forensic sciences

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Review

Iatrogenic Sigma Perforation in a Patient with Localized Rectal and Sigma AL Amyloidosis: A Forensic Case and a Literature Review

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Abstract: Amyloidosis is defined as a rare group of 30 protein-folding diseases characterized by the extracellular deposition of a specific soluble precursor protein that aggregates in the form of insoluble fibrils. The gastrointestinal tract (GI) is a common site for amyloid deposits: Among patients with systemic amyloidosis, at least 70% present with gastrointestinal deposition. Rarely, the deposition is exclusively localized in this area, leading to various gastrointestinal symptoms (bleeding, weight loss, etc.). In this case report, we present a rare and unusual form of localized gastrointestinal amyloidosis, diagnosed after a post-mortem examination of an 83-year-old woman who died due to septic shock resulting from post-colonoscopy iatrogenic perforation of the sigma, in a suspected medical liability case. Morphological examination revealed AL amyloid deposits within the muscular wall of the submucosal vessels of the rectum, which caused increased friability of the vessels and ischemic changes in the intestinal mucosa. A renal cell carcinoma (RCC) was found, which might be related to amyloid deposits, as reported by the literature. Amyloid deposits are an unknown and unpredictable pathological substrate that increase the risk of iatrogenic perforation. Analysis of the medical documentation did not reveal any censurable conduct in terms of prescribing the procedure, technical execution, or subsequent management of the patient following the perforation. GI amyloidosis should be part of the risk stratification of patients with rectal bleeding and gastrointestinal symptoms, and awareness is essential to guide subsequent diagnostic and therapeutic approaches and investigate underlying causes.

Keywords: autopsy; diagnosis; gastrointestinal amyloidosis; malpractice; sigma perforation

Citation: Albano, G.D.; Zerbo, S.; Di Franco, S.; Orlando, E.; Formisano, E.; Argo, A.; Belmonte, B. Iatrogenic Sigma Perforation in a Patient with Localized Rectal and Sigma AL Amyloidosis: A Forensic Case and a Literature Review. *Forensic Sci.* **2024**, *4*, 453–462. https://doi.org/10.3390/forensicsci4030029

Academic Editor: Dominic Gascho

Received: 25 July 2024
Revised: 7 September 2024
Accepted: 11 September 2024
Published: 13 September 2024

1. Introduction

Amyloidosis is defined as a rare group of 30 protein-folding diseases characterized by the extracellular deposition of a specific soluble precursor protein that aggregates in the form of insoluble fibrils [1]. These fibrils deposit in tissues, causing architectural disruption and altering their function. These abnormal protein aggregates can accumulate locally, causing relatively limited symptoms, or more diffusely, involving multiple organs and leading to severe multi-organ failure, characterizing the disease as either systemic or localized (most commonly in the kidneys, heart, or gastrointestinal tract) [2,3]. Systemic amyloidosis is more common than localized amyloidosis, and the annual incidence of primary systemic amyloidosis is 78%, while that of secondary systemic amyloidosis is only 6% each year in the United States [4,5]. Among many forms of amyloidosis, the most

common ones are the AL and AA types. Systemic AL amyloidosis ("primary amyloidosis") is the most common form of clinical amyloid disease in developed countries and it is usually related to hematological conditions, such as benign low-grade monoclonal gammopathy, and it may also complicate multiple myeloma or other clonal B-cell diseases. Alternatively, reactive systemic AA amyloidosis ("secondary amyloidosis") is a complication of chronic infections and inflammatory conditions, characterized by a sustained acute-phase response in which there is a persistently increased production of serum amyloid A protein (SAA) [6]. Localized forms of amyloidosis are most commonly caused by foci of monoclonal plasma cells that produce immunoglobulin light chains [5]. The diagnosis of the disease can be performed histologically through the biopsy of the affected tissue: Hematoxylin and eosin staining locate amyloid deposits in tissue, while further confirmation is provided by Congo red histochemical staining, displaying the typical apple-green birefringence under polarized light in the bioptic specimen [7].

Gastrointestinal amyloidosis (GIA) is complex, with multiple etiologies and presentations which are usually associated with amyloid deposition in other organs. Among patients with systemic amyloidosis, at least 70% present with gastrointestinal deposition [8]. The main symptoms are weight loss, diarrhea, abdominal pain, malabsorption, esophageal reflux, and varying degrees of upper and lower GI bleeding [9].

