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Characteristics and Treatment Outcomes of Small-bowel Angioectasia in Systemic Sclerosis Patients: A Retrospective Observational Study

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Abstract:

Objective Systemic sclerosis (SSc) is defined as an autoimmune disease presenting with fibrosis of various organs and vascular endothelial damage. Vascular lesions, including small-bowel angioectasias, are also frequently detected in SSc patients. Polidocanol injection (PDI) is a safe and effective hemostatic treatment for gastrointestinal bleeding. We evaluated the outcomes of PDI for small-bowel angioectasia in SSc patients.

Methods We retrospectively evaluated 65 consecutive SSc patients (61 women; mean age, 64.3 years old) who underwent capsule endoscopy (CE) and/or double-balloon endoscopy at Hiroshima University Hospital between April 2012 and December 2019.

Patients Patients were stratified according to the presence of small-bowel angioectasia. Among patients who underwent CE during the same period, those with small-bowel angioectasia without concomitant diseases were compared with SSc patients with small-bowel angioectasia. Clinical and endoscopic characteristics, treatment outcomes, and the incidence of metachronous small-bowel angioectasia after PDI were evaluated.

Results SSc patients with small-bowel angioectasia exhibited significantly lower hemoglobin levels and a significantly higher incidence of skin telangiectasia than those without small-bowel angioectasia. On a multivariate analysis of the presence of small-bowel angioectasia, anemia and skin telangiectasia were significant independent factors. SSc patients with small-bowel angioectasia included a higher proportion of women and exhibited a significantly higher incidence of metachronous small-bowel angioectasia than X. The characteristics of small-bowel angioectasia and outcomes of PDI were not significantly different between the two groups. No post-treatment rebleeding cases or adverse events were noted.

Conclusion CE should be performed for SSc patients with anemia and/or skin telangiectasia. PDI is effective for SSc patients with small-bowel angioectasia.

Key words: capsule endoscopy, systemic sclerosis, small-bowel, angioectasia, polidocanol injection

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Introduction

Systemic sclerosis (SSc) is defined as an autoimmune disease presenting with vascular endothelial damage and fibrosis of various organs, including the skin and gastrointestinal tract. In SSc, the distribution of skin sclerosis and progression of the disease vary among patients, and SSc can be

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classified into two types from this perspective: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) (1). In dcSSc, patients present with typical symptoms of SSc. Skin sclerosis is frequently distributed throughout the body and often rapidly progresses after the onset of SSc. Anti-Scl-70 and anti-RNA polymerase III antibodies are often detected in dcSSc patients. In lcSSc patients, the distribution of skin sclerosis is often localized to the face and distal portion of the extremities. The progression of lcSSc is very slow, and the detection frequency of anti-centromere antibodies is relatively high. A large number of cases of nailfold bleeding are found among lcSSc patients, while it is often absent in dcSSc patients as the disease progresses. Using capillaroscopy, the capillary of the nail in lcSSc patients is meandering and dilated.

SSc patients often present with symptoms derived from gastrointestinal motility impairments, such as reflex esophagitis, small-intestinal bacterial overgrowth (SIBO), and constipation (2, 3). These symptoms are caused by fibrosis of the gastrointestinal tract. In addition, vascular lesions are also frequently observed in SSc patients. Notably, capsule endoscopy (CE) and balloon endoscopy, including double-balloon endoscopy (DBE), are useful modalities for diagnosing small-bowel vascular lesions (4-12). Vascular lesions are thought to be caused by chronic hypoxia in the microcirculation (13-15). Approximately 5% of all gastrointestinal bleeding cases originate in the small bowel (16), and 23-52% of small-bowel bleeding cases are caused by vascular lesions, such as small-bowel angioectasia (17-19). Furthermore, small-bowel angioectasia accounts for about half of obscure gastrointestinal bleeding (OGIB) cases (20).

