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CLINICAL CASE REPORT

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Endoscopic Findings of Small-Bowel Lesions in Familial Amyloid Polyneuropathy

A Case Report

Kensuke Asakura, MD, Shunichi Yanai, MD, PhD, Shotaro Nakamura, MD, PhD, Keisuke Kawaski1, MD, Makoto Eizuka, MD, Kazuyuki Ishida, MD, PhD, Tamotsu Sugai, MD, PhD, Mitsuharu Ueda, MD, PhD, Taro Yamashita, MD, PhD, Yukio Ando, MD, PhD, and Takayuki Matsumoto, MD, PhD

Abstract: Familial amyloid polyneuropathy (FAP) is an autosomal dominant disease associated with the mutations in the transthyretin gene. To date, the endoscopic findings of the small-bowel lesions of FAP have never been described. We report a rare case of FAP with gastrointestinal involvement.

A 71-year-old woman complaining of refractory diarrhea for 1 year was referred to our institution. She had sensory disturbance, movement disorder due to muscle weakness, and autonomic nervous system disorders including orthostatic hypotension and dysuria. Her eldest sister had cardiac amyloidosis. Small-bowel radiography and retrograde double-balloon endoscopy (DBE) revealed that fine granular protrusions were diffusely observed both in the jejunum and ileum. Histologic examination of the biopsy specimens obtained from the small bowel revealed perivascular amyloid deposits mainly in the muscularis mucosae and submucosa, which were immunoreactive with transthyretin antibodies. Analysis of the genomic DNA showed a heterozygous Gly47Val mutation in the transthyretin gene. Thus a diagnosis of FAP was established.

Diffuse fine granular protrusions in the jejunum and the ileum visualized by small-bowel radiography and DBE may be characteristic of FAP. Multiple biopsies from the gastrointestinal mucosa are recommended for the definitive histologic diagnosis of FAP.

(*Medicine* 95(11):e2896)

Abbreviations: $A\beta_2$ = β_2-microglobulin amyloidosis, AA = amyloid A protein amyloidosis, AL = immunoglobulin light chain-derived amyloidosis, DBE = double-balloon endoscopy, EGD = esophagogastroduodenoscopy, FAP = familial amyloid polyneuropathy, TTR = transthyretin.

Editor: Gilbert Fruhwirth.
Received: September 27, 2015; revised and accepted: January 27, 2016.
From the Division of Gastroenterology, Department of Internal Medicine (KA, SY, SN, KK, TM); the Division of Molecular Diagnostic Pathology, Department of Pathology; School of Medicine, Iwate Medical University, Morioka (ME, KI, TS); and Department of Neurology, Graduate School of Medical Sciences, Kumamoto University (MU, TY, YA), Honjo, Kumamoto, Japan.
Correspondence: Kensuke Asakura, Division of Gastroenterology, Department of Internal Medicine, Iwate Medical University School of Medicine, Uchimaru 19-1, Morioka 020-8505, Japan (e-mail: asaken@iwate-med.ac.jp).
Written informed consent was obtained from the patient for publication of this case report and accompanying images.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002896

INTRODUCTION

Familial amyloid polyneuropathy (FAP) is an autosomal dominant disease associated with the mutations in the transthyretin (TTR) gene.[1–3] Pathologically, FAP is characterized by amyloid deposition in various organs and tissues, including peripheral nerves, heart, kidney, and gastrointestinal tract.[1,4] Clinically, the disease usually begins in the third to fifth decade of life, and the most frequent symptoms are sensorimotor neuropathy, autonomic dysfunction, and cardiopathy.[1] Whereas the involvement of the gastrointestinal tract wall, especially the gastrointestinal autonomic nerves, by TTR amyloid is common in FAP,[4–6] the endoscopic findings of FAP have rarely been described.[6] To date, the endoscopic findings of the small-bowel lesions of FAP have never been described. In the present study, we report the first case of FAP in whom the characteristic findings in the small bowel were detected by double-contrast radiography and double-balloon endoscopy (DBE).

CASE REPORT

A 71-year-old Japanese woman was referred to our institution in September 2014, complaining of recurrent diarrhea for 1 year and weight loss of 6 kg during 1 month. The patient also complained of muscle weakness, peripheral paresthesia, and subjective distal hypoesthesia in her lower extremities. Her eldest sister had been diagnosed as cardiac amyloidosis. On physical examination, no abnormalities were noted in her breath or cardiac sounds. A neurological examination revealed muscle weakness and decreased deep tendon reflexes in the lower extremities. Autonomic nervous system disorders including orthostatic hypotension and dysuria were noted. The laboratory and urinalysis data showed mild hypoalbuminemia (3.7 g/dL). Neither serum M-protein, amyloid A protein, nor urine Bence-Jones protein was detected. The electrocardiogram revealed low voltages in the limb lead.

