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Clinical, Endoscopic, and Histopathologic Observations in Gastrointestinal Amyloidosis

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ABSTRACT

Background & Aims: Amyloidosis is a group of systemic disorders caused by extracellular deposition of misfolded serum proteins. Gastrointestinal (GI) involvement is associated with a higher risk of GI bleeding, especially if mucosal lesions are present. Our study aims to evaluate the frequency of GI manifestations in patients with amyloidosis, to clinically characterize these patients and to describe the endoscopic and histopathologic findings in GI amyloidosis.

Methods: A retrospective, single-center study of all patients admitted with amyloidosis and GI manifestations was conducted at a German University Hospital between July 2003 and June 2023. Clinical, endoscopic, and histopathological data was retrieved from medical records.

Results: Between July 2003 and June 2023, 63 patients with different types of amyloidosis were included into the study. Twenty-three (36,5%) were diagnosed with GI involvement of amyloidosis (60.9% male, median age 62 ± 18.28 years). The distribution of the types of amyloidosis were amyloid light chain (AL) at 52.5%, transthyretin (ATTR) at 21.7%, amyloid A (AA) at 13.0%, and unknown at 18%. Initial GI symptoms were present in 78.3% of the patients and included mainly diarrhea (34.8%), and abdominal pain (30.4%) Affected GI organs were primarily the colon (60,8%) and the stomach (39.1%). Endoscopic findings were ulcerations (47.8%), mucosal inflammation (43.5%), polyps (26.1%), erosions (13.0%), vascular malformation, polypoid protrusion, submucosal hematoma, erythema, metaplasia, and diverticulum. Histopathological findings included vascular wall thickening, (peri-)vascular and interstitial amyloid deposition. Gastrointestinal bleeding occurred in 39.1% of the patients. The mortality rate 5 years after diagnosis was 47.8%.

Conclusions: Gastrointestinal amyloidosis can present with multiple symptoms and endoscopic findings, rendering diagnosis a challenge. Of clinical relevance, GI bleeding was a frequent event in our patient cohort. Therefore, clinicians must be aware of GI bleeding as a manifestation of amyloidosis and definite diagnosis should be achieved based on biopsy results.

Key words: gastrointestinal amyloidosis – amyloid deposition – gastrointestinal bleeding – orphan disease.

Abbreviations: AA: amyloid A; AATR: transthyretin; AL: amyloid light chain; GI: gastrointestinal.

INTRODUCTION

Amyloidosis is a generic term for extracellular tissue deposition of insoluble aggregates of amyloid fibrils composed of low molecular weight subunits of a variety of primarily misfolded serum proteins [1, 2]. Amyloid deposition can be confined to a single organ, which is referred to as localized amyloidosis [3-6] or can cause a systemic disorder with the appearance of deposits distant from the synthesizing location [7-9], resulting in multiple organ dysfunction. Often, underlying predisposing conditions become apparent before the diagnosis of amyloidosis is established. Clinically relevant examples are multiple myeloma [10], monoclonal gammopathy of undetermined significance [11-13], Waldenström macroglobulinemia [14, 15], and chronic uncontrolled inflammatory diseases such as inflammatory bowel disease [16, 17], rheumatoid arthritis [8, 18, 19], familial Mediterranean fever [20, 21], and tumor necrosis factor-associated periodic syndrome [22]. The clinical manifestations of amyloidosis are determined by the type of precursor protein involved as well as the amount and the location of the amyloid deposits [2]. Frequent systemic forms of amyloidosis are primary amyloid light chain (AL),

secondary serum-amyloid A (AA) and senile/hereditary transthyretin (ATTR) amyloidosis [3, 23, 24]. In patients with AA and AL amyloidosis, nephropathy is common [7], while ATTR amyloidosis is mainly associated with cardiomyopathy and neuropathy in the form of carpal tunnel syndrome [8]. AL amyloidosis can also manifest with cardiomyopathy, hepatomegaly, and neurological disorders [7, 25-27]. Gastrointestinal (GI) involvement is common in AL amyloidosis and can be present in AA and ATTR amyloidosis [24, 28]. In some cases of ATTR amyloidosis GI manifestations are present even before the onset of polyneuropathy [29]. However, GI amyloidosis with biopsy verification is rare. Associated manifestations are GI bleeding [24, 30-32], malabsorption [33-35], protein-losing enteropathy [36, 37], and motility disorders [23, 24, 38, 39], presenting as gastroparesis, nausea or vomiting, diarrhea, bacterial overgrowth, constipation, or chronic intestinal pseudo-obstruction. Ischemia, infarction or mucosal lesions such as erosions, erythema, ulcerations, nodularity, polypoid protrusions and submucosal hematomas are possible endoscopic findings [23, 39, 40] and may constitute causes of GI bleeding [23, 30, 41, 42]. In cases of vascular or hepatic amyloid deposition, vascular friability and impaired liver function may occur, increasing the risk of GI bleeding [43, 44]. Patients with AA amyloidosis frequently present with diarrhea and malabsorption, whereas patients with AL amyloidosis typically present with mechanical obstruction or intestinal pseudo-obstruction [45]. Although amyloidosis can be clinically suspected, performing a biopsy with the detection of amyloid deposition is mandatory to establish the diagnosis [29, 46]. In cases of suspected amyloidosis of the GI tract, rectal or duodenal mucosal biopsies are preferred [24, 40]. Characteristic histopathologic findings include extracellular hyaline deposits with distinct Congo red staining and apple-green birefringence in polarized light [7, 23, 47]. For the most part, GI manifestation results from either mucosal or neuromuscular amyloid infiltration [48]. Sites of mucosal infiltration include tongue, esophagus, stomach, small intestine, and the colorectum [24, 40]. Neuromuscular deposition can lead to uncoordinated, low or high amplitude smooth muscle contractions, which can either generate a prolonged or accelerated transit time [48]. A study with amyloidosis patients and clinical signs of intestinal pseudo-obstruction revealed extensive amyloid deposition in the muscularis propria, especially in the small intestine, in AL amyloidosis patients, whereas in AA amyloidosis patients, amyloid deposits were primarily localized in the myenteric plexus [49]. Hence, the localization of amyloid depositions is dependent on the precursor protein but can lead to similar symptoms. In wild-type ATTR amyloidosis, deposits are usually discovered in the veins of the subserosa of the large and small intestine [50, 51]. Survival rates differ between the types of amyloidosis. In AL amyloidosis, the 4-year survival rate is reported to be between 40% and 60% [52] with an overall survival increasing steadily within the last 4 decades to a median value of 4.6 years [53]. In patients with wild-type ATTR cardiac amyloidosis, the median survival time was demonstrated to be 3.6 years after the diagnosis [54]. In a study among AA amyloidosis patients, the estimated 5-year survival rate was 31.3% in patients with cardiac involvement and 63.3% in patients without cardiac involvement [55]. In AL amyloidosis with hepatic involvement, the median survival was 8.5 months [27], and in patients with GI involvement 10 months [33]. In another study, the 3-year survival rate of patients with gastric amyloidosis was reported to be 60% independent of the type of amyloidosis [39].