Angioectasia is a localized dilation and tortuosity of abnormal blood vessels in the mucosa or submucosa. SSc patients have a high frequency of vascular lesions, including small-bowel angioectasia, but few studies have investigated the treatment outcomes for small-bowel angioectasia in SSc patients (21). Although we previously reported the usefulness of polidocanol injection (PDI) for small-bowel vascular lesions (4, 5), few studies have reported its usefulness for small-bowel angioectasia in SSc patients.

Therefore, in the present study, we evaluated the characteristics and treatment outcomes of small-bowel angioectasia in SSc and non-SSc patients.

Materials and Methods

Patients

At Hiroshima University Hospital, 65 consecutive patients with SSc (61 women; mean age, 64.3 years old) underwent CE between April 2012 and December 2019. Before undergoing CE, patients were checked for the presence of small-bowel stenosis using transabdominal ultrasonography and/or abdominal computed tomography. Patients were retrospectively classified according to the presence or absence of small-bowel angioectasia, and the Yano-Yamamoto classification (21) of small-bowel vascular lesions was used to classify small-bowel angioectasia. Small-bowel angioectasia was subclassified as follows: Type 1a angioectasia was defined as spotty redness (<1 mm) with or without oozing, and Type 1b was defined as patchy redness (2-3 mm). In addition, in patients who underwent CE during the same period (3,374 CE cases in total), patients with small-bowel angioectasia but without concomitant diseases or history of medications (non-SSc patients) were compared with SSc patients with small-bowel angioectasia.

CE procedure

A PillCam™ SB2 or SB3 video capsule (Covidien, Mansfield, USA) was used at Hiroshima University Hospital. The capsule was swallowed with a solution of dimethicone after 8-hour fasting. After swallowing the capsule, patients were able to spend their time as usual, except for refraining from engaging in intense exercises. Capsule images were analyzed using the Rapid Reader 6.5 software program on a RAPID 8 workstation (Covidien). The CE image stream was reviewed by 2 experienced endoscopists with >200 cases of experience independently, and the final diagnosis was made by consensus between them.

DBE Procedure

The FUJIFILM system (Saitama, Japan) with a FUJIFILM EN-450 P5, EN-450 T5, EI-580BT, or EN-580T-type endoscope was used. In cases with per-oral insertion, patients needed to fast for 8-12 hour, similar to the preparation for upper gastrointestinal endoscopy. In cases with rectal insertion, patients had to undergo bowel preparation similar to that for colonoscopy. Pentazocine (15 mg) and midazolam (0.05 mg/kg) were used for sedation. The insertion route was selected according to the results of CE. If we were unable to identify the bleeding source during DBE, we marked the most distal point of the small-bowel with pure carbon for follow-up.

Endoscopic treatment for small-bowel angioectasia

Lesions were punched out under direct visualization with DBE, and 1% polidocanol was injected using a 25-gauge local injection needle for small-bowel (TOP Corporation, Tokyo, Japan). The indications for PDI were Type 1a angioectasia with oozing and Type 1b angioectasia. The treatment strategies for small-bowel angioectasia were as follows: 1) Type 1a angioectasia without oozing was carefully followed up, 2) PDI was performed for Type 1a angioectasia with oozing, and 3) Type 1b angioectasia was treated using PDI alone or in combination with PDI and argon plasma coagulation (APC) or clipping based on the condition of lesions, as previously reported (4).

Evaluations

The characteristics of small-bowel angioectasia [number, main location, and Yano-Yamamoto classification (21)] and incidence of metachronous small-bowel angioectasia were

Table 1. Characteristics of SSc Patients Classified According to the Presence or Absence of Small-bowel Angioectasia.

