

Amyloidosis Presenting as Lower Gastrointestinal Hemorrhage

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ABSTRACT

AL-Amyloid rarely presents in the gastrointestinal tract as acute gastrointestinal hemorrhage, especially in the absence of clinical disease elsewhere in the body. There are no reported cases of monoclonal gammopathy of undetermined significance progressing to AL-Amyloid presenting as lower gastrointestinal hemorrhage. We report a case of a patient initially diagnosed with monoclonal gammopathy of undetermined significance who progressed to AL-Amyloid over the course of 1 year. His progression resulted in primary colonic amyloidosis that manifested as lower gastrointestinal hemorrhage. The diagnosis was made by biopsy of a sigmoid plaque demonstrating necrotic material on histopathology. Amyloid deposition was seen on congo red and on birefringence. The bleeding stopped spontaneously without intervention and he was discharged his fourth day in the hospital. Further evaluation revealed no involvement in other organ systems. The plan is to treat with melphalan and dexamethasone.

We conclude that early endoscopic examination and biopsy of the surrounding intestinal tissue is indicated when patients with monoclonal gammopathy of undetermined significance present with gastrointestinal hemorrhage to evaluate for the progression to AL-Amyloidosis. Treatment to prevent recurrent hemorrhage and further progression of the disease should be considered.

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INTRODUCTION

Early recognition of AL-Amyloidosis (AL) is important in an attempt to limit significant long-term effects. AL is a disorder characterized by the extracellular deposition of homogeneous, fibrillar monoclonal immunoglobulin light chains in various organs and tissues. The presentation of AL is protean with symptoms reflecting the sites of amyloid deposition. The organs most commonly involved are the heart and kidney.¹

Monoclonal gammopathy of undetermined significance (MGUS) has a prevalence of 3%-6% in those 70 years old or older and can be a clinical precursor to AL.^{2,3} MGUS is the presence of small amounts of monoclonal protein in the serum and urine without clinical manifestations. Patients with MGUS have the same life expectancy as the general population. However, MGUS is not static and can progress to multiple myeloma (MM), plasmacytoma, macroglobulinemia, AL, or chronic lymphocytic leukemia. This occurs at a rate of approximately 1% per year.⁴

AL rarely presents in the gastrointestinal (GI) tract as acute GI hemorrhage, especially in the absence of clinical disease elsewhere in the body. We present a case report of a patient initially presenting as MGUS who 1 year later progressed to AL with primary colonic involvement presenting as a lower GI hemorrhage. The incidence and pathophysiology for AL-associated gastrointestinal hemorrhage and the emphasis for early recognition of AL in an attempt to limit progression and prevent further organ involvement is discussed.

CASE REPORT

In January 2006, a 70-year-old white man was found to have a monoclonal gammopathy while being evaluated for anemia. Serum protein electrophoresis (SPEP) revealed a monoclonal IgG-lambda spike of 1.33 g/dL. Workup for MM was negative, and he was diagnosed with MGUS. His anemia was felt to be secondary to the chronic inflammation.

The remainder of his medical history included coronary artery disease, diabetes, hyperlipidemia, hypertension, and chronic obstructive pulmonary disease from longstanding tobacco use. His status is post radical prostatectomy with external radiation therapy for prostate cancer. Current medications include glyburide, lisinopril, metoprolol, niacin, and simvastatin.

Approximately 4 months prior to this admission for GI hemorrhage, the patient had a screening colonoscopy that revealed 2 tubular adenomas and was without other remarkable findings. A histopathologic review of biopsies obtained at that colonoscopy revealed no amyloid involvement, suggesting the development of the amyloid plaque was rapid and localized in its colonic involvement.

He was doing well until January 2007 when he presented with multiple episodes of painless hematochezia, which represents the passage of bright red blood primarily from the lower GI tract. This is contrasted with melena, which is the passage of oxidized (black and tarry) blood primarily from the upper gastrointestinal tract. The patient was hemodynamically stable and did not require transfusion. Colonoscopy revealed a large plaque with adherent clot in the sigmoid colon that encompassed nearly a third of the circumference of the lumen (Figure 1). Multiple biopsies were obtained, which were described as necrotic material on histopathology. Amyloid deposition was seen on congo red and on birefringence (Figure 2). The bleeding stopped spontaneously without intervention and the remainder of his hospitalization was uneventful without further hemorrhage. He was discharged on day 4.