In this case report and literature review, we present a rare form of gastrointestinal localized amyloidosis, diagnosed after a post-mortem examination of an 83-year-old woman who died due to septic shock resulting from post-colonoscopy iatrogenic perforation of the sigma, in a suspected medical liability case, and we discuss and summarize the most recent and updated literature in this field.

2. Case Report

2.1. History

The woman died in a hospital at the age of 83. Past medical history was positive for an undefined valvopathy and paroxysmal atrial fibrillation, treated with Propafenone. Due to isolated rectal bleeding, the patient underwent a proctological examination, and subsequently a recommendation for a diagnostic colonoscopy was made by a general practitioner. Mucosal hyperemia along with blood and mucus was observed, leading to the diagnostic suspicion of active ulcerative colitis. Following the examination, the patient experienced abdominal pain. A CT scan of the abdomen was performed, revealing a significant amount of free air in the abdomen, indicative of a perforation. The patient was urgently transferred to another hospital, where she was admitted with a diagnosis of suspected perforation. Upon admission, the physical examination revealed diffuse abdominal pain and an acute abdomen. Blood tests and blood gas analysis were conducted, showing mild acidosis (pH 7.32) and elevated levels of lactate and CRP (5.2 mmol/L and 31.06, respectively). An emergency exploratory laparotomy was performed, confirming an iatrogenic perforation of the sigmoid colon and leading to the patient being treated surgically (a laparotomy, resection of the area affected by the perforation, and then an anastomosis). After surgery, she was admitted to an intensive care unit department where her conditions worsened due to the occurrence of septic shock. After two days the woman died. Ten days after her death, an autopsy was requested by the Prosecutor Office to investigate both the cause of death and hypothetical medical liability. The resected gastrointestinal tract and its relative slides were also requested in order to perform a microscopic investigation.

2.2. Autopsy

The autopsy was performed by a forensic pathologist who is an assistant professor of forensic medicine and has ten years of experience in autopsy (GDA). The findings were discussed and shared with an associate and a full professor of forensic medicine (S.Z. and A.A., respectively). During the autopsy, the selection of organs for sampling was guided by the patient's clinical history, along with random organ samplings for histopathological evaluation and, most importantly, for determining the cause of death. The external examination

revealed only abdominal surgical sutures, with the body measuring 161 cm in height and weighing 80 kg. Upon opening the thoracic cavity, both lungs exhibited significant vascular congestion and a spongy appearance. Cardiac morphology was assessed, revealing no abnormalities. Given the clinical history of rectal bleeding that led to the colonoscopy, the abdominal cavity was examined with particularly close attention. The liver and spleen showed no significant macroscopic alterations, but a region of slight redness was observed in the gastric mucosa. In the proximal and distal ileocolic tract, several areas exhibited thinning of the walls and a flattened, blackish mucosa indicative of hemorrhagic infarction; these areas were sampled along with regions of healthy mucosa. The duodenal mucosa did not show significant macroscopic alterations. Notably, the integrity of the colonic anastomosis performed during the laparotomy was confirmed, with no alterations observed in the superior and inferior mesenteric vessels. The rectal and transverse colonic mucosa showed erythematous changes, with the rectum displaying a more intense grade of inflammation and friable mucosa; samples were taken for histological examination. In the urinary system, a yellowish neoformation measuring 5.5 × 6 × 3.5 cm, suggestive of renal heteroplasia, was detected at the lower pole of the left kidney, while the right kidney displayed mild, non-significant cortical vascular congestion. Both adrenal glands appeared unremarkable. Finally, the encephalon and cerebellum showed no significant alterations. All gross anatomical details, including the gastrointestinal hemorrhagic areas and the renal neoformation, were confirmed during the macroscopic examination of the organs after fixation in 10% buffered formalin for 30 days following the autopsy. After fixation, atomical reduction and tissue sampling were performed for further analysis.

