

The 13-year bleed: Exuberant amyloid angiopathies, angiodysplasias, and acquired coagulopathies of the gut

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Abstract

Amyloidosis is a disorder characterized by extracellular deposits of proteins that are prone to aggregate and form insoluble fibrils. Amyloid deposits limited to a single organ or tissue without the involvement of any other site in the body is uncommon. We report a 75-year-old man with previously treated non-Hodgkin's lymphoma who presented with recurrent gastrointestinal hemorrhage. Histopathology showed amyloid deposition within vascular malformations. His bleeding continued with the cause rooted in the fundamental building blocks—clotting factors. We discuss the interplay of the pathophysiology of lymphoma, amyloidosis, and factor X deficiency in a patient with preexisting angiodysplasias leading to refractory gastrointestinal bleeding. To our knowledge, there are only 3 reported cases of concomitant amyloidosis and angiodysplasia in the colon, and none involving the small bowel.

Keywords

Amyloidosis, angiodysplasia, factor X deficiency, hemorrhage

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Introduction

Amyloidosis is a disorder characterized by extracellular deposits of proteins that are prone to aggregate and form insoluble fibrils, causing distortion to the tissue architecture and organ dysfunction. Gastrointestinal (GI) involvement may present with nonspecific symptoms related to dysmotility, malabsorption, and bleeding.^{1,2} The cause of bleeding becomes more complex in the setting of multiple predisposing factors involving the GI tract such as angiodysplasia. We report a 75-year-old man with a history of previously treated non-Hodgkin's lymphoma (NHL) who presented with recurrent GI bleeding. We will then discuss the interplay of the pathophysiology of lymphoma, amyloidosis, and factor X deficiency in angiodysplasias leading to refractory GI bleeding. To our knowledge, there are only 3 reported cases of concomitant amyloidosis and angiodysplasia in the colon, and none involving the small bowel.

Case description

A 75-year-old man presented with recurrent painless, dark-red rectal bleeding, and fatigue. His first episode was

13 years prior, for which he was eventually diagnosed with a lambda light chain predominant lymphoplasmacytic lymphoma following resection of a portion of his small bowel due to unrelenting hemorrhage. Remission was achieved after chemotherapy.

Upon admission, the examination was remarkable for tachycardia, frank blood on rectal examination: lab workup: prothrombin time (PT)=11.9 (normal=9–13), international normalized ratio (INR)=1.1, partial thromboplastin time (PTT)=36.2 (normal=25.5–37), and hemoglobin (Hb)=7.1 g/dL. Computed tomography of the abdomen did not reveal hepatosplenomegaly or lymphadenopathy. Colonoscopy revealed a polypoid cecal mass

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with an adjacent ulcer (Figure 1). Biopsies showed submucosal eosinophilic material with apple green birefringence under polarized light when stained with Congo red dye, consistent with amyloid deposition. Due to massive

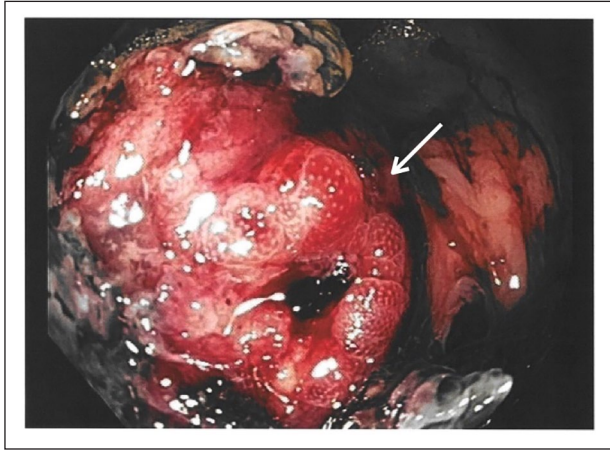


Figure 1. Colonoscopy finding of a polypoid 4-cm cecal mass (white arrow) underneath a clot. Endoscopic features of AL amyloidosis include thickening of the valvulae conniventes, mucosal ulcerations, multiple polypoid protrusions, and tumor-like lesions.

hemorrhage refractory to blood transfusions, laparoscopic cecectomy and primary ileocolic anastomosis were performed. There was no evidence of lymphoma noted on the surgical specimen; however, primary light chain amyloidosis was confirmed by immunochemistry with lambda chain predominance (Figure 2). Protein electrophoresis and immunofixation of serum and urine were undetectable. He improved, but declined reinitiation of chemotherapy or further workup such as a bone marrow biopsy.

