

Endoscopic and histopathological features of gastrointestinal amyloidosis

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orders. Although GI symptoms are usually nonspecific, histopathological patterns of amyloid deposition are associated with clinical and endoscopic features. Amyloid deposition in the muscularis mucosae, submucosa, and muscularis propria has been dominant in AL amyloidosis, leading to polypoid protrusions and thickening of the valvulae conniventes, whereas granular amyloid deposition mainly in the propria mucosae has been related to AA amyloidosis, resulting in the fine granular appearance, mucosal friability, and erosions. As a result, AL amyloidosis usually presents with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction while AA amyloidosis presents with diarrhea and malabsorption. Amyloidotic GI symptoms are mostly refractory and have a negative impact on quality of life and survival. Diagnosing GI amyloidosis requires high suspicion of evaluating endoscopists. Because of the absence of specific treatments for reducing the abundance of the amyloidogenic precursor protein, we should be aware of certain associations between patterns of amyloid deposition and clinical and endoscopic features.

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Abstract

Amyloidosis is a rare disorder, characterized by the extracellular deposition of an abnormal fibrillar protein, which disrupts tissue structure and function. Amyloidosis can be acquired or hereditary, and systemic or localized to a single organ, such as the gastrointestinal (GI) tract. Clinical manifestations may vary from asymptomatic to fatal forms. Primary amyloidosis (monoclonal immunoglobulin light chains, AL) is the most common form of amyloidosis. AL amyloidosis has been associated with plasma cell dyscrasias, such as, multiple myeloma. Secondary amyloidosis is caused by the deposition of fragments of the circulating acute-phase reactant, serum amyloid A protein (SAA). Common causes of AA amyloidosis are chronic inflammatory dis-

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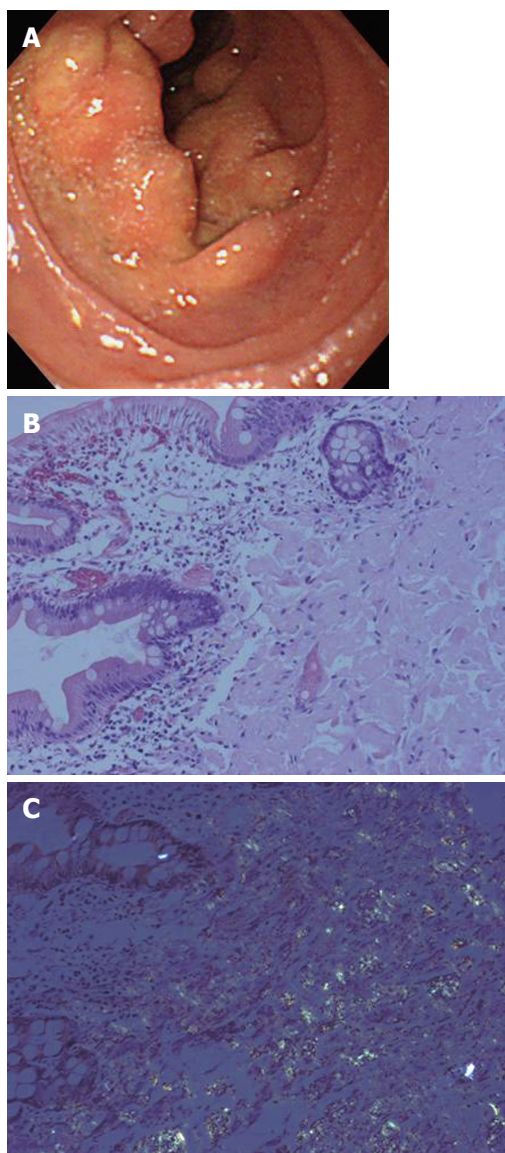


Figure 1 Endoscopic view of amyloid light chains amyloidosis in a 64-year-old man without multiple myeloma presenting abdominal fullness. A: Characteristic multiple yellowish-white polypoid protrusions and thickening of the folds in the descending duodenum are presented; B: Biopsy specimens showed marked homogenous eosinophilic deposition in the mucosae and submucosa (HE, $\times 40$); C: Congo red stain confirmed a unique "apple-green" birefringence of the amyloid deposition under polarized light ($\times 40$). All figures and legends are reproduced from^[6] with permission from Elsevier.