Esophagogastroduodenoscopy (EGD) showed no localized lesions in the stomach except for several fundic gland polyps, whereas fine granular mucosa with various-sized protrusions was recognized in the duodenal bulb (Figure 1A). Biopsy specimens from the normal-appearing mucosa of the stomach and granular mucosa of the duodenal bulb revealed amyloid depositions around small vessels and in the stroma of the submucosa, which was confirmed by Congo red and direct fast scarlet stains (Figure 1B). Colonoscopy showed no definite

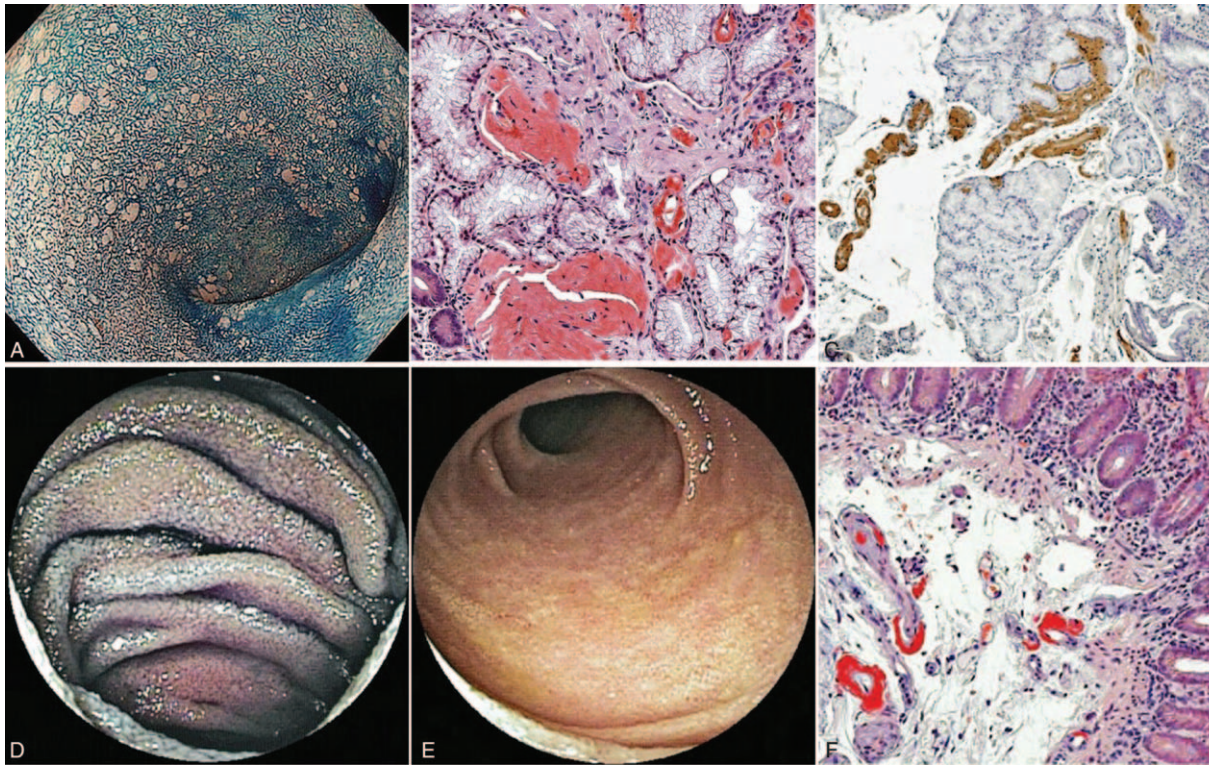

FIGURE 1. Endoscopic and histologic findings of FAP. A, Endoscopic image of duodenal bulb showing fine granular mucosa with numerous various-sized protrusions. B, C, Histologic pictures of the biopsy specimen reveals amorphous amyloid deposits around small blood vessels and the stroma of the submucosa, which are highlighted by Congo red stain (B) and the immunohistochemical staining for antitransthyretin antibody (C). D, E, Double-balloon endoscopic images of the jejunum (D) and the ileum (E); fine granular protrusions can be diffusely observed. F, Histologic pictures of the biopsy specimens from the jejunum reveal amorphous amyloid deposition around small blood vessels in the submucosa (Congo red stain, ×200). FAP = familial amyloid polyneuropathy.