Variables	Total, n=65	Small-bowel angioectasia		p values
		(+), n=13	(-), n=52	
Sex, female	61 (94)	11 (85)	50 (96)	0.1447
Mean age (years)	64.3 [36-81]	65.7 [42-81]	64.5 [36-80]	0.6303
Subclassification (lcSSc)	34 (52)	9 (69)	25 (48)	0.1485
History of abdominal surgery	0 (0)	0 (0)	0 (0)	
Medications				
Antiplatelet drugs	8 (12)	1 (8)	7 (13)	0.6102
NSAIDs	10 (15)	1 (8)	9 (17)	0.2168
Chief complaints				
Abdominal symptoms	18 (28)	0 (0)	18 (38)	
OGIB	14 (22)	9 (69)	5 (10)	
No symptoms	33 (50)	4 (31)	29 (56)	
mRSS	11.1 [0-43]	14.8 [0-34]	13.9 [0-43]	0.6522
Hemoglobin (g/dL)	12.0 [6.0-15.9]	6.9 [6.0-12.6]	12.2 [6.0-15.9]	0.0026
Telangiectasia on the skin	18 (28)	8 (62)	10 (19)	0.0023
Disease duration (months)	64.1 [7-192]	43.3 [16-131]	60.1 [7-192]	0.2241
Concomitant diseases				
Cardiovascular disease	14 (22)	5 (38)	9 (17)	0.1145
Respiratory disease	13 (20)	2 (15)	11 (21)	0.6336
Hypertension	7 (11)	1 (2)	6 (12)	0.6783
Diabetes	5 (8)	1 (2)	4 (8)	1.0000
Dyslipidemia	3 (5)	0 (0)	3 (6)	0.2410
Cerebrovascular disease	1 (2)	0 (0)	1 (2)	0.5023

Data are presented as frequency (percentage) or mean [range], as appropriate. SSc: systemic sclerosis, lcSSc: limited cutaneous SSc, NSAID: non-steroidal anti-inflammatory drug, OGIB: obscure gastrointestinal bleeding, mRSS: modified Rodnan's total skin thickness score

evaluated in patients with and without SSc. In addition, the sex, age, SSc subclassification, abdominal surgical history, medication, chief complaint, modified Rodnan's total skin thickness score (mRSS), telangiectasia on the skin, and SSc duration were also assessed. Treatment-related outcomes for small-bowel angioectasia, including the treatment method, treatment success rate, adverse events, and rebleeding rate, were compared between SSc and non-SSc patients.

In this study, all patients were followed up using CE or DBE at three to six months after endoscopic hemostasis to ensure that there were no lesions to treat. We defined rebleeding as when bleeding observed again from the treated lesions. The incidence of metachronous small-bowel angioectasia was defined as small-bowel bleeding from lesions indicated for treatment other than those detected or treated previously and/or hemoglobin levels subsequently decreased by >2 g/dL relative to baseline, after confirming the absence of a bleeding source in the small bowel using CE or DBE.

This study was performed in accordance with the tenets of the Declaration of Helsinki. All patients received a detailed explanation of the contents of CE and DBE before the examination. None of them refused the examination during the study period. All patients provided their written informed consent for the use of their de-identified data for research purposes. The study protocol was approved by the Hiroshima University Hospital Institutional Review Board.

Statistical analyses

To compare the characteristics of patients and outcomes of initial treatment for small-bowel angioectasia, we used Pearson's chi-square test or Fisher's exact test for quantitative variables and Student's t-test or the Mann-Whitney U test for continuous variables. All tests were two-sided, and p values <0.05 were considered significant. To examine predictive factors for small-bowel angioectasia, a logistic regression analysis was used to calculate the odds ratio, p values, and 95% confidence intervals. The incidence of metachronous small-bowel angioectasia was estimated using the Kaplan-Meier method. All analyses were performed using the JMP software program, version 15 (SAS Institute, Cary, USA).

Results

Table 1 shows the characteristics of the 65 SSc patients according to the presence or absence of small-bowel angioectasia. Both groups of SSc patients (with and without small-bowel angioectasia) included more women than men, with similar proportions of women in both groups [85% (11/13) and 96% (50/52), respectively]. No significant differences were observed in the age or proportion of lcSSc cases between the two groups, and none of the patients in either

Table 2. Multivariate Analysis of Predictive Factors for Small-bowel Angioectasia in Patients with Systemic Sclerosis.