INTRODUCTION

Amyloidosis is a rare disorder, characterized by the extracellular deposition of an abnormal fibrillar protein, which disrupts tissue structure and function. Types of amyloidosis are classified based on the identity of the respective precursor protein^[1]. Amyloidosis can be acquired or hereditary, and systemic or localized to a single organ, such as the gastrointestinal (GI) tract. Clinical manifestations may vary from asymptomatic to fatal forms. We review the endoscopic and histopathological characteristics of GI amyloidosis with the presentation of our experiences.

TYPES OF AMYLOIDOSIS

Primary amyloidosis (monoclonal immunoglobulin light chains, AL) is the most common form of amyloidosis. AL amyloidosis has been associated with plasma cell dyscrasias, such as multiple myeloma. Secondary amyloidosis is caused by the deposition of fragments of the circulating acute-phase reactant, serum amyloid A protein (SAA). Common causes of AA amyloidosis are chronic inflammatory disorders and infections, including rheumatoid arthritis, Crohn's disease, familial Mediterranean fever, leprosy and tuberculosis^[1,2]. Due to a predominance of infections before 1990, the AA/AL ratio was 1:3; however, the ratio has been 1:17 to 1:38 due to fewer chronic infections and an increasing recognition of AL amyloidosis^[3]. Other types of amyloidosis are dialysis-related amyloidosis with the deposition of β_2 -microglobulins, and autosomal dominant systemic amyloidosis, such as familial amyloidotic polyneuropathy (FAP) with the deposition of genetically variant transthyretin^[1,2]. The incidence of the former has declined with the use of high flux hemodialysis.

THE ASSOCIATION OF CLINICAL FEATURES AND ENDOSCOPIC FINDINGS

Presentations of systemic amyloidosis include weakness, weight loss, neuropathy, cardiopathy, nephropathy and arthropathy, all of which can be refractory^[1,2]. Among patients with systemic amyloidosis, the involvement in the GI tract is very common. The small intestine is most commonly affected in the GI tract^[4,5]. Diagnosis requires confirmation of the presence of amyloid by histopathology using Congo red staining (Figure 1). Although GI symptoms are usually nonspecific and include macroglossia, dysphagia, abdominal pain, hemorrhage, constipation, diarrhea and malabsorption, patterns of amyloid deposition are associated with clinical and endoscopic features^[6,7]. Amyloid deposition in the muscularis mucosae, submucosa and muscularis propria has been dominant in AL amyloidosis, leading to polypoid protrusions and thickening of the valvulae conniventes, whereas granular amyloid deposition mainly in the propria mucosae has been related to AA amyloidosis, resulting in the fine granular appearance, mucosal friability and erosions^[6]. As a result, AL amyloidosis usually presents with constipation, mechanical obstruction or chronic intestinal pseudo-obstruction, while AA amyloidosis presents with diarrhea and malabsorption^[6]. Typical endoscopic images of duodenal lesions in AL amyloidosis at our institute^[8] are shown in Figure 1. Characteristic polypoid protrusions and thickening of the folds are presented. In Figure 2, gastroduodenal lesions in AA amyloidosis caused by rheumatoid arthritis are depicted. More friable duodenal mucosa and reddish colonic mucosa of AA amyloidosis caused by familial Mediterranean fever are disclosed in Figures 3 and 4. Table 1 shows a brief comparison of characteristics of AL and AA amyloidosis. In addition,

