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Case Report

Light-Chain (AL) Amyloidosis as a Rare Cause of Upper Gastrointestinal Bleeding: A Case Report and Systematic Literature Review

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Keywords
Case report · Systematic review · AL-amyloidosis · Upper gastrointestinal bleeding

Abstract
Introduction: Amyloidosis is a rare disease characterized by the deposition of misfolded proteins in different organs leading to tissue damage and organ failure. The immunoglobulin light chain produced by a monoclonal B-cell is one of more than 30 proteins identified to cause amyloidosis. Most commonly affecting the heart and kidneys, AL (amyloid, light chain) -amyloidosis can occur in any organ except for the central nervous system and carries a high morbidity and mortality. Gastrointestinal involvement is observed rather rarely and can present with intestinal obstruction, weight loss, hematochezia, malabsorption, or hematemesis. In this case report and systematic review, we present a 76-year-old male patient with new onset recurrent hematemesis and melena due to duodenal AL-amyloidosis and give a summary on the reported cases of upper gastrointestinal bleeding caused by the disease. ***Case Report:*** The report of this case was guided by the CARE guidelines and served as an example to allow for a discussion of the specific aspects of upper gastrointestinal bleeding in AL-amyloidosis. A comprehensive literature search was conducted using the databases PubMed, Embase and Google Scholar. After applying the eligibility criteria, a total count of 26 were included into the systematic review which was reported according to the PRISMA checklist. The reported case showed recurrent hematemesis as the initial symptom of AL-amyloidosis due to B-cell dyscrasia and appeared to be characteristic of patients presenting with primary gastrointestinal involvement. Summarizing the biometric and clinical details of the individuals included into the systematic review, we observed a mean age of 66 years, a slight female predominance and a preferred clinical manifestation in the stomach and duodenum with localized disease in 38% of all cases. ***Conclusion:*** Although being a rare cause of upper gastrointestinal bleeding, AL-amyloidosis should be considered in patients with

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endoscopic findings of systemic disease and a clinical condition of suspected or known B-cell dyscrasia. An early diagnosis is crucial for patients with AL-amyloidosis as the disease often shows a rapid progression and treatment with combined personalized-/chemotherapy is usually well tolerated and highly efficient.

Introduction

Amyloidosis is a systemic disease caused by the extracellular deposition of misfolded fibrillar proteins leading to dysfunction of the affected organ. The most common subgroup is AL (amyloidosis, light chain) -amyloidosis with an incidence of 5–13 in one million person-years [1]. A median age of 63 years and a slight male predominance are reported [2]. The disease results from the clonal proliferation of B-cells producing immunoglobulin light chains with mutations in the variable region. This is most commonly observed in the setting of plasma cell dyscrasia with symptomatic multiple myeloma accounting for about 10% of cases and is rarely seen in B-cell lymphoma, immunocytoma, or mantle cell lymphoma [3, 4].

The mutation in the immunoglobulin light chain is about to be three times more likely to occur in the λ compared to the κ subtype [5] and causes low folding stability and impaired protein aggregation. These proteins deposit in the extracellular space as rigid, non-branching amyloid fibrils [6] which may exhibit a toxic effect and cause physical damage to the tissue parenchyma [7]. The heart and kidneys are most commonly affected and cardiac involvement is consistently related to an adverse clinical outcome and is therefore referred to in prognostic staging systems [8]. Gastrointestinal manifestations are observed only in about 3–8% of patients with AL-amyloidosis and span a wide range of symptoms including intestinal obstruction, weight loss, hematochezia, malabsorption, or hematemesis [9]. Common endoscopic findings are polypoid mucosal protrusions and thickened folds which result from the mass-like submucosal deposition of amyloid fibrils. These fibrils exhibit a strong affinity for Congo red staining and show apple-green birefringence under polarized light which is considered pathognomonic for amyloidosis during pathological examination. Upper gastrointestinal bleeding is less commonly observed in AL-amyloidosis and can be attributed to multiple factors including vascular damage and acquired coagulopathy [10]. Fibril deposition occurs preferentially around submucosal vessels thereby inducing ischemic changes of the vessel wall leading to vasculature fragility. Besides immediate endoscopic interventions, the treatment of AL-amyloidosis intends to reverse the underlying condition by inhibiting the proliferation of monoclonal B-cells. Given the rapid progression of the disease, treatment with combined personalized-/chemotherapy should be initiated once the diagnosis has been made [11–13]. In this case report and systematic review, we present a patient with recurrent hematemesis and melena due to duodenal AL-amyloidosis and summarize the existing literature on upper gastrointestinal bleeding caused by the disease.

