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**Gastrointestinal amyloidosis: A focused review**

Dahiya DS *et al*. Gastrointestinal amyloidosis

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**Abstract**

Amyloidosis, a heterogenous group of disorders, is characterized by the extracellular deposition of autologous, insoluble, fibrillar misfolded proteins. These extracellular proteins deposit in tissues aggregated in ß-pleated sheets arranged in an antiparallel fashion and cause distortion to the tissue architecture and function. In current literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been associated with human disease. Classified as a rare disease, amyloidosis is known to have a wide range of possible etiologies and clinical manifestations. The exact incidence and prevalence of the disease is currently unknown. In both systemic and localized amyloidosis, there is infiltration of the abnormal proteins in the layers of the gastrointestinal (GI) tract or the liver parenchyma. The gold standard test for establishing a diagnosis is tissue biopsy followed by Congo Red staining and apple-green birefringence of the Congo Red-stained deposits under polarized light. However, not all patients may have a positive tissue confirmation of the disease. In these cases additional workup and referral to a gastroenterologist may be warranted. Along with symptomatic management, the treatment for GI amyloidosis consists of observation or localized surgical excision in patients with localized disease, and treatment of the underlying pathology in cases of systemic amyloidosis. In this review of the literature, we describe the subtypes of amyloidosis, with a primary focus on the epidemiology, pathogenesis, clinical features, diagnosis and treatment strategies available for GI amyloidosis.

**Key Words:** Gastroenterology; Hepatology; Amyloidosis; Dysmotility; Endoscopy; Therapeutics

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**Core Tip:**This manuscript focuses on a rare disease entity that can cause significant morbidity and mortality, especially amongst the elderly patient population. Lack of awareness regarding the possibility of gastrointestinal amyloidosis, which presents with vague symptoms common to a host of disorders, can lead to unnecessary testing and delays in diagnosis, contributing to poor outcomes. Physicians should consider the presence of gastrointestinal amyloidosis, especially in elderly patients with conditions predisposing them to the development of amyloid deposition.

**INTRODUCTION**

In 1853, Rudolf Virchow first used the term “amyloid” to describe tissue deposits which showed close similarity to starch after they were dyed with iodine and sulphuric acid[1]. Amyloidosis encompasses a heterogenous group of disorders characterized by the extracellular deposition of autologous fibrillar proteins, which aggregate into a three-dimensional ß-lamina disposition (ß-pleated sheets aligned in an anti-parallel fashion) in tissues, disrupting normal tissue architecture and function[2,3]. According to the Genetic and Rare Disease Information Center (GARD) of the National Institute of Health (NIH), amyloidosis is a rare disease. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. According to the data available from NIH, AL (amyloid light chain) amyloidosis has an incidence of 1 case per 100000 person-years in Western countries[4]. Systemic amyloidosis is more common than localized disease, and the annual incidence of primary systemic amyloidosis is 78% whereas that of secondary systemic amyloidosis is only 6% every year in the United States[4]. In the literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 are associated with known disease in humans[5].Based on the location of production of amyloidogenic precursor protein and its deposition within the tissues, it can be classified into two distinct subtypes: systemic and localized amyloidosis[6]. GI tract involvement may be a feature of both subtypes[6]. Gastrointestinal (GI) amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease. However, as per the current literature, GI amyloidosis with direct biopsy verification from the GI tract may be a rare phenomenon. Hence, in this review, we describe the different subtypes of amyloidosis with associated amyloid precursor proteins deposited in tissues. We also describe the incidence rates of amyloidosis reported in different healthcare systems throughout the world. Additionally, we detail the pathogenesis, clinical presentations, methods to establish diagnosis and the treatment strategies available for GI amyloidosis.