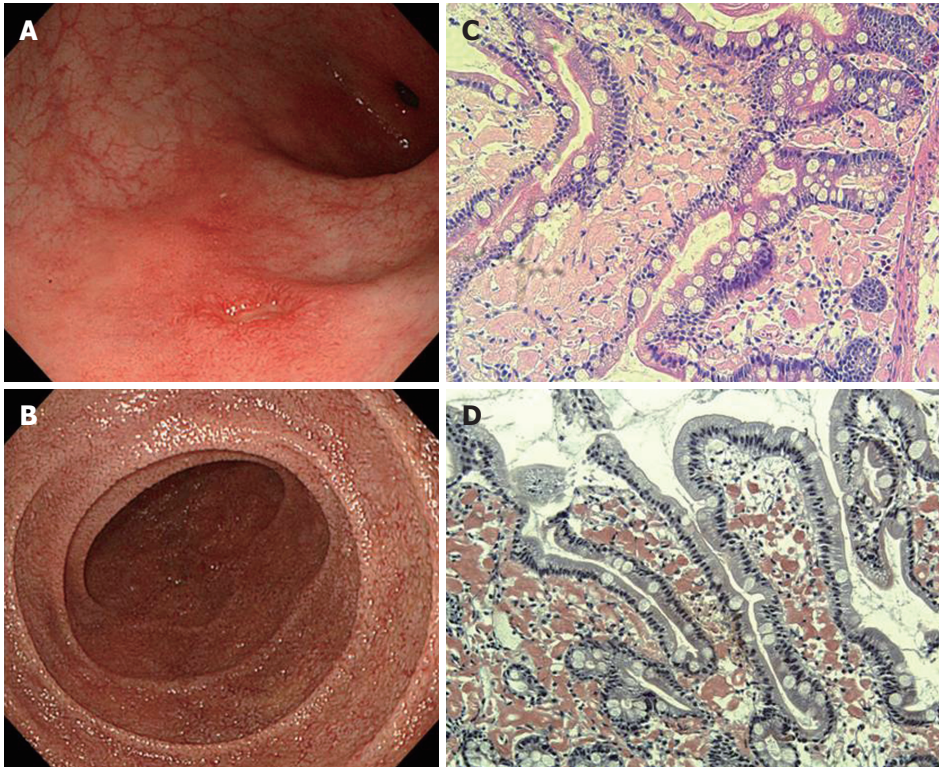


Figure 2 Endoscopic views of amyloid A amyloidosis in a 45-year-old woman with rheumatoid arthritis. A: A round ulcer surrounded by longitudinal reddish mucosa is presented in the gastric antrum. Histopathological examination confirmed amyloid deposition; B: Fine granular mucosa in the descending duodenum; C: Biopsy of the duodenal lesion showing marked amorphous eosinophilic deposition in the lamina propria mucosae (HE, $\times 100$); D: Congo red staining showing amyloid deposition ($\times 100$).

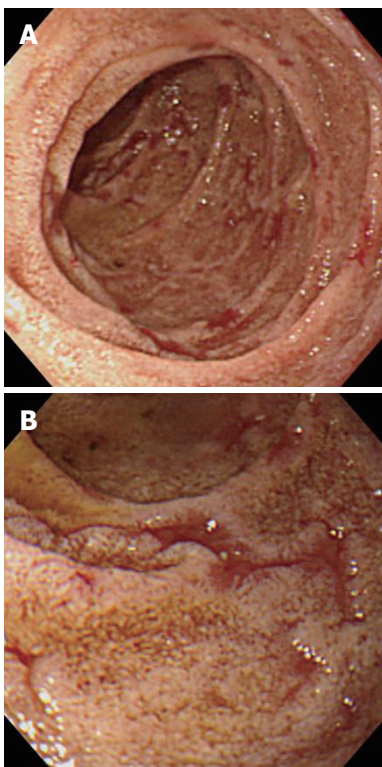


Figure 3 Endoscopic views of amyloid A amyloidosis in a 45-year-old man with familial Mediterranean fever. A: Friable granular mucosa with in the descending duodenum; B: Closer observation revealing whitish dilated villi with multiple reddish erosions.

