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【 CASE REPORT 】

Localized Gastric Amyloidosis that Displayed Morphological Changes over 10 Years of Observation

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Abstract:
We herein report an extremely rare case of localized gastric amyloidosis (LGA) with morphological changes during the follow-up. A 71-year-old woman who had a depressed lesion with central elevation in the gastric lower body was diagnosed with LGA. Esophagogastroduodenoscopy at 10 years after the initial examination showed that the lesion had grown and changed morphologically, exhibiting a submucosal tumor-like appearance. Since the lesion was confined to the submucosa, the patient underwent endoscopic submucosal dissection. The final pathological diagnosis was amyloid light-chain (AL)-type LGA. This case may provide useful information regarding the natural history of AL-type LGA.

Key words: localized gastric amyloidosis, morphological change

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Introduction

Amyloidosis is a spectrum of diseases that leads to the dysfunction of various organs due to extracellular deposits of insoluble and fibrillar amyloid proteins (1). This disease commonly manifests as systemic involvement of multiple tissues and organs, but amyloidosis limited to the stomach is relatively rare (2). Although cases regarding localized gastric amyloidosis (LGA) have been reported, there have been no cases with long-term observation and morphological changes.

We herein report a case of LGA that displayed increased size and morphological changes over an extended follow-up duration of 10 years.

Case Report

A 71-year-old woman with a depressed lesion in the anterior wall of the gastric lower body was referred to our institution for a further examination. She had no subjective symptoms and no relevant medical history. Esophagogastroduodenoscopy (EGD) showed a reddish and partially yellowish depressed lesion with central elevation (Fig. 1A). Biopsy specimens revealed amyloid deposits in the gastric mucosa (Fig. 2A, B). A biopsy from the duodenum was negative for amyloid. Laboratory data, such as blood, biochemistry, tumor marker and urinalysis, were within normal limits. *Helicobacter pylori* was positive in the serum IgG antibodies (40 U/mL). Serum protein electrophoresis did not reveal monoclonal spikes, and there was no proteinuria.

An electrocardiogram and echocardiogram were normal and computed tomography revealed no abnormal findings. Colonoscopy also showed no abnormalities, and biopsy specimens from the rectum revealed no amyloid deposits. Several erosions were found in the ileum, but no amyloid deposits were present in the biopsy specimen. Based on these results, LGA was suspected, and no treatment but instead a follow-up at an interval of one year by EGD and two to three years by computed tomography was selected.

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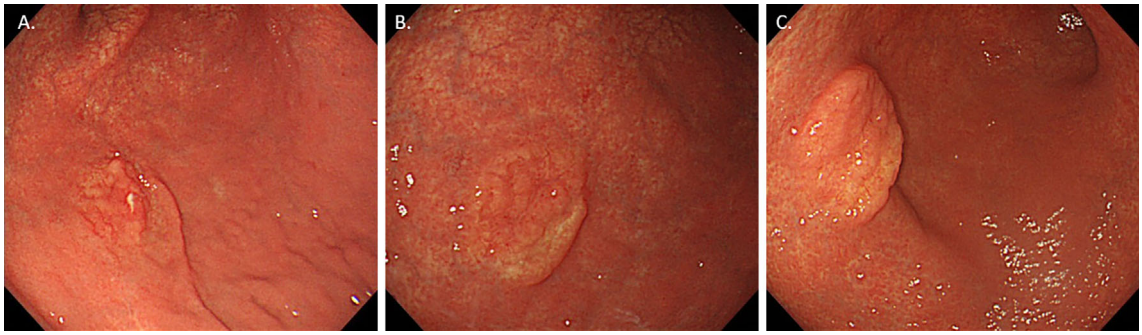

Figure 1. **Natural history of LGA. A, B, and C are conventional white light endoscopy findings at the initial endoscopy and 5 and 10 years after the initial examination, respectively. Initial endoscopy showed a reddish and partially yellowish depressed lesion with central elevation, but the lesion had grown and changed morphologically to exhibit a SMT-like appearance at later evaluations. LGA: localized gastric amyloidosis, SMT: submucosal tumor**

