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CASE REPORT | COLON

Systemic Amyloid A Protein Amyloidosis With Gastrointestinal Involvement

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ABSTRACT

Systemic amyloidosis is a multiorgan deposition of misfolded amyloid protein fibrils. The systemic amyloid A protein (AA) amyloidosis type predominantly involves the kidney and is mostly an under-recognized complication among persons who inject drugs. Gastrointestinal involvement in systemic AA amyloidosis that is associated with illicit drug use is uncommon. In this report, we present a case of a 40-year-old man with history of injection drug use, recurrent skin and soft-tissue infection, and renal AA amyloidosis that presented with painless bloody bowel movement, which initially resolved with conservative management. Upon further evaluation, the patient was found to have empyema that required antibiotic therapy and bilateral pleural drain. His hospital course was further complicated by multiple episodes of hematochezia requiring gastrointestinal consultation. Subsequent gastrointestinal biopsy revealed amyloid deposit.

KEYWORDS: GI amyloidosis; renal AA amyloidosis; skin and soft tissue infection; PWID; biopsy

INTRODUCTION

Systemic amyloidosis is the deposition of misfolded amyloid proteins in multiple tissues or multiple organs at a site remote from the production of the amyloid precursor proteins, leading to organ failure.[1,2] There are several forms of systemic amyloidosis. Commonly encountered forms are monoclonal light chain Primary or light chain amyloid (AL), serum amyloid A protein (AA), hereditary Transthyretin amyloidosis (ATTR), and beta 2 microglobulin (dialysis-related) amyloidosis.[2,3] Systemic AA amyloidosis is characterized by the deposition of serum amyloid A (SAA) protein in tissues/organs in response to inflammation or infection.[4,5] The SAA protein is an acute-phase reactant produced by hepatocytes during inflammation, and its deposition levels in tissue are associated with the chronicity of the inciting factor.[6,7] Although AA amyloidosis is less prevalent in developed countries possibly due to good access to effective treatment of inflammatory conditions, several chronic inflammatory conditions have been associated with AA amyloidosis, with rheumatoid arthritis been recognized as the most common etiology in the developed countries.[6,8] Injection drug use is a global health problem, and persons who inject drug (PWID) are prone to diverse medical conditions which include but are not limited to soft-tissue infection, endocarditis, overdose intoxication and withdrawal, hepatitis B virus infection, HIV, and hepatitis C virus infection.[9] Renal organ involvement is prevalent among PWID who present with AA amyloidosis. There is a plethora of information on AA amyloidosis involving the gastrointestinal (GI) tract associated with PWID. Thus, we present here a case report of systemic AA amyloidosis with GI involvement from Intravenous (IV) drug use.

CASE REPORT

A 40-year-old man presented to the emergency department with complaints of 3 episodes of painless bloody bowel movement, associated with fatigue and weakness. Medical history was significant for end-stage renal disease secondary to tissue-confirmed renal AA amyloidosis with positive immunohistochemistry demonstrating amyloid A staining in the glomeruli, arterioles, and interstitium; chronic obstructive pulmonary disease negative for alpha-1 antitrypsin deficiency; multiple skin and soft-tissue infections; and subcutaneous and intravenous drug use. He abused fentanyl, heroin, and cocaine. On presentation, he had stable vital signs with a systolic blood pressure of 120/70. The physical examination was notable for generalized pallor, bilateral pitting edema, and multiple atrophic scars on bilateral upper and lower extremities from injection drug use.

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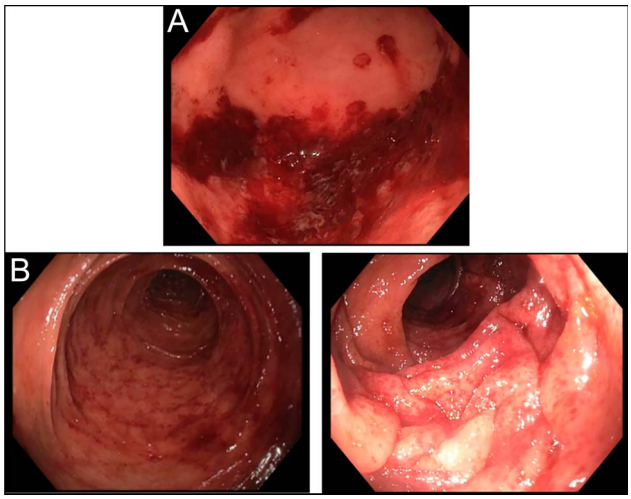

Figure 1. (A) Esophagogastroduodenoscopy: gastric body with congestion and friability with clot. (B) Colonoscopy: inflamed transverse colon. (C) Colonoscopy: inflamed sigmoid colon.