Case Report

Methods

The writing of the case report was guided by the CARE guidelines [14] and the systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P 2015) [15] checklist.

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Eligibility Criteria

The systematic review only included case reports of patients with upper gastrointestinal bleeding due to AL-amyloidosis. No restrictions were defined with regard to publication date or language of published articles. Case reports were only included if the diagnosis was made based on pathological examination and endoscopic or clinical evidence of upper gastrointestinal bleeding were reported.

Search Strategy and Study Selection

A comprehensive literature search was conducted using the electronic databases PubMed, Embase, and Google Scholar until October 1, 2024. The keywords and Medical Subject Heading (MeSH) terms "amyloidosis" and "gastrointestinal bleeding" were combined by Boolean operator. The search strategy was restricted to the search terms being contained in the title and/or abstract. References were exported with the Citavi© software (Lumivero, Denver, USA) and duplicates were removed. The identified records were screened for eligibility by reading the titles and abstracts of each article. If the eligibility criteria were met, the full text was obtained and investigated for inclusion into the systematic review (Fig. 1).

Report of Case

A 76-year-old male patient presented to our emergency department with exertional shortness of breath and melena for 4 days. The patient was on ongoing Bismuth quadruple therapy (bismut-III-oxid, metronidazole, tetracycline, omeprazole) which had been prescribed for *Helicobacter pylori* positive duodenitis after his first admission about 10 days before. On physical examination, we noted pitting edematous ankles, a height of 173 cm, weight of 68 kg, and vital signs within normal range. The past medical history included insulin dependent diabetes mellitus type 2, arterial hypertension and hypercholesterinemia. His home medication included insulin glulisine, atorvastatin, hydrochlorthiazide, lercanidipine, and lisinopril. Laboratory assessment revealed normocytic, normochromic, hyperregeneratory anemia with a hemoglobin concentration of 9.9 mg/dL, an erythrocyte count of 3.7/pl and reticulocytes of 2.7%. Symptoms of decompensated congestive heart failure were consistent with an elevated NT-proBNP of 837 mg/dL. On echocardiography, an enhanced echo texture with hypertrophy of the septum and inferior wall was observed. Neither significant valvular pathology nor diastolic or systolic dysfunction with an estimated left ventricular ejection fraction of 70% were demonstrated. On esophago-gastro-duodenoscopy, multifocal polypoid lesions with mucosal protrusions from the distal bulbus to the pars descendens of the duodenum were observed (Fig. 2a, b). During the investigation the mucosa appeared highly friable with recurrent oozing on contact. Overall, the endoscopic findings were suspicious for an underlying systemic disease. The pathological examination of duodenal biopsies revealed submucosal mass-like deposits which stained positive for Congo red with birefringence under polarized light (Fig. 3a, b). Immunohistochemistry showed positive staining for p53, CD31, pan+ cytokeratin. In addition, subtyping of amyloid deposits showed positivity for both λ-light chains and AL7 while being negative for κ-light chain, serum protein A amyloid and transthyretin. The investigation of serum free light chains showed elevated levels for the λ fraction 182.85 mg/dL (5.71–26.30 mg/dL) with normal concentrations for κ 10.89 mg/dL (3.30–19.40 mg/dL) and a ratio of 0.06. Monoclonal production of free light chains of the λ subtype was confirmed by urine immunofixation which showed an elevated concentration of 13.17 mg/dL (<3.79 mg/dL) and a level of 18.77 mg/dL (<32.90 mg/dL) for κ free light chains resulting in a ratio of 1.43 (2.04–10.37). Based on the pathological examination and levels of free light chains, the diagnosis of systemic AL-amyloidosis with isolated organ involvement of the duodenum was made. Cardiac involvement was not confirmed by cardiac MRI on which no global subendocardial contrast enhancement and

