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Peritoneal Amyloidosis as a Presenting Manifestation of AL Amyloid

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CASE REPORT

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Abstract

Amyloid is a systemic disease characterized by extracellular deposition of misfolded protein. Gastrointestinal and peritoneal deposition of light chain (AL) amyloid is an under-recognized manifestation of this systemic disease, usually as a late sequela. Here we present a case of recently diagnosed AL peritoneal amyloid that presented in the context of recurrent, acute onset abdominal discomfort and was found to have bowel obstruction complicated by perforation in the setting of AL-mediated gastrointestinal tract infiltration and dysmotility.

Keywords: Misfolded protein, AL amyloid Gastrointestinal amyloid, Late sequela of disease

1. Introduction

Amyloid is a generic term for extracellular tissue deposition of insoluble fibrils composed of low molecular weight subunits of a variety of proteins, most of which circulate within plasma.[1-3] To date, 18 systemic and 22 localized forms of amyloid have been identified.[4] The most common systemic types include AL, AA, and transthyretin (ATTR) amyloid. AL amyloid occurs due to deposition of protein derived from immunoglobulin light chain fragments and is the most common type of amyloid in the United States with an approximate incidence of 6−10 cases per million person-years.[5,20] AA amyloid usually occurs in context of chronic infection and inflammation secondary to deposition of serum amyloid A protein. [21] ATTR amyloid arises from the extracellular deposition of amyloid fibrils formed by transthyretin, a liver-derived transport protein, resulting a late-onset acquired amyloid.[54] While AA amyloid has a predilection for the gastrointestinal (GI) tract with an incidence rate of approximately 60%, AL amyloid affects the GI tract in only 1−8% of patients.[5-10] The pathophysiologic mechanisms of this dichotomy and predilection for specific organ involvement remains unknown. AL amyloid of the GI tract presents with unexplained and nonspecific complaints such as abdominal pain, esophageal reflux, constipation/diarrhea, nausea, weight loss, and early satiety.[53]

Gastrointestinal AL amyloid is an under-recognized disease manifestation that may be further compounded by peritoneal involvement, usually as a late sequela of the disease.[11-14] The prognosis of patients with AL amyloid and GI involvement is poorer than those without GI involvement, and these patients generally present with advanced disease with more organ involvement.[15] A number of studies have described amyloid affecting the GI tract or peritoneum separately, but cases of AL amyloid involving both organs are rare.[13]

2. Case presentation

A 60-year-old woman presented to the emergency department with worsening lower extremity swelling and acute on chronic abdominal pain for 2 weeks. Her abdominal pain was gradual in onset, crampy, 8/10 in intensity, and involved the epigastric area with radiation to the back and bilateral upper abdominal quadrants. Her pain was

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associated with several episodes of non-bloody, non-bilious emesis. She denied aggravating factors and reported some relief with staying still.

Her medical history was notable for hypertension, papillary thyroid adenocarcinoma status post thyroidectomy, and recent biopsy-confirmed peritoneal AL amyloid. With respect to her peritoneal AL amyloid, she was noted to have a history of chronic abdominal pain for which upper GI endoscopy was unremarkable and computed tomography (CT) of abdomen and pelvis (Fig. 1, Panel A) demonstrated peritoneal calcifications concerning for carcinomatosis and a soft tissue mass within the sigmoid mesentery concerning for a neoplastic process. Interventional Radiology-guided peritoneal biopsy was positive for AL amyloid deposition involving fibro-adipose tissue and skeletal muscles (Fig. 2). Additional serological workup and marrow biopsy was deferred to an outpatient basis. She was scheduled to follow up with an outpatient oncologist but unfortunately, she was lost to follow-up during the COVID-19 pandemic. Her home medications included Synthroid and Nifedipine. Family history was remarkable for a maternal history of stomach cancer, a paternal history of prostate cancer, and a sister with breast cancer.

