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Review

Intestinal Amyloidosis: A Comprehensive Review

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Abstract

Amyloidosis is a rare yet significant condition characterized by the deposition of amyloid proteins in various tissues, resulting in a wide range of clinical manifestations. Although typically systemic, amyloidosis can occasionally present with isolated gastrointestinal involvement. Patients with this condition may experience symptoms such as nausea, vomiting, and weight loss. Small bowel involvement is most commonly observed; however, the stomach, colon, and, in rare cases, the esophagus may also be affected. Histopathological examination of the affected organ demonstrates red staining with Congo red dye and birefringence under polarized light, appearing as green reflexes. While primary amyloidosis (AL) often necessitates aggressive chemotherapy regimens, the treatment for secondary amyloidosis focuses on managing the underlying disease.

Keywords: Diarrhea, intestinal amyloidosis, weight loss

INTRODUCTION

Amyloidosis encompasses a group of diseases caused by the abnormal accumulation of amyloid proteins in the extracellular spaces of various tissues and organs, ultimately leading to organ dysfunction. The condition may be systemic or localized, as well as genetic or acquired. Commonly affected organs include the kidneys, heart, nervous system, and gastrointestinal tract. Although less prevalent than systemic forms, intestinal amyloidosis can have a profound impact on gastrointestinal function and significantly affect the quality of life.[1]

The International Amyloidosis Society's classification of amyloidosis is based on the structure of the accumulated amyloid fibrils.[2] The most common types of amyloidosis are AL (primary) amyloidosis, associated with monoclonal gammopathies; AA (secondary) amyloidosis, often linked to chronic inflammatory conditions; and Aβ2 amyloid, associated with hemodialysis. Recent research has emphasized the role of genetic factors in certain cases of amyloidosis, particularly familial amyloidosis caused by mutations in the transthyretin (TTR) gene.[3]

AL amyloidosis is the most prevalent form, with an estimated annual incidence of 10–12 per million people. The median age of patients diagnosed with AL amyloidosis is 63 years. Some studies indicate a slight male predominance, though findings vary. Geographic variations in amyloidosis prevalence have also been noted, influenced by genetic, environmental, and socioeconomic factors.

AL amyloidosis is a malignant condition often associated with multiple myeloma, in which monoclonal immunoglobulin light chains, typically lambda and less commonly kappa, are produced in the bone marrow. These monoclonal immunoglobulin light chains accumulate extracellularly as misfolded, insoluble protein complexes known as amyloids. The heart and kidneys are the most commonly affected organs, followed by the autonomic nervous system, liver, and gastrointestinal system.[4,5]

AA amyloidosis is linked to infectious, neoplastic, or inflammatory disorders, with rheumatoid arthritis being one of the most common associated conditions. Other causes include tuberculosis, chronic osteomyelitis, bronchiectasis, familial Mediterranean fever (FMF), and inflammatory bowel disease. The accumulated protein in AA amyloidosis consists of serum amyloid A protein (SAA), a hepatic acute-phase reactant.[6]

Gastrointestinal involvement frequently occurs as part of systemic amyloidosis, although it may sometimes present as isolated gastrointestinal involvement. The digestive system is affected in 3–28% of diagnosed patients, aside from cardiac, renal, or neurological involvement. In the gastrointestinal tract, amyloid deposition primarily occurs in the muscularis mucosa near vascular and nerve plexuses, which is likely responsible for the symptoms. However, amyloid deposition does not produce specific findings on endoscopic examination. Data indicate that AL amyloidosis (52.8–83.3%) is the most common type observed in endoscopic biopsies, followed by AA amyloidosis (1.5–16.2%) and ATTR amyloidosis (4.2–12.5%).[7,8] In the liver, amyloid accumulation can activate the fibrinogenic process, leading to liver fibrosis.[9]

