Journal of Community Hospital Internal Medicine Perspectives

Volume 13 | Issue 3 Article 11

2023

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Mohammed Rifat Shaik
University of Maryland Medical Center Midtown Campus, Baltimore, Maryland, United States, shaikrifat13@gmail.com

Nishat Anjum Shaikh
Guntur Medical College, Guntur, Andhra Pradesh, India

Elvina Yunasan
University of Maryland Medical Center Midtown Campus, Baltimore, Maryland, United States

Erika Wheeler
University of Maryland Medical Center Midtown Campus, Baltimore, Maryland, United States

Robert T Chow
University of Maryland Medical Center, Baltimore, Maryland, United States

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Recommended Citation

Shaik, Mohammed Rifat; Shaikh, Nishat Anjum; Yunasan, Elvina; Wheeler, Erika; and Chow, Robert T (2023) "Gastrointestinal Bleeding as Initial Manifestation of Injection Drug Use-Associated Amyloidosis," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 3, Article 11.
DOI: 10.55729/2000-9666.1179
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss3/11

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CASE REPORT

Gastrointestinal Bleeding as Initial Manifestation of Injection Drug Use-Associated Amyloidosis☆

Mohammed R. Shaik [a,*], Nishat A. Shaik [b], Elvina Yunasan [a], Erika Wheeler [c], Robert Td Chow [a,d]

[a] Department of Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, MD, United States
[b] Department of Medicine, Guntur Medical College, Guntur, Andhra Pradesh, India
[c] Department of Pathology, University of Maryland Medical Center, Baltimore, MD, United States
[d] Department of Medicine, University of Maryland Medical Center, Baltimore, MD, United States

Abstract

Systemic amyloidosis has been reported in the context of injection drug use, usually related to ongoing chronic inflammation and persistent cutaneous infections. The kidneys are almost always the first organs affected in that setting. Involvement of the gastrointestinal tract is less common and rarely the initial site of presentation. We present a case of systemic amyloidosis that primarily manifested in the gastrointestinal tract, occurring in the setting of chronic injection drug use. The patient's hemoglobin level dropped progressively over time due to ongoing, slow gastrointestinal bleeding, prompting an endoscopic examination that ultimately confirmed the presence of gastrointestinal amyloidosis. As the overall prognosis for gastrointestinal amyloidosis is poor, early diagnosis and treatment are essential to decelerate the progression of the disease.

Keywords: Gastrointestinal amyloidosis, Injection drug use, Endoscopy

1. Introduction

AA amyloidosis, also known as reactive or secondary amyloidosis, arises in the context of persistent inflammation caused by chronic inflammatory disorders, autoinflammatory diseases, malignancies, or persistent infections. It has an estimated incidence of 1−2 cases per million person-years. Cytokines that are involved in the chronic inflammatory process stimulate liver cells and upregulate the production of serum amyloid A (SAA), which is then transformed into amyloid through a series of mechanisms and deposits in body tissues.[1]

The association of skin-popping and injection drug usage with AA amyloidosis has been described in the literature dating back to the 1970s.[2] In a study of subcutaneous drug users versus intravenous (IV) users, 44% of subcutaneous abusers had renal AA amyloidosis in contrast to only 1% of IV drug users. This remarkable difference has been attributed to the inflammatory process associated with chronic skin ulcerations and active chronic suppurative cutaneous infections in subcutaneous injection drug use.[2,3] While renal impairment, typically advanced renal failure or severe nephrotic syndrome, is the primary presentation of AA amyloidosis, gastrointestinal involvement is uncommon, and it is extremely rare as an initial presentation.[4] We describe a case of gastrointestinal amyloidosis in a long-time injection drug user, in which occult gastrointestinal bleeding prompted an endoscopy leading to the diagnosis of AA amyloidosis.