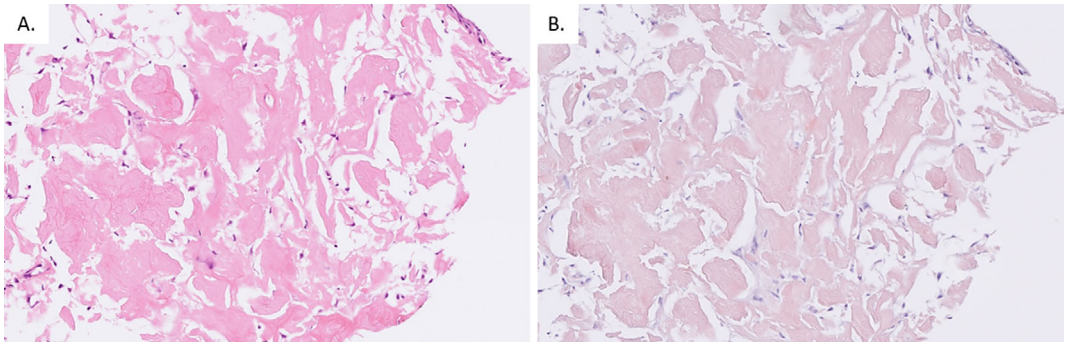

Figure 2. **Pathological findings of LGA in biopsy specimen at the initial diagnosis. Hematoxylin and Eosin staining showed eosinophilic amorphous material (A). Congo red staining was positive for the material (B). LGA: localized gastric amyloidosis**

The lesion gradually grew and changed morphologically (Fig. 1B), and EGD at 10 years after the initial examination showed that the lesion now exhibited a submucosal tumor (SMT)-like appearance (Fig. 1C). Magnifying endoscopy with narrow-band imaging showed a dilated vessel but neither microvessel nor microsurface irregularity (Fig. 3A), with this lesion being covered with normal epithelium. On endoscopic ultrasonography (EUS), the lesion was mainly localized in the third layer (Fig. 3B), corresponding to the submucosa. Although narrowing of the third layer was observed, there was no evidence of interruption. The lesion consisted of a relatively uniform hyperechoic finding in the superficial part and a gradual hypoechoic finding in the deeper part.

A biopsy specimen from the lesion showed amyloid deposits. Laboratory data, including serum alkaline phosphatase and immunoglobulin levels, serum and urinary immunoelectrophoresis, electrocardiogram, echocardiogram, whole-body computed tomography, gallium scintigraphy, and biopsy specimen from the rectum, ileum, duodenum and stomach other than LGA, at that time showed no abnormal findings. Bence-Jones protein in the urine was negative. Since a case in which the initial diagnosis by a biopsy was gastric amyloidosis but the final diagnosis was plasmacytoma with amyloid deposits in the stomach had been reported (3), our patient underwent endoscopic submucosal dissection (ESD) to obtain the whole pathology.

The lesion was 25 mm in maximal diameter, and hematoxylin and eosin staining showed an aggregation of eosinophilic amorphous material from the lamina propria to the submucosal layer (Fig. 4A, B). Infiltration of many plasma cells was present in the lamina propria mucosa, but there was no monoclonal light chain of immunoglobulin. No findings indicated gastric cancer, malignant lymphoma, or plasmacytoma. Congo red staining was positive for the material (Fig. 4C), and polarizing microscopy showed green birefringence (Fig. 4D). Immunohistochemical staining of amyloid light-chain (AL) for λ was positive (Fig. 4E), while that for κ, anti-amyloid A (AA) component antibody, and anti-transthyretin antibody was negative. No amyloid deposits were observed in the horizontal or vertical margin.

The final diagnosis of this lesion was amyloid AL-type LGA. No recurrence or progression to systemic amyloidosis has been confirmed during the six-year follow-up after ESD.