Our study aims to evaluate the frequency of GI manifestation in patients with amyloidosis. In addition, we investigate the clinical, endoscopic, and histopathological characteristics and outcomes of patients with amyloidosis and GI manifestations.

METHODS

Statement of Ethics

This study was reviewed and approved by the Ethics Committee of the University of Regensburg, Regensburg, Germany (22-3044-104). This is a retrospective study. All patient-related data was acquired from our hospital databases and was subsequently pseudonymized. Due to the retrospective character of the study, written informed consent was not required.

Clinical Data

Clinical data was retrieved from the medical records of the hospital information system. This included age at diagnosis, gender, type of amyloidosis, underlying predisposing disease, affected organs, initial gastrointestinal symptoms, endoscopic and histopathological findings as well as outcome parameters such as the occurrence of GI bleeding and mortality.

Statistical Analysis

The data was analyzed using the descriptive statistics techniques in IBM SPSS Statistics (version 28.0.1.1.).

Histopathological Analysis

Histopathological samples were fixed in formalin and embedded in paraffin for vertical microcuts (4 μm thickness). The cuts were mounted on glass slides, deparaffined with xylene and ethanol and stained with hematoxylin-eosin (HE) and Congo Red according to standard protocols.

RESULTS

Study Design and Patient Characteristics

This is a retrospective, 20-year single-center study of patients with GI amyloidosis. Patients with known GI manifestation of amyloidosis or a typical finding of amyloid deposition in the GI tract were included. All patients were treated at the department of Internal Medicine I of the University Hospital Regensburg, Regensburg, Germany between July 2003 and June 2023. Overall, 63 patients with diagnosed amyloidosis were identified. Most of the patients had AL amyloidosis (20 patients, 31.7%), followed by ATTR amyloidosis (19 patients, 30.1%), AA amyloidosis (12 patients, 19.0%) and wild-type TTR (1 patient, 1.5%). In 11 patients the type of amyloidosis was not documented. Twenty-three (36.5%) patients had proven GI depositions of amyloid. The clinical characteristics, outcome, GI amyloid localization and other organ manifestation in the patient cohort are summarized in the Supplementary file (Table I).

Table I. Clinical characteristics of study population (n=23)

Clinical characteristics	N (%)
Age at diagnosis [years], median ± SD (range)	62 ± 18.28 (10-87)
Gender, n (%)	
Female	9 (39.1)
Male	14 (60.9)
Type of amyloidosis, n (%)	
AL amyloidosis	12 (52.5)
TTR amyloidosis	5 (21.5)
AA amyloidosis	3 (13.0)
Unknown	3 (13.0)
Underlying predisposing disease, n (%)	
MGUS	8 (34.8)
Plasmacytoma	4 (17.3)
Multiple myeloma	1 (4.3)
RA and B-cell NHL	1 (4.3)
Vasculitis	1 (4.3)
None	8 (34.7)
Results of initial endoscopy available, n (%)	20 (87.0)
Clinical outcomes, n (%)	
GI bleeding	9 (39.1)
Upper	5 (21.7)
Lower	4 (17.4)
Death during study period	16 (69.5)
Mortality 6 months after diagnosis	8 (34.7)
Mortality 5 years after diagnosis	11 (47.8)
Cause of death	
Cardiovascular	3 (18.7)
Multiple organ failure	3 (18.7)
Pneumonia	1 (6.2)
Liver failure	1 (6.2)
SIRS	1 (6.2)
Amyloidosis-associated	7 (43.7)

SD: standard deviation; AL: amyloid light chain; AA: serum-amyloid A; TTR: transthyretin; MGUS: monoclonal gammopathy of undetermined significance; RA: rheumatoid arthritis, NHL: non-Hodgkin's lymphoma: SIRS: systemic inflammatory response syndrome.

Patients with Gastrointestinal Amiloidosis

Twenty-three patients (36.5%) had a GI manifestation of their amyloidosis and were further characterized (Table I). The median age of the patients with amyloidosis and GI manifestation at the time of diagnosis was 62±18.28 years. Two-thirds of the study population were male (14 patients, 60.9%). Twelve patients (52.5%) had AL amyloidosis. Five patients (21.5%) had ATTR amyloidosis, 3 patients (13%) had AA amyloidosis, and in another 3 cases (13%) the type of amyloidosis was unknown. 12 of 20 patients (60.0%) with AL amyloidosis showed GI involvement, whereas in ATTR and AA patients, only 5 of 19 patients (26.3%) and 3 of 12 patients (25%), presented with GI involvement, respectively. Out of the 23 patients with GI involvement, 15 patients (65.2%) had an underlying predisposing disease, with MGUS being the most common (8 patients, 34.8%), followed by plasmacytoma (4 patients, 17.3%). One patient had rheumatoid arthritis, and B-cell non-Hodgkin's lymphoma, and one patient had vasculitis. Another patient suffered from multiple myeloma. During the study period, 16 patients (69.5%) died. The 5-year mortality rate was 47.8%. The leading cause of death was cardiovascular or multiple organ failure (3 patients, 18.7% respectively). In 7 cases (43.7%) the cause of death was found to be amyloidosis-associated. One patient died of septic shock due to pneumonia, one due to liver failure, one due to systemic inflammatory response syndrome and one due to gastric ischemia.

Initial Clinical Presentation

The data regarding GI symptoms is summarized in Table II. In 78.3% of the patients, GI symptoms at the time of first presentation were documented. The symptoms included diarrhea (34.8%), abdominal pain (30.4%), weight loss (26.1%), nausea/vomiting (21.7%), loss of appetite (21.7%), abdominal distension (8.7%) and GI bleeding (8.7%). In cases where no GI symptoms were documented, we classified patients as having "no initial GI symptoms".

Table II. Initial gastrointestinal symptoms (n=23)

	N, %
Diarrhea	8 (34.8)
Abdominal pain	7 (30.4)
Weight loss	6 (26.1)
Nausea/ vomiting	5 (21.7)
Loss of appetite	5 (21.7)
Abdominal distension	2 (8.7)
Gastrointestinal bleedingNone	2 (8.7)
	5 (21.7)

Organ System Involvement

Affected organs are listed in Table III. The main GI localization in the study cohort was the colon with 60.8%, followed by the stomach (39.1%), duodenum (21.7%), jejunum and ileum (each 17.3%), and rectum (13%). In 19 of the 23 patients, multiple GI manifestations were present. Other affected organs included primarily the heart and the kidneys (60.8%, respectively 43.4%), followed by the liver (17.4%), nervous system (17.4%), spleen (4.3%), skin (4.3%), omentum (4.3), and gallbladder (4.3%). The defined category "nervous system" included two patients with involvement of the peripheral nervous system, one patient with the autonomic nervous system involved and one patient with amyloid depositions in the brain.