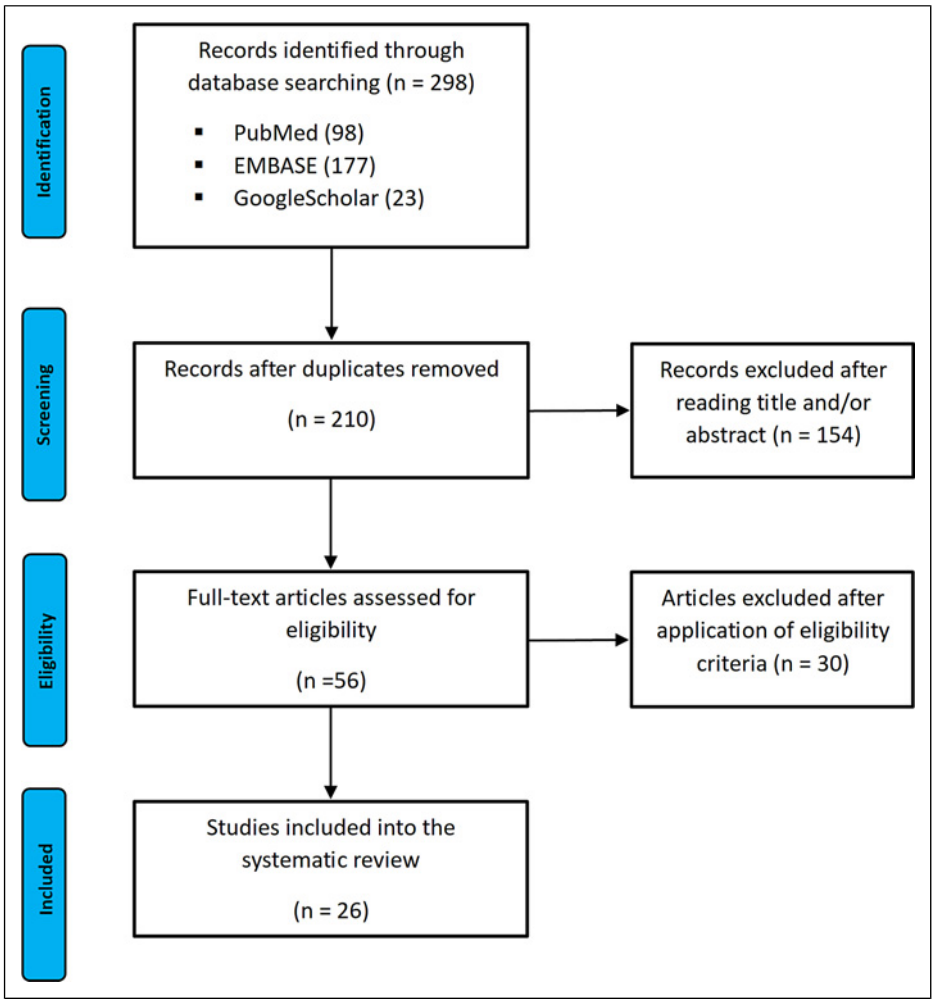

Fig. 1. Flowchart of the study selection according to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA).

rather diffuse late gadolinium enhancement consistent with hypertrophic cardiomyopathy were observed. Computed tomography revealed a localized thickening of the duodenal wall (Fig. 4a, b). Retention parameters were within the normal range and ultrasound showed no evidence of renal involvement. In addition, there were no sonographic signs of organomegaly or clinical evidence for peripheral polyneuropathy. Therefore, our patient was diagnosed with isolated duodenal manifestation in systemic AL-amyloidosis of the duodenum and was planned for treatment initiation with combined personalized-/chemotherapy. According to current recommendations, treatment with daratumumab (1,800 mg s.c.)-bortezomib (1.3 mg/m^3 s.c.) and dexamethasone (20 mg p.o.) was initiated and cyclophosphamide was omitted due to its hematotoxic effects.

Study Selection

The study selection process is illustrated in the flowchart in Figure 1. There was a total count of 298 records after the initial search including 98 from PubMed, 177 from Embase, and 23 from Google Scholar. After removing all duplicates, 154 of the 210 remaining records were excluded after reading the title and/or abstract. A total count of 56 articles was then screened for eligibility. Finally, 26 studies were included into the systematic review.

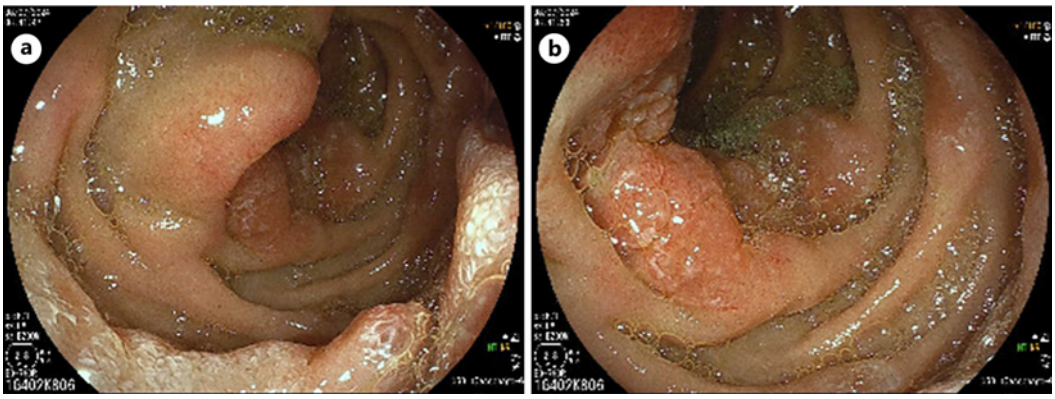

Fig. 2. a, **b** Polypoid protrusions, thickened folds, and friable mucosa of the duodenum.