**Methods**

A thorough literature search was performed to identify articles on amyloidosis of the GI tract and its clinical presentations. The authors used search engines such as PubMed, Google Scholar, and Ovid MEDLINE to search for published literature on GI amyloidosis between the years 1960 and 2020. A detailed literature search of the articles referenced in the identified publications was also performed. Furthermore, data and statistics available from national organizations such as the GARD were also researched. The keywords used in the literature search included, but are not limited to: “amyloidosis”, “gastrointestinal amyloidosis”, “localized amyloidosis”, “systemic amyloidosis”, “amyloid pathogenesis”, “hepatic amyloidosis”, “amyloidosis treatment”, “gastrointestinal amyloidosis treatment”, and “gastrointestinal amyloidosis prognosis”. The inclusion criteria set by the authors consisted of articles published between the years 1960 and 2020, published articles available in the English language, data and statistics available from national organizations such as NIH, and published articles or guidelines related to the therapeutic options available for the management of GI amyloidosis in all clinical settings. The exclusion criteria consisted of duplicate articles or abstracts only, articles published before the year 1950, articles published in a language other than English, and unpublished research on GI amyloidosis. Application of the inclusion and exclusion criteria yielded a total of 3197 articles which were carefully reviewed by all the authors for this review of the literature. A total of 65 references ultimately were used for the purposes of drafting this narrative review.

**Discussion**

As described earlier, amyloidosis refers to a heterogenous group of disorders characterized by extracellular deposition of fibrillar proteins, which can disrupt tissue structure and function. On electron microscopy, amyloid fibrils are approximately 10 nm in diameter, and on polarized light microscopy after staining with Congo Red (CR) dye, they have the characteristic apple green-birefringence appearance[5]. According to the 2010 recommendations from the Nomenclature Committee of the International Society of Amyloidosis, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been found to be associated with known human disease[7].

**CLASSIFICATION**

Amyloidosis can be classified into two main subtypes based on the location of production of the amyloidogenic precursor protein and its deposition within the tissues (Table 1)[6]. The classification is as follows[6,8].

***Systemic amyloidosis***

The most common subtype. It is characterized by the production of amyloidogenic precursor proteins at a site remote from the organ of amyloid deposition. It can either be due to acquired conditions such as plasma cell dyscrasias, or hereditary conditions due to modifications in the transthyretin (TTR) gene. Table 2 summarizes the common forms of systemic amyloidosis along with organ-specific involvement[8].

***Localized amyloidosis***

It is characterized by the production of amyloidogenic precursor proteins at the same location as its deposition. It may commonly involve the respiratory tract, urinary bladder, breast, skin, or the GI tract. A single center retrospective analysis by Cowan *et al*[6] reported that out of the 3.3% of patients with biopsy proven amyloidosis, only 21% had amyloidosis restricted to the GI tract[6]. Hence, localized amyloidosis is an uncommon entity.

**EPIDEMIOLOGY**

According to the GARD, amyloidosis is a rare disease entity. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. Furthermore, regional variations in the environment *i.e.,* prevalence of local infections and autoimmune diseases which predispose to chronic inflammation, and genetic factors such as polymorphisms in the genes encoding for amyloid precursors may also contribute significantly to the likelihood of developing the disease[9]. Studies, although limited, have been conducted to evaluate the epidemiology of the disease in the United States and worldwide. According to the latest statistics available from the NIH, AL amyloidosis has an incidence of 1 case per 100000 person-years in Western countries, and in the United States approximately 1275 to 3200 new cases are reported every year[4]. Systemic amyloidosis is more common than localized amyloidosis, and the annual portion of new cases with primary systemic amyloidosis (AL) is 78% whereas secondary systemic amyloidosis (AA) represents only 6% of these cases every year in the United States[4]. Familial transthyretin-associated amyloidosis, believed to be less common and with a currently unknown incidence rate, constitutes approximately 10% to 20% of diagnosed cases at tertiary hospitals in the United States[4]. Outside the United States, similar trends in incidence have been observed. In the United Kingdom, Pinney *et al*[10] reported a global incidence of amyloidosis of 5 cases per million person-years, out of which 3 cases per million person-years were attributed to the AL amyloidosis and 1 case per million person-years to AA amyloidosis[10]. Similarly, Hemminki *et al*[11] estimated the incidence of amyloidosis to be 8 patients per million person-years in Sweden, from which 3 cases per million person-years were credited to AL amyloidosis and 2 cases per million person-years to AA amyloidosis[11]. Typically, amyloidosis manifests later in life and more commonly affects the older demographic (mean age for the AL subtype is 63 years)[12]. A higher incidence and prevalence of the disease has been reported in males as compared to females[12]. In the United States, the literature also reported a substantial increase in amyloidosis-related mortality from 1.77 to 3.96 per million between 1979 and 2015, with the highest mortality rates noted in the African-American population[13].