Table III. Organ system involvement (n=23)

Affected organs	Total study population (n=23)
GI tract	23 (100)
Colon	14 (60.8)
Stomach	9 (39.1)
Duodenum	5 (21.7)
Ileum	4 (17.3)
Jejunum	4 (17.3)
Rectum	3 (13.0)
Heart	14 (60.8)
Kidney	10 (43.4)
Liver	4 (17.4)
Nervous system	4 (17.4)
Spleen	1 (4.3)
Omentum	1 (4.3)
Gallbladder	1 (4.3)
Skin	1 (4.3)

Endoscopic Findings

Twenty-one (91,3%) of the 23 patients showed GI lesions in the performed endoscopy. Detailed data is given in Table IV. The most common lesions were ulcerations with 47.8% (Fig. 1).

Table IV. Endoscopic and histopathological findings (n-23)

	N, (%)
Gastrointestinal lesions, n (%)	
Ulcerations	11 (47.8)
Mucosal inflammation	10 (43.5)
Polyp	6 (26.1)
Erosions	3 (13.0)
Vascular malformation	2 (8.7)
Polypoid protrusion	2 (8.7)
Submucosal hematoma	2 (8.7)
Erythema	1 (4.3)
Metaplasia	1 (4.3)
Diverticulum	1 (4.3)
Histopathological findings, n (%)	
Vascular wall thickening	6 (26.1)
(Peri-)Vascular amyloid deposition	18 (78.3)
Interstitial amyloid deposition	10 (43.5)
Polyp with amyloid deposition	1 (4.3)
Congo red stain positive	22 (95.7)
Green birefringence	16 (69.6)

Data of Congo red stain only available for 22 patients.

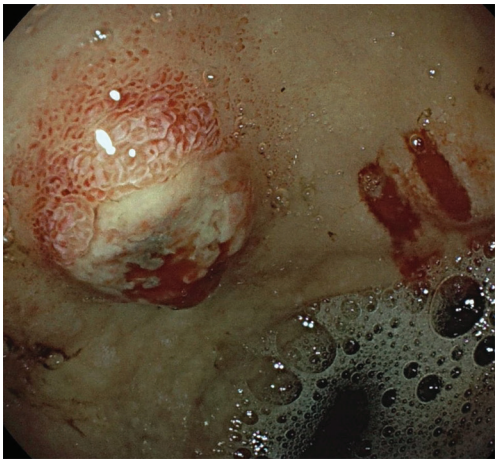

Fig. 1. Ulcer in the duodenal bulb in a patient with AL amyloidosis.

Mucosal inflammation (43.5%), polyps (26.1%), and erosions (13.0%) were also frequent. Less common were vascular malformation (8.7%), polypoid protrusion (8.7%, Fig. 2), and submucosal hematoma (8.7%, Fig. 3), as well as erythema (4.3%), metaplasia (4.3%), diverticulum (4.3%), and ischemia (4.3%, Fig. 4). Furthermore, and of clinical importance, GI hemorrhage occurred in 39.1 % of the patients during the course of the disease. Endoscopic investigations showed diffuse bleeding due to mucosal friability, ulcerations, and submucosal hematoma (Figs. 1, 3 and 5).

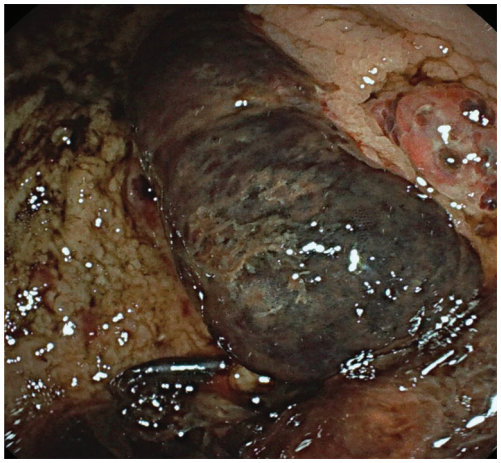

Fig. 3. Gastric submucosal hematoma in a patient with AL amyloidosis and severe gastrointestinal hemorrhage.

Gastrointestinal Bleeding

Gastrointestinal bleeding occurred in 9 patients (39.1%) during the course of the disease, with upper GI bleeding being slightly more frequent than bleeding in the lower GI tract (5 patients, 55.5%). In most of the patients (7 cases, 77.7%), the GI bleeding was mild and did not necessitate admission to the intensive care unit. However, 2 female patients (22.2%) needed emergency admission to the intensive care unit due to hematemesis, arterial hypotension, and low hemoglobin value. For airway protection both patients were endotracheally intubated. Also, both patients required vasopressor therapy and red blood cells concentrates for achieving hemodynamic stability. In one patient endoscopy revealed ulceration in the duodenal bulb, gastric submucosal hematoma, and polypoid structures with amyloid deposits (Figs. 1-3). The patient could be safely extubated after biopsy was taken to diagnose GI amyloidosis and discharged from the hospital one week

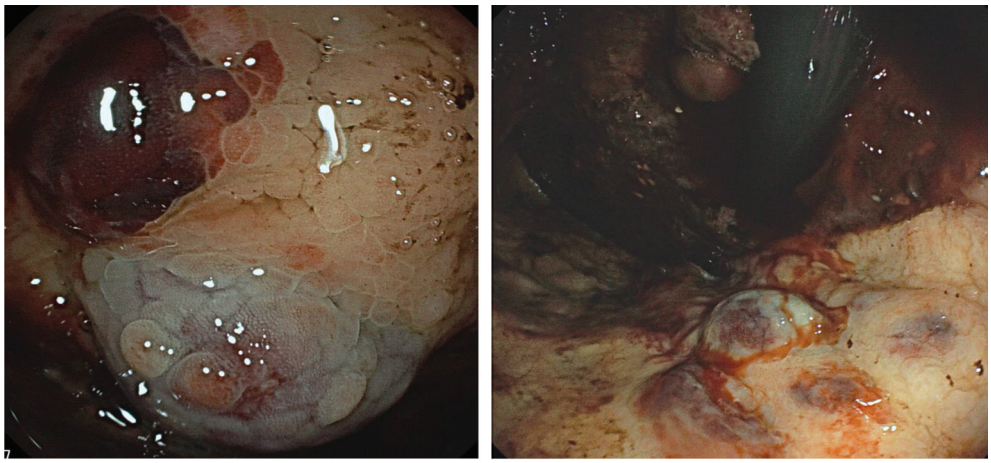

Fig. 2. Polypoid structures with amyloid deposits in the stomach.

after the bleeding episode. The second case presenting with hematemesis and arterial hypotension was a 66-year-old female with previously unknown GI amyloidosis. The initial gastroscopy showed diffuse gastric bleeding (Fig. 5). Upon increasing lactate another gastroscopy was immediately performed. This gastroscopy revealed an extensive gastric ischemia (Fig. 4). The patient underwent gastrectomy, but despite surgical and intensive care efforts the patient did not survive. The histopathological report revealed a pronounced gastric amyloidosis.

Histopathological Diagnosis

Histopathological findings of GI amyloidosis included peri- or vascular amyloid deposition in 78.3% of the cases, with vascular wall thickening in 26.1%, whereas interstitial amyloid deposition was demonstrated in 43.5%. Positive Congo red stain was found in 95.7% of the patients with typical apple-green birefringence in polarized light in 69.6% (Figs. 6 and 7).