2.3. Histopathology

Histopathological examination of tissue samples on hematoxylin- and eosin-stained slides was performed. The histopathological examination was performed by B.B, Assistant Professor in Pathology and Expert in Forensic Pathology, with the support of E.O., Pathology Specialist. During morphological analysis, the lungs presented widespread anthracosis, interstitial and intraparenchymal vessel congestion, and exhibited pulmonary edema, panlobular emphysema, and subpleural and intraparenchymal fibrosis associated with chronic bronchitis foci. The heart showed intraparenchymal fibrosis in the anterior left ventricle wall, extending to the papillary muscle, with anisotropy, myocardial fiber disarray in the lateral wall suggestive of hypertrophic cardiomyopathy, and lipomatous infiltration in the right ventricle. Gastric mucosa presented partial autolytic changes and was characterized by mild chronic lymphocytic inflammation and vascular congestion. In the small intestine, particularly the ileum, we observed intestinal infarction characterized by hemorrhagic necrosis of the mucosa, which was largely deepithelialized, and a moderate lympho-macrophagic chronic inflammatory infiltrate, occasionally containing neutrophils. Foci of coagulative necrosis, edema, and marked ectasia and vascular congestion of the submucosa were also noted. Extensive autolysis observed in the duodenum prevented histological evaluation. The transverse colon specimen displayed partial autolytic changes along with dilatation and vascular congestion of the submucosal layer.

Histological examination of the rectum, mainly in the medium and distal regions, revealed erosive–ulcerative mucosal changes, associated with a lympho-macrophagic inflammatory infiltrate and varying from a moderate to a severe grade, occasionally forming microaggregates. Ectasia and congestion of vessels in the submucosal layer were also noted. Additionally, within the muscular wall of these vessels, deposition of amorphous eosinophilic material resembling amyloid was detected (Figure 1).

Due to the suspicion of amyloid deposits, a Congo red staining was performed on the intestinal samples (small intestine, sigma, and rectum). The results were negative for amyloid in the small intestine but positive in the sigma and the rectum, which exhibited the characteristic green birefringence, confirming the presence of amyloid deposits (Figure 1).