Involvement of the GI tract can be seen in both localized (limited only to the gut) and systemic (most commonly AL subtype) amyloidosis. GI amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease[14]. It is more commonly seen in elderly males. Yen *et al*[15] conducted a single center retrospective cohort study from 2008 to 2017 in 583 amyloid patients and observed that only 96 (16.8%) patients had GI signs and symptoms[15]. Out of these 96 patients, 82 underwent esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy, and it was reported that only 37 (45%) patients had biopsy proven GI amyloidosis, whereas 45 (55%) patients had absence of GI amyloidosis on biopsy[15]. Similarly, another retrospective study which evaluated 2337 patients in a 13-year period using the Boston University Amyloid Treatment and Research Program database reported biopsy proven GI Amyloidosis in only 76 (3.3%) of the patients[6]. Furthermore, on EGD or colonoscopy, the site of highest diagnostic yield from biopsy specimens was found to be the duodenum, followed by the stomach, colon and rectum, and esophagus[6,15]. Hence, it can be concluded that GI amyloidosis with direct biopsy verification from the GI tract is a rare phenomenon. There is also a significant paucity of data on GI amyloidosis with most of it available either from small, retrospective single center studies, or isolated case reports. Therefore, we strongly advocate for the need for additional large multi-center prospective studies to capture the impact of GI amyloidosis globally and its burden on the healthcare system.

**PATHOGENESIS**

The basic pathogenic mechanism of amyloidosis involves the extracellular deposition of insoluble protein fibrils derived from amyloid precursor proteins in tissues[16]. These are composed of low molecular weight subunits arranged in antiparallel ß-pleated sheets[16]. In GI amyloidosis, infiltration of extracellular misfolded proteins can be seen in the different layers of the GI tract.

***Mucosal infiltration***

The most common site of mucosal infiltration is the duodenum, followed by the stomach, colorectum and the esophagus[17]. Furthermore, the subtype of amyloid protein deposited governs the clinical presentation[18,19].

AL amyloid deposition is usually seen in the muscularis mucosa, submucosa and muscularis propria, often leading to the formation of protrusions. It may present with symptoms of bowel obstruction.

AA amyloid deposition is seen mainly in the mucosa, which may lead to increased friability and erosions in the involved area. It may present with diarrhea and clinical features of malabsorption.

β2-microglobulin amyloid (Aβ2M) deposition is usually seen in patients on hemodialysis and corresponds to increased mean time on dialysis. Aβ2M deposits can be seen in the blood vessels of the GI tract, mucosa, submucosa, and muscularis propria. It may present with features of mucosal ulceration.

***Neuromuscular infiltration***

It is characterized by the deposition of the amyloid proteins in the neuromuscular layer of the GI tract. This can affect the intrinsic nerve plexus (myenteric or submucosal nerve plexus) and the muscularis externa (longitudinal and circular muscles) leading to abnormal peristalsis, abnormal GI transit times and dysmotility[20-22].

Hepatic amyloidosis, a manifestation of systemic amyloidosis, has a similar pathogenic mechanism and is characterized by the extracellular deposition of fibrillar amyloid protein (AL) in the hepatic parenchyma[23]. It is a diagnostic challenge as it shares numerous clinical manifestations with other common chronic liver diseases, and has a poor prognosis particularly in patients with jaundice[23].

**CLINICAL MANIFESTATIONS**

The clinical manifestations of GI amyloidosis depends on the amount and location of the amyloid deposits, irrespective of whether it is primary or secondary systemic amyloidosis[17]. Patients with localized amyloidosis may have similar clinical features as those with systemic disease. All patients with amyloidosis share common presenting symptoms such as fatigue, light-headedness, anorexia, and weight loss[24]. The common GI-specific abnormalities include.