Summary of Included Studies

A summary of each included study is given in Tables 1–4. All articles were written in English and published between 1998 and 2022 in scientific journals. The mean age of the 26 presented patients was 66.0 ± 12.5 years. The female-to-male ratio was 15:11 showing a slight female predominance. The most frequent initial symptoms for which patients referred to the hospital were melena (38%), hematemesis (35%), and epigastric pain (19%). Localized disease where the production and deposition of amyloid fibrils is within the same organ was reported in 10 cases (38%). The disease manifested most frequently in the stomach (77%) and duodenum (50%) while the jejunum (12%), the tongue, esophagus, and the colon were only rarely involved (8%). Endoscopic findings included ulcers (58%), fragile or friable mucosa (15%), erosions (12%), polypoid lesions (12%), hematoma (12%), and active bleeding (8%). Besides urgent treatment with proton pump inhibitors, volume substitution and packed RBCs, patients received immunomodulating and personalized-/chemotherapy.

Discussion

This case report and systematic review intended to give a case-based overview on upper gastrointestinal bleeding as the primary symptom in AL-amyloidosis. Being categorized as a rare disease, AL-amyloidosis most commonly presents with a cardiac or renal manifestation and involves the gastrointestinal system only in about 3–8% of patients [9].

Regarding biometric data, the systematic review confirms epidemiological studies reporting a mean age within the 7th decade of life. The gender distribution with a female to male ratio of 1:0.73 was not entirely consistent with most studies on AL-amyloidosis indicating an overall male predominance [2].

The symptoms can vary depending on the affected organ and can occur as part of systemic amyloidosis or as localized disease where production and deposition site of amyloid fibrils are within the same tissue. In the initially reported case, the duodenum was the only affected organ presenting with melena and polypoid lesions as the main clinical and endoscopic findings. The duodenum was involved in half of all reported cases and was the second most frequent organ manifestation.

Endoscopically, multilocular polypoid lesions were observed throughout the entire duodenum in our patient which is consistent with a study by Tada et al. [42] who reported polypoid protrusions as the main endoscopic finding occurring in 75% of patients with gastrointestinal involvement of AL-amyloidosis. However, in this systematic review

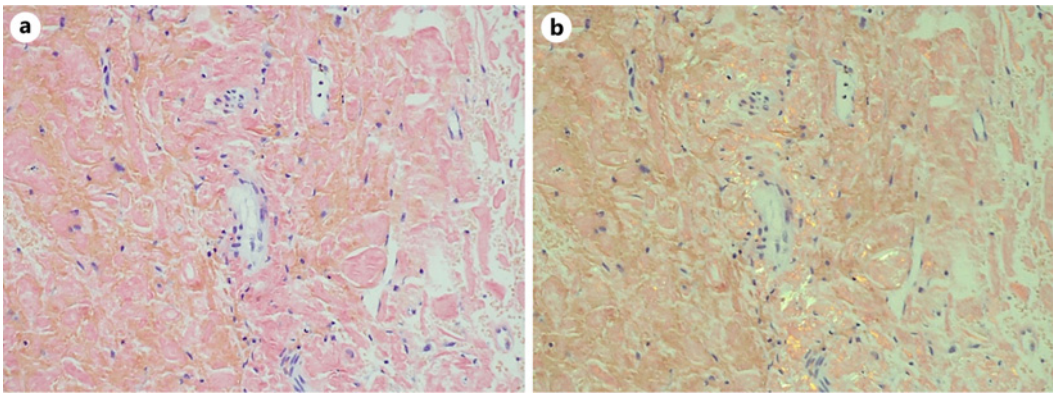

Fig. 3. a, **b** Amyloid deposits positive for Congo red staining with birefringence under polarized light.