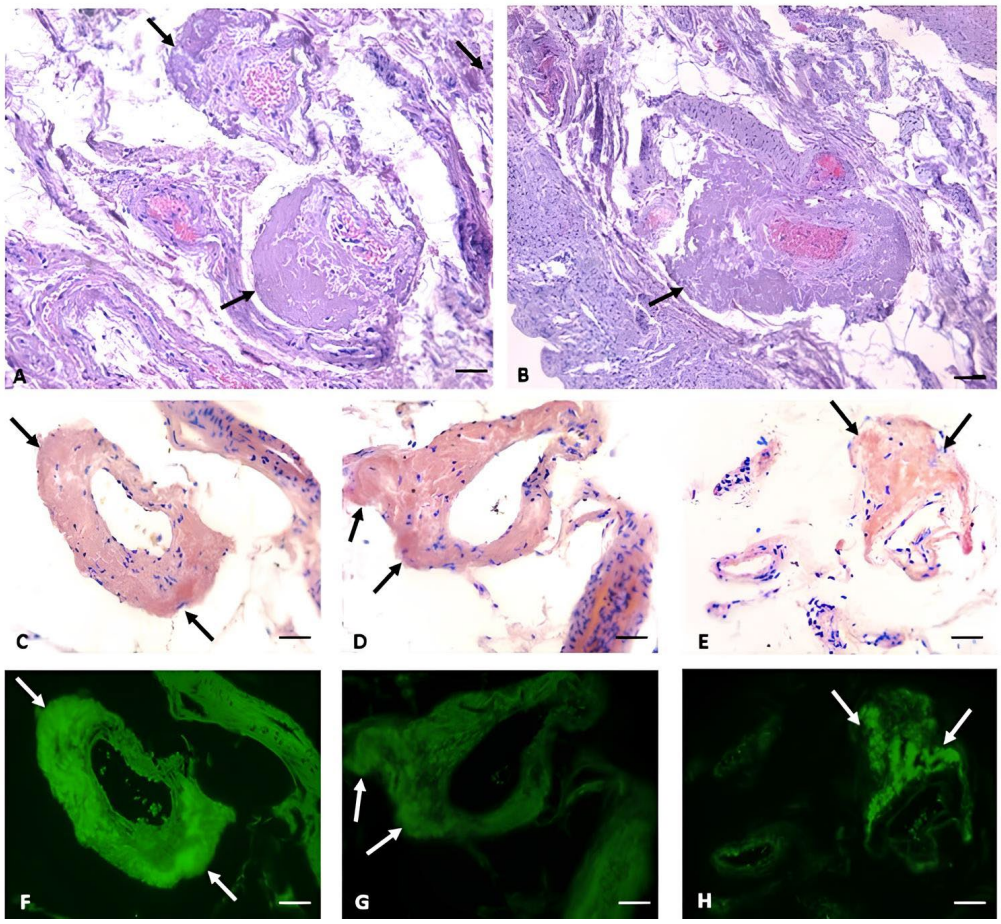

Figure 1. (**A**,**B**) Representative microphotographs showing the amyloid deposits (black arrows) within the muscular wall of submucosal vessels in rectum. Sampled using hematoxylin and eosin staining. Scale bars: 50 μm. (**C**–**H**) Presence of amyloid deposited within the muscular wall vessels of the rectal mucosa (black arrows in the top images under bright field; white arrows in the bottom images under dark field). Scale bars: 50 μm.

Moreover, immunohistochemical (IHC) analysis confirmed the presence of light chain lambda (λ), leading to the diagnosis of immunoglobulin light chain (AL) amyloidosis of the rectum (Figure 2).

Histopathological examination of the resected sigma revealed focal hemorrhagic ulceration of the mucosa with transmural involvement, displaying irregular margins and accompanied by a sparse neutrophilic granulocytic infiltrate and identified the colonic segment as having an iatrogenic perforation (Figure S1). Ectasia and congestion of vessels in the submucosal layer were also observed. In the muscular wall of these vessels, deposition of amorphous eosinophilic material resembling amyloid was detected. We also evaluated the urinary system. The adrenal glands showed normal cortical and medullary zones with partial autolysis and no significant histological alterations. The right kidney exhibited slight basement membrane thickening and mild mesangial thickening of glomerules and acute tubular necrosis associated with hemorrhagic infarction. The left kidney samples showed a multinodular neoplasm with cystic and hemorrhagic areas, characterized by a neoplastic proliferation with a solid growth pattern showing the morphological features of clear cell carcinoma. The neoplasm extended up to the capsule without breaching it. No clear evidence of vascular invasion was observed. In the renal parenchyma not affected by the neoplasm, there were noted foci of arteriolosclerosis. IHC examination showed CD10 positivity, confirming the diagnosis of renal cell carcinoma (RCC) (Figure 3).