2. Case presentation

A 37-year-old woman with a long history of injection drug use and bilateral chronic forearm

☆ The ACG (American College of Gastroenterology) 2022 Annual Scientific Meeting held in Charlotte featured portions of the manuscript presented in the form of an abstract poster

Received 21 December 2022; revised 9 February 2023; accepted 22 February 2023.
Available online 8 May 2023

* Corresponding author at. University of Maryland Medical Center Midtown Campus, Baltimore, MD, 21201, United States.
E-mail address: shaikrifat13@gmail.com (M.R. Shaik).

https://doi.org/10.55729/2000-9666.1179
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wounds was admitted with diarrhea and opioid overdose. She reported a moderate quantity of watery diarrhea for three-week duration. The patient denied hematochezia, melena, or hematemesis. She also reported increased purulence in her bilateral forearm wounds for the prior week.

Her past medical history was significant for active injection of heroin on a daily basis into her upper extremity wounds; chronic, untreated hepatitis B infection (serology from a year prior showed HBsAg positive and HBc Ab positive with HBV DNA detected); and bilateral chronic forearm wounds that were noted during a prior hospitalization during which the patient was found to have subacute osteomyelitis of the humerus and completed a treatment course of oral trimethoprim-sulfamethoxazole.

On physical examination, she was hypotensive with a blood pressure of 80/40. The bilateral forearm wounds measured 12 cm × 7 cm and 12 cm × 7 cm (Fig. 1A and B). Laboratory test results are shown in Table 1. CT scan of bilateral upper extremities showed progressive soft tissue ulceration without evidence of abscess. However, periosteal reactions were seen along the shafts of the radius and ulna bilaterally, suggestive of osteomyelitis. Magnetic Resonance Imaging (MRI) of the upper extremities and lumbar spine showed no evidence of ulnar, radial, or spinal osteomyelitis. CT scan of the abdomen showed emphysematous cystitis and the presence of ascites, pleural effusions, and diffuse body wall edema.

Intravenous (IV) vancomycin and cefepime were initiated. Wound care was consulted, and regular dressings were performed. Transthoracic echocardiography (TTE) showed normal biventricular size and function with an ejection fraction of 55–60%. These findings were corroborated by transesophageal echocardiography (TEE), which additionally showed no evidence of valve vegetation. Repeat blood cultures were negative. The patient showed signs of clinical improvement and was transitioned to cefazolin to complete a total of 2-week antibiotic course. Entecavir was initiated for chronic hepatitis B infection.

During the hospitalization, multiple units (6 units) of packed red cell transfusions were required to maintain Hgb> 7 g/dL. With concern for a gastrointestinal (GI) bleed, CT angiography of mesenteric circulation was pursued, which revealed no obvious source of bleeding. An urgent gastroduodenoscopy revealed erythematous, friable gastric mucosa and duodenal mucosal atrophy (Fig. 1C, D, and E). Colonoscopy showed similar findings, with friable mucosa throughout the entire colon (Fig. 1F). Random gastric, duodenal, and colon biopsies demonstrated extensive amyloid deposition in the lamina propria, confirmed with Congo red stain (Fig. 2). Liquid chromatography-tandem mass spectrometry detected a peptide profile consistent with serum amyloid A (AA).

The underlying etiology for amyloidosis was thought to be secondary to long-standing, chronic forearm wounds resulting from injection drug use as well as chronic hepatitis B infection. The patient was transfused to a Hgb goal of greater than 7 g/dL and repleted with IV ferric gluconate. She was treated with IV pantoprazole and was discharged on oral pantoprazole. Chemical dependency service was