At a follow-up visit 2 months after discharge, the patient had experienced no further episodes of GI hemorrhage. Colonoscopy at that time revealed a healed scar where the amyloid plaque had been, suggesting this lesion had healed without intervention. However, there was another plaque that had developed distally. Further evaluation for AL included a transthoracic echocardiogram, which revealed an ejection fraction (50%) without presence of diastolic dysfunction or right heart failure. He had no complaints of diarrhea, intestinal bleeding, weight loss, swollen legs, shortness of breath, or rash. His renal function remained normal. Based on these findings, a therapeutic regimen of melphalan and dexamethasone in an attempt to prevent further progression of amyloidosis is planned.

DISCUSSION

Our patient was initially diagnosed with MGUS and within 1 year progressed to AL with primary colonic

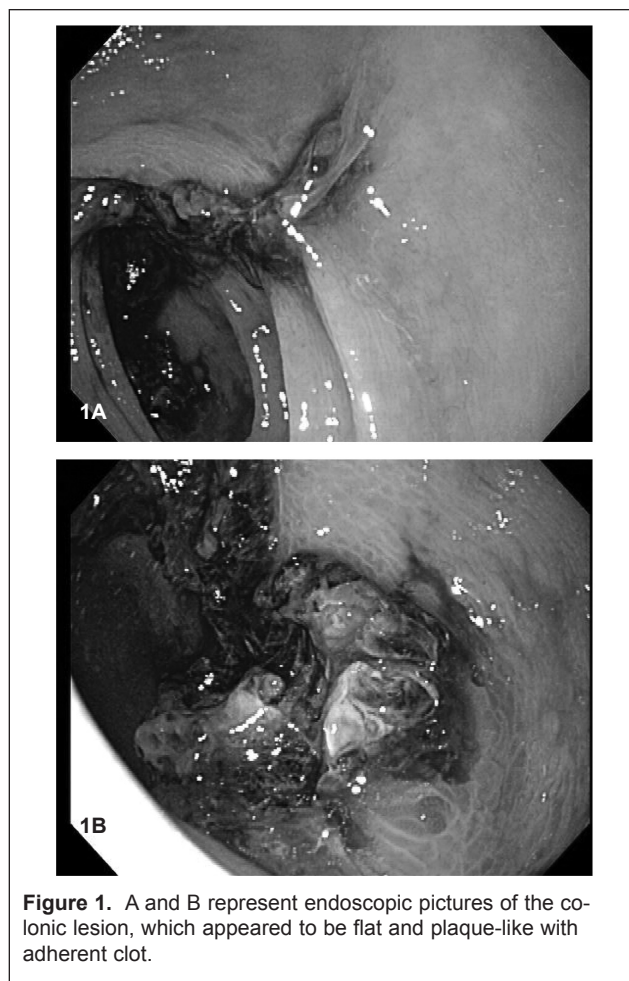


Figure 1. A and B represent endoscopic pictures of the colonic lesion, which appeared to be flat and plaque-like with adherent clot.

involvement manifested as lower gastrointestinal hemorrhage. This specific progression of MGUS to AL presenting as a lower GI hemorrhage has not been reported. GI involvement in AL is common, and has been found in up to 98% in some autopsy series, depending on the detection technique used.⁵ However, AL can present initially as GI hemorrhage and has only been reported 5 times in the literature.⁶⁻¹⁰ Conversely, there is a well-established association of AL patients experiencing GI hemorrhage at some point in the course of the disease. In 1 retrospective study of 337 patients with AL over an 8-year period, Mumford et al found a 5% incidence of GI hemorrhage.¹¹

Several mechanisms have been reported in the literature by which AL can induce GI hemorrhage. The best-established mechanism is the well-recognized association between AL and coagulation abnormalities, which can increase the risk of intestinal hemorrhage. In the study by Mumford et al, a prolongation of thrombin time, prothrombin time, or activated partial thromboplastin time was observed 51% of the time.¹¹ Acquired deficiency of fac-