DISCUSSION

Amyloidosis of the GI tract is an orphan disease. During our study period over 20 years, 23 patients out of 63, corresponding to 36.5% of all amyloidosis patients treated at our institution with a definite diagnosis of GI amyloidosis, were identified. Furthermore, we performed a literature search in view of the paucity of data on GI involvement of amyloidosis.

Regarding the prevalence of a GI involvement in patients with amyloidosis, a previous retrospective 13-year single-center analysis found a smaller percentage of only 3.2% of their amyloidosis patients to have biopsy-proven GI involvement [56]. Another review reported a series of 445 patients with AL amyloidosis, with 7% of the patients having GI involvement [1].

Amyloidosis can involve multiple organs, including the kidney, heart, and nervous system [7, 8, 25-27], but rarely presents with primarily GI symptoms [57]. In a study with 20 patients with AL amyloidosis and GI involvement, primarily the heart, followed by the peripheral nervous system, kidney, and autonomic nervous system were listed as involved organs [58]. Similarly, our analysis revealed the heart, but also the kidneys as additionally involved organs, followed by the liver, nervous system, spleen, skin, omentum, and gallbladder.

Regarding the GI localization of amyloidosis, we identified the colon as the major manifestation site in 60.8% of the patients. The second most common localization site was the stomach (39.1%), and the third most common being the duodenum (21.7%). Less common were the ileum, the jejunum, and the rectum. A prospective study with 37 patients suffering from amyloidosis with systematically performed biopsies of the esophagus, stomach, duodenum, and colorectum detected amyloid deposition primarily in the duodenum within 100% of the patients, whereas amyloid deposition in the colon and rectum were found in 91% of the patients [59]. The frequency of depositions in the stomach and esophagus was 95 and 72%,

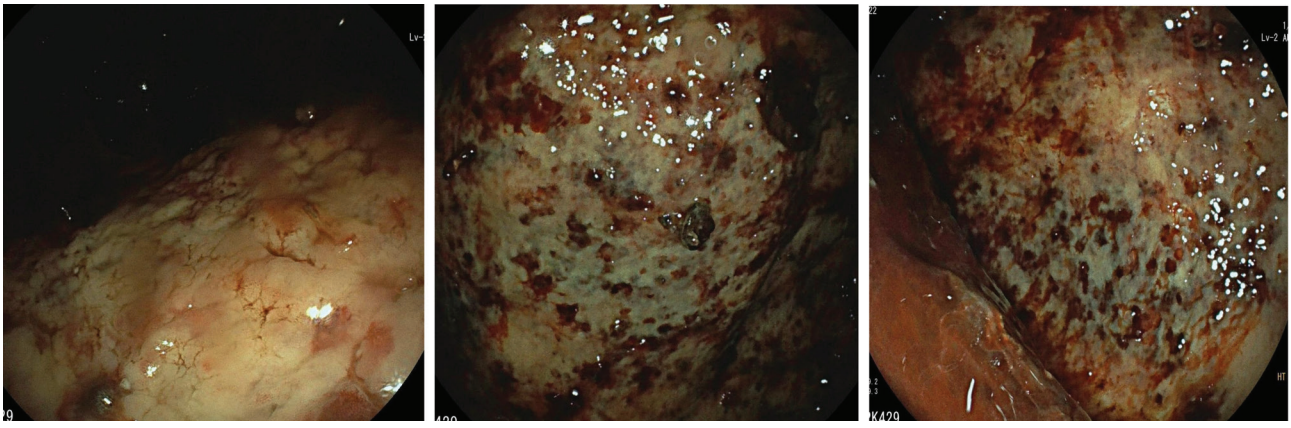

Fig. 4. Endoscopic images of gastric ischemia in a patient with AL amyloidosis.

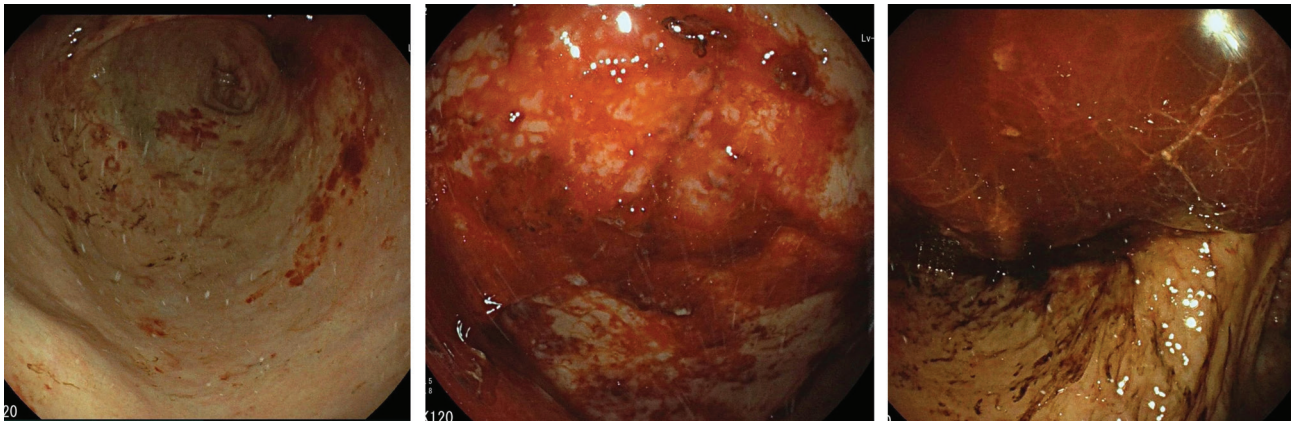

Fig. 5. Endoscopic images of diffuse gastric bleeding in a patient with AL amyloidosis.