CLINICAL MANIFESTATION

The clinical presentation of intestinal amyloidosis is highly variable, often resulting in delays in diagnosis. It can range from being asymptomatic to presenting with severe complications, such as intestinal masses or spontaneous perforation. Symptoms may include the following:

- **Diarrhea:** Diarrhea is the most frequently reported symptom, occurring in 11–46% of cases.[7] In patients with unexplained diarrhea, weight loss, or malabsorption, amyloidosis should be considered. Chronic, nonspecific watery diarrhea-often postprandial and malabsorptive-can lead to incontinence.[7,10] Less commonly, patients may experience bloody diarrhea accompanied by fever and abdominal pain. Although the exact cause of diarrhea in amyloidosis is unclear, neuropathy and impaired motility are believed to play a role. Impaired motility may also contribute to diarrhea by promoting bacterial overgrowth.[11]
- **Malnutrition and Weight Loss:** Although diarrhea is commonly reported as the most frequent symptom, weight loss is also prevalent. Inflammation associated with the disease likely contributes to weight loss. Additional factors such as malabsorption, nausea, and vomiting further exacerbate weight loss. Intestinal dysmotility is thought to be the primary cause of nausea and vomiting in these cases.
- **Intestinal Bleeding:** Intestinal bleeding occurs in 4–36% of patients with amyloidosis. The close relationship between amyloid proteins accumulated in the muscularis mucosa and the vascular and nerve beds may contribute to these hemorrhages. Endoscopy may reveal erosions, ulcerations, or bleeding in the form of leakage (Figure 1). In some cases, despite the presence of melena or hematemesis, the bleeding focus cannot be identified. 8 Another factor predisposing patients to bleeding may be the accumulation of amyloid proteins and the bleeding diathesis caused by Factor X deficiency.[12]
- **Intestinal Dysmotility and Pseudo-obstruction:** Prolonged abdominal pain, bloating, and distension may sometimes manifest as pseudo-obstruction. In suspected cases, standing direct abdominal radiography can be a useful diagnostic tool.
- **Perforation:** Although rare, some patients may present with intestinal perforation. The underlying mechanism is likely related to vascular stenosis and intestinal ischemia caused by the accumulation of amyloid proteins. Diagnosis requires obtaining a tissue sample during surgery.[13]

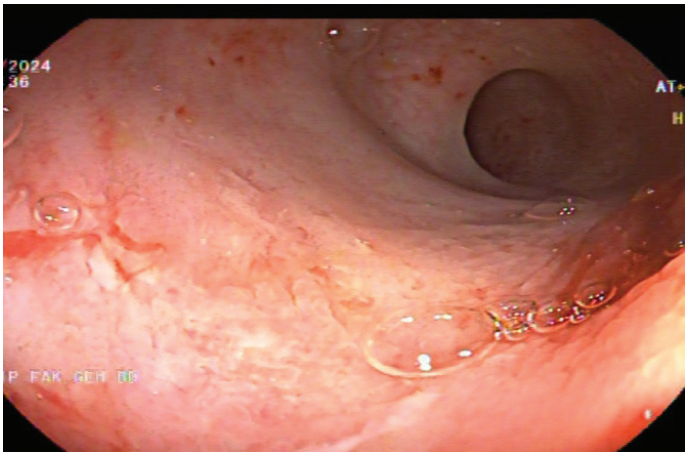

Figure 1. Ulceration in the terminal ileum (Image courtesy of the Istanbul Medicine Faculty Hospital Gastroenterohepatology Department archive; patient consent required).