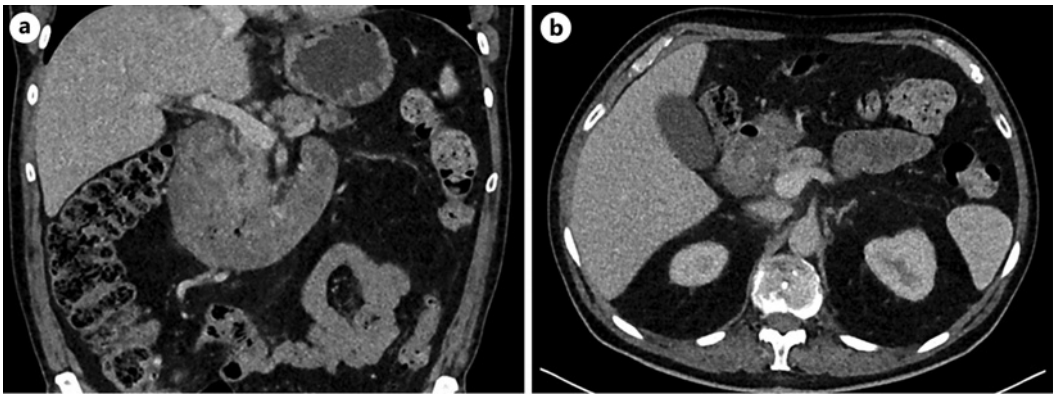

Fig. 4. a, **b** Thickened and hazy duodenum in sagittal and transversal CT abdomen.

polypoid protrusions were observed in only 12% of patients while ulcers were the most frequently reported lesion (58%). This may be explained by variable endoscopic reporting and the stomach being the most common manifestation site. Pathological examinations show that amyloid deposition in AL-amyloidosis occurs as a mass in the submucosal and muscular layer thereby protruding the mucosa and presenting as polypoid lesions and thickened folds [42]. In contrast, AA (amyloidosis, serum amyloid A) -amyloidosis which is related to inflammatory diseases shows a diffuse deposition pattern involving the mucosal layer causing friability of the mucosa. This may partly explain the difference in gastrointestinal symptoms between both entities. While AL-amyloidosis presents with a wide range of clinical signs including intestinal obstruction, weight loss, hematochezia, malabsorption, or hematemesis, AA-amyloidosis is more often associated with intestinal bleeding occurring both in the small and large intestine [42]. The pathophysiology of upper gastrointestinal bleeding is multifactorial and can result from mucosal damage, vascular fragility or acquired coagulopathy. Amyloid deposition in AL-amyloidosis begins in submucosal vessels which induces ischemia of the vessel wall. As illustrated in Figure 3a and b, the amyloid fibrils seem to accumulate preferentially around vessels of the intestinal wall which may lead to vascular fragility. In addition to vascular lesions, direct mechanical damage by amyloid deposits which present as rigid, non-branching fibrils measuring about 10 nm under electron microscopy can be assumed [43]. Another cause of

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Table 1. Summary of the included studies on upper gastrointestinal bleeding in AL-amyloidosis

Study author (year)	Patient characteristic					Endoscopy	Histology	Treatment
	age, years	gender	symptoms	localized or systemic disease	organ involvement			
Lau et al. [16] (1998)	60	Female	Vomiting of food for 3 days, hematemesis for 1 day	Systemic (plasma cell dyscrasia)	Stomach	1 cm ulcer of gastric ulcer	Eosinophilic amyloid-like material in the submucosa, apple-green birefringence in the submucosa	PPI, TPN, melphalan 0.15 mg/kg bodyweight, prednisone 0.8 mg/kg bodyweight for 7 days
Chang et al. [17] (2001)	75	Female	Generalized malaise, lower back pain, hematemesis, tarry stool, hematochezia	Systemic (MM)	Stomach, duodenum	Several erosions, erythematous streaks over the antrum and duodenum, uneven duodenal mucosa with protruding vessels	Amyloid deposition in the submucosa, green birefringence	24 courses of melphalan and prednisolone
Alvares et al. [18] (2003)	45	Female	Fatigability and body ache, upper gastrointestinal bleeding, macroglossia	Systemic (MM)	Tongue, esophagus, stomach	Hematoma of the lower esophagus, Large nodular folds, ulcer in the antrum	Positive for Congo red stain	PPI, melphalan and prednisolone for 3 years
Dias et al. [19] (2009)	66	Male	Fatigue, exertional dyspnea, melena for 3 days	Localized	Duodenum	Mucosal thickening and clots in the duodenal bulb, polypoid protrusions with erosions in the second half of the duodenum		
Rehman et al. [20] (2010)	60	Male	Crampy abdominal pain	Systemic (MM)	Tongue, stomach	Inflamed, infiltrated mucosa along the greater curvature, ulcerations into the prepyloric area	Positive Congo red staining of gastric biopsies with green birefringence	Bortezomib
Patel et al. [21] (2012)	83	Female	1 week of melenic stool	Localized	Duodenum	2 cm non-bleeding ulcerative duodenal mass	Congo red staining exhibited apple-green birefringence under polarized light	Not reported

MM, multiple myeloma; PPI, proton pump inhibitor; TPN, total parenteral nutrition.