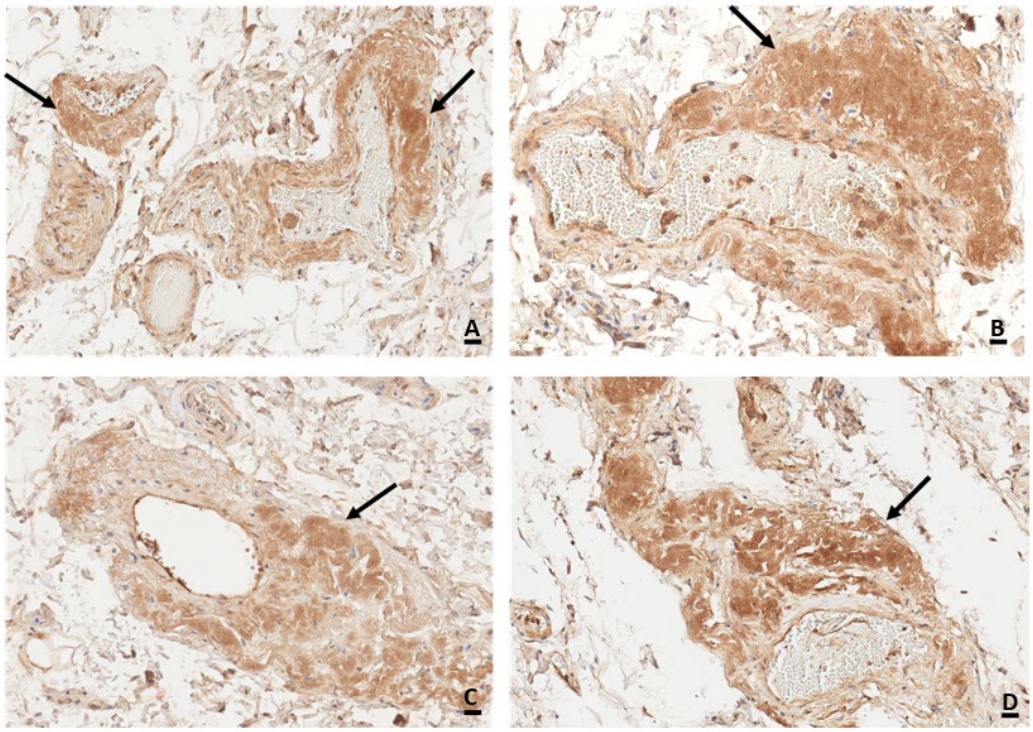

Figure 2. (**A**–**D**) Presence of amyloid deposits, lambda light chains-positive, within the muscular wall vessels of the rectal mucosa (black arrows). Sampled using DAB chromogen. Scale bars: 50 μm.

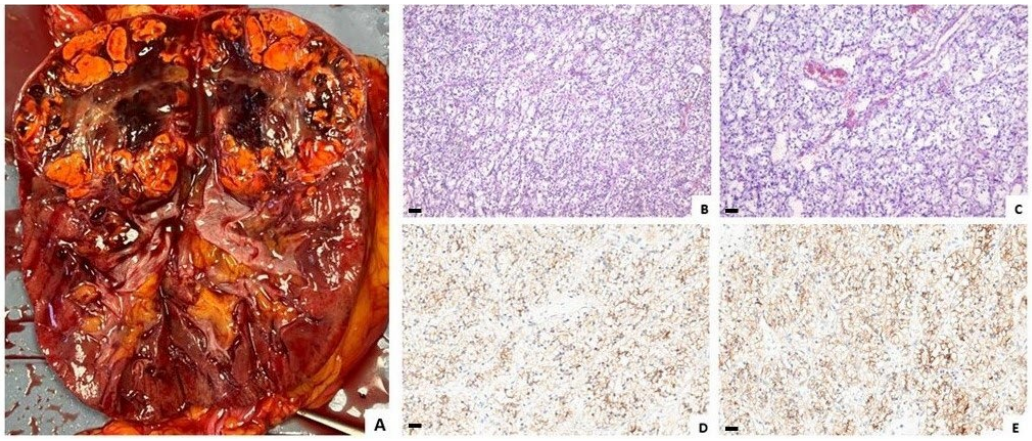

Figure 3. Representative pictures of renal carcinoma. (**A**) Macroscopic appearance, (**B**,**C**) Hematoxylin- and eosin-stained sections, and (**D**,**E**) CD10 immunostaining of clear cell renal carcinoma. Scale bars: 50 μm.

Lastly, histopathological examination of the content of the cranial cavity showed cytotoxic neuronal edema and congestion of intraparenchymal and leptomeningeal vessels, with no evidence of ischemic pathology of the brain. No significant histological alterations were detected in the cerebellum.

3. Discussion

The initial purpose of our investigation was to identify the patient's cause of death and evidence of malpractice. The combination of multiple elements acquired through collaboration with the judicial authority and other specialists (a forensic physician, pathologist, and general surgeon) allowed us to reach the diagnosis of septic shock due to post-colonoscopy iatrogenic perforation of the sigma.

The present case demonstrates the importance of a multidisciplinary approach in the investigation of forensic autopsy cases, including assessing the causal relationship between healthcare assistance and death [10–13]. Toxicological analyses for alcohol and drugs were negative. The integration of histopathological, histochemical, and immunohistochemical investigations, along with the study of the scientific literature and medical records, led to the suspicion and diagnosis of amyloidosis; therefore, this integrative approach should direct future research.

Colonoscopy is generally a safe and accurate procedure, well-tolerated by patients [12] whose main complications are bleeding and perforation of the colon–rectum [13]. Perforation can be related to direct trauma to the intestinal wall by the instrument itself or to barotrauma, which has an incidence of 0.3% among endoscopic procedures.