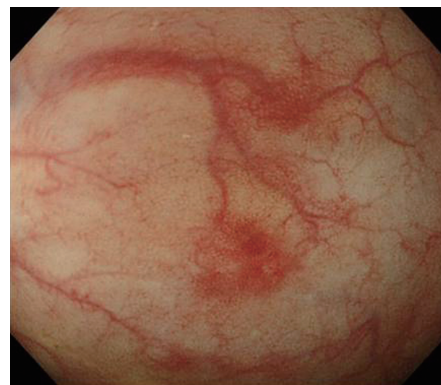


Figure 4 Endoscopic views of amyloid A amyloidosis in a 55-year-old man with familial Mediterranean fever. Patchy reddish mucosa was presented along with submucosal veins. Histopathological examination confirmed amyloid deposition.

submucosal hematoma, ulcers and hemorrhagic bullous colitis, which may be caused by amyloid infiltration, are other features in the setting of GI bleeding in AL amyloidosis^[9,10]. Our experience with hemorrhagic colonic lesions in AL amyloidosis^[11] is shown in Figure 5. Characteristic yellowish plaque-like infiltrative lesions, submucosal hematoma and ulceration are presented.

As for other types of amyloidosis, dialysis-related β_2 -microglobulin amyloidosis has a similar presentation to AL amyloidosis^[12]. In FAP, endoscopic findings of GI tract are mostly a mild, fine, granular appearance and the

Table 1 Comparison of characteristics of amyloid light chains and amyloid A amyloidosis^[1,2,6,7]

| | amyloid light chains amyloidosis | amyloid A amyloidosis |
|---|--|--|
| Causes | Idiopathy and plasma cell dyscrasias | Chronic inflammatory disorders and infections |
| Deposition | Monoclonal immunoglobulin light chains | Serum amyloid A protein |
| Gastrointestinal site of amyloid deposition | The muscularis mucosae, submucosa and muscularis propria | The propria mucosae |
| Gastrointestinal symptoms | Constipation, mechanical obstruction and chronic intestinal pseudo-obstruction | Diarrhea, malabsorption and weight loss |
| Endoscopic and radiological features | Polypoid protrusions and thickening of the folds | Fine granular appearance and mucosal friability |
| Treatments | Prokinetic agents and myeloma-type chemotherapy | Control of the underlying inflammatory disorders |