Discussion

We described a case of LGA that showed growth and

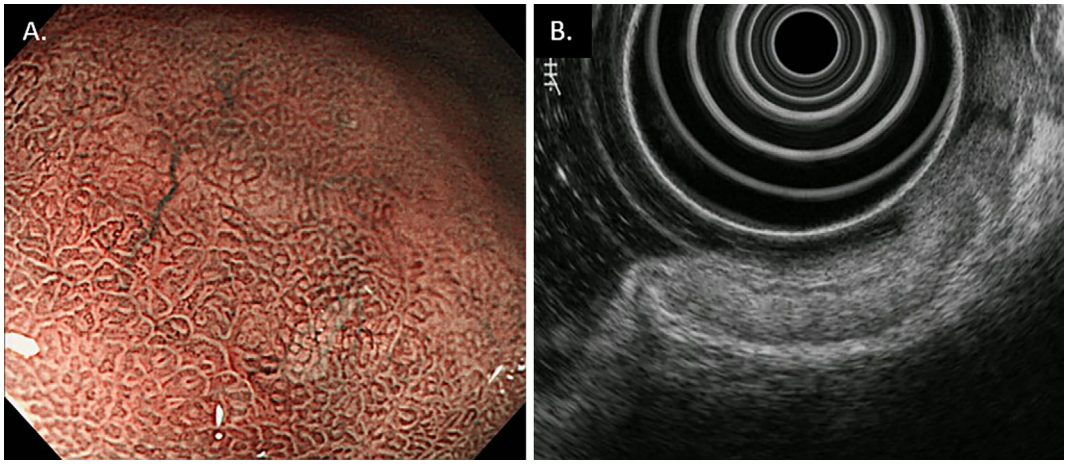

Figure 3. **Endoscopic images of LGA at 10 years after the initial examination. Magnifying endoscopy with narrow-band imaging showed a dilated vessel but neither microvessel nor microsurface irregularity (A). In EUS, the lesion in the third layer consisted of a relatively uniform hyperechoic finding in the superficial part and gradual hypoechoic findings in the deeper part (B). LGA: localized gastric amyloidosis, EUS: endoscopic ultrasonography**

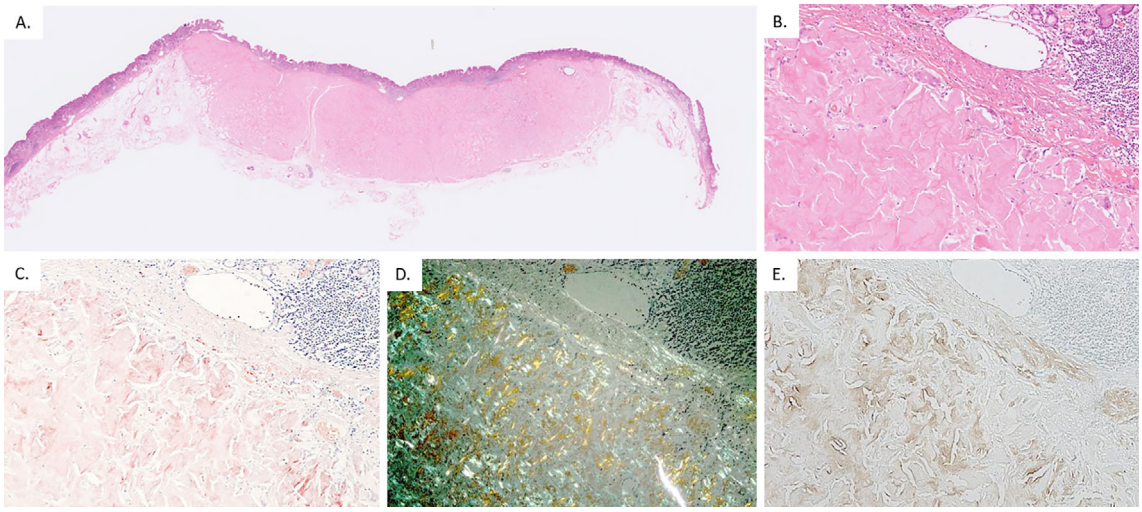

Figure 4. **Pathological findings of LGA in the ESD specimen. Hematoxylin and Eosin staining showed an aggregation of eosinophilic amorphous material from the lamina propria to the submucosal layer (A, B). Congo red staining was positive for the material (C), and polarizing microscopy showed green birefringence (D). Immunohistochemical staining of AL for λ was positive (E). LGA: localized gastric amyloidosis, ESD: endoscopic submucosal dissection, AL: amyloid light-chain**

morphological change during a long-term observation. In addition, no recurrence of amyloidosis appeared during the long-term follow-up after ESD.

According to the classification system proposed by the International Society of Amyloidosis, amyloidosis is classified into systemic and localized types based on the deposition of amyloid fibrils in the extracellular spaces of organs and tissues (4). Gastrointestinal involvement is common in amyloidosis; however, most cases are systematic amyloidosis, and local deposits of amyloid in the gastrointestinal tract without systemic involvement is uncommon (5). Amyloidosis limited to the stomach is relatively rare (2, 5-17). To our knowledge, there have been 11 case reports with follow-up after the initial diagnosis (Table) (2, 5-8, 10, 11, 13-15), but all of them showed a relatively short natural history, and there have been no reports describing morphological changes during the follow-up.

The present case showed morphological changes during 10 years of follow-up. Although Biewend et al. reported that 98% of patients with localized amyloidosis in various organs, not including LGA, remained free of systemic disease on follow-up evaluations from 6 months to 23 years (18), Koike et al. reported a case that was initially diagnosed as LGA but finally diagnosed as plasmacytoma with amyloid deposits at 2 years after the initial diagnosis (3). In the present case, there was no evidence of progression to systemic

Table. Reports of LGA with the Follow-up.