Variables	Odds ratio	p values	95% confidence interval
Sex			
Female	Reference	0.2327	0.29-173.74
Male	7.04		
Age (years)			
<65	Reference	0.2856	0.33-41.94
≥65	3.73		
Subclassification			
dcSSc	4.95	0.3586	0.16-150.58
lcSSc	Reference		
mRSS			
Severe-very severe (≥20)	Reference	0.3173	0.35-25.58
Normal-moderate (0-19)	2.99		
Hemoglobin levels (g/dL)			
Anemia (+)	31.42	0.0014	3.79-260.62
Anemia (-)	Reference		
Telangiectasia on the skin			
(+)	29.79	0.0008	4.10-216.62
(-)	Reference		
Disease duration (months)			
≥56	Reference	0.7216	0.14-16.84
<56	1.54		

SSc: systemic sclerosis, dcSSc: diffuse cutaneous SSc, lcSSc: limited cutaneous SSc, mRSS: modified Rodnan's total skin thickness score

group had a history of abdominal surgery. No significant differences were found in the use of antiplatelet drugs or nonsteroidal anti-inflammatory drugs (NSAIDs), chief complaints, mRSS, disease duration, or concomitant diseases. Antiplatelet drugs were used by one SSc patient with small-bowel angioectasia and seven SSc patients without small-bowel angioectasia. NSAIDs were used by one SSc patient with small-bowel angioectasia and nine SSc patients without small-bowel angioectasia. Hemoglobin levels were significantly lower in SSc patients with small-bowel angioectasia than in those without small-bowel angioectasia (p=0.0026). The presence of telangiectasia on the skin differed significantly between SSc patients with and without small-bowel angioectasia (p=0.0023). No significant difference was noted in the disease duration or presence of concomitant diseases between SSc patients with and without small-bowel angioectasia.

Table 2 shows the results of the multivariate analysis of predictive factors for small-bowel angioectasia in SSc patients. This analysis was performed using the following factors considered important in a previous report (22): sex, age, subclassification, mRSS, hemoglobin levels (g/dL), telangiectasia on the skin, and disease duration. Older adults were defined as those ≥65 years old. mRSS was classified as normal-moderate (0-19) and severe-very severe (≥20) based on the severity of skin thickening. Hemoglobin levels <12 g/dL for women and <13 g/dL for men were considered to indicate anemia. The disease duration was classified based on the median number of months (56 months). Anemia and telangiectasia on the skin were identified as significant independent factors.

Table 3 shows the characteristics of SSc and non-SSc patients with small-bowel angioectasia. Patients with small-bowel angioectasia were classified into the SSc and non-SSc groups, and non-SSc patients had no concomitant diseases or history of medications. Consistent with the high proportion of women in the SSc group, SSc patients with small-bowel angioectasia included a larger proportion of women than non-SSc patients with small-bowel angioectasia [85% (11/13) vs. 41% (7/41); p=0.0272]. No significant differences were noted in the age, medications (antiplatelet drugs and NSAIDs), or chief complaints between these two groups, but the hemoglobin level was lower in SSc patients with small-bowel angioectasia than in non-SSc patients with small-bowel angioectasia. The characteristics of small-bowel angioectasia were similar in both groups. Single small-bowel angioectasia was more common than multiple small-bowel angioectasias in both groups [SSc patients, 77% (10/13) vs. 23% (3/13); non-SSc patients, 65% (11/17) vs. 35 (6/17)]. The main location of small-bowel angioectasia in both groups was the jejunum [SSc patients, 69% (9/13); non-SSc patients, 59% (10/17)]. There were no significant between-group differences in the type of small-bowel angioectasia indicated for treatment (p=0.0906) or the incidence of Type 1a angioectasia without oozing (p=0.7941).

Table 4 presents the initial treatment outcomes of small-bowel angioectasia in SSc and non-SSc patients. No cases of posttreatment adverse events or hemorrhaging were noted.

Table 3. Characteristics of Patients with Small-bowel Angioectasia.