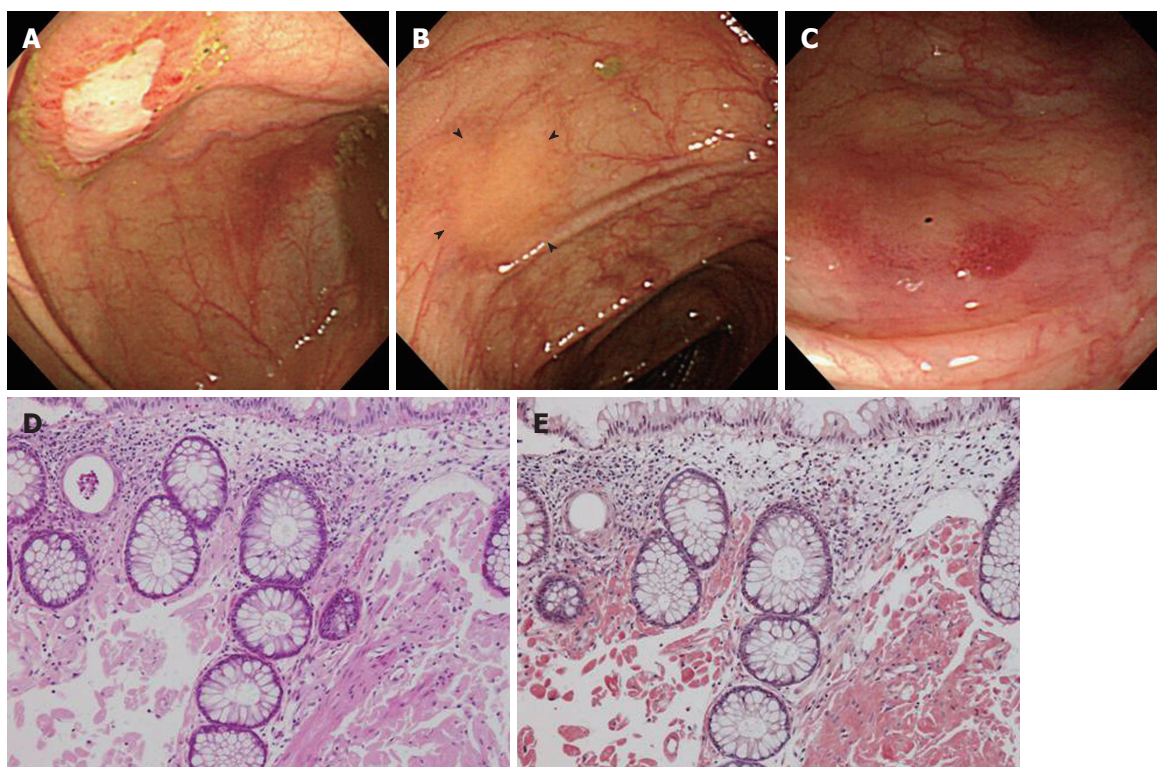


Figure 5 Endoscopic views of amyloid light chains amyloidosis in an 80-year-old woman without multiple myeloma presenting hematochezia. A: Colonoscopy showing a round ulcer in the cecum; B: A patchy yellowish plaque-like infiltrative lesion (arrowheads) relatively normal-appearing intervening mucosae in the transverse colon; C: A tiny submucosal hematoma within pinky plaque-like erythema in the sigmoid colon; D: Biopsy of the colonic lesion showing marked amorphous eosinophilic deposition in the mucosa and submucosa (HE, $\times 100$); E: Congo red staining showing amyloid deposition ($\times 100$). All figures and legends are reproduced from^[11] with permission from BMJ Publishing Group Ltd.

amount of amyloid deposition in the mucosa is small compared with that in AL and AA amyloidosis. However, a significant amount of deposition is evident in the nerves of the GI tract, which may be the cause of severe diarrhea and malabsorption occasionally observed in FAP patients despite the mild macroscopic findings^[13]. Although recent advances in endoscopy, including narrow-band imaging^[14], capsule endoscopy^[15,16] and double-balloon enteroscopy^[17], have been widely applied to diagnose GI amyloidosis, plain radiographs and radiological barium examination, basic techniques, are still useful in evaluating GI amyloidosis, especially in the small intestine^[18,19]. These methods can clearly reveal fold thickening of AL amyloidosis or fine granular mucosa of AA amyloidosis, which corroborate well with the histopathological findings^[19,20].

TREATMENT OF AMYLOIDOSIS

Because of the absence of specific treatments for GI amyloidosis, therapy is aimed at reducing the abundance of the amyloidogenic precursor protein, leading to the improvement of amyloidotic organ dysfunction^[1]. Treatment of AL amyloidosis includes myeloma-type chemotherapy with melphalan and prednisone and high-dose chemotherapy with hematopoietic stem cell transplantation. Prokinetic agents may benefit dysmotility-related symptoms. Treatment of AA amyloidosis is control of the underlying inflammatory disorders, leading to the reduction of SAA. Diarrhea and malabsorption are often refractory. Supportive measures such as total parenteral nutrition and antidiarrheal agents can be beneficial^[1]. GI

tract surgery should be performed only if the benefits clearly outweigh the risks.

CONCLUSION

Amyloidotic GI symptoms are mostly refractory and have a negative impact on quality of life and survival. Diagnosing GI amyloidosis requires a high level of suspicion by the evaluating endoscopists; therefore, we should be aware of certain associations between patterns of amyloid deposition and clinical and endoscopic features.

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