***Gastrointestinal bleeding***

May occur from any site of amyloid deposition and can be seen in up to 57% of patients[25]. The underlying cause is commonly mucosal lesions (amyloidoma ulcers, erosions, polypoid lesions, hematomas or submucosal hemorrhage), vascular friability, or in some cases bowel ischemia[25,26]. Massive occult bleeding from the GI tract is usually seen with dialysis-related amyloidosis[27].

***Malabsorption***

May present with symptoms such as diarrhea, weight loss, steatorrhea, anorexia, or dizziness and is usually secondary to mucosal infiltration, pancreatic insufficiency, or bacterial overgrowth[28,29].

***Protein-losing gastroenteropathy***

GI specific manifestations include diarrhea, edema, and ascites. It is secondary to mucosal lesions which may lead to abnormal protein loss from the GI tract[30].

***Chronic gastrointestinal dysmotility (Stasis syndrome)***

May present with nausea, vomiting, dysphagia, gastroparesis, gastro-oesophageal reflux, loss of appetite, constipation, abdominal pain, bloating, or clinical features of chronic intestinal pseudo-obstruction[20,21,25]. Dysmotility can be secondary to myopathic and neuropathic dysfunction[25]. Some patients may present with persistent diarrhea due to rapid transit times secondary to dysmotility, intestinal inflammation and bacterial overgrowth[25,31,32].

***Hepatic amyloidosis***

Has no clinical significance in most patients due to mild clinical manifestations[33]. Hepatomegaly and mild elevations in alkaline phosphatase (ALP) are the most frequent findings[34]. Other symptoms include weight loss (72%), fatigue (60%), abdominal discomfort (53%) and anorexia (26%)[25]. Elevated direct serum bilirubin levels (> 2 mg/dL) are often associated with a poor prognosis[25,34].

***Uncommon symptoms***

Some patients with GI Amyloidosis may have features of cholangitis, pneumatosis intestinalis (gas pockets within the bowel wall), or bowel perforation[35-37].

The physical examination findings in patients with amyloidosis depend on the organ specific infiltration by abnormal proteins[9]. However, from a purely GI perspective, physical examination may reveal macroglossia (enlarged tongue) in up to 50% of the cases[25]. On abdominal examination, hepatosplenomegaly and ascites may be the most frequent findings[34,38].

**ESTABLISHING DIAGNOSIS**

A high degree of clinical suspicion is necessary to establish a definitive diagnosis of GI amyloidosis. Due to the rarity of the condition coupled with non-specific signs and symptoms at the time of presentation, these patients usually undergo extensive and unnecessary testing to identify the cause of clinical presentation. GI amyloidosis should be high on the list of possible differential diagnoses in patients presenting with non-specific GI symptoms and a past medical history of disorders commonly associated with amyloidosis, such as plasma cell dyscrasia, chronic renal failure on hemodialysis, and other chronic inflammatory conditions (*e.g.* rheumatoid arthritis and inflammatory bowel disease). A positive family history of amyloidosis should also alert the provider to suspect GI amyloidosis[9]. Laboratory investigations in these patients may reveal anaemia, mild elevations in ALP levels, elevations of acute phase reactants (due to the underlying chronic inflammatory condition) and deficiencies from malabsorption. Radiological investigations in GI amyloidosis are usually non-specific[39]. Some common features seen on computer tomography (CT) or magnetic resonance imaging (MRI) include[25,39-41]: (1) Diffuse or nodular wall thickening of the involved bowel segment; (2) Dilatation depending upon the degree of hypomotility; (3) Presence of fluid levels in dilated bowel loops; (4) Luminal narrowing secondary to amyloid infiltration or ischemia; (5) Attenuation due to cluster of calcifications or mucosal ulcerations; (6) Presence of polyploid protrusions or masses mimicking cancer; (7) Loss of haustrations; (8) Mesenteric thickening or adenopathy; and (9) Decreased hepatic attenuation with or without areas of calcification (Ultrasound may demonstrate heterogenic hepatic echotexture).