Laboratory diagnostics revealed a normocytic anemia with a hemoglobin level of 5.6 mg/dL (reference range 11–14.5 mg/dL), mild hyponatremia with a sodium concentration of 133 (136–145 mmol/L), hyperphosphatemia with a phosphorus concentration of 6 mg/dL (reference range 2.4–5.1 mg/dL), elevated blood urea nitrogen of 65 mg/dL (reference range of 9–23 mg/dL), and an elevated creatinine at 8.48 mg/dL (reference range 0.5–0.80 mg/dL). Workup of chronic inflammatory conditions such as HIV, Hepatitis B virus (HBV), and Hepatitis C virus (HCV) were negative. Chest computed tomography revealed bilateral loculated pleural effusion.

On presentation, he was transfused with 2 units of packed red blood cells with improvement of hemoglobin to 7.3 mg/dL. Evaluation of bilateral loculated pleural effusion revealed empyema with pleural fluid culture demonstrating streptococcus intermedius. He underwent bilateral pleural drainage and received antibiotic therapy. Further workup with transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) ruled out bacterial endocarditis. Serial chest x-ray was performed to monitor improvement in the empyema. His hospital course was extensive and complicated by multiple episodes of bright red blood per rectum requiring multiple transfusions.

He was evaluated by the gastroenterology team. He underwent upper endoscopy and colonoscopy. Upper endoscopy revealed normal esophagus and gastritis with hemorrhage (Figure 1). No biopsy was obtained from the upper endoscopy. He was recommended to follow up outpatient for repeat upper endoscopy in 1 month. Colonoscopy showed moderate inflammation found in the entire colon (Figure 1). The different segments of the colon were biopsied, and the result was significant for amyloidosis. Congo red stain demonstrated apple green birefringence on the histopathology report (Figures 2 and 3). He was started on a proton pump inhibitor (pantoprazole) and advised to follow up with gastroenterology as an outpatient.

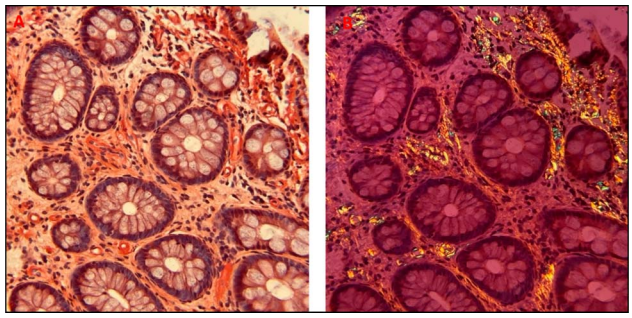

Figure 2. (A) Congo red stain showing amyloid deposits in the ascending colon. (B) Congo red stain showing amyloid deposits in the transverse colon.

DISCUSSION

AA amyloidosis is a result of overproduction of serum AA in response to inflammation.[4,7,10] Reported causes of AA amyloidosis in developed countries, such as the United States, have been associated with chronic inflammatory conditions—rheumatoid arthritis, juvenile idiopathic arthritis, ankylosis spondylitis, familial Mediterranean fever, inflammatory bowel disease, chronic infection, and some malignancies.[3,5,6,8] AA amyloidosis is an unrecognized complication among PWIDs. However, recent studies have shown an increase in the incidence of AA amyloidosis secondary to chronic skin and soft-tissue infection among PWIDs, particularly in heroin users.[11] AA amyloidosis predominantly affects the kidney in PWID as indicated in studies performed in San Francisco, United States, and meta-analyses conducted in London, United Kingdom.[10,12,13] In the San Francisco study conducted between 1998 and 2013, 24 patients were described to have renal AA amyloidosis secondary to injection drug use, ultimately resulting in end-stage renal disease.[12] Kidney involvement in AA amyloid commonly presents as nephrotic range proteinuria.[5–7]

The GI tract and heart are rarely affected.[4–6] Infiltration of SAA proteins in the GI tract results in GI AA amyloidosis. Clinical manifestations in patients vary and depend on the degree of amyloid deposition. Common symptoms include fatigue, weight loss, nausea, vomiting, diarrhea, constipation, abdominal pain, dysmotility, and GI bleeding.[6,14,15] Our patient had

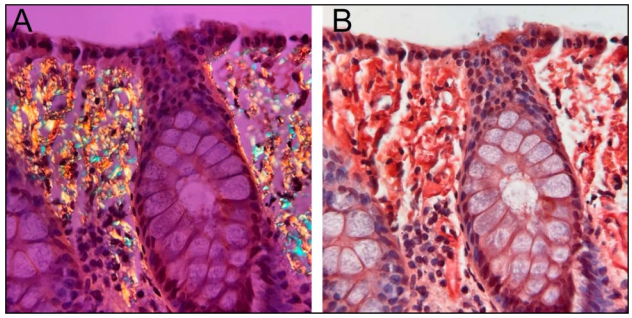

Figure 3. (A) Congo red stain showing amyloid deposits in the sigmoid colon. (B) Congo red stain showing amyloid deposits in the rectum.

renal AA amyloidosis from injection drug use. It appears his AA amyloidosis progressed to a systemic disease with GI involvement about 8 to 9 months after he was diagnosed with renal AA amyloidosis, manifesting as hematochezia. This progression may have resulted from persistent injection drug abuse causing a continuous state of inflammation further worsened by empyema, leading to increased SAA protein deposition in the affected organ.