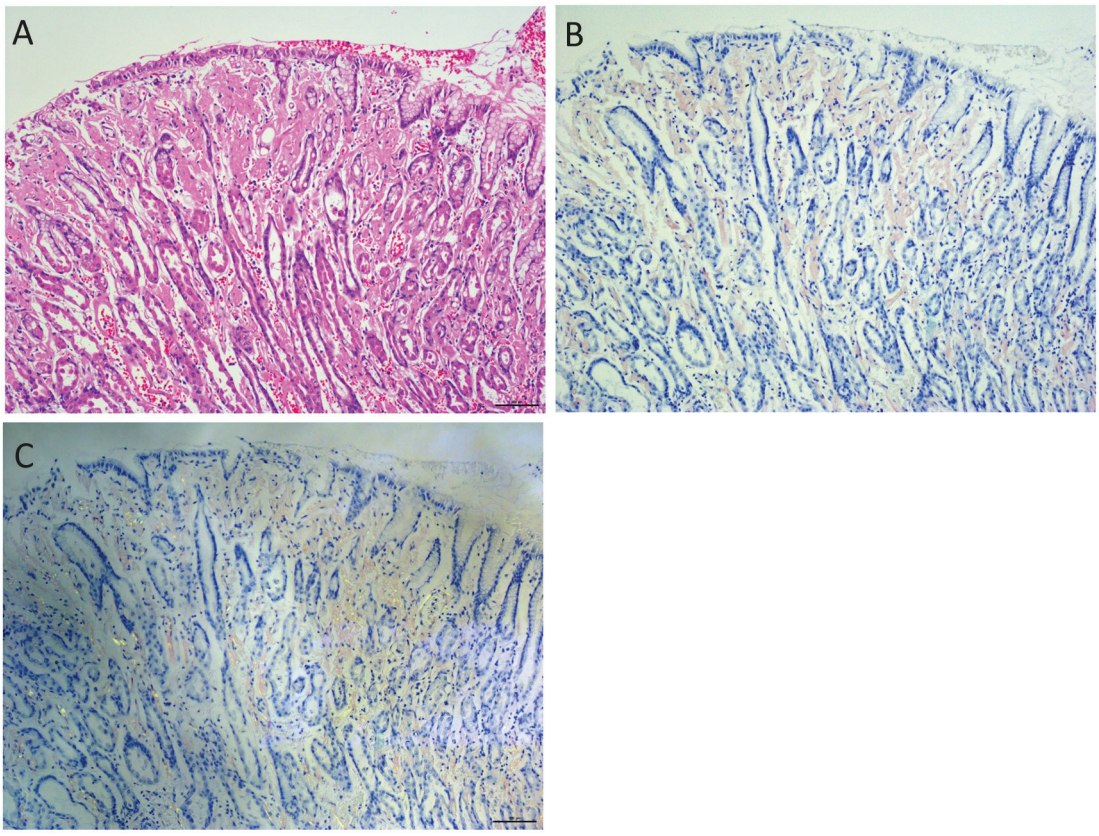

Fig. 6. A) Gastric mucosa with extensive hyaline deposits in the interstitium (HE stain); B) Amyloid deposits showing Congo red staining; C) Apple green birefringence in polarised light (magnification: 100x).

respectively. In this context, the duodenum was the main site of GI involvement. Several other studies also assessed the distribution of amyloid deposition in the GI tract, but the results differed significantly from each other. For patients with systemic AL amyloidosis, the frequency of amyloid deposition in the biopsy specimens was reported at 50% in the small intestine, 44% in the stomach, and 32% in the colon in one study [56]. Other authors detected amyloid deposition in only 5% in the small intestine, 55% in the stomach, and 45% in the colon and 35% in the rectum [58]. Freudenthaler et al. [60] found a distribution of 38% in the colon, followed by the stomach (23%), rectum (17%), duodenum (16%), and jejunum/ileum (6%). But comparable to our study, due to the retrospective design of these three studies, no systematic biopsy regimen was conducted. Yilmaz et al. [61] investigated 36 patients with AA amyloidosis confirmed by renal biopsy and performed upper and lower GI endoscopies to obtain biopsies from the gingiva, esophagus, antrum, duodenum, and rectum. Duodenal, antral, rectal, esophageal, and gingival amyloidosis was present in 97%, 76%, 76%, 59%, and 32%, respectively.

An early autopsy study by Briggs [62] reviewed cases of 53 patients with secondary amyloidosis, and 20 patients with primary amyloidosis. His findings indicate a frequency distribution of 57% in the tongue, 43% in the small bowel,

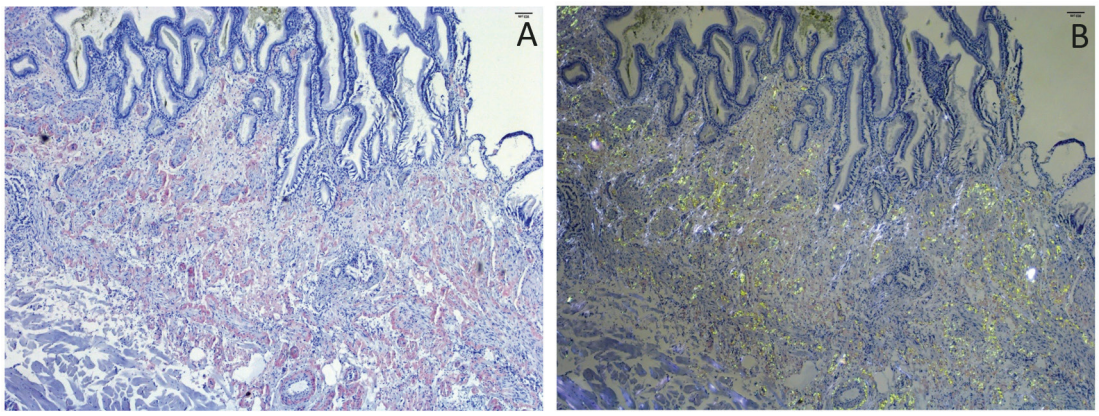

Fig. 7. A) Congo red staining of a gallbladder wall with hyaline deposits in the interstitium and vascular walls. B) Apple green birefringence in polarised light (magnification: 40x).

Table V. Existing studies regarding gastrointestinal amyloidosis

Study name	Authors, Year, reference	Study period/ patient cohort	Described features
Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: a single-center experience	Young Lim et al., 2015 [58]	18 years / 24 patients	Clinical findings and outcomes
Clinical and endoscopic findings in gastrointestinal amyloidosis: a single-center experience	Dias et al., 2022, [67]	10 years / 11 patients	Clinical, and endoscopic findings
Gastrointestinal amyloidosis in Australian indigenous patients	Frommer et al., 2014, [68]	4 years / 9 patients	Clinical findings, outcomes, and histopathological findings
Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience	Cowan et al., 2013, [56]	13 years / 76 patients	Clinical, endoscopic, and histopathological findings
Clinical implications of gastrointestinal symptoms in systemic amyloidosis	Yen et al., 2017, [57]	9 years / 37 patients	Clinical findings
Gastrointestinal amyloidosis: radiologic features by chemical types	Tada et al., 1994, [69]	14 years / 49 patients	Radiologic and histopathological findings
Clinical recognition of Al type amyloidosis of the luminal gastrointestinal tract	James et al., 2007, [70]	14 years / 19 patients	Clinical, endoscopic, and histopathological findings (only AL amyloidosis)
Intestinal involvement in amyloidosis is a sequential process	den Braber-Ymker et al., 2018 [71]	Autopsy study / 14 patients	Histopathological findings
Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis	Tada et al., 1990, [59]	10 years / 37 patients	Endoscopic and histopathological findings
Amyloid in biopsies of the gastrointestinal tract - a retrospective observational study on 542 patients	Freudenthaler et al., 2016, [60]	10 years / 542 patients	Demographical and histopathological findings
Primary systemic amyloidosis: a cause of malabsorption syndrome	Hayman et al., 2001, [35]	38 years / 19 patients	Clinical findings
Gastric amyloidosis: clinicopathological correlations in 79 cases from a single institution	Said et al., 2015 , [39]	6 years / 79 patients	Clinical and histopathological findings
Clinical outcome and survival of secondary (AA) amyloidosis	Tanaka et al., 2003, 55]	18 years / 42 patients	Clinical findings and outcomes
Primary (AL) amyloidosis with gastrointestinal involvement	Madsen et al., 2009 [33]	6 years / 11 patients	Clinical findings
Gastrointestinal manifestations in hereditary transthyretin amyloidosis associated with Glu89Gln Mutation	Nakov et al., 2019, [63]	6.5 years/ 78 patients	Clinical findings
Gastrointestinal manifestations in hereditary transthyretin amyloidosis: a single-centre experience	Luigetti et al., 2020 [64]	39 patients	Clinical findings