Eight months later, he was readmitted due to recurrence of massive bleeding for which colonoscopy, capsule endoscopy, abdominal imaging, and angiogram were inconclusive. Nuclear bleeding scan was suggestive of active bleeding in the ileus. Further intensive workup revealed a factor X level of 15% (normal=50%–150%) in keeping with a factor X deficiency for which he received a total of 3 fresh frozen plasma (FFP) and 6 prothrombin complex concentrate (PCC). Amyloidosis was considered as one of the likely causative factors; thus, dexamethasone, bortezomib, and cyclophosphamide were initiated. Due to hemodynamic compromise, exploratory laparotomy resulting to small bowel resection was performed. Histopathology demonstrated extensive thick fragile, dilated vessels in the mucosa with diffuse amorphous depositions in the vessel wall and submucosa. Postoperatively, however, he continued to have

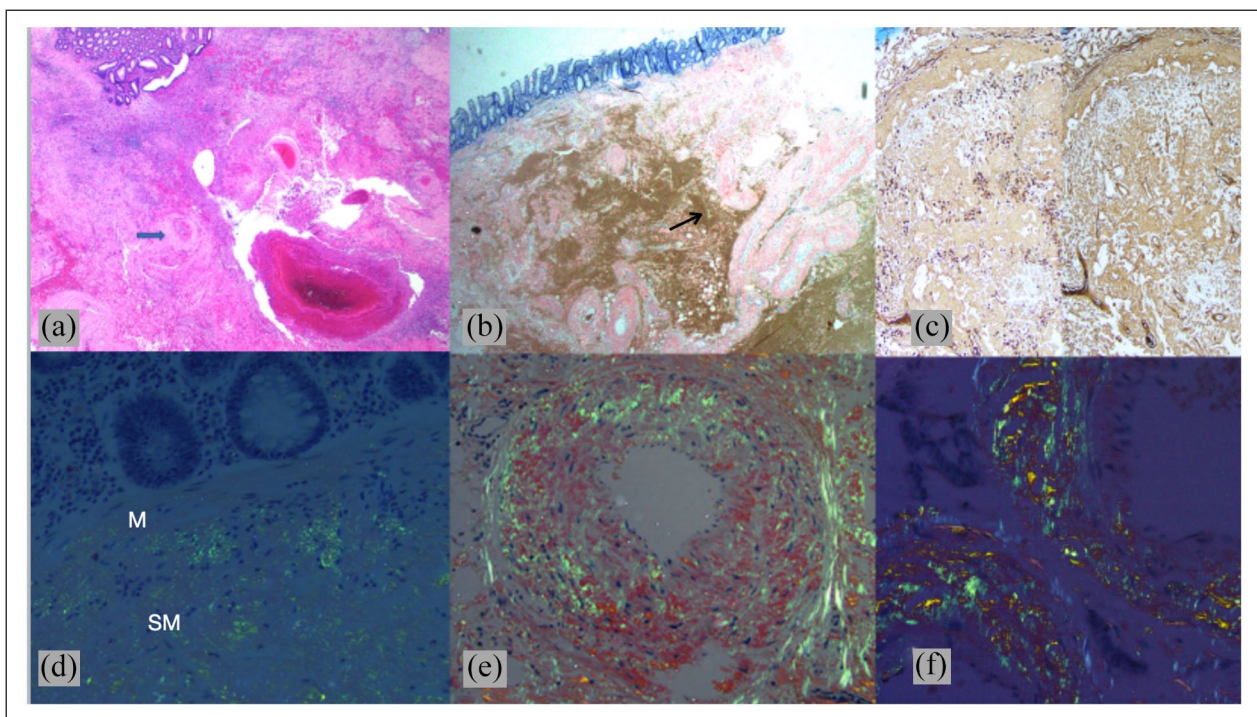


Figure 2. Histology of the cecal mass. (a) Hematoxylin-eosin-stained section showing thrombosed blood vessels demonstrating abundant homogeneous pink deposits in its walls (blue arrow). (b) Congo red stain positive material demonstrated in the walls of a vascular malformation (green arrow). (c) Abundance of lambda light-chain deposits in the pericecal lymph node. (d) Apple green birefringence under polarized light showing amyloid aggregates in the submucosa (SM) below the muscular mucosa (M). (e) Apple green birefringence reflected under polarized light within the arterial walls. (f) Apple green birefringence reflected under polarized light within the walls of the malformations.

refractory bleeding and had episodes of ventricular tachycardia which led to his eventual demise.

Discussion

The vicious cycle of extensive amyloid deposition, consequent acquired factor X deficiency, concomitant amyloid deposition on vascular malformations, and recurrent bleeding all contributed to this patient's demise.

Amyloidosis is a group of disorders characterized by the extracellular deposition of pathologic proteinaceous substances in various tissues and organs of the body.³ Given its insidious onset, a high index level of clinical suspicion is required to prevent delayed histological diagnosis of the apparently affected organ. Amyloid deposits encroaching on the perivascular and vascular walls lead to fragility, impaired vasoconstriction which can manifest as mucosal erosions and hemorrhage.