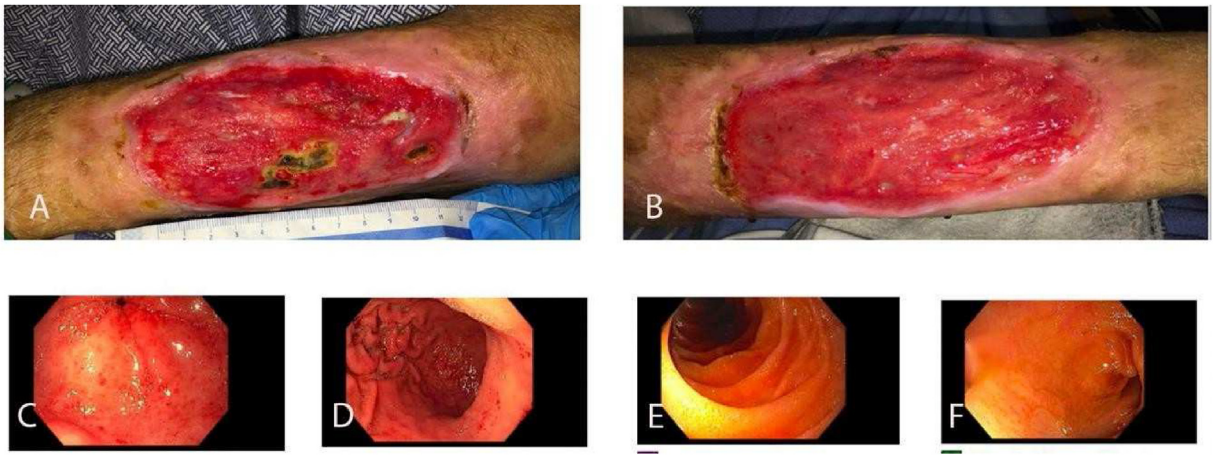

Fig. 1. A and B are images demonstrating right and left forearm wounds measuring 12 cm × 7 cm and 12 cm × 7 cm respectively. C, D and E are images from esophagogastroduodenoscopy (EGD) with C and D demonstrating inflammation in the pylorus and gastric body respectively. E shows mucosal atrophy in the second portion of the duodenum. F is a colonoscopy image demonstrating a normal terminal ileum.

Table 1. Laboratory test results.

Hemoglobin (Hgb)	4.6 g/dL (baseline: 7–8 g/dL)	HBV viral load	6626 IU/mL
White cell count	11,100/mm3	HCV antibody	Positive
Creatinine	1.0 mg/dL	HCV viral load	Undetectable
Blood cultures	Methicillin-sensitive *Staphylococcus aureus* (MSSA)	HIV	Non-reactive
Urine microscopic examination	>50 WBC/hpf	Urine toxicology	Positive for cocaine and fentanyl
Urine dipstick	2+ protein, positive nitrites, and positive leukocyte esterase	Urine legionella antigen	Negative
Urine cultures	Mixed microbial flora	Urine pneumococcal antigen	Negative
Fecal occult blood test (FOBT)	Positive	Stool for *Clostridium difficile* toxin	Negative
Serum ferritin	17 ng/mL (Ref: 6.2–137 ng/mL)	Serum iron	11 mcg/dL (Ref: 23–170 mcg/dL)
Serum transferrin	388 mg/dL (Ref:206–381 mg/dL)	Serum percentage iron saturation	6 (Ref: 15–50)

HBV: hepatitis B virus, HCV: hepatitis C virus.

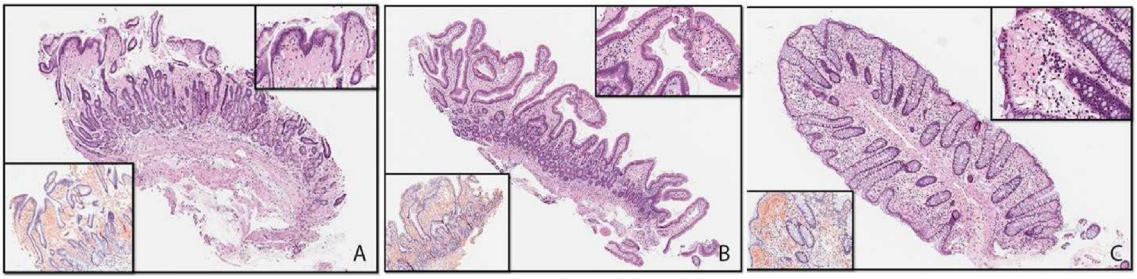

Fig. 2. A, B and C are low power images of gastric, duodenal and colon biopsies showing increased deposition of an amorphous pink material within the lamina propria (see insets, upper right of each image, 20x). A Congo red special stain confirms the amorphous material is comprised of amyloid protein (see insets, orange coloring, bottom left).

consulted, and drug rehabilitation was provided. Outpatient follow-up with wound care was arranged.