Although radiological investigations may provide a clue to the extent and area of involvement, the gold standard test to establish a diagnosis of GI amyloidosis is tissue biopsy followed by CR staining and visualization under polarized light microscopy[42]. Based on the patients presenting symptom, an EGD or colonoscopy should be performed to obtain the biopsy specimen. As mentioned earlier, the site of highest diagnostic yield from biopsy specimen in the GI tract has been found to be the duodenum, followed by the stomach, colorectum, and the esophagus[6,15]. A liver biopsy may also be performed to confirm hepatic infiltration of the amyloid proteins; however, a transjugular route should be used to prevent fatal bleeding complications[43,44]. Additionally, the study by Yen *et al*[15] reported biopsy negative disease in 55% of the patients. However, these patients met the Rome IV criteria for several functional bowel disorders, but only 23.2% underwent additional diagnostic studies for functional assessment of the luminal gastrointestinal tract (such as esophageal or anorectal manometry, capsule endoscopy, or gastric emptying studies)[6]. Hence, the authors recommend the need for additional diagnostic studies to evaluate for motility disorders in patients with clinical features of GI amyloidosis but a negative result on biopsy.

Amyloid fibrils appear as amorphous, eosinophilic deposits on routine hematoxylin-eosin stained preparations, which may sometimes be confused with hyaline changes or sclerosis[45]. Hence, CR staining with the characteristic apple-green birefringence of CR-stained deposits under polarized light has been considered the gold standard for a definitive diagnosis since its inception[45]. However, despite a high sensitivity and specificity of the CR-staining method, false negative results may be seen due to the quantity of amyloid deposition in the tissue, the age of the deposits, thickness of the sections for visualization, fixation of the tissues on the slide, or the staining procedure itself[46]. Therefore, newer methods are being developed to act as an adjunct for diagnosis. Digitally reinforced hematoxylin-eosin polarization (DRHEP), a newly introduced technique which uses both routine light microscopy and digital photography, can detect weak birefringence which is not recognized through the microscope objective[45]. Although the use of DRHEP is currently limited to kidney biopsies, its role for GI amyloidosis is currently under investigation[45].

**TREATMENT**

Once the diagnosis of GI amyloidosis is established, the biopsy specimen needs further analysis to determine the subtype of amyloid deposition which can then help guide therapy[47]. The management of GI Amyloidosis includes:

***Symptomatic management***

Symptom control in patients with GI amyloidosis is tailored to the clinical presentation. In patients with symptoms of dysmotility (stasis syndrome), dietary modifications, adequate hydration, and the use of pro-kinetic and anti-emetic agents is advised. Dietary modification consists of frequent, small-volume liquid or homogenized foods with low soluble fibre and fat content along with additional nutritional supplementation when necessary[48]. Prokinetic agents such as metoclopramide, erythromycin or domperidone (if indicated) are the mainstay of therapy for dysmotility[48]. Parenteral nutrition is indicated in severe cases of chronic GI dysmotility. Patients with dysphagia may be successfully treated with balloon dilation[49]. For patients with diarrhea or bloating, anti-diarrheal agents such as loperamide should be initiated[50]. Empiric antibiotic therapy should be considered in patients with diarrhea and suspected bacterial overgrowth. In patients with severe diarrhea associated with protein-losing enteropathy, literature reports good response to corticosteroid and octreotide therapy[51,52]. The management for GI bleeding includes triage to appropriate settings, supportive measures, volume resuscitation if needed, and source control through ligation of the bleeding blood vessel. Surgical intervention may be necessary in cases of severe obstruction, uncontrolled GI hemorrhage or bowel ischemia[8,53]. Patients with macroglossia causing airway obstruction or obstructive sleep apnea may need partial resection of the tongue to alleviate symptoms[54].