Variables	Patients		p values
	SSc, n=13	Non-SSc, n=17	
Sex, female	11 (85)	7 (41)	0.0272
Mean age (years)	65.7 [42-81]	72.9 [44-98]	0.1833
History of abdominal surgery history (+)	0 (0)	2 (12)	0.1228
Medication			
Antiplatelet drugs	1 (8)	0 (0)	0.1900
NSAIDs	1 (8)	0 (0)	0.1900
Chief complaints			
Abdominal symptoms	0 (0)	5 (29)	
OGIB	9 (69)	12 (71)	
No symptoms	4 (31)	0 (0)	
Hemoglobin (g/dL)	6.9 [6.0-12.6]	10.5 [4.5-15.9]	0.3259
Small-bowel angioectasia			
Number			
Single	10 (77)	11 (65)	0.4657
Multiple	3 (23)	6 (35)	
Main localization of small-bowel angioectasia			
Jejunum	9 (69)	10 (59)	0.5562
Ileum	4 (31)	7 (41)	
Yano-Yamamoto classification			
Type 1a without oozing (follow-up) *	4 (31)	6 (35)	0.7941
Small-bowel angioectasia indicated for treatment			
Type 1a with oozing	7 (54)	14 (82)	0.0906
Type 1b	6 (46)	3 (18)	

* Overlapping data

Data are presented as frequency (percentage) or mean [range], as appropriate. SSc: systemic sclerosis, NSAID: non-steroidal anti-inflammatory drug, OGIB: obscure gastrointestinal bleeding

Table 4. Outcomes of Initial Treatment for Small-bowel Angioectasia in SSc and Non-SSc Patients.

Variables	Patients		p values
	SSc, n=13	Non-SSc, n=17	
Treatment method			
PDI	7 (54)	14 (82)	0.0906
PDI combined with APC or clipping	6 (46)	3 (18)	
Average amount of injected polidocanol per each angioectasia (mL)	0.73 [0.5-1.0]	0.59 [0.5-1.0]	0.0969
Treatment success rate	13 (100)	17 (100)	
Adverse events	0 (0)	0 (0)	
Hemorrhage after treatment	0 (0)	0 (0)	

Data are presented as frequency (percentage) or mean [range], as appropriate. SSc: systemic sclerosis, PDI: polidocanol injection, APC: argon plasma coagulation

The treatment strategy, average amount of injected polidocanol, and treatment success rate did not differ significantly between the two groups.

The details of a case of lcSSc with small-bowel angioectasia are shown in Fig. 1. Telangiectasia is found on the lips and hands. CE revealed that multiple angioectasias were predominantly located in the jejunum. These lesions were treated with PDI combined with APC. No adverse events or rebleeding were noted after endoscopic treatment.

Fig. 2 shows the incidence of metachronous small-bowel angioectasia in SSc and non-SSc patients. The incidence of metachronous small-bowel angioectasia was significantly higher in SSc patients than in non-SSc patients. New lesions indicated for treatment (Type 1a angioectasia with oozing: 4 patients, Type 1b angioectasia: 1 patient) were observed only in SSc patients, even after a prolonged period following treatment. No new lesions were observed in non-SSc patients.