3. Discussion

While gastrointestinal (GI) symptoms are not uncommon in the setting of amyloidosis, biopsy-proven GI amyloidosis is rare, with an incidence of only 3%, according to a large retrospective case series. With regards to GI involvement, ALλ is the most common type (53%), followed by ATTR (16%), with AA being less common.[5] Having GI symptoms as the first sign of systemic amyloidosis is exceedingly unusual, especially in the absence of clinical signs of the disease elsewhere in the body.[6] Although any segment of the gastrointestinal tract is theoretically susceptible, the small intestine remains the most commonly affected.[6] In terms of the wall layers involved, all amyloid types have a propensity for vascular deposition in the submucosa; however, AL preferentially deposits in the muscularis propria and muscularis mucosa, and AA deposits in the lamina propria (as in our patient). The typical deposition pattern for AL is a nodule or mass, which contrasts with the macular or perivascular form of deposits seen with AA.[6,7]

Clinical GI manifestations result from infiltration in the GI tract or the autonomic nervous system. Symptoms include impaired motility (leading to esophageal reflux, delayed gastric emptying, chronic intestinal pseudo-obstruction), malabsorption (leading to steatorrhea, diarrhea), and vascular insufficiency (presenting as bleeding, infarction, or perforation).[6] Weight loss is frequent and an early sign.[8] Related to the pattern of deposition within the gut wall as described above, AA amyloidosis usually presents with diarrhea, malabsorption, and gastrointestinal bleeding, whereas AL amyloidosis is characterized by mechanical obstruction and chronic intestinal pseudo-obstruction.[6] Gastrointestinal bleeding results from vascular occlusion and gut fragility induced by amyloid infiltration in the tunica media/intima.[6] Other contributing reasons to bleeding include diminished motility and increased rigidity, making the musculature more susceptible to shearing forces from coprostasis and colonoscopy, bleeding diatheses, such as prolonged PT/INR, prolonged aPTT, prolonged TT, low factor X concentration, and portal hypertension.[6] In our patient, AA amyloid accumulated in the lamina propria, causing mucosal fragility and slow bleeding. As a result, the patient developed iron-deficiency anemia and a positive fecal occult blood test.

Diagnostic confirmation of amyloid is made by histopathology of biopsy specimens obtained via endoscopy and positive staining with Congo red; apple green birefringence is demonstrated under cross-polarized light by light microscopy.[6] Endoscopic abnormalities are nonspecific and include mucosal friability, erosions, shallow ulcers, fine granular appearance (predominant in AA amyloidosis), polypoid protrusions, and thickening of valvular conniventes (seen with AL amyloidosis). The duodenum was shown to have the highest positive biopsy yield rate compared to other locations and is, therefore, the most favored site for endoscopic biopsy. It is important to limit the number of biopsies to reduce potential bleeding. Techniques such as push enteroscopy, double balloon enteroscopy, and capsule endoscopy can be used to explore potential bleeding sites in the small intestine. In rectal amyloidosis, optical filter techniques such as narrow-band imaging may be beneficial.[9] Immunohistochemistry should be used to determine the amyloid protein type once a diagnosis is established. Mass spectrometry and serum amyloid P component scintigraphy are more recent amyloid typing techniques.[10]

The SAA level has a direct influence on patient survival, amyloidotic organ survival, and the change in amyloid burden.[6] Treatment is aimed at reducing the abundance of the amyloidogenic precursor protein by managing the underlying cause, i.e., wound infection and drug rehabilitation, as in our case.[6] Because the fragility of small blood vessels leads to the impairment of hemostasis, endoscopic treatment is ineffective. Therefore, management of the underlying illness is crucial to decelerating the course of amyloidosis. The risk of hemorrhage can be reduced with close surveillance, which includes monitoring of prothrombin time with the repletion of vitamin K and maintaining platelet counts greater than 50,000/mcL and hemoglobin greater than 7 g/dL. Proton pump inhibitors can reduce the potential for bleeding related to hyperacidity. Aspirin, antiplatelet agents, and nonsteroidal anti-inflammatory drugs other than acetaminophen should be avoided.[11]

Conflict of interest

The above authors have no potential conflicts of interest or sources of financial support.

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