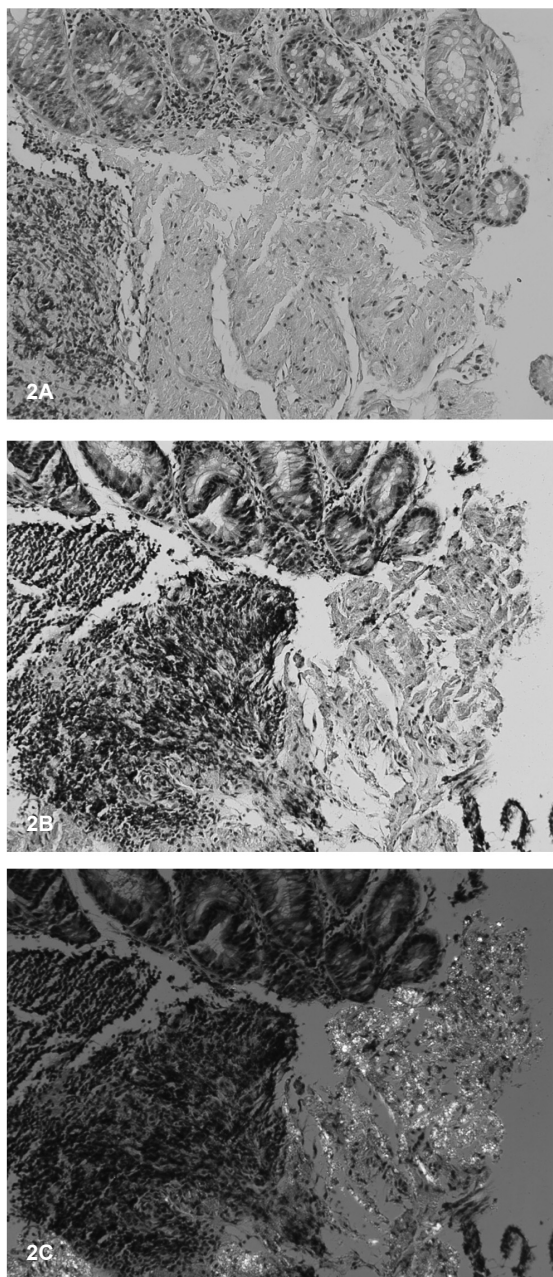


Figure 2. A. H&E stained sections of biopsied specimen revealing amorphous, eosinophilic material deposited within the submucosa. B. Congo red stained section revealing positive staining for amyloid protein. C. Apple-green birefringence as viewed through polarized lenses.

tor X is the most common coagulation factor deficiency in AL. Choufani et al performed a retrospective analysis of 368 patients with AL and found 32 (8.7%) patients with an acquired deficiency of factor X, correlating well with other studies that found 6.3%¹³ and 14%.¹¹ The authors concluded that all patients with AL should be screened for reduced factor X levels due to the increased risk of hemorrhage, especially prior to surgical proce-

dures.¹² Mechanistically, the acquired factor X deficiency appears to result when amyloid binds selectively to factor X, impairing the clotting cascade.¹⁴

Other less well-defined mechanisms for AL induced hemorrhage involve localized intestinal ischemia, which occurs when all layers of the intestine and blood vessel walls are infiltrated. This can lead to diffuse mucosal oozing as described by Mallory et al.¹⁵ This is the most likely scenario in our case, as necrosis with amyloid deposition in the submucosa and surrounding vessel walls was seen on biopsy (Figure 2). Also described is heavy focal amyloid deposition causing ulcerations.¹⁶ Lastly, amyloid deposition in the mesenteric and submucosal vessel walls can induce fragility and subsequent hemorrhage.¹⁷⁻¹⁸

Given the nonspecific nature of GI manifestations and the rarity of AL presenting as GI hemorrhage, it is important to have a high index of suspicion for progression of patients with MGUS if they present with hemorrhage or GI symptoms as this may be the initial sign of progression.¹⁹⁻²¹ If patients with MGUS present with either upper or lower intestinal bleeding, endoscopic examination should be performed to determine the source of bleeding. Further, mucosal biopsies should be obtained at the time of endoscopy with special stains performed for the presence of amyloid.

Diagnosis of AL is important after the initial bleeding has been controlled, as there are treatment options available that can have a significant impact on their disease course. Therapy is generally directed at management of specific organ system complications and, when possible, reduction of the amount of circulating amyloid protein to prevent or slow the rate of additional amyloid deposition. Thus, the presence of AL with primary GI involvement only, as in our case, should prompt consideration for treatment because the cause of death in most patients is cardiac related, and usually reflects the extent of cardiac involvement.²² Patients with AL have improved survival over placebo when treated with autologous or allogeneic hematopoietic cell transplants, and various regimens including melphalan, dexamethasone, thalidomide, and interferon.²³ In addition, our patient has recurrence of amyloid plaques, thus increasing his likelihood to rebleed.

CONCLUSION

In conclusion, we report a case of MGUS progressing to AL and presenting as GI hemorrhage. Though primary presentation with GI hemorrhage is rare, a high degree of suspicion is required with early endoscopic examination, and biopsy of the surrounding intestinal

tissue is recommended. Survival in patients with AL is largely dependent on the degree of cardiac and renal involvement, and immediate referral to a hematologist for consideration of treatment should be undertaken when the involvement is limited to the GI tract.

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