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Table 2. Summary of the included studies on upper gastrointestinal bleeding in AL-amyloidosis

Study author (year)	Patient characteristic					Endoscopy	Histology	Treatment
	age, years	gender	symptoms	localized or systemic disease	organ involvement			
Ali et al. [22] (2014)	58	Female	Epigastric pain, coffee-ground emesis for 2 days	Localized	Stomach, duodenum	Punctate, erythematous lesions of the stomach, small bowel mucosa scalloped, ulcerated, and hemorrhaged on contact	Infiltration and expansion of the lamina propria und submucosa, deposits around blood vessels	RBC, FFP, PPI
Anand et al. [23] (2015)	78	Male	Anemia, gastrointestinal bleeding, fever	Localized	Duodenum	Erythematous, granular and atrophic mucosa in the entire stomach, multiple inflamed and friable nodules	Positive Congo red stain	Lenalidomide and decadron
Mittal et al. [24] (2015)	82	Male	Anemia secondary to gastrointestinal bleeding	Systemic (MM)	Stomach, duodenum, jejunum, kidneys	Erosions in the gastric antrum, duodenitis, jejunal ulcers	Amyloid deposition in jejunal ulcers, IHC staining positive for Cong red and lambda light chain	PRBC, platelets, long-term treatment not reported
Gjeorgjievski et al. [25] (2015)	92	Female	Progressive weakness, lethargy, orthostatic dizziness, and melena during the prior few days	Systemic (SMM)	Stomach	Clot attached to the gastric body, eight small sessile polyps in the gastric fundus	Positive Congo red stain deposits in the lamina propria, apple-green birefringence	RBC, PPI
Dugan et al. [26] (2015)	50	Female	Recurrent hematemesis	Systemic (MM)	Stomach	Gastric mucosal ulcers and submucosal hematomas	Not reported	Lenalidomide
Siau et al. [27] (2016)	55	Male	Abdominal pain, weight loss, meleana, anemia	Systemic (MGUS)	Duodenum, jejunum	Mucosal congestion and friability within the distal duodenum, jejunitis	IHC showing plasma cells with λ-light chain expression. Congo red stain was positive with apple-green birefringence under polarized light in the mucosa and submucosa	Cyclophosphamide, bortezomib and dexamethasone

FFP, fresh frozen plasma; ICH, immunohistochemistry; MGUS, monoclonal gammopathy of unclear significance; PPI, proton pump inhibitor; RBC, red blood cells; SMM, smoldering multiple myeloma.

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Table 3. Summary of the included studies on upper gastrointestinal bleeding in AL-amyloidosis

Study author (year)	Patient characteristic					Endoscopy	Histology	Treatment
	age, years	gender	symptoms	localized or systemic disease	organ involvement			
Singh et al. [28] (2016)	61	Male	Hematemesis and melena	Systemic (MM)	Stomach	Ulcers in the fundus and body of the stomach	Diffuse amyloid deposition in the antrum, body, distal body of the stomach	PPI, oncology follow-up
Katagiri et al. [29] (2017)	64	Female	Petechial hemorrhage of the skin, melena	Systemic (MM)	Jejunum	Small ulcers in the jejunum	Congo red deposits around blood vessels, apple-green birefringence	Induction therapy not specified
Chahal [30] (2017)	46	Male	Melena for 2 weeks	Systemic (MM)	Duodenum, kidneys	Hemorrhagic, nodular, ulcerated mucosa of stomach and proximal duodenum	Biopsies positive for AL-amyloid	Bortezomib, cyclophosphamide, dexamethasone
Suchartlikitwong et al. [31] (2017)	59	Female	Syncope, periorbital purpura, macroglossia, gastrointestinal bleeding	Systemic (MM)	Stomach, duodenum	Foveolar hyperplasia of mucosa with submucosal amorphous deposition	Positive Congo red stain, apple-green birefringence	RBC, bortezomib, dexamethasone
Zhou [32] (2017)	63	Female	Hematemesis, anemia	Systemic (MM)	Stomach, colon	Ulceration in the angulus of the stomach	Positive Congo red staining with deposits below the epithelium	Cyclophosphamide, dexamethasone, thalidomide
Gupta et al. [33] (2019)	60	Female	Epigastric pain, vomiting, diarrhea, tachycardia, macroglossia	Systemic (MM)	Stomach, duodenum, colon	Diffuse discontinuous congestion, friability, and ulceration of the mucosa	Mucosal cells with extracellular amorphous deposits, staining positive for Congo red stain	Bortezomib, elotuzumab
Guijula et al. [34] (2019)	81	Female	Hematemesis for 1 day, epigastric pain	Localized	Stomach	Oozing of blood on contact with air insufflation from the lesser curvature, body and fundus	Dilated and congested blood vessels suggestive of AVM and positive Congo red stain and apple-green birefringence	TPN, sucralfate for 10 days

AL, amino light chain; AVM, arteriovenous malformation; MM, multiple myeloma; PPI, proton pump inhibitor; RBC, red blood cells; TPN, total parenteral nutrition.