On presentation, the patient was afebrile and with preserved saturations on room air, but was noted to be hypotensive (87/50 mm Hg) and mildly tachycardic (100 beats per minute). Physical examination showed decreased bowel sounds, epigastric tenderness without guarding or rebound tenderness, 3+ pitting edema of bilateral lower extremities extending to the knees, and jugular venous distension to the angle of mandible. Laboratory diagnostics (Table 1) were remarkable for transaminitis, a normocytic anemia, a positive ANA (1:200), and a positive B2 microglobulin. CT of abdomen and pelvis with IV contrast showed diffuse hepatic hypoattenuation and small ascites (new since prior CT abdomen and pelvis 3 months ago) and persistent peritoneal/retroperitoneal infiltration with associated calcifications consistent with amyloid (Fig. 1, Panel B). MRCP showed fatty hepatic infiltration without bile duct pathology. Echocardiogram showed hyperdynamic LVEF of 80–85%, grade II diastolic dysfunction, and a speckled pattern suggestive of infiltrative cardiomyopathy.

Additional workup included a SPEP and UPEP demonstrating a monoclonal peak in the gamma region with immune subtraction showing a free lambda light chain monoclonal pattern. Free kappa was within normal limits with marked elevation of free lambda and a markedly abnormal kappa/lambda ratio (Table 1). To confirm the diagnosis, a bone marrow biopsy (Fig. 3) of right iliac crest was performed. Histology demonstrated 5–10% plasma cells with lambda predominance and perivascular amyloid deposition. She also underwent esophagogastroduodenoscopy for a down trending hemoglobin that showed linear red stripes in the gastric antrum. Congo red staining of antral biopsies showed amyloid protein in perivascular area (Fig. 4).

The patient was started on furosemide for volume overload, pantoprazole for probable peptic ulcer disease, and dexamethasone for presumed autoimmune hepatitis with symptomatic improvement in both her abdominal discomfort and lower extremity

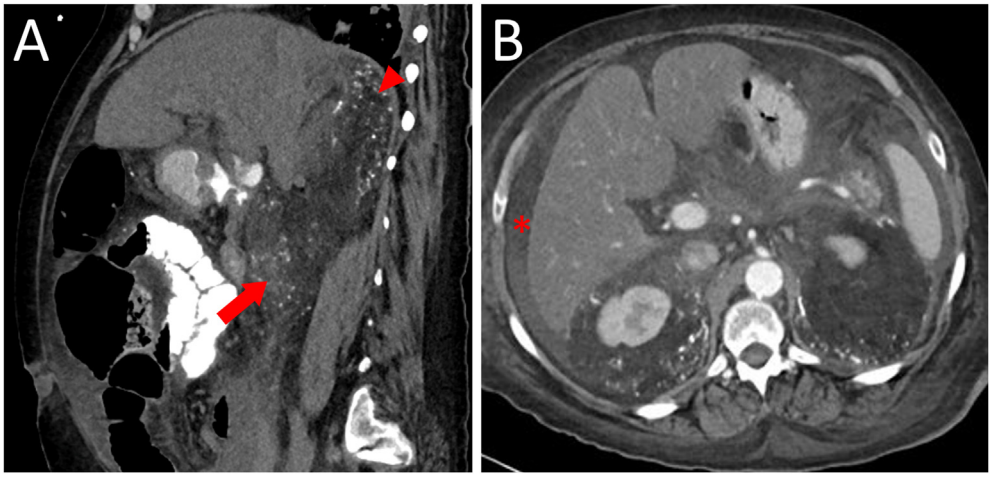

Fig. 1. Computed Tomography of the Abdomen and Pelvis without and with contrast. (A) CT without contrast demonstrates diffuse punctate calcifications throughout the peritoneum (arrows) and retroperitoneum (arrowhead). (B) CT with contrast demonstrates diffuse hepatic hypoattenuation and small ascites (new since prior CT abdomen and pelvis) and persistent peritoneal/retroperitoneal infiltration with associated calcifications consistent with amyloid. Additionally, new ascites was appreciated (asterix).