INVOLVEMENT IN THE GASTROINTESTINAL TRACT

Intestinal amyloidosis primarily affects the small intestine but can also involve other parts of the gastrointestinal (GI) tract, including the colon and, less frequently, the esophagus and stomach. A study conducted in Kiel found that the site of GI tract involvement depends on the type of amyloidosis. According to this study, AL lambda amyloidosis can occur in any region of the GI tract, with its prevalence increasing slightly from proximal to distal regions, similar to amyloidosis TTR. AL kappa and AA amyloidosis were most commonly identified in biopsies from the stomach and duodenum.[14] The deposition of amyloid fibrils can lead to various structural and functional changes in the GI tract, significantly impacting digestion and absorption. The small intestine is the most common site of amyloid deposition, particularly in AL amyloidosis. Accumulated amyloid can cause mucosal thickening, resulting in malabsorption and diarrhea. Malabsorption often occurs due to damage to the intestinal villi, reducing the surface area available for nutrient absorption.[15] Amyloid accumulation in the colon may cause symptoms such as constipation or diarrhea. Colonic involvement is sometimes associated with more severe disease and may lead to complications such as gastrointestinal bleeding. Although the stomach is less commonly affected, amyloid deposits can cause gastric dysmotility, leading to symptoms such as nausea, vomiting, and early satiety.[15] Esophageal involvement is rare but can result in motility disorders, causing symptoms like dysphagia.[16] On endoscopic examination, lesions may present as ulcerations and mucosal fragility, which can lead to bleeding. Other findings include finely granular or nodular mucosa, polypoid protrusions, and thickening of the intestinal wall.[17]

DIAGNOSIS

The gold standard for diagnosing amyloidosis is the identification of amyloid protein in affected tissues using Congo red staining, which produces an apple-green birefringence under polarized light microscopy (Figure 1). In addition to this hallmark finding, amyloid fibrils infiltrate the lamina propria, leading to thickening of the intestinal wall, destruction of vascular structures that cause ischemia and ulceration, and motility defects resulting from nervous system damage. [18] However, reaching this diagnostic stage is not always straightforward. Diagnosis may be delayed due to the rarity of the disease and its nonspecific findings, which can easily be mistaken for other conditions. Amyloidosis should be considered, particularly in cases of unexplained weight loss, diarrhea, and intestinal dysmotility. For secondary amyloidosis, the presence of a chronic underlying disease associated with these symptoms may serve as a diagnostic clue. Isolated gastrointestinal tract involvement can make diagnosis more challenging. However, in systemic disease with the involvement of other organs, such as the kidneys and heart, amyloidosis should be prioritized as a differential diagnosis. In such cases, biopsies of subcutaneous fat tissue or the rectum may also confirm the diagnosis.

Although not diagnostic on their own, imaging methods can help exclude other conditions. For instance, endoscopic ultrasound examination can theoretically detect amyloid deposits in the intestinal wall.

DIFFERENTIAL DIAGNOSIS

The symptoms of intestinal amyloidosis can closely mimic those of other gastrointestinal disorders, including inflammatory bowel disease (IBD), celiac disease, and gastrointestinal infections. This overlap necessitates comprehensive investigations to ensure an accurate diagnosis (Table 1).