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Table 4. Summary of the included studies on upper gastrointestinal bleeding in AL-amyloidosis

Study author (year)	Patient characteristic					Endoscopy	Histology	Treatment
	age, years	gender	symptoms	localized or systemic disease	organ involvement			
Gregory and Kachru [35] (2019)	64	Female	Fatigue, dyspnea for 1 day, melena and dizziness for 1 week	Systemic (MM)	Stomach	Localized gastropathy in the proximal stomach	Deposition of amorphous, eosinophilic material, Congo red stain showed apple-green birefringence	Oncology follow-up
Tanaka et al. [36] (2020)	65	Male	Hematemesis	Localized	Esophagus, stomach	Fragile mucosa, submucosal hematoma	Eosinophilic substance in the lamina propria, Congo red stain, apple-green birefringence	Not reported
Singh et al. [37] (2021)	47	Female	Chronic bleeding, anemia	Systemic (MM)	Stomach	3 cm ulcer on the lesser curve of the stomach	Amyloidogenic component was immunoglobulin light chains	Not reported
Akusoba et al. [38] (2021)	70	Male	Melena and hematochezia, hypotonia, tachycardia	Systemic	Stomach, duodenum	Mucosal friability of the stomach and duodenum	Congo red stain, deposits in the vasculature of the ulcer, apple-green birefringence	RBCs, FFP, crystalloids infusion
Chan and Carpentier [39] (2021)	76	Male	Hematemesis, melena, reduced consciousness	Systemic (MM)	Stomach, duodenum	Diffuse gastritis, nodularity, ulceration of the cardia and natrum, duodenal ulcer	Congo red staining, apple-green birefringence	Cyclophosphamide, bortezomib, dexamethasone
Fang et al. [40] (2021)	80	Female	Decreased appetite, weight loss, paleness	Systemic (MM)	Stomach	Irregular thickened gastric folds, ulcers, polypoid masses of the fundus	Eosinophilic material in the lamina propria, apple-green birefringence in Congo red staining	PPI, RBC, 9 cycles of melphalan, prednisolone, thalidomide
Merrill et al. [41] (2022)	74	Male	Chest pain, dyspnea, melena	Systemic (plasma cell dyscrasia)	Stomach, duodenum	Gastric mucosal bleeding, mosaic pattern of gastric mucosa	Congo red staining, apple-green birefringence	Daratumumab, cyclophosphamide, and bortezomib

FFP, fresh frozen plasma; MM, multiple myeloma; PPI, proton pump inhibitor; RBC, red blood cells.

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upper gastrointestinal bleeding in AL-amyloidosis may be acquired coagulopathy due to clotting factor deficiency which has been most frequently described for factor X deficiency. It is hypothesized that clotting factors get absorbed by amyloid deposits in the spleen which could be reversed by splenectomy or successful treatment of monoclonal B-cell proliferation [44, 45]. However, in none of the presented cases any association with underlying coagulopathy as the cause of bleeding was reported.

Diagnostic Biopsies from the Gastrointestinal Tract

In accordance with the hemorrhagic predisposition in AL-amyloidosis, tissue sampling of the gastrointestinal tract carries a particularly high risk of bleeding associated complications and should be performed with great caution. However, organ biopsy is mandatory in patients with localized manifestation and is required if bone marrow biopsy and fat pad aspiration are negative. This is the case in 11% of all patients presenting with AL-amyloidosis. The sensitivity of organ biopsies in AL-amyloidosis of the upper or lower gastrointestinal tract is 88% and 80%, respectively. Gastrointestinal tissue sampling is also mandatory to make a diagnosis in localized forms of AL-amyloidosis and limited organ involvement is a predictor for the necessity of organ biopsy [46]. In gastrointestinal amyloidosis, the occurrence of amyloid deposition shows an anatomical distribution with increasing probability from the lamina propria to the muscularis mucose, and the submucosa of the affected organ [47]. This especially applies to AL-amyloidosis of the lambda subtype and indicates a necessity for deeper endoscopic tissue sampling which in turn increases the risk of bleeding associated complications.