41% in the esophagus, 30% in the large bowel and 23% in the stomach. But the author emphasized that the actual frequency distribution among the organs might have been different in reality because of the insufficient number of organs examined in many cases. The tongue, for instance, was only examined in 7 of the 73 patients. A more recent study by Iida et al. [40] described the frequency of amyloid deposition in different parts of the GI tract for 36 of their patients. They further evaluated the differences in the biopsy results in the presence or absence of endoscopic findings. They found that the percentage of positive biopsy results in the stomach and colon were significantly higher than in those without endoscopic findings, with 80% versus 44%, and 88% versus 42%, respectively. On the contrary, the yield of positive biopsy results in the duodenum and rectum was high regardless of endoscopic findings, with 89% versus 90%, and 88% versus 78%, respectively.

In our study cohort, the majority of patients with GI involvement had AL amyloidosis. Even though the percentage of AL patients was also the highest among all treated 63 patients, the proportion of GI involvement was also considerably higher within the AL patients compared to the ATTR and AA patients. In line with our findings, Cowan et al. [56] reported AL to be the most frequent type of amyloidosis in patients with GI involvement.

Diarrhea and weight loss were two of the most frequent GI symptoms in our study population. This observation is in accordance with prior reports [33, 35, 56, 58, 63, 64]. In addition, our patients presented with abdominal pain as the second most frequent symptom. GI bleeding as an initial symptom was only present in two patients but occurred in 9 cases (39.1%) of the patients with GI manifestation of amyloidosis in the further course of the disease.

Our endoscopic findings were comparable to previous studies [40, 48] and included mostly ulcers, mucosal inflammation, polyps, and erosions. Tada et al. [59] suggested that the most characteristic endoscopic features of GI amyloidosis might be a fine granular appearance and polypoid protrusions since those two findings remained unchanged

during the follow-up period of their patients, and biopsy specimens revealed marked deposits of amyloid in the mucosa and submucosa of the duodenum. However, in our patients, fine granular appearances were not described, and polypoid protrusions were only found in two patients.

Histopathologic findings showed vascular amyloid deposition in the majority of our patients, with vascular wall thickening in about a quarter of the study population. Interstitial amyloid deposition was observed in about two-fifths of the patients. The Congo red stain was positive in all patients except one. In this patient, there was no data available regarding Congo red staining, but amyloid deposition was described in the histopathological report. Moreover, in approximately 70% of the patients, typical apple-green birefringence was described. Characteristic green birefringence under cross-polarized light following Congo red staining is the gold standard for confirming the diagnosis of amyloidosis [7, 65, 66].

Among our patients, the overall 5-year survival rate was 38.1% irrespectively of the type of amyloidosis. Here is to mention that two patients were diagnosed with GI amyloidosis 13 and 36 months before the end of the follow-up period and are still alive. These two patients were excluded from this analysis. Previous studies showed 3 years survival rates for patients with gastric amyloidosis up to 60% [39]. Another study showed a 5-year survival among patients with AA amyloidosis and without cardiac involvement of 60% [55]. In AL patients with GI involvement, however, others found that 50 % of the patients only lived 10 months on average after the diagnosis was established [33]. In accordance with that, another study with primarily AL patients with GI amyloidosis reported a median survival of approximately 8 months [58]. As common causes of death, we observed mostly cardiovascular events or multiple organ failure, whereas GI complications seem to be rarely the cause of death in these patients. In our study, none of the patients died due to GI bleeding. This is consistent with previous clinical data [23].

Compared to the existing literature, our study is one of the longest studies on GI amyloidosis with 20 years of observation. There is only one study by Hayman et al. [35] with 38 years of observation. However, only clinical findings were described in this study. Our study is one of the few to have investigated all three aspects namely clinical, endoscopic, and histological findings in the same cohort of patients. Furthermore, our study includes critically ill patients, who suffered from direct complications of GI amyloidosis like severe GI bleeding or gastric ischemia requiring intensive care treatment. Not only that we report the clinical, endoscopic, and histopathologic findings in these critically ill patients but also, we describe the intensive care treatment steps as well as the outcomes.

An overview of existing literature on GI amyloidosis is given by Table V.

The retrospective character may have limited our study. Due to the retrospective character, the sites of performed biopsies to establish the diagnosis of amyloidosis were not standardized. Therefore, the frequency distribution of GI localizations might be biased by preferred sampling sites and GI involvement might be underdiagnosed. Furthermore, there was no standardized questionnaire that explicitly asked for GI symptoms on admission like it could have been provided in a prospective study. Consequently, documented data on GI symptoms was limited to medical history.

CONCLUSIONS

We report the clinical, endoscopic, and histopathological characteristics of 23 patients with amyloidosis and GI involvement within a time span of 20 years. To our knowledge, this is the longest study analyzing clinical, endoscopic, and histopathological aspects as well as patient outcome of GI amyloidosis. Furthermore, based on our information, this is the first study characterizing also critically ill patients with complications of GI amyloidosis. The gold standard to diagnose GI amyloidosis is endoscopic biopsy and histopathological examination.

Conflicts of interest: None to declare.

Authors' contribution: M.M., V.P., and S.S. conceived the study. L.K., S.S., and V.P revised the literature, collected the data, and performed the statistical analyses. L. K., S.S., and V.P drafted the manuscript. M.M., S. S., K. U., P. M., C.K., and V. P. revised the manuscript. M.M., V.P., and S.S. supervised the study. All the authors read and approved the final version of the manuscript.