^{4,5} The peculiarity of this case rests in the discovery of amyloid deposits within angiodysplasias. Angiodysplasias occur in 1% of the population and are ectatic nests of submucosal tortuous veins, venules, and capillaries. They may be separated from the intestinal lumen by only the vascular wall and a layer of attenuated epithelial cells, as such limited injury can result in significant hemorrhage.⁶

The pathophysiology of angiodysplasias is unknown; however, various theories have been proposed. The mechanical theory postulates that obstruction of low-grade submucosal veins causes increased muscular contractions resulting in congestion and occlusion within the muscular propria. This leads to dilated and tortuous veins which result in loss of precapillary sphincter functionality, causing small arteriovenous communications. The angiogenic theory suggests that intermittent hypoxia from muscular contractions stimulate growth factors which trigger pathological neovascularization.⁷ In the event of amyloidosis, globular deposition within the submucosa becomes a nidus for obstruction, increased vascular contraction, and hypoxia-induced vascular malformations.

Amyloidosis can be classified based on the precursor protein such as light chains, SAA (serum protein A), beta-2 microglobulin, or ARRT (transthyretin amyloid). Light chain (AL) amyloidosis occurs from the deposition of transformed kappa or lambda light chains.⁸ AA amyloidosis occurs due to the deposition of acute phase reactants often related to chronic inflammatory diseases and malignancy. Amyloidosis involving the gastrointestinal tract occurs as part of systemic amyloidosis in 80% of cases and as a localized entity in 20%.⁹

AL amyloidosis is customarily associated with plasma cell disorders; however, amyloidosis arising in the setting of B-cell lymphoma is rare and accounts for only 2%–4% of cases. The deposits are almost always associated with circulating monoclonal proteins which are typically indolent or slowly progressive. When low-grade NHL have localized

involvement, they tend to have low to undetectable circulating serum and urine levels of monoclonal protein, thus making this entity a diagnostic challenge.¹⁰ Accurate identification of the underlying low-grade NHL and its type is important in initiating management.