***Treatment of the underlying condition for systemic amyloidosis***

No specific treatment protocols currently exist for the management of GI amyloidosis. Therapy varies significantly depending on the cause and type of amyloid protein deposited within the tissues (Table 3). The current management strategies based on the type of amyloid deposits available in literature include:

**AL amyloidosis:** The therapy is aimed at suppressing the production of monoclonal immunoglobulin light chains through eradication of the malignant plasma cells[55]. Autologous stem cell transplantation is the standard of care for plasma cell dyscrasias in eligible patients[55]. For patients not eligible to receive autologous stem cell transplantation, the management guidelines are unclear; however, the use of combination therapy with Bortezomib, Melphalan and Dexamethasone has shown improved hematologic response rate and overall survival[56]. The addition of Daratumumab (human monoclonal antibody against CD38) to bortezomib-based therapy has been evaluated but the results are yet to be published[55]. Furthermore, a fully humanized monoclonal IgG1 anti-serum amyloid P component antibody (Dezamizumab) is also under evaluation for AL amyloidosis[57].

**AA Amyloidosis:** Therapy is specifically directed at controlling the underlying disease which in turn helps reduce the acute phase response and production of serum amyloid A protein. Colchicine is used in the treatment of patients with Familial Mediterranean Fever[58]. Biologic agents (activity against pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6), cytotoxic agents and immunosuppressants have a key role to play in the management of underlying chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriatic arthritis among others.

**Hereditary amyloidosis:** Therapy is aimed to eliminate the source of production of the genetically variant protein. The liver produces most of the circulating TTR in the body. Orthotopic liver transplantation can be used to significantly reduce the production of the mutant protein in patients where the liver is the culprit[59]. Other disease modifying therapies such as TTR Stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may also be considered on a case-to-case basis[59]

**Dialysis-related amyloidosis:** No medical or pharmacological therapy currently exists for dialysis-related amyloidosis[60]. The prevention and treatment consists of removal of plasmatic Aβ2M through hemodialysis or peritoneal dialysis using ultrapure dialysate or with more biocompatible and high-flux membranes[60]. Furthermore, early and successful renal transplantation leads to reduction in Aβ2M levels, which after a few years may lead to regression of the already deposited amyloid proteins[61].

**Treatment of localized amyloidosis:** It is characterized by deposition of AL amyloid restricted to the GI tract. For patients who are asymptomatic, no intervention may be needed, and observation may be the key; however, patients with recurrent or severe symptoms may require localized surgical excision.

Moreover, the treatment strategies for GI amyloidosis are consistently evolving with a better understanding of the disease pathology and the development of newer agents with target specific actions. Clinical trials to assess the efficacy and the toxicity profile of newer agents are currently ongoing and available at clinicaltrials.gov[62].

**PROGNOSIS**

The prognosis of GI amyloidosis depends on the extent of involvement of the GI tract, the quantity of deposition and the type of amyloid deposition. Literature reports that patients with AL amyloidosis and GI tract involvement had a worse prognosis than those without GI involvement[63]. Additionally, patients with GI amyloidosis had involvement of additional organs, an increased number of poor prognostic factors, and a more advanced disease than those without the involvement of the GI tract[63]. Patients with AA amyloidosis were reported to have better median survival outcomes[64]. Involvement of the liver was associated with poor prognosis and increased mortality, particularly in patients with jaundice at the time of initial presentation and those with elevated direct serum bilirubin levels (> 2 mg/dL)[25,34].

**CONCLUSION**

Amyloidosis is characterised by the extracellular deposition of autologous fibrillar proteins aggregated into three-dimensional ß-pleated sheets aligned in an anti-parallel fashion. Based on the location of production of amyloidogenic precursor protein and its deposition in tissues, it can be divided into two distinct subtypes, systemic and localized amyloidosis. Involvement of the GI tract (GI amyloidosis) may be seen with both subtypes. Patients with GI amyloidosis commonly present with fatigue, light-headedness, anorexia, weight loss, GI bleeding, features of malabsorption, protein-losing enteropathy, or chronic GI dysmotility. Infiltration of amyloid proteins in the liver may also be seen, often presenting with hepatomegaly and mild elevations of ALP. Presence of jaundice with liver involvement (elevated direct bilirubin levels > 2 mg/dL) is associated with a poor prognosis. Radiological investigations are usually non-specific, and a definitive diagnosis is established with a tissue biopsy followed by CR-staining. The characteristic apple-green birefringence of the CR-stained deposits under polarized light is diagnostic. In patients with a negative biopsy from the GI tract, the authors recommend for the need of additional investigations for motility disorders and referral to a gastroenterologist. The use of DRHEP, a newly introduced technique, is also being explored to aid in diagnosis. For all patients with localized GI amyloidosis, the management consists of observation or localized surgical excision; however, for those with systemic GI amyloidosis, therapy is directed towards the underlying disease pathology. Symptomatic management in these patients is tailored to the presenting symptoms. The overall survival outcome depends on the extent of involvement of the GI tract, the quantity, and type of amyloid deposition.