Reference	Age/ sex	Type	Location	Symptom	Endoscopic finding	Treat-ment	Follow-up duration	Findings at follow-up
6	68/F	Unknown	Antrum	Pain, nausea	Scirrhous	Surgery	10 months†	No recurrence
7	60/F	AL	Body	Hematemesis	Thickened folds	Surgery	4.5 years	No recurrence
8	52/F	AL (λ)	Lower body	None	Erosion	EMR	2 years	No progression
5	50/F	AA	Lower body	Epigastric discomfort	Ulcer	Surgery	9 months	No recurrence
10	55/M	Unknown	Lower body	Epigastric pain	White-yellowish area	PPI	10 months	No symptom
2	76/F	AL (λ)	Upper to lower body	Epigastric discomfort	Scirrhous	Follow	6 years	No progression
11	33/F	Unknown	Body, fundus	Epigastric pain	Erosion, SMT	ESD with DMSO	1.5 years	No recurrence
13	75/M	AL	Lower body	None	Depressed	Follow	2 years	No progression
14	64/M	AL (λ)	Middle body	None	SMT	Follow	5 years	No progression
15	59/M	Unknown	Whole	None	Pale-colored depressed	Follow	3 years	No progression
Present case	71/F	AL (λ)	Lower body	None	Depressed with internal nodule SMT	Follow →ESD	10 years →6 years	Morphological change →no recurrence

† Death by breast cancer.

LGA: localized gastric amyloidosis, AL: amyloid light-chain, EMR: endoscopic mucosal resection, AA: amyloid A, PPI: proton pump inhibitor, SMT: submucosal tumor, ESD: endoscopic submucosal dissection, DMSO: dimethyl sulfoxide

amyloidosis during the 10-year follow-up. However, since morphological changes were observed and EUS showed that this lesion was confined to the submucosa, we performed ESD, resulting in the final diagnosis of AL-type LGA. Thus, this case revealed that LGA could show morphological change during the follow-up.

Local progression of localized amyloidosis has been reported in some organs (18, 19). Hazenberg et al. indicated that local progression of amyloid slows down after six years of follow-up (19). A theory concerning a toxic effect on plasma cells that creates a self-limiting neoplasm was suggested in localized AL amyloidosis (20), and the slowing-down of this disease was speculated to have been caused by exhaustion of the underlying clonal plasma cells (19). However, our case showed progression even six years after the initial diagnosis, although many plasma cells had infiltrated the lamina propria mucosa in the ESD specimen. Based on the previous theory (19), the presence of many plasma cells may have been due in part to the continuous local progression of amyloid, and LGA may have further progressed when follow-up with no treatment was selected.

Thus far, 36 human amyloid proteins have been identified, of which 14 appear to be associated only with systemic amyloidosis while 19 are localized forms (4). Among them, AA- and AL-type amyloidosis are frequently encountered in clinical practice, and the latter in particular is associated with localized amyloidosis. In addition, the most frequent type of LGA is AL-type, and this was also true in the present case. AL-type amyloid is mainly deposited below the muscularis mucosa, whereas AA-type amyloid is mainly deposited in the lamina propria mucosa (21). Thus, AL-type LGA tends to form submucosal tumors, which are sometimes difficult to diagnose by an endoscopic biopsy. In the present case, we did not obtain amyloid tissue from several endoscopic biopsies during the follow-up, and EGD at 10 years after the initial EGD showed an SMT-like appearance. Therefore, deeper tissue sampling may be required when LGA is suspected endoscopically.

The EUS findings of LGA are not consistent (8, 11, 12), and few studies have compared EUS images with the pathology. In the present case, ESD enabled us to compare the EUS findings with the corresponding pathology. As a result, we noted an interesting EUS finding in this case of LGA: EUS showed relatively uniform hyperechoic findings in the superficial part of the lesion and gradual hypoechoic findings in the deeper part of the lesion. This may be due to the presence of amyloid deposits without a cell component. Indeed, this finding differs from the typical EUS findings of gastric cancer (hypoechoic) (22) or malignant lymphoma (hypoechoic or very hypoechoic) (23). Although further studies will be required to reach a definitive conclusion, this finding may be helpful for diagnosing amyloidosis.

In summary, we experienced an extremely rare case of AL-type LGA that grew and changed shape to resemble an SMT-like lesion over an extended follow-up duration of 10 years. This case may provide valuable information regarding the natural history of AL-type LGA.

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

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