Primary Localized Small Bowel Amyloidosis: A Rare Cause of Diarrhea Detected by Balloon-Assisted Enteroscopy

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Abstract
Gastrointestinal involvement occurs in approximately 4% of cases of systemic amyloidosis and may be associated with heterogeneous and nonspecific clinical manifestations and endoscopic findings, which poses important diagnostic challenges. A 76-year-old female with previous medical history of breast cancer, hypertension, dyslipidemia, asthma, and depression presented to emergency department with a 1-month history of diarrhea, abdominal pain, anorexia, asthenia, and weight loss. Physical examination revealed dehydration and abdominal tenderness. Stool microbiologic studies, Clostridium difficile toxin, fecal leukocyte count, stool fat, and celiac serology were all negative. Remarkably, an axillary lymphadenopathy was also noted and its investigation revealed multiple myeloma, which raised suspicion for gastrointestinal amyloidosis. However, upper digestive endoscopy and colonoscopy did not reveal abnormalities and both gastric and colon biopsies were negative for amyloid, as was abdominal fat biopsy. As the patient also presented hypoproteinemia and hypoalbuminemia suggestive of protein-losing enteropathy, videocapsule endoscopy was performed where petechiae, villous atrophy, and fissures were seen along jejunal mucosa. These findings were confirmed with double-balloon enteroscopy and jejunal biopsies revealed extensive deposition of an amorphous hyaline material in lamina propria and muscularis mucosae that exhibited apple-green birefringence under polarized light after Congo red staining, consistent with localized small bowel amyloidosis secondary to multiple myeloma. Chemotherapy was started, but she would die after 3 weeks. This case illustrates the role of balloon-assisted enteroscopy in diagnosis of localized small bowel amyloidosis with jejunal involvement.
Introduction

Amyloidosis consists of a heterogeneous group of complex diseases where abnormal protein metabolism results in the conversion of proteins from their soluble functional states into highly organized fibrillar aggregates termed “amyloid” with extracellular deposition and progressive organ damage. The most common are AL amyloidosis, which is associated with plasma cell disorders and deposition of the variable region of immunoglobulin light chains, and AA amyloidosis, which results from chronic inflammatory, immunological, and neoplastic conditions and deposition of amyloid A fibrils derived from the serum AA precursor protein [1].

Amyloidosis is usually a systemic disease that can affect virtually any organ, most commonly heart, kidney, and peripheral nerves. The gastrointestinal tract is involved in approximately 4% of cases. Patients usually present with variable and heterogeneous clinical symptoms and endoscopic findings. Management is primarily directed at the treatment of the underlying cause, with supportive measures to alleviate specific gastrointestinal symptoms [2].

We report a rare case of diarrhea where diagnostic work-up revealed localized small bowel amyloidosis secondary to multiple myeloma. Balloon-assisted enteroscopy played a key role for its diagnosis after negative gastric, duodenal, and colon biopsies.

Case Report

A 76-year-old female with previous medical history of breast cancer (diagnosed 2 years earlier and currently with cure criteria after mastectomy and lymphadenectomy and adjuvant radiation therapy), hypertension, dyslipidemia, asthma, and depression presented to emergency department with a 1-month history of diarrhea, abdominal pain, asthenia, and weight loss (8 kg). She denied fever, hematochezia, nausea, or vomiting. Her current usual medications included anastrozole, valsartan, hydrochlorothiazide, amlodipine, simvastatin, sertraline, diazepam, zolpidem, and inhaled budesonide plus formoterol, none of which she had started taking recently. There was also no history of recent traveling or antibiotic use. Physical examination revealed dehydration and abdominal tenderness. She was afebrile (auricular temperature: 36.2°C) and hemodynamically stable (blood pressure: 108/67 mm Hg; heart rate: 93 bpm). Laboratory studies revealed acute kidney injury (creatinine: 1.61 mg/dL, urea: 77 mg/dL) and elevated C-reactive protein (20.8 mg/dL). Hemoglobin, leukocyte and platelet counts, liver tests, electrolytes, and coagulation studies were all normal. Abdominal ultrasound was also unremarkable.

The patient was admitted and started fluid therapy with progressive normalization of creatinine levels. She referred improvement in general well-being although diarrhea remained stable with approximately 4-5 bowel movements per day with watery stool. Stool microbiologic studies, Clostridium difficile toxin, fecal leukocyte count, stool fat, thyroid hormone level, and celiac serology were all negative. Upper digestive endoscopy and colonoscopy did not reveal significant endoscopic abnormalities. Gastric biopsies only revealed mild Helicobacter pylori-negative gastritis, whereas duodenal and colon biopsies were normal. Abdominal ultrasound was also unremarkable.

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Remarkably, an axillary lymphadenopathy was noted and she performed computed tomography scan of thorax, abdomen, and pelvis where enlarged lymph nodes in axillae, abdomen, and thoracic cavity were detected. Increased levels of serum and urine light chains with decreased ratio kappa/lambda and increased levels of serum beta-2 microglobulin were
also found and she performed bone marrow biopsy that revealed monoclonal proliferation of plasma cells consistent with multiple myeloma. This raised suspicion for gastrointestinal amyloidosis as a possible cause for diarrhea. However, specific search for amyloid in gastric, duodenal, and colon biopsies using Congo red stain was negative. Colon biopsies had been performed from ascending, transverse, sigmoid, and rectum as part of our protocol for exclusion of microscopic colitis in colonoscopies performed for diagnostic work-up of diarrhea when no significant macroscopic findings are detected. Additionally, she performed abdominal fat biopsy where amyloid was also not detected. As the patient also presented hypoproteinemia and hypoalbuminemia suggestive of protein-losing enteropathy, videocapsule endoscopy was performed where petechiae, villous atrophy, and fissures were seen along jejunal mucosa (Fig. 1). These findings were confirmed with double-balloon enteroscopy (Fig. 2) and jejunal biopsies revealed extensive deposition of an amorphous hyaline material in lamina propria and muscularis mucosae (Fig. 3) that exhibited apple-green birefringence under polarized light after Congo red staining, consistent with localized small bowel amyloidosis secondary to multiple myeloma. Chemotherapy was started, but she would die after 3 weeks from septic shock.