Localized Amyloidosis

Other than in our patient and the majority of the presented cases, localized amyloidosis, which is defined as amyloid fibrils produced and deposited within the same organ, requires an individualized treatment approach often involving surgical or endoscopic resection and is generally not treated with systemic chemotherapy. Only six of the included cases reported a localized manifestation which is consistent with epidemiological data indicating that a localized form occurs in about 12% all newly diagnosed gastrointestinal amyloidosis [48]. In all patients reported in this systematic review, a local deposition of AL-amyloid fibrils was observed which is the most common subtype in localized amyloidosis being about five times more prevalent than AA-amyloidosis according to a recent review. Unlike systemic amyloidosis, the prognosis in localized disease is remarkably good since removal of amyloid deposit may be curative and transition to systemic disease is not observed. While surgical resection of the affected manifestation site is the most frequently applied therapeutic approach in gastrointestinal amyloidosis [49] successful treatment with less invasive procedures like endoscopic submucosal resection [50] are reported. Endoscopic laser resection is frequently applied in tracheobronchial amyloidosis as it does not only remove amyloid deposits but eliminates plasma cells [51].

Systemic Amyloidosis

The presence of systemic amyloidosis in which the location of production of amyloid fibrils is different from the deposition site is associated with precursor proteins circulating in the blood and urine. It requires a systemic therapeutic approach involving treatment of an underlying inflammatory condition in AA-amyloidosis or chemotherapy of B-cell clones in AL-amyloidosis. Systemic amyloidosis due to B-cell dyscrasia was present in our patient and in 20 of the reported cases which corresponds with the existing literature naming it as the predominant subtype of gastrointestinal amyloidosis [52]. Its prognosis is generally worse than

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in localized forms and depends on the underlying condition and the amount of amyloid deposition. The treatment choice should be made depending on the patient's risk profile which can be stratified according to the Mayo Clinic Staging System (2012) [53] including cardiac and renal biomarkers.

According to current recommendations, a combination of daratumumab/cyclophosphamide/bortezomib/dexamethasone is recommended as first-line treatment in patients with systemic AL-amyloidosis [54]. The addition of daratumumab, a human monoclonal CD38 antibody, has shown to cause a stronger treatment response compared with cyclophosphamide/bortezomib/dexamethasone alone [13]. It has been demonstrated to induce long-lasting hematological and organ specific responses with comparably good tolerability.

High-dose melphalan, a nitrogen mustard alkylating agent, and subsequent autologous stem cell transplantation (ASCT) used to be the only treatment option to achieve sustained remissions before the approval of daratumumab/cyclophosphamide/bortezomib/dexamethasone in AL-amyloidosis. In none of the presented cases conduction of ASCT was reported [55]. Instead, a combination of melphalan with prednisone was chosen in 4 patients. Before the introduction of ASCT, treatment with melphalan (0.15 mg/kg) and prednisone (0.8 mg/kg) daily for 1 week has been the standard treatment for many years [3].

A mono- or combination therapy with the immunomodulators thalidomide or lenalidomide has proved to be efficient in AL-amyloidosis and was applied in 4 patients. The therapeutic effects include direct cytoxicity, immunostimulation, and antiangiogenic effects [56]. Its clinical use is limited due to its narrow therapeutic index with a wide range of side effects [57].

Treatment with bortezomib, a proteasome inhibitor, was prescribed in 7 patients as either monotherapy or in combination with dexamethasone, daratumumab, or cyclophosphamide. In the reported case, a treatment cycle with daratumumab (1,800 mg s.c.) and bortezomib (1.3 mg/m^3) on day 1 and 8 followed by daratumumab (1,800 mg s.c.) on day 15 with dexamethasone (20 mg) every 2 days was initiated. Due to its hematotoxic side effects [58], localized disease of the duodenum and high treatment efficacy of daratumumab and bortezomib, application of cyclophosphamide was omitted.

Conclusion

In this work, we presented 27 patients with upper gastrointestinal bleeding due to either systemic or localized manifestation of AL-amyloidosis. In each case, the diagnosis was made on pathological exam with positive staining for Congo red and birefringence under polarized light. Treatment wise, a trend toward more tolerable medication including the monoclonal CD38 antibody daratumumab and the proteasome inhibitor bortezomib which could induce long-lasting hematological remissions was observed. Clinicians should be aware of AL-amyloidosis as a rare cause of upper gastrointestinal bleeding since early diagnosis and treatment initiation are crucial for clinical outcome.

Statement of Ethics

Ethical approval is not required for this study in accordance with local and national guidelines. Written informed consent was obtained for the publication of this case report. The CARE Checklist for this case report is available as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545586).

Conflict of Interest Statement

All authors declare to have no conflict of interest.

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Author Contributions

C.M. conducted the systematic review and wrote the manuscript. C.M. and A.W. prepared figures. Both authors interpreted the results and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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