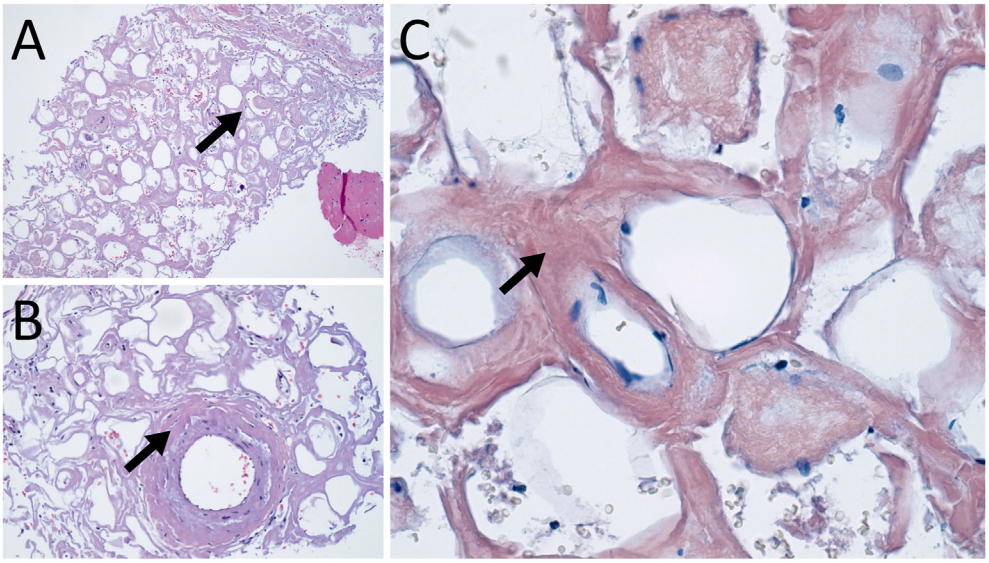

Fig. 2. Peritoneal Histopathology. (A) H&E staining of the peritoneum in 100x magnification demonstrates fibroadipose tissue with diffuse infiltration of acellular amorphous material surrounding fat lobules (arrow). (B) 200x magnification demonstrates diffuse acellular amphophilic material infiltrating fibroadipose tissue and a blood vessel (center/right, lower), with vessel wall involvement (arrow). (C) Congo red staining of the peritoneum in 400x magnification demonstrates amyloid (staining pink/red; arrow).

swelling. She was subsequently discharged with planned outpatient initiation of chemotherapy - Cyclophosphamide, Bortezomib and Daratumumab.

Approximately one month after the aforementioned hospitalization, the patient was readmitted in the context of severe, generalized, crampy abdominal pain, with associated nausea and vomiting. Abdominal examination demonstrated a distended abdomen that was markedly tender to palpation in all quadrants with positive rebound tenderness and involuntary guarding. CT of abdomen and pelvis demonstrated free air and fluid within the peritoneum with an indeterminate site of perforation and diffuse small bowel distension with a transition point in pelvis, compatible with partial small bowel obstruction. She underwent exploratory laparotomy; however, the perforation was unable to be localized and her abdomen was closed after peritoneal lavage. She was transferred to hospice care.

3. Discussion

Amyloid, while a systemic disease, rarely affects the peritoneum and is oftentimes asymptomatic, diagnosed as a mimic of peritoneal carcinomatosis.[15] GI amyloid, while slightly more common, also remains rare, positive in only 3.2% of all amyloid cases,[25] and historically has an increased incidence in AA amyloid when compared to the other subtypes; the pathophysiologic mechanisms of this predisposition remain unknown. AL amyloid involving both the peritoneum and GI tract is an extremely rare entity[13] with only sporadic reports noted in the literature.[16,18,28]