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REFERENCES

1 Merlini G, Bellotti V. Molecular Mechanisms of Amyloidosis. N Engl J Med 2003;349:583–596. doi:10.1056/NEJMra023144
2 Franck C, Venerito M, Weigt J, Roessner A, Malfertheiner P. Recurrent diffuse gastric bleeding as a leading symptom of gastrointestinal AL amyloidosis. Z Gastroenterol 2017;55:1318–1322. doi:10.1055/s-0043-120924
3 Bansal R, Syed U, Walfish J, Aron J, Walfish A. Small Bowel Amyloidosis. Curr Gastroenterol Rep 2018;20:11. doi:10.1007/s11894-018-0616-y
4 Kyle RA, Gertz MA, Lacy MQ, Dispenzieri A. Localized AL amyloidosis of the colon: An unrecognized entity. Amyloid 2003;10:36–41. doi:10.3109/13506120308995256
5 Paccalin M, Hachulla E, Cazalet C, et al. Localized amyloidosis: A survey of 35 French cases. Amyloid 2005;12:239–245. doi:10.1080/13506120500351174
6 Biewend ML, Menke DM, Calamia KT. The spectrum of localized amyloidosis: A case series of 20 patients and review of the literature. Amyloid 2006;13:135–142. doi:10.1080/13506120600876773
7 Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641–2654. doi:10.1016/S0140-6736(15)01274-X

8 Muchtar E, Dispenzieri A, Magen H, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med 2021;289:268–292. doi:10.1111/joim.13169

9 Gertz MA, Dispenzieri A. Systemic Amyloidosis Recognition, Prognosis, and Therapy: A Systematic Review. JAMA 2020;324:79–89. doi:10.1001/jama.2020.5493

10 Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and Management of Multiple Myeloma: A Review. JAMA 2022;327:464–477. doi:10.1001/jama.2022.0003

11 Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance. Clin Lymphoma Myeloma 2005;6:102–114. doi:10.3816/CLM.2005.n.036

12 Bladé J. Monoclonal Gammopathy of Undetermined Significance. N Engl J Med 2006;355:2765–2770. doi:10.1056/NEJMcp052790

13 Mouhieddine TH, Weeks LD, Ghobrial IM. Monoclonal gammopathy of undetermined significance. Blood 2019;133:2484–2494. doi:10.1182/blood.2019846782

14 Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenstrom's macroglobulinemia. J Clin Oncol 2005;23:1564–1577. doi:10.1200/JCO.2005.03.144

15 Gertz MA. Waldenström macroglobulinemia: 2021 update on diagnosis, risk stratification, and management. Am J Hematol 2021;96:258–269. doi:10.1002/ajh.26082

16 Cuquerella JT, Bosca-Watts MM, Ausejo RA, Alonso ST, De Miguel FM, Perez MM. Amyloidosis in inflammatory bowel disease: A systematic review of epidemiology, clinical features, and treatment. J Crohn's Colitis 2016;10:1245–1253. doi:10.1093/ecco-jcc/jjw080

17 Sattianayagam PT, Gillmore JD, Pinney JH, et al. Inflammatory bowel disease and systemic AA amyloidosis. Dig Dis Sci 2013;58:1689–1697. doi:10.1007/s10620-012-2549-x

18 Husby G. Amyloidosis and rheumatoid arthritis. Clin Exp Rheumatol 1985;3:173–180.

19 Nakamura T. Amyloid a amyloidosis secondary to rheumatoid arthritis: Pathophysiology and treatment. Clin Exp Rheumatol 2011;29:850–857.

20 Ben-Chetrit E. Familial Mediterranean fever (FMF) and renal AA amyloidosis - Phenotype-genotype correlation, treatment and prognosis. J Nephrol 2003;16:431–434.

21 Alghamdi M. Familial Mediterranean fever, review of the literature. Clin Rheumatol 2017;36:1707–1713. doi:10.1007/s10067-017-3715-5

22 Cudrici C, Deuitch N, Aksentijevich I. Revisiting TNF receptor-associated periodic syndrome (TRAPS): Current perspectives. Int J Mol Sci 2020;21:3263. doi:10.3390/ijms21093263

23 Petre S, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis - clinical features, diagnosis and therapy. Aliment Pharmacol Ther 2008;27:1006–1016. doi:10.1111/j.1365-2036.2008.03682.x

24 Syed U, Ching Companioni RA, Alkhawam H, Walfish A. Amyloidosis of the gastrointestinal tract and the liver. Eur J Gastroenterol Hepatol 2016;28:1109–1121. doi:10.1097/MEG.0000000000000695

25 Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. Blood 2020;136:2620–2627. doi:10.1182/blood.2020006913

26 Dittrich T, Kimmich C, Hegenbart U, Schönland SO. Prognosis and staging of AL amyloidosis. Acta Haematol 2020;143:388–400. doi:10.1159/000508287

27 Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA. Primary (AL) hepatic amyloidosis: Clinical features and natural history in 98 patients. Medicine (Baltimore) 2003;82:291–298. doi:10.1097/01.md.0000091183.93122.c7

28 Wixner J, Mundayat R, Karayal ON, Anan I, Karling P, Suhr OB. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. Orphanet J Rare Dis 2014;9:61. doi:10.1186/1750-1172-9-61

29 Nakov R, Suhr OB, Ianiro G, et al. Recommendations for the diagnosis and management of transthyretin amyloidosis with gastrointestinal manifestations. Eur J Gastroenterol Hepatol 2021;33:613–622. doi:10.1097/MEG.0000000000002030

30 Chang HS, Myung SJ, Yang SK, et al. Massive small bowel bleeding in a patient with amyloidosis. Gastrointest Endosc 2004;59:126–129. doi:10.1016/s0016-5107(03)02352-6

31 Yood RA, Skinner M, Rubinow A, Talarico L, Cohen AS. Bleeding Manifestations in 100 Patients With Amyloidosis. JAMA 1983;249:1322–1324.

32 Kim SH, Kang EJ, Park JW, et al. Gastrointestinal amyloidosis presenting with multiple episodes of gastrointestinal bleeding. Cardiovasc Intervent Radiol 2009;32:577–580. doi:10.1007/s00270-008-9429-y

33 Madsen LG, Gimsing P, Schiødt FV. Primary (AL) amyloidosis with gastrointestinal involvement. Scand J Gastroenterol 2009;44:708–711. doi:10.1080/00365520902783717

34 Suhr O, Danielsson Å, Steen L. Bile acid malabsorption caused by gastrointestinal motility dysfunction? an investigation of gastrointestinal disturbances in familial amyloidosis with polyneuropathy. Scand J Gastroenterol 1992;27:201–207. doi:10.3109/00365529208999949

35 Hayman SR, Lacy MQ, Kyle RA, Gertz MA. Primary systemic amyloidosis: A cause of malabsorption syndrome. Am J Med 2001;111:535–540. doi:10.1016/s0002-9343(01)00919-6

36 Kawaguchi M, Koizumi F, Shimao M, Hirose S. Protein-losing enteropathy due to secondary amyloidosis of the gastrointestinal tract. Pathol Int 1993;43:333–339. doi:10.1111/j.1440-1827.1993.tb02576.x

37 Shin JK, Jung YH, Bae MN, Baek IW, Kim KJ, Cho CS. Successful treatment of protein-losing enteropathy due to AA amyloidosis with octreotide in a patient with rheumatoid arthritis. Mod Rheumatol 2013;23:406–411. doi:10.1007/s10165-012-0675-0

38 Wixner J, Törnblom H, Karling P, Anan I, Lindberg G. Abnormal small bowel motility in patients with hereditary transthyretin amyloidosis. Neurogastroenterol Motil 2018;30. doi:10.1007/s10165-012-0675-0

39 Said SM, Grogg KL, Smyrk TC. Gastric amyloidosis: Clinicopathological correlations in 79 cases from a single institution. Hum Pathol 2015;46:491–498. doi:10.1016/j.humpath.2014.12.009