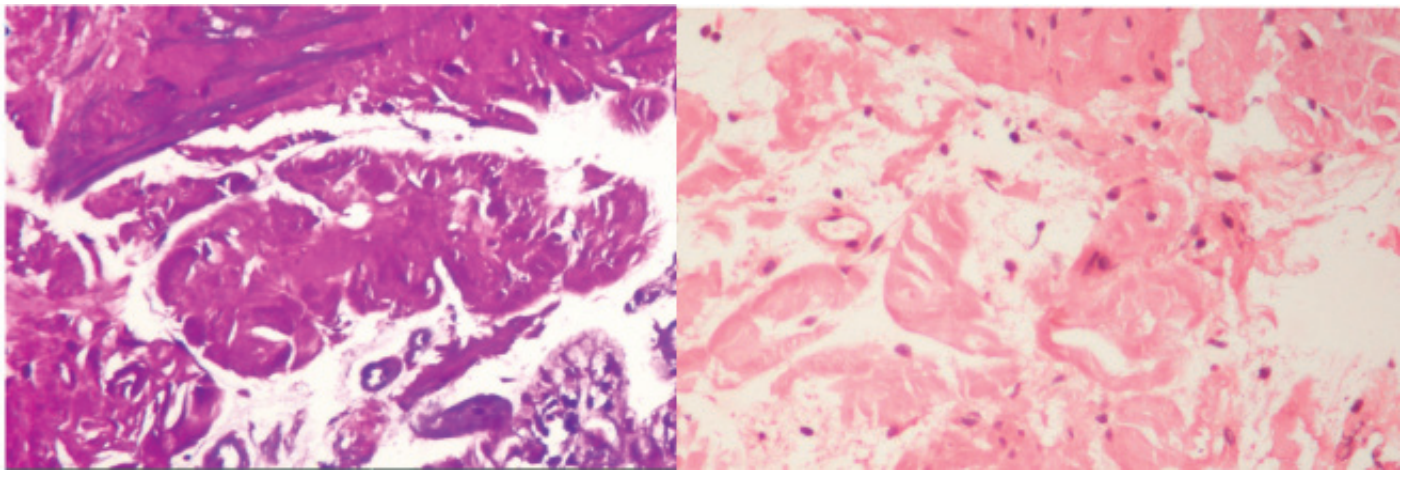

Figure 2. Duodenal biopsy of a patient with amyloidosis (Image courtesy of the Istanbul Medicine Faculty Hospital Gastroenterohepatology Department archive; patient consent required).

Table 1. Amyloidosis mimicking disease

Inflammatory Bowel Disease (IBD)	Lymphoma
Celiac Disease	Tuberculosis
Ischemic colitis	Cytomegalovirus
Collagenous colitis	Radiation colitis

TREATMENT

Management of intestinal amyloidosis focuses on addressing the underlying cause, alleviating symptoms, and preventing complications.

For patients with AL amyloidosis, treatment strategies often involve chemotherapy to reduce the clonal plasma cell population. Agents such as bortezomib and immunomodulatory drugs have shown promise.[19]

In AA amyloidosis, controlling the underlying inflammatory condition is essential. Treatment options include IL-6 receptor antibody tocilizumab for rheumatoid arthritis, colchicine for familial Mediterranean fever (FMF) and Behçet's disease, and anti-TNF therapies for inflammatory bowel diseases.

Symptomatic treatment may include dietary modifications, such as low-fat and low-fiber diets, to manage diarrhea and abdominal pain. Nutritional support, including enteral feeding, may be required in severe cases.[17] Antibiotics can be prescribed for bacterial overgrowth.[11] Neostigmine may be used to alleviate acute colonic pseudo-obstruction.[20] Diarrhea has been effectively managed with loperamide or octreotide. The approach to treating intestinal bleeding is consistent with standard treatments for bleeding from other causes.

PROGNOSIS

The prognosis of intestinal amyloidosis depends on the underlying cause and the extent of organ involvement. Early diagnosis and timely intervention are critical for improving patient outcomes.

Intestinal amyloidosis is associated with significant morbidity, as it can result in malnutrition and severe gastrointestinal complications. Studies indicate that patients with amyloidosis often face poor outcomes due to multi-organ involvement and complications such as bowel obstruction and perforation.[21]

Gertz et al.[21] reported that patients with AL amyloidosis involving the gastrointestinal tract had a median survival of approximately 24 months, with severe gastrointestinal symptoms being strongly associated with increased mortality. Patients with significant gastrointestinal involvement also experienced higher rates of hospitalization and required more aggressive nutritional support, both of which negatively impacted their quality of life.

CONCLUSION

Intestinal amyloidosis is a complex condition that necessitates a multidisciplinary approach for effective diagnosis and management. Recent advancements in understanding its pathophysiology and treatment options provide hope for improved patient outcomes. Ongoing research is essential to further elucidate the mechanisms of amyloid deposition and to develop more targeted and effective therapies.

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