abnormalities. Double-contrast small-bowel radiography demonstrated fine barium flecks and granular appearance in the jejunum and in the ileum (Figure 2). Retrograde DBE revealed that fine granular protrusions were diffusely observed both in the jejunum (Figure 1D) and the ileum (Figure 1E). Histologic examination of the biopsy specimens from the fine granular protrusions of the jejunum and ileum, and the normal-appearing mucosa of the colorectum revealed perivascular amyloid depositions in the muscularis mucosae and submucosa (Figure 1F). Immunohistochemically, the amyloid depositions in the specimens from both the duodenum and the small bowel were positive for polyclonal anti-TTR antibody (DAKO; Figure 1C). Table 1 summarizes the distribution of amyloid deposition in the gastrointestinal tract of the patient. A marked amount of amyloid deposition was observed in the stroma and the vessels predominantly in the submucosa with or without muscularis mucosae of most parts of the gastrointestinal tract, except for the esophagus, ascending colon, transverse colon, and the sigmoid colon.

A heterozygous Gly47Val mutation in the *TTR* gene was identified by DNA analysis. Based on these findings, we made a diagnosis of FAP in this patient. The patient is presently getting a follow-up examination.

DISCUSSION

Systemic amyloidosis is characterized by the involvement of multiple organs and the presence of an amyloid precursor

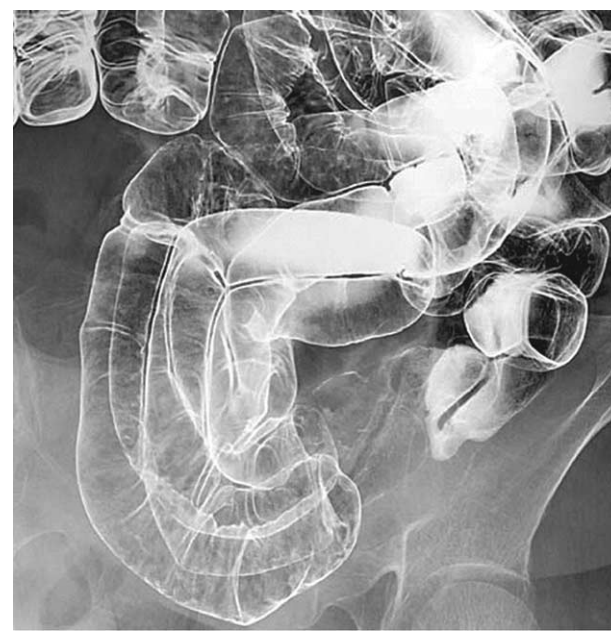

FIGURE 2. Small-bowel lesions of FAP. Double-contrast radiography demonstrates fine barium flecks and granular appearance in the ileum. FAP = familial amyloid polyneuropathy.

TABLE 1. Distribution of Amyloid Deposition in Gastrointestinal Tract of the Patient

	Epithelium	Lamina Propria	Muscularis Mucosae	Submucosa
Esophagus	Negative	Negative	Negative	Negative
Gastric antrum	Negative	2+ (S)	2+ (S, V)	NE
Gastric corpus	Negative	2+ (S, V)	2+ (S, V)	NE
Duodenal bulb	Negative	2+ (S, V)	2+ (S, V)	2+ (S, V)
Duodenal second portion	Negative	Negative	2+ (S)	2+ (S, V)
Jejunum	Negative	Negative	Negative	2+ (S, V)
Ileum	Negative	Negative	2+ (S, V)	NE
Cecum	Negative	Negative	2+ (S, V)	2+ (V)
Ascending colon	Negative	Negative	Negative	Negative
Transverse colon	Negative	Negative	Negative	Negative
Descending colon	Negative	Negative	Negative	2+ (S, V)
Sigmoid colon	Negative	Negative	Negative	Negative
Rectum	Negative	Negative	Negative	2+ (S)

1+ = moderate, 2+ = marked, NE = not evaluated, S = stroma, V = vessels.