Amyloidosis diagnosis is made when there is a presence of symptoms of organ involvement with histopathology confirmation of amyloidosis demonstrating apple green birefringence under polarized light with Congo red stain of the tissue.[6,14,15] A high index of suspicion is needed to accelerate the diagnosis of amyloidosis due to rareness of the condition and its nonspecific presentation. Patients with GI sequelae, especially those with symptoms, often require diagnostic endoscopy, either with esophagogastroduodenoscopy or colonoscopy, as seen in the index patient who had multiple episodes of bleeding per rectum that required evaluation with esophagogastroduodenoscopy and colonoscopy. Endoscopic findings in GI amyloidosis vary and are nonspecific. These include erosions, ulcers, submucosal tumor-like masses, and loss of normal architecture of GI lining.[16] AA amyloid deposit in the GI tract is commonly seen in the mucosa layer, with the involved area presenting as mucosal friability, erosions, and fine granular appearance that are typically seen in endoscopic findings of AA amyloidosis.[2,16] The commonest site of GI amyloid deposits with a high biopsy rate has been shown to be in the duodenum, followed by the stomach, colorectum, and esophagus.[1,17,18] Biopsy confirmation of GI AA amyloidosis is rare. Our patient had proven renal AA amyloidosis that later involved the GI tract as proven by the amyloid deposition in the colon and rectum shown in the biopsy. Although immunohistochemistry was not performed on the patient's GI biopsy to further confirm a GI AA amyloidosis, the previous confirmation of the patient's' renal AA amyloidosis with immunohistochemistry substantiated our conclusion of GI AA amyloidosis and not Primary or light chain amyloid (AL) or ATTR. Most studies in the literature have only reported biopsy-proven AL and ATTR amyloidosis. In a retrospective study performed at the Amyloid Treatment and Research Program at Boston University where over 2,000 patients (none were PWIDs) were evaluated during a 13-year period, 3.2% of the patients had biopsy-proven amyloid involvement of the GI tract, in which the forms of the amyloidosis identified were AL and ATTR, with AL noted to be the most common cause of GI amyloid involvement.[1] In another retrospective study conducted by Yen et al on 583 amyloid patients, 37 of 82 endoscopically biopsied patients had biopsy-proven GI amyloid (18). Similar to the study in Boston, most of the confirmed cases were AL amyloidosis. In both studies, AA amyloidosis was not observed as one of the causes of biopsy-proven GI amyloidosis

Treatment of systemic AA amyloidosis is directed at the underlying inflammatory disorder to suppress production of serum AA.[3] Biological and immunosuppressive therapies have been shown to improve outcomes in the management of the disease in underlying conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriatic arthritis. Similarly, antibiotic therapy for infection has been reported to improve outcomes in the management of the disease.[2,6,14] No specific treatment directed to the management of GI AA amyloidosis exists till date. For patients with GI features, supportive therapy is provided for symptomatic management.[14,15] In this index case, the patient was managed with blood transfusion and was initiated on a proton pump inhibitor and antibiotic to treat the underlying infection. He was also counseled on cessation of illicit drug use. Patients with AA amyloidosis from recurrent skin and soft-tissue infection in the setting of injection drug use is often difficult to treat, which poses a poor prognosis in this population. The disease is better prevented with prompt treatment of skin and soft-tissue infection and sensitization on complications of injection drug use along with cessation of drugs.

In the other common subtypes of GI amyloidosis, which include the AL and ATTR, treatment is also directed at the underlying etiology. Treatment of AL amyloidosis is directed at elimination of plasma cell dyscrasia with chemotherapy. Overall prognosis of AL amyloidosis is poor when there is cardiac involvement.[3,5] In ATTR, treatment is targeted at reducing the production of amyloid protein at the site of production, which is mostly in the liver. Liver transplantation has been used significantly to reduce the production of mutant proteins. The 5-year survival rate after liver transplant is approximately 100%.[2,6]

In summary, this case study highlights a rare case of biopsy-proven GI amyloidosis that progressed from patient's renal AA amyloidosis from injection drug use. A high clinical suspicion should be maintained in this population given its increasing incidence. Early diagnosis and prompt treatment of the underlying etiology of systemic AA amyloidosis is important due to the progressive nature of the disease. Safe prescribing and harm-reduction strategies should be enforced to prevent complications of injection drug use including AA amyloidosis.

DISCLOSURES

Author contributions: A. Olubunmi, O. Solabomi: manuscript writing, proofreading, figures and review of data. HA Naqvi: overall supervision and proofreading. HA Naqvi is the article guarantor.

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