 83.9)

Abbreviations: CI, confidence interval; SD, standard deviation.

^aMann-Whitney *U* test.

**P* < .05.

whether purpura spread above the waist.⁸ Our study indicated that extensive purpura on the upper extremities was related to severe erosive/ulcerative GI lesions in adult IgAV patients, as similar to the French cohort.⁷

It was commonly thought that GI endoscopic observations including extensive edema, blood clotting, and hematoma in the bowel walls of patients with IgAV are caused by an abnormal reaction to certain substances in capillaries, resulting in enhancement of capillary permeability.⁹ The most common endoscopic finding is erythema/petechiae, followed by erosion and ulceration.⁹ Typical CT findings were reported as bowel thickening with mucosal hyperenhancement and the presence of skip areas, which reflected the endoscopic observations.¹⁰

The rate of leukocytoclastic vasculitis in the biopsies taken from the GI system is 30%–40%.^{11,12} It was reported that prednisone reduced the duration and severity of abdominal pain,¹³ and factor XIII substitution therapy markedly improved abdominal symptoms.¹⁴ Blood coagulation factor XIII is a transglutaminase cross-linking fibrin in the coagulation cascade, which also maintains angiogenesis, vascular remodeling, and cardiovascular health.¹⁵ A low activity of factor XIII has been observed in the acute phase of IgAV, presumably due to degradation by proteolytic enzymes released during inflammation,¹⁵ and related to the severities of GI lesions and arthralgia of adult IgAV cases¹⁴ as well as observed in our series.

In conclusion, widespread purpura on the upper extremities accompanied by a low factor XIII activity is a suggestive factor for severe GI lesions. Our study is a single-center retrospective study involving a small number of Japanese cases, which need to be considered as limitations.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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