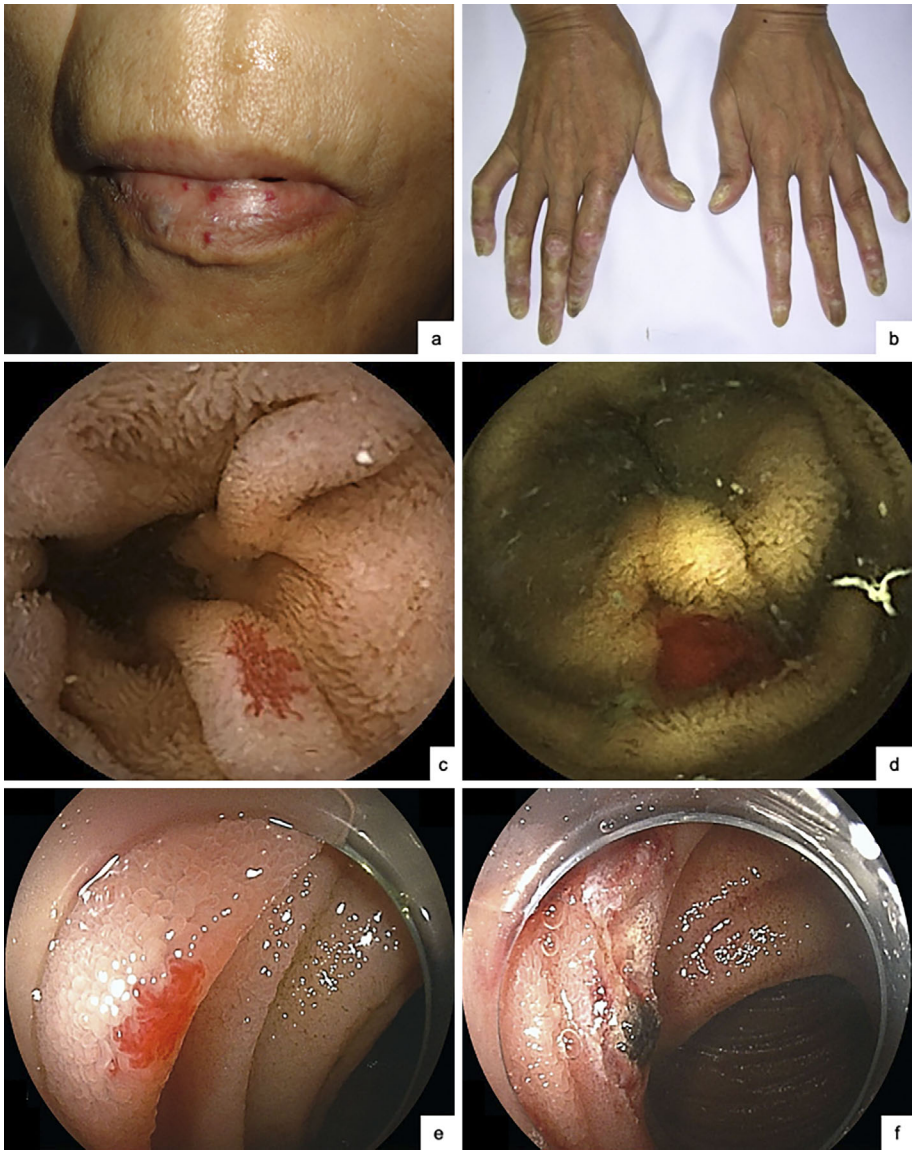

Figure 1. **A case of lcSSc with small-bowel angioectasia. Telangiectasia on the lips and hands was also noted (a, b). Representative images of Type 1b angioectasia are shown in (c-e). This lesion was treated with PDI combined with APC (f). lcSSc: limited cutaneous systemic sclerosis, PDI: polidocanol injection, APC: argon plasma coagulation**

Discussion

This study revealed that PDI was a useful treatment method for small-bowel angioectasia in SSc patients and that metachronous vascular lesions occurred after a long period of time following endoscopic hemostasis in SSc patients compared with non-SSc patients. Anemia and telangiectasia on the skin were predictive factors for small-bowel angioectasia in SSc patients. Gastrointestinal diseases manifest as esophageal dysmotility, gastroparesis, colonic dysmotility, and constipation, and these symptoms have a profound influence on patients' quality of life.

Notably, the gastrointestinal tract is one of the most commonly affected organs in SSc patients (2, 3), and gastrointestinal tract involvement frequently leads to substantial morbidity. SSc patients are characterized by gastrointestinal dysfunction, including SIBO (23, 24). SSc patients have a high incidence of small-bowel lesions, especially vascular lesions (22). However, few studies have reported the cause of gastrointestinal angioectasia in SSc patients. A previous study suggested that chronic hypoperfusion stimulates the sympathetic nerve system, which causes the intestinal vascular smooth muscle to relax, resulting in localized vascular dilation (25). In addition, it is believed that gastrointestinal angioectasia is an acquired vascular lesion caused by chronic hypoxia in the microcirculation (13-15). A previous study also reported that the overexpression of angiogenic factors, such as vascular endothelial growth factor, is involved in the development of angioectasia (26).