40 Iida T, Yamano H, Nakase H. Systemic amyloidosis with gastrointestinal involvement: Diagnosis from endoscopic and histological views. J Gastroenterol Hepatol 2018;33:583–590. doi:10.1111/jgh.13996

41 Marques M, Sarmento JA, Rodrigues S, Guimarães S, Fonseca E, MacEdo G. Gastric amyloidosis: Unusual cause of upper gastrointestinal hemorrhage. Endoscopy 2011;43(SUPPL. 2). doi:10.1055/s-0030-1256080

42 Rodriguez AC, Clayton S, Brady P, Mamel J. Images of the Month: A Rare Cause of Overt Gastrointestinal Bleeding. Am J Gastroenterol 2016;111:171. doi:10.1038/ajg.2015.213

43 Sucker C, Hetzel GR, Grabensee B, Stockschlaeder M, Scharf RE. Amyloidosis and Bleeding: Pathophysiology, Diagnosis, and Therapy. Am J Kidney Dis 2006;47:947–955. doi:10.1053/j.ajkd.2006.03.036

44 Mumford AD, O'donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol. 2000;110:454–460. doi:10.1046/j.1365-2141.2000.02183.x

45 Tada S, Iida M, Yao T, et al. Endoscopic features in amyloidosis of the small intestine: Clinical and morphologic differences between chemical types of amyloid protein. Gastrointest Endosc 1994;40:45–50. doi:10.1016/s0016-5107(94)70008-7

46 Ihne S, Morbach C, Sommer C, Geier A, Knop S, Störk S. Review article amyloidosis—the diagnosis and treatment of an underdiagnosed disease. Dtsch Arztebl Int 2020;117:159–166. doi:10.3238/arztebl.2020.0159

47 Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010;17:101–104. doi:10.3109/13506129.2010.526812

48 Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol 2008;103:776–787. doi:10.1111/j.1572-0241.2007.01669.x

49 Tada S, Iida M, Yao T, Kitamoto T, Yao T, Fujishima M. Intestinal pseudo-obstruction in patients with amyloidosis: Clinicopathologic differences between chemical types of amyloid protein. Gut 1993;34:1412–1417. doi:10.1136/gut.34.10.1412

50 Röcken C, Saeger W, Linke RP. Gastrointestinal amyloid deposits in old age: Report on 110 Consecutive Autopsical Patients and 98 Retrospective Bioptic Specimens. Pathol Res Pract 1994;190:641–649. doi:10.1016/S0344-0338(11)80742-9

51 Matsutani H, Hoshii Y, Setoguchi M, et al. Vascular amyloid of unknown origin and senile transthyretin amyloid in the lung and gastrointestinal tract of old age: Histological and immunohistochemical studies. Pathol Int 2001;51:326–332. doi:10.1046/j.1440-1827.2001.01213.x

52 Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood 2016;128:159–168. doi:10.1182/blood-2016-01-629790

53 Staron A, Zheng L, Doros G, et al. Marked progress in AL amyloidosis survival: a 40-year longitudinal natural history study. Blood Cancer J 2021;11:139. doi:10.1038/s41408-021-00529-w

54 Grogan M, Scott CG, Kyle RA, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol 2016;68:1014–1020. doi:10.1016/j.jacc.2016.06.033

55 Tanaka F, Migita K, Honda S, et al. Clinical outcome and survival of secondary (AA) amyloidosis. Clin Exp Rheumatol 2003;21:343–346.

56 Cowan AJ, Skinner M, Seldin DC, et al. Amyloidosis of the gastrointestinal tract: A 13-year, single-center, referral experience. Haematologica 2013;98:141–146. doi:10.3324/haematol.2012.068155

57 Yen T, Chen FW, Witteles RM, Liedtke M, Nguyen LA. Clinical implications of gastrointestinal symptoms in systemic amyloidosis. Neurogastroenterol Motil 2018;30:e13229. doi:10.1111/nmo.13229

58 Lim AY, Lee JH, Jung KS, et al. Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: A single-center experience. Korean J Intern Med 2015;30:496–505. doi:10.3904/kjim.2015.30.4.496

59 Tada S, lida M, Iwashita A, et al. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. Gastrointest Endosc 1990;36:10–14. doi:10.1016/s0016-5107(90)70913-3

60 Freudenthaler S, Hegenbart U, Schönland S, Behrens HM, Krüger S, Röcken C. Amyloid in biopsies of the gastrointestinal tract - a retrospective observational study on 542 patients. Virchows Arch 2016;468:569–577. doi:10.1007/s00428-016-1916-y

61 Yilmaz M, Unsal A, Sokmen M, et al. Duodenal biopsy for diagnosis of renal involvement in amyloidosis. Clin Nephrol 2012;77:114–118. doi:10.5414/CN107139

62. Briggs GW. Amyloidosys. Ann Intern Med 1961;55:943-957. doi:10.7326/0003-4819-55-6-943

63 Nakov R, Sarafov S, Nakov V, et al. Gastrointestinal Manifestations in Hereditary Transthyretin Amyloidosis associated with Glu89Gln Mutation. J Gastrointestin Liver Dis 2019;28:421–426. doi:10.15403/jgld-362

64 Luigetti M, Tortora A, Romano A, et al. Gastrointestinal Manifestations in Hereditary Transthyretin Amyloidosis: a Single-Centre Experience. J Gastrointestin Liver Dis 2020;29:339–343. doi:10.15403/jgld-2474

65 Lee AYS, Bayly A, Lin MW. Evaluation of Polarized Light and Fluorescence Microscopy of Congo Red Stain in the Diagnosis of Renal Amyloidosis. Lab Med 2021;52:574–577. doi:10.1093/labmed/lmab022

66 Clement CG, Truong LD. An evaluation of Congo red fluorescence for the diagnosis of amyloidosis. Hum Pathol 2014;45:1766–1772. doi:10.1016/j.humpath.2014.04.016

67. Dias E, Santos-Antunes J, Marques M, et al. Clinical and endoscopic findings in gastrointestinal amyloidosis: a single-center experience. Rev Esp Enferm Dig 2022 Jul;114(7):425-427. doi:10.17235/reed.2022.8656/2022

68. Frommer DJ, Fernandes D, Pawar G, Goud R. Gastrointestinal amyloidosis in Australian Indigenous patients. Intern Med J 2014;44:605-609. doi:10.1111/imj.12450

69. Tada S, Iida M, Yao T, et al. Gastrointestinal amyloidosis: radiologic features by chemical types. Radiology 1994;190:37-42. doi:10.1148/radiology.190.1.8259424

70. James DG, Zuckerman GR, Sayuk GS, Wang HL, Prakash C. Clinical Recognition of AL Type Amyloidosis of the Luminal Gastrointestinal Tract. Clin Gastroenterol Hepatol 2007;5:582-588. doi:10.1016/j.cgh.2007.02.038

71. den Braber-Ymker M, Heijker S, Lammens M, Croockewit S, Nagtegaal ID. Intestinal involvement in amyloidosis is a sequential process. Neurogastroenterol Motil 2018;30:e13469. doi:10.1111/nmo.13469