The histopathological findings from the autoptic and the surgical samples led to the diagnosis of localized gastrointestinal amyloidosis, with negative results in other areas. The involvement of the large bowel in the amyloidosis led to a higher fragility of the wall, facilitating the perforation. Clinical negligence and risk of malpractice due to the procedure have been excluded. The autopsy was performed under the charge of the Prosecutor Office together with a specialist in general surgery. The Italian law on medical malpractice (Law n. 24/2017) focuses on reducing the number of medical-malpractice claims against HCWs by introducing a better regimen of professional liability that emphasizes the necessity to follow clinical practice guidelines and good clinical practices to prevent medical malpractice litigation [14]. According to the literature, current clinical practices, and expert opinion, no medical errors were performed: The exam was performed according to the underlying symptoms, there were no contraindications, no intraoperative errors were observed, the perforation was immediately detected, and after the perforation was detected, the patient underwent surgery that was performed correctly. The perforation has not been considered avoidable, considering also the underlying amyloidosis. The alteration of intestinal walls, macroscopically visualized during the colonoscopy examination as ulceration and bleeding of the sigma and confirmed after histopathological investigations, configured a particular substratum of fragile and more susceptible mucosa, increasing the risk of perforation. This is an unknown and unpredictable pathological substrate that increases the risk of iatrogenic perforation. Analysis of the medical documentation did not reveal any censurable conduct in terms of prescribing the procedure, technical execution, or subsequent management of the patient following the perforation.

Gastrointestinal amyloidosis is a pathological condition characterized by signs and symptoms in the gastrointestinal tract, confirmed histologically through biopsy sampling. However, the current literature indicates that gastrointestinal amyloidosis diagnosis may not always be confirmed upon biopsy. A retrospective analysis by Cowan et al. reported that among approximately 3.3% of patients with biopsy-confirmed amyloidosis, only 21% presented with amyloidosis limited to the gastrointestinal tract. Several studies have reported cases of amyloidosis involving the gastrointestinal tract or peritoneum [15–24] and classified as systemic or localized amyloidosis based on the presence of amyloidogenic protein and its tissue deposition. In our case, the amyloid deposition was exclusively localized in the sigma, as confirmed by the histopathological examination through a Congo red stain and the identification of lambda (λ) light chain during the IHC investigation (AL amyloidosis) of the gastrointestinal tract samples. In the literature, cases with an exclusive GI localization of amyloid deposits have been reported [25–34] (Table 1).

Clinical manifestations, which depend on the amount of amyloid deposits [35], are usually characterized by gastrointestinal bleeding, which can be seen in up to 57% of patients and is commonly caused by mucosal lesions, vascular friability or bowel ischemia, malabsorption, and protein-losing gastroenteropathy [36].

Table 1. Summary of the studies about amyloidosis of the GI tract.

Reference	Article Type	Autopsy/ Biopsy	GI Symptoms	Clinical Findings	Histopathologic Findings	Amyloid Type
Cowan et al. [15]	Retrospective review	Biopsy	GI bleeding, heartburn		Amyloid deposits	AL (11), Undefined (5)
Groisman et al. [18]	Case report	Autopsy	Enterorrhagia	Diverticula [ultrasound]	Amyloid deposits; ischemia-related changes, mainly mucosal	AL
Coulier et al. [20]	Case report	Biopsy	None	Infiltration of the fat tissue of greater omentum, mesentery, retroperitoneum [CT]	Amyloid deposits	AL
Choi et al. [26]	Case report	Biopsy	Epigastric pain, nausea, constipation	Lesions with central erosion in duodenum [colonoscopy]	Amyloid deposits	AL
Nagaaki et al. [27]	Case report	Biopsy	Gastralgia, hematemesis, melena	Nodular lesions (upper GI); ulcers; submucosal hemorrhage (lower GI) [endoscopy]	Amyloid deposits	AL
Wu et al. [28]	Case report	Biopsy	Epigastric discomfort	Gastric ulcer on the posterior wall of small curvature [endoscopy]	Amyloid deposits	AA
Wetwittayakhlang et al. [29]	Case report	Biopsy	Colic pain, unable to pass feces and flatus, progressive abdominal distension	Small bowel obstruction [endoscopy]	Amyloid deposits	AL
Kyle et al. [30]	Case reports	Biopsy	Rectal bleeding (all)	Purpuric lesions in the sigmoid colon (case 1); patchy erythema of the sigmoid colon (case 2); polyps (case 3) [colonoscopy]	Amyloid deposits in lamina propria and submucosa	AL
Tokoro et al. [31]	Case report	Biopsy	None	10 submucosal tumors scattered from the rectum to the sigmoid colon [colonoscopy]; several hyperechoic submucosal lesions, suggestive of lipomas [EUS]	Amyloid deposits	AL
Chen et al. [32]	Case report	Biopsy	Periumbilical pain, bloody stool, weight loss	Narrowing of the lumen of the transverse colon, multiple polypoid lesions, ulceration [colonoscopy]; annular lesion with disrupted mucosa [barium enema]	Amyloid deposits in perivascular regions of the mucosa	AL
Hemmer et al. [33]	Case report	Biopsy	Progressive microcytic anemia	Polyps, from duodenal bulb to jejunum [EGDS]	Amyloid deposition, rounded and globular in submucosa	AL
Garcia et al. [34]	Case report	Biopsy	Chronic constipation, history of benign colonic polyps	Nodular erythema in ascending colon, polyp in transverse colon [endoscopy]	Amyloid deposits in mucosa	AL