Small-bowel angioectasia is known to lead to OGIB (6, 7). Because the wall of the small bowel is thinner

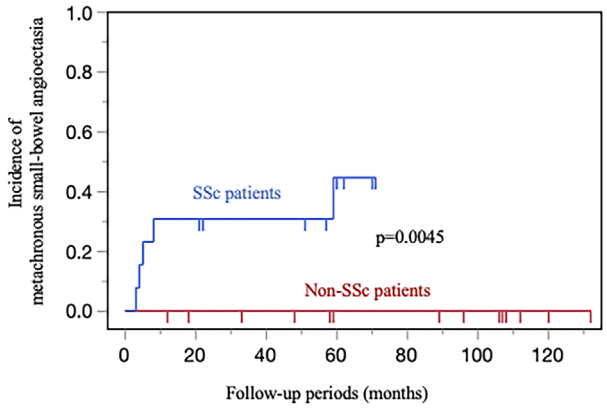

Figure 2. Incidence of metachronous small-bowel angioectasia in SSc and non-SSc patients. The Kaplan-Meier curve revealed a significant difference in the incidence of metachronous small-bowel angioectasia between the SSc and non-SSc patients. Recurrence of angioectasia was observed in SSc patients, even after a prolonged period following treatment. SSc: systemic sclerosis

than that of other parts of the gastrointestinal tract, endoscopists need to consider the possibility of perforation after treatment for small-bowel angioectasia. APC uses a jet of ionized argon gas that is directed through a probe, thus allowing the gas to be transmitted to the small-bowel angioectasia without directly contacting the mucosa (27). The superficial mucosal layer alone can be coagulated by controlling the power setting, gas flow, and duration of coagulation. APC can safely treat small-bowel angioectasia, which improves the patient's quality of life by reducing the need for transfusion (28). However, the rebleeding rate after treatment for small-bowel angioectasia was approximately 43% according to a recent meta-analysis (29). Notably, PDI has been demonstrated to be useful for treating SSc patients with small-bowel angioectasia. For example, the usefulness of PDI for treating gastrointestinal bleeding has been reported in several studies (30-33). Consistently, we previously reported the usefulness of PDI for treating Type 1a angioectasia and PDI combined with APC or clipping for treating Type 1b angioectasia (4, 5). Furthermore, in the present study, the outcomes of PDI for small-bowel angioectasia in SSc patients were also good.

In addition, several studies have reported on the hemostatic properties of polidocanol in dogs (34, 35). Immediately after injection, polidocanol causes thrombus formation in small blood vessels and edema in the submucosal layer, resulting in a localized decrease in blood flow. Furthermore, late hemostatic effects were associated with vascular inflammation, which causes thrombus formation. Moreover, fibrosis in the submucosal layer and a slight reduction in the capillary density occurred after the improvement of vascular inflammation, resulting in a sustained hemostatic effect.

Several limitations associated with the present study warrant mention. First, it was a single-center retrospective study. A possibility of bias in terms of patient selection could not be excluded. Second, the number of participants was relatively small. The reliability of the multivariate analysis may not be sufficient. Third, our observation period was relatively short, although surveillance CE is necessary for SSc patients. Therefore, further large-scale and long-term studies are needed to address these limitations.

In conclusion, our data showed that CE should be performed in SSc patients with anemia and/or telangiectasia on the skin. Because small-bowel angioectasia in SSc patients occurs after a long period following endoscopic hemostasis, it is necessary to perform CE on a regular basis. In addition, PDI might be a useful treatment for patients with small-bowel angioectasia.

The authors state that they have no Conflict of Interest (COI).

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