Discussion

The prevalence of gastrointestinal involvement in patients with systemic amyloidosis is approximately 4%. It has been described in both AL and AA amyloidosis and is most commonly part of a spectrum of systemic disease with involvement of other organs, although rarely it may be localized to gastrointestinal tract [3]. Clinical manifestations and endoscopic findings associated with gastrointestinal amyloidosis are nonspecific and variable according to the segments involved and may sometimes be subtle or inexistent. In fact, patients may be asymptomatic and endoscopic abnormalities may be absent which poses diagnostic challenges that require a high index of clinical suspicion [2].

The small bowel is the most frequently involved location in gastrointestinal amyloidosis [4]. The most common clinical manifestations are malabsorption and chronic diarrhea that may be caused either by direct amyloid infiltration of the small bowel mucosa or neural damage to autonomic neurons and subsequent motility disturbances. It may also be associated with severe complications such as massive small bowel bleeding [5], pseudo-obstruction [6], perforation [7], or acute pancreatitis [8]. Endoscopic features are variable ranging from subtle erosive changes, mucosal friability and granularity to diffuse polyposis, or small bowel diverticula [9].

Remarkably, balloon-assisted enteroscopy played a key role in our case as the diagnosis was established from jejunal biopsies after exclusion of more common causes of diarrhea such as infection, drugs, inflammatory bowel disease, celiac disease, hyperthyroidism, or pancreatic diseases and even after gastric, duodenal, and colon biopsies without evidence of amyloid deposition. It is possible that those biopsies were too superficial and did not demonstrate submucosal amyloid deposits. However, abdominal fat biopsy was also negative for amyloid which supports the hypothesis that amyloidosis was indeed restricted to jejunum and balloon-assisted enteroscopy played an essential role in diagnostic work-up. Besides, this technique has proved essential in previous cases of small bowel amyloidosis affecting segments distal to the duodenum as jejunal polyposis after normal upper and lower digestive endoscopy [10, 11]. These include 1 patient presenting with obscure gastrointestinal bleeding where push enteroscopy revealed jejunal polyoid protrusions [10]. The other had AL amyloidosis and presented with intestinal obstruction caused by jejunal polyps [11].
Fig. 1. Videocapsule endoscopy revealed petechiae, villous atrophy, and fissures diffusely involving jejunal mucosa. In contrast, duodenal and ileal mucosa were normal.

Fig. 2. Double-balloon enteroscopy was performed confirming the findings of videocapsule endoscopy, with severe atrophy along jejunal mucosa, and allowing endoscopic biopsies.

Fig. 3. Histopathological examination of a jejunal biopsy showing extensive deposition of an amorphous hyaline material in lamina propria and muscularis mucosae after Congo red staining consistent with amyloidosis.
It is important to note that the patient was taking valsartan and this was an important differential diagnosis, since angiotensin II receptor blockers have been associated with severe enteropathy, particularly recognized for olmesartan [12]. In fact, olmesartan-associated enteropathy is a rare disorder that usually manifests with chronic diarrhea after months to years of exposure. Diagnostic criteria include symptom development while taking olmesartan, supportive histological findings on gastrointestinal biopsies, and exclusion of other causes of diarrhea. The mainstay of treatment is discontinuation of olmesartan and replacement with an antihypertensive drug from a different class [12]. Although olmesartan is the most commonly implicated agent, other angiotensin II receptor blockers have been occasionally implicated, including valsartan [13]. Therefore, this drug was a potential cause for the patient’s symptoms that was carefully excluded after complete diagnostic work-up and endoscopic biopsies.

Congo red stain of tissue demonstrating apple-green birefringence under polarized light has long been considered the hallmark for the diagnosis of amyloidosis. Although other staining methods besides Congo red may be used, such as crystal violet, those are less specific for detection of amyloid deposits and Congo red remains the gold standard [14]. Therefore, our protocol for detection of amyloid deposits is based in positive staining after application of Congo red dye and apple-green birefringence under polarized light and we do not usually use other stains for this purpose although they can be considered according to the experience of each center.

Systemic amyloidosis is usually associated with high mortality rate and short-term survival. There is evidence that patients with AL amyloidosis and gastrointestinal involvement present more organ involvement and more advanced diseases with worse prognosis than those without gastrointestinal involvement [15]. This was reflected in our case where, despite starting chemotherapy, the patient exhibited poor survival.

In conclusion, small bowel amyloidosis is a rare cause of chronic diarrhea that should be considered after exclusion of more common causes. Balloon-assisted enteroscopy should be considered when there is clinical suspicion for gastrointestinal amyloidosis despite normal upper and lower digestive endoscopy, especially if the capsule endoscopy shows pathological findings.

**Statement of Ethics**

Written informed consent from the next of kin was obtained to publish this case and accompanying images. Ethical approval is not required for this study in accordance with Centro Hospitalar Universitário de São João guidelines, considering that it is a descriptive case report and patients’ anonymity was maintained.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: Emanuel Dias and Patricia Andrade. Analysis and interpretation of data: Emanuel Dias; Patricia Andrade; Helder Cardoso; and Elsa Fonseca. Drafting of the article: Emanuel Dias. Critical revision of the article for important intellectual content: Patricia Andrade; Helder Cardoso; Elsa Fonseca; and Guilherme Macedo. Final approval of the article: all authors.

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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