protein in serum, which is classified into the following 4 major forms: amyloid A protein (AA) amyloidosis, immunoglobulin light chain-derived (AL) amyloidosis, dialysis-related β_2-microglobulin ($A\beta_2$) amyloidosis, and TTR-associated (ATTR) amyloidosis.[7] ATTR amyloidosis is further classified into 2 types—one is senile systemic amyloidosis (SSA), which affects around 25% of the population over 80 years of age, and the other is FAP, which affects approximately 1 in 100,000 persons.[8] Whereas wild-type TTR deposition is associated with the sporadic SSA, variant TTR deposition causes hereditary ATTR amyloidosis. More than 120 variants of *TTR* gene mutations have been associated with FAP.[1] Among them, Val30Met is the most common, accounting for approximately 50% of mutations in global populations.[1] The mutation at position 47 with substitution of Gly with Val in our patient was very rare, and our present patient was the first case of FAP with Gly47Val TTR mutation in Japan. The main symptoms of FAP are peripheral and autonomic neuropathies.[1–3] In addition, digestive, orthostatic, urinary, and cardiac symptoms often appear.[1,9]

Gastrointestinal involvement is common in systemic amyloidosis, and the small bowel is one of the most frequently involved sites.[10,11] Endoscopic findings of gastrointestinal amyloidosis include various findings such as a fine granular appearance, erosions, ulcerations, mucosal friability, diffusely distributed petechiae, thickened mucosal folds, and/or multiple protrusions.[10–13] These endoscopic features correlate to the chemical types of amyloid fibril protein.[10,13] In patients with AA amyloidosis, amyloid protein deposits mainly in the lamina propria mucosaes and perivascular walls in the subumudosa of the gastrointestinal tract. Therefore, fine granular appearance with or without mucosal friability is endoscopically observed in most cases with AA amyloidosis,[11,13] and the disease frequently causes refractory diarrhea, intestinal bleeding, and malnutrition. By contrast, in patients with AL amyloidosis, amyloid protein tends to deposit massively in the muscularis mucosa, submucosa, and muscularis propria. Endoscopically, multiple polypoid protrusions resembling submucosal tumors and thickening of the folds are characteristic of AL amyloidosis, and frequent symptoms include mechanical obstruction, intestinal pseudoobstruction, and bleeding.[10–13] In patients with Aβ2 amyloidosis, extensive infiltration and replacement of the muscularris propria by amyloid deposits is characteristic,[10,14] and the resected specimens macroscopically show a distinctive feature of rippled appearance with serosal wrinkles along the muscle layer arrangement.[14]

Endoscopic findings of FAP have been described only in a few publications.[6,11] In a study by Tada et al,[11] 1 patient with FAP underwent small-bowel endoscopy, which showed normal-appearing jejunal mucosa, and slight amyloid deposits in the musularis mucosae and submucosal vessels were detected by biopsy. Yoshimatsu et al[6] reported that endoscopic abnormalities including fine granular appearance, lack of lustre, or mucosal friability in the stomach, duodenum, and/or colorectum were observed in 5 of 9 patients (56%) with FAP. In our present case, EGD showed normal-appearing gastric mucosa and fine granular appearance with various-sized protrusions was recognized in the duodenal bulb, from both of which amyloid deposits were detected by biopsy. In addition, we could visualize diffuse fine granular protrusions in the jejunum and the ileum by double-contrast radiography and DBE, which is considered as characteristic findings for FAP (Figure 2). To the best of our knowledge, the present report is the first in the literature describing a patient with FAP whose small-bowel lesions were detected by both radiography and endoscopy.

It should be noted that the quantity of amyloid deposition in our patient was predominant in the submucosa, whereas it was none or little in the mucosa (Table 1). This finding is compatible with that in a previous literature,[6] which accounts for the fact that amyloid deposit was detected in the biopsy specimens taken from the normal-appearing mucosa. Therefore, biopsy samples should be taken not only from obviously abnormal lesions, such as granular appearance, erosions, ulcerations, mucosal friability, diffusely distributed petechiae, thickened mucosal folds, or protrusions, but also from the normal-appearing mucosa for the definitive diagnosis and evaluation of FAP.

We speculate that the cause of refractory diarrhea in our patient was probably due to autonomic neuropathy, because histologic examinations of the biopsy specimens detected only a small amount of amyloid depositions in the submucosa (Figure 1F), and a detailed histopathological analysis of autopsy specimens revealed that significant amount of amyloid deposition in the nerves in the gastrointestinal tract was frequently observed in all the patients with FAP, but not in those with AA or AL amyloidosis.[6]

CONCLUSIONS

Detailed endoscopic findings in a rare case of FAP have been presented. In addition to EGD findings showing fine granular mucosa with various-sized protrusions in the duodenum, diffuse fine granular protrusions in the jejunum and the ileum visualized by double-contrast radiography and DBE are considered as characteristic findings for FAP. Multiple biopsies, not only from such obviously abnormal lesions, but also from normal-appearing gastrointestinal mucosa, are recommended for the definitive histologic diagnosis of FAP.

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