ACG CASE REPORTS JOURNAL

CASE REPORT | SMALL BOWEL

Malabsorption Secondary to Gout-Induced Amyloidosis

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ABSTRACT

Many chronic inflammatory conditions can lead to systemic amyloidosis. However, secondary amyloidosis has rarely been associated with gout, and the literature reports only a handful of cases, all presenting with renal disease. We report a patient with a history of poorly controlled gout who presented with malabsorption. Endoscopic biopsies confirmed a diagnosis of small intestinal amyloidosis. This was believed to be a consequence of gout. Interestingly, renal involvement was subclinical. Our case raises awareness of this rare association and highlights the importance of considering a diagnosis of amyloidosis in patients who present with the combination of gout and gastrointestinal symptoms.

INTRODUCTION

Amyloidosis is the general term used to describe the extracellular tissue deposition of β-sheet fibrils composed of a variety of proteins, which usually circulate in their native form as constituents of plasma. These deposits may result in a wide range of clinical manifestations depending upon the type, location, and amount of deposition.

Gastrointestinal (GI) amyloidosis may cause a wide spectrum of symptoms, including diarrhea, steatorrhea, hemorrhage, weight loss, and abdominal pain.[1] Amyloid light (AL), amyloid A (AA), and amyloid transthyretin (ATTR) are the usual subtypes that cause symptomatic GI amyloidosis. However, the diagnosis of AA amyloidosis is rare in patients presenting with GI symptoms and chronic inflammatory conditions. Furthermore, in the clinical course, radiological and endoscopic findings are often non-specific. Therefore, without a high clinical suspicion for amyloidosis, the underlying pathology can be missed on a traditional hematoxylin and eosin stain, and often special stains are necessary to highlight amyloid deposits in biopsied tissue.

CASE REPORT

A 48-year-old Samoan man underwent a colonoscopy and endoscopy to evaluate a history of chronic diarrhea and recent significant weight loss of >20 kilograms. His past medical history was significant for recurrent polyarticular gout for >7 years, which had caused significant physical impairment. On clinical examination his weight was 84 kg (body mass index, 25 kg/m^2). Inspection of the hands revealed swelling and enlargement of the proximal interphalangeal joints, and a gouty tophus was visible on the tragus of the right ear. The systemic examination was otherwise normal.

Biochemical analysis showed mild anemia (124 g/L) and leukocytosis (12.7 x 10^9/L) with lymphocytosis (5.75 x 10^9/L). C-reactive protein was elevated at 71 mg/L. Liver function tests showed elevated alkaline phosphotase (351 U/L) and gamma-glutamyl transpeptidase (277 U/L) with hypoalbuminemia (25 g/L). The urate level was 0.68 mmol/L,

ACG Case Rep J 2017;4:e32. doi:10.14309/crj.2017.32. Published online: March 1, 2017.

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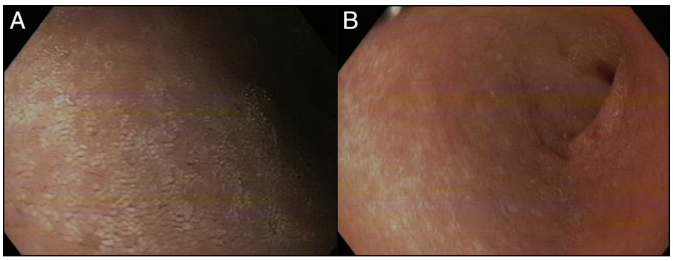

Figure 1. Endoscopy of the duodenum showing blunted villi.

and microbiological investigations of stool samples were negative. A joint aspiration showed negatively birefringent monosodium urate crystals with sterile cultures. A liver ultrasound was normal.

Esophagogastroduodenoscopy identified gastric mucosal atrophy and blunted villi in the duodenum (Figure 1). Duodenal mucosal biopsies showed preserved villous architecture with some deposition of eosinophilic material within the lamina propria and vessel walls. The eosinophilic material stained positive with Congo red (Figure 2). A colonoscopy was macroscopically normal. Biopsies from the terminal ileum showed mild villous blunting, fibrosis of submucosa, and eosinophilic material that stained positive with Congo red within the lamina propria and vessel walls. Immunohistochemistry of duodenal and terminal ileum sections tested positive for serum AA protein. Kappa and lambda immunoglobulin light chain and transthyretin immunohistochemical stains were negative. Proteomic analysis demonstrated the amyloid deposits to be comprised of serum amyloid A (SAA)-2 protein.