Treatment for gastrointestinal amyloidosis consists of observation for asymptomatic patients or, alternatively, localized surgical excision for localized disease and treatment of the underlying pathology for systemic amyloidosis cases. Prognosis depends on the extent of gastrointestinal tract involvement, the amount of deposit, and the type of amyloid deposit [37]. It has been reported that patients with AA amyloidosis have a better prognosis. AA amyloid tends to deposit in the lamina propria of the mucosa and submucosal layer with a diffuse or perivascular distribution, while AL amyloid tends to deposit in the submucosal layer and/or muscularis propria as a mass [38]. Furthermore, amyloid

deposition in the arteriolar muscular wall can induce an increased friability of the vessels 8 and ischemic changes in the intestinal mucosa, such as mucosal denudation and sometimes ulceration [39].

As a matter of fact, the colonoscopy performed on the patient showed hyperemia of the gastrointestinal mucosa, associated with blood and mucus, leading to the diagnostic suspicion of active ulcerative colitis. However, the histopathological examination of the gastrointestinal samples showed no microscopic signs compatible with active colitis, such as the presence of neutrophil-mediated epithelial injury, in the form of cryptitis, crypt abscesses, or by infiltration of surface epithelium with or without mucosal ulceration [40].

Furthermore, although some authors have highlighted that a solid malignant neoplasm can be a cause of AA amyloidosis, with RCC being the most common carcinomatous cause for different possible production mechanisms (the secretion of amyloidogenic substance or the modification by partial proteolysis of a serum precursor protein into an amyloidogenic fragment by the tumor cells themselves [41]), few reports in the literature also showed a correlation between RCC and AL amyloidosis, as in this case [42,43].

4. Conclusions

The patient presented a rare case of amyloidosis exclusively localized in the gastrointestinal tract. Indeed, the negative results after microscopic investigation of the organs commonly involved in the amyloid deposition led to the diagnosis of the exclusively localized form of amyloidosis. The perforation was considered an unavoidable complication and, therefore, not attributable to medical malpractice in light of the autopsy and histopathological findings that exposed the underlying amyloidosis disease as a predisposing condition. Medical liability was excluded as a result of the performed forensic approach. Gastrointestinal amyloidosis should be part of the risk stratification of patients with rectal bleeding and gastrointestinal symptoms, and awareness is essential to guide subsequent diagnostic and therapeutic approaches and investigate underlying causes.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/forensicsci4030029/s1, Figure S1: Representative photographs of Hematossyline & Eosin stain of sigmoid perforation.

Author Contributions: Conceptualization, G.D.A. and B.B.; methodology, S.D.F.; validation, A.A. and S.Z.; investigation, E.O. and E.F.; resources, A.A. and B.B.; writing—original draft preparation, G.D.A. and S.D.F.; writing—review and editing, B.B., A.A. and S.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Our investigations were carried out following the rules of the Declaration of Helsinki of 1975, revised in 2013. According to Italian legislation, ethical approval for a single case is not required, as long as the data are kept anonymous and the investigations performed do not imply genetic results.

Informed Consent Statement: Because summoning the parents was not possible, as it would badly interfere with the grieving process, the parents' consent was completely waived, according to the Italian Authority of Privacy and Data Protection ("Garante della Privacy": GDPR nr 679/2016; 9/2016 and recent law addition number 424/19 July 2018).

Data Availability Statement: All data are available on request to to the corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest as there's no financial/personal interest or belief that could affect their objectivity.

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