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**Table 1 Differences in systemic and localized gastrointestinal amyloidosis**

|  |  |
| --- | --- |
| **Systemic gastrointestinal amyloidosis** | **Localized gastrointestinal amyloidosis** |
| * More common subtype | * Less common subtype |
| * Amyloid production at a remote location with subsequent deposition in the GI tract | * Amyloid production in the GI tract with subsequent deposition locally. |
| * Presence of amyloid precursor proteins in the blood | * Amyloid precursor proteins absent in the blood |
| * Associated with plasma cell dyscrasia, chronic inflammatory conditions, dialysis, or hereditary conditions | * Not associated with an underlying disease pathology |
| * Amyloid precursor protein deposited include AL, AA, Aβ2M and ATTR | Amyloid precursor protein most deposited is AL |
| * Management consists of symptomatic management and treatment of the underlying etiology | * Management consists of observation or surgical excision of the localised deposition |
| * Prognosis depends on the type and amount of amyloid deposition | * Good prognosis. No transition to systemic type |

AL: Monoclonal light chain; AA: Serum amyloid A; Aβ2M:β2-microglobulin amyloid; ATTR: Familial transthyretin-associated amyloidosis; GI: Gastrointestinal.

**Table 2** **The common forms of systemic amyloidosis with organ involvement**

|  |  |  |
| --- | --- | --- |
| **Type of systemic amyloidosis** | **Causative protein** | **Organ involvement** |
| Primary systemic amyloidosis | Monoclonal light chain (AL) | Heart, Kidneys, Liver, Peripheral nervous system, Autonomic nervous system, and Gastrointestinal tract |
| Senile systemic amyloidosis | Wild-type transthyretin (ATTR) | Heart |
| Hereditary systemic amyloidosis | Mutant transthyretin (ATTR); Apolipoprotein 1 (AApoA1); Mutant fibrinogen A alpha (AFib); Lysozyme (ALys) | Heart; Heart, Kidneys, Liver, Peripheral nervous system, and Skin; Kidneys and Liver; Kidneys and Liver |
| Isolated Atrial Systemic Amyloidosis | Atrial natriuretic factor (AANF) | Heart |
| Secondary Systemic Amyloidosis | Serum amyloid A (AA) | Kidneys, Heart, and Gastrointestinal tract |
| Dialysis-Related Systemic Amyloidosis | β2-microglobulin (Aβ2M) | Osteoarticular tissue, Circulatory system, and Gastrointestinal tract |
| Finnish-type Systemic Amyloidosis | Gelsolin (AGel) | Lattice dystrophy of cornea, and Corneal neuropathy |

**Table 3** **Management of gastrointestinal amyloidosis based on the amyloid protein**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gastrointestinal amyloidosis** | **AL amyloidosis** | **AA amyloidosis** | **Hereditary amyloidosis** | **Dialysis-related amyloidosis** |
| Treatment strategy | Systemic: eligible: Autologous stem cell transplantation (ASCT) for plasma cell dyscrasias. Non-eligible: No standard protocol; combination of Bortezomib, Melphalan and Dexamethasone has shown improved survival. Localized: Observation or localized surgical excision | Chronic inflammatory conditions: Biologics (anti-TNF antibodies, humanized anti-IL6 receptor antibody) and immunosuppressants. Familial mediterranean fever: Colchicine. | Liver production of transthyretin: Orthotopic liver transplantation (OLT). Disease modifying therapy: Transthyretin stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may be used on case-to-case basis | Prevention: Removal of plasmatic β2-microglobulin (Aβ2M) through hemodialysis or peritoneal dialysis. Early renal transplant |