The results were consistent with a diagnosis of AA amyloidosis. A search for additional causes of secondary amyloidosis failed to identify any other immune-mediated diseases such as rheumatoid arthritis or chronic infections including tuberculosis. Thus, the final diagnosis was systemic AA amyloidosis with GI involvement due to polyarticular tophaceous gout.

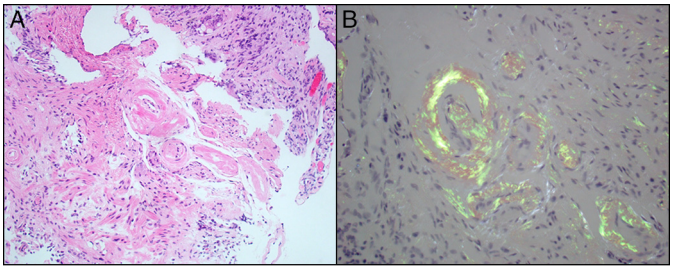

Figure 2. Duodenal mucosal biopsy showing (A) eosinophilic material within vessel walls and (B) Congo red birefringence highlighting the eosinophilic material.

Echocardiogram and cardiac magnetic resonance imaging showed no evidence of cardiac amyloid infiltration, and renal investigations revealed proteinuria of 450 mg/day with normal glomerular filtration rate (GFR). The patient was commenced on a weaning course of prednisolone, and colchicine was started at 500 μg. His dose of allopurinol was increased from 100 mg to 300 mg once daily. During outpatient follow-up, he reported that the GI symptoms had started to improve gradually following the resolution of the gout exacerbations.

DISCUSSION

Gout is a crystal arthropathy characterized by the deposition of uric acid in the joints and commonly involves the first metatarsal joint, knees, fingers, and ears. It is characterized by recurrent attacks of acute inflammatory arthritis, chronic arthropathy, and accumulation of urate crystals in the form of tophaceous deposits.

Despite the high prevalence of gout (approximately 3% in the adult population),[2] association with AA amyloidosis is very rare, and there are only a few reported cases.[3,4] All of the previously published cases had renal involvement, which manifested as a reduced GFR or nephrotic syndrome. Indeed, only 3% of patients with AA amyloidosis present without proteinuria (>500 mg/day) or renal impairment.[5] Neither of these abnormalities were present in our patient. This is the first reported case of a patient with AA amyloidosis due to gout presenting with primary GI symptoms.

AA amyloidosis occurs secondary to chronic inflammatory conditions, which result in prolonged and increased expression of the acute phase reactant SAA protein. In the largest reported series of AA amyloidosis, the median duration of symptomatic inflammatory disease before the diagnosis of amyloidosis was 17 years.[5] A possible explanation for the rarity of the association between gout and secondary amyloidosis may be due to the nature of waxing and waning inflammation in gout with short duration of an intense episode. This prohibits the sustained elevation of SAA proteins that is required for significant amyloid formation.[6] Alternatively, the association between gout and secondary amyloidosis may be uncommon as gout often responds well to pharmacotherapy. Therefore, depending on the chronicity of the illness, severity of the inflammation, frequency of relapse, and duration of remission, the expression of acute phase reactants and subsequent conversion to amyloid deposits will vary.[4,6]

Involvement of systemic amyloidosis in the GI tract can be diverse, leading to a range of symptoms including gastroesophageal reflux disease, nausea, and abdominal pain. Additionally, malabsorption symptoms can manifest as diarrhea, weight loss, hypoproteinemia, and other nutritional deficiencies. Localized amyloidosis of the GI tract has also been reported.[1] Protein-losing enteropathy can also occur in

amyloidosis, and therefore amyloidosis should be suspected in patients presenting with low albumin[7] and associated diarrhea.[8]

Our patient presented with an unusual combination of chronic gout with diarrhea, epigastric pain, weight loss, and hypoalbuminemia. He was found to have AA amyloidosis of the GI tract due to his uncontrolled chronic inflammation. Our case also highlights that this phenomenon can occur in the absence of significant renal pathology, contrary to previous reports.[5] While the patient did not meet the traditional definition for renal involvement in amyloidosis (>500 mg/d proteinuria), we suspect that kidney biopsy would reveal early amyloid deposits. We postulate that he has subclinical renal involvement and for some reason his amyloid is depositing preferentially in the bowel. Our case raises awareness of this rare association and highlights the importance of considering a diagnosis of amyloidosis in patients who present with the combination of gouty arthropathy and GI symptoms.

DISCLOSURES

Author contributions: A. Azzam and R. Balasubramaniam reviewed the literature and wrote the manuscript. A. Azzam is the article guarantor. S. Safa provided the images. C. McIvor and P. Mollee reviewed the literature and supervised the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received June 12, 2016; Accepted November 4, 2016

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