Hemostatic abnormalities such as coagulation factor deficiencies, hyperfibrinolysis, and platelet dysfunction are associated with AL amyloidosis. Factor X deficiency occurs because of the entrapment of this factor within the amyloid fibrils as they are exposed to plasma. This is reflected by an elevated international normalized ratio and activated partial thromboplastin time.^{11,12} When present, factor X deficiency suggests advanced disease and poor outcomes.¹³ In the setting of acute bleeding, rapid correction of the deficiency with FFP, PCC, or recombinant factors may play a role. In the systemic form of light chain amyloidosis, multiagent chemotherapy targeting plasma cells to inhibit light chain production is necessary. It is prudent to discern between localized and systemic form of AL amyloidosis as systemic therapy is not indicated for localized amyloidosis. Novel agents such daratumumab are currently being added to the standard of therapy, cyclophosphamide, bortezomib, and dexamethasone (CyBORd) in patients with newly diagnosed AL amyloidosis. On the ANDROMEDA trial, daratumumab-CyBORd was well tolerated, with no new safety concerns versus the intravenous formulation, and demonstrated robust hematologic and organ responses.^{14,15}

Conclusion

The implications of amyloid depositions on vascular aberrations and its effect on hemostasis are crucial given its potential to cause lethal bleeding. Awareness of the correlation of lymphoma, amyloidosis, and factor X deficiency in a patient with angiodysplasia and eventual prompt diagnosis and treatment can significantly alter the natural course of the disease and be lifesaving.

Author contributions

L.N.S. and L.S.K.S. conceptualized, gathered data, performed literature review, and drafted the report. J.P. provided clinical expertise. K.D. critically reviewed the paper. All authors reviewed the final manuscript.

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Informed consent

Written consent was obtained from the legally authorized representative of the deceased subject.

Patient consent

Written consent was taken from the legally authorized representative of the deceased subject.

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References

1. Sakai E, Ohata K, Nakajima A, et al. Diagnosis and therapeutic strategies for small bowel vascular lesions. *World J Gastroenterol* 2019; 25(22): 2720–2733.
2. Dahiya DS, Kichloo A, Singh J, et al. Gastrointestinal amyloidosis: a focused review. *World J Gastrointest Endosc* 2021; 13(1): 1–12.
3. Hoda SA and Cheng E. Robbins basic pathology. *Am J Clin Pathol* 2017; 148(6): 557–557.
4. Oyasiji T and Yood S. Jejunal amyloidoma—a rare cause of gastrointestinal bleeding. *Cases J* 2009; 2: 9100–9100.
5. Bansal R, Syed U, Walfish J, et al. Small bowel amyloidosis. *Curr Gastroenterol Rep* 2018; 20(3): 11.
6. Jackson CS and Strong R. Gastrointestinal angiodysplasia: diagnosis and management. *Gastrointest Endosc Clin N Am* 2017; 27(1): 51–62.
7. García-Compeán D, Del Cueto-Aguilera AN, Jiménez-Rodríguez AR, et al. Diagnostic and therapeutic challenges of gastrointestinal angiodysplasias: a critical review and view points. *World J Gastroenterol* 2019; 25(21): 2549–2564.
8. Cowan AJ, Skinner M, Seldin DC, et al. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. *Haematologica* 2013; 98(1): 141–146.
9. Díaz Del Arco C and Fernández Aceñero MJ. Globular amyloidosis of the colon. *Arab J Gastroenterol* 2018; 19(2): 96–99.
10. Wechalekar AD, Chakraborty R and Lentzsch S. Systemic amyloidosis due to low-grade lymphoma. *Hematol Oncol Clin North Am* 2020; 34: 1027–1039.
11. Patel G, Hari P, Szabo A, et al. Acquired factor X deficiency in light-chain (AL) amyloidosis is rare and associated with advanced disease. *Hematol Oncol Stem Cell Ther* 2019; 12(1): 10–14.
12. Bruserud Ø, Tvedt THA, Ahmed AB, et al. Spontaneous splenic artery rupture as the first symptom of systemic amyloidosis. *Case Rep Crit Care* 2021; 2021: 6676407.
13. Abdallah N, Muchtar E, Dispenzieri A, et al. Coagulation abnormalities in light chain amyloidosis. *Mayo Clin Proc* 2021; 96(2): 377–387.
14. Godara A and Palladini G. Monoclonal antibody therapies in systemic light-chain amyloidosis. *Hematol Oncol Clin North Am* 2020; 34(6): 1145–1159.
15. Palladini G, Kastiris E, Maurer MS, et al. Daratumumab plus CyBORd for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *Blood* 2020; 136(1): 71–80.