Peritoneal amyloid presents with two distinct patterns - nodular and diffuse[22] – exclusively based upon imaging findings, with an as of yet unknown clinical significance. The diffuse pattern demonstrates generalized peritoneal thickening with amorphous or irregular calcifications.[56] Our patient's initial CT abdomen and pelvis showed diffuse punctate calcifications of the peritoneum and retroperitoneum that prompted an initial peritoneal biopsy. GI amyloid, in contrast to the asymptomatic nature of peritoneal amyloid, presents with nonspecific symptoms[15] ranging from esophageal reflux, abdominal pain, constipation/diarrhea, nausea, weight loss, early satiety to more severe hemorrhage and obstruction.[48] These symptoms are hypothesized to occur secondary to the deposition of amyloid in the submucosal layer and/or muscularis propria of GI tract[49,55] with associated involvement of blood vessels and nerves and subsequent autonomic neuropathy, mucosal friability, malabsorption, infarction, and bowel perforation.[46] The second portion of the duodenum (100%), stomach (90%), colon and rectum (90%), and esophagus (70%) are commonly affected.[14,25,30] Indeed, our patient demonstrated mucosal friability in the gastric antrum which correlated with amyloid deposition in that area, with histologic involvement of perivascular areas.

In our case, the initial suspicion was for autoimmune hepatitis as our patient was a female, who

Table 1. Laboratory diagnostics.

Parameters	Normal range	Result
Hemoglobin (gm/dl)	11–14.5	6 (Baseline Hb: 10)
AST (units/l)	0–33	4017
ALT (units/l)	10–49	942
Alkaline phosphatase (units/l)	46–116	287
Total bilirubin (mg/dl)	0.3–1.2	1.1
Total protein (gm/dl)	5.7–8.2	4.9
Albumin (gm/dl)	3.2–4.8	3.2
Globulin (gm/dl)	1.3–4.7	1.8
Free K level (mg/l)	3.3–19.4	29.8
Free Lamda level (mg/l)	5.71–26.3	4067.5
Free Kappa/Lamda	0.26–1.65	0.007
SPEP	0	Spike in gamma region measuring 0.2 gm/dl, suspicious for a monoclonal protein
UPEP	0	Monoclonal peak in gamma region, comprising 62% of total urine protein
Immunosubstraction	None	Free Lamda light chain monoclonal pattern
B2 microglobulin	0	7.9 mcg/ml
Anti-smooth antibody	Negative	Negative
Anti dsDNA ab	Negative	Negative
IgA (mg/dL)	40–350	164.9
IgM (mg/dL)	50–300	58
IgG (mg/dL)	650–1600	1160
HAV IgM	Non-reactive	Non-reactive
HBsAg, anti HBc IgM	Non-reactive	Non-reactive
HCV	Non-reactive	Non-reactive

AST: Aspartate aminotransferase; ALT: Alanine transaminase; SPEP: Serum protein electrophoresis; UPEP: Urine protein electrophoresis; Anti ds DNA ab: Anti-double-stranded deoxyribonucleic acid antibodies; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G; HAV IgM: Hepatitis A virus immunoglobulin M; HBsAg: Hepatitis B virus surface antigen; anti HBc IgM: IgM antibody to Hepatitis B virus core antigen; HCV: Hepatitis C virus.

presented in the context of acute abdomen with marked transaminitis, negative hepatitis panel, and positive ANA, however negative further immunological workup (anti dsDNA, anti-smooth antibody) and normal level of serum globulin and immunoglobulins mainly IgG, excluded the possibility of autoimmune hepatitis. The elevated liver enzymes were thought to be in context of ischemic hepatitis given her persistent hypotension. Her imaging of abdomen and pelvis was negative for decreased contrast uptake by hepatocytes as well as absence of hepatomegaly and normalization of liver enzymes showed less likelihood of hepatic amyloid infiltration, thus making a liver biopsy unnecessary.

Early diagnosis of amyloid relies upon a high index of suspicion. The combination of serum and urine testing with immunofixation electrophoresis and measurement of serum free light chain is required to detect the monoclonal protein subtype of AL amyloid.[17,21] Our patient demonstrated an elevated free lambda level without associated heavy chain involvement, a lack of classic CRAB symptomatology, and 5–10% plasma cells on marrow biopsy, which in combination with the noted positive Congo red staining of the peritoneum and gastric antrum was strongly suggestive of a diagnosis of a lambda-restricted AL amyloid. Alternative diagnoses such as a light chain multiple myeloma and light chain monoclonal gammopathy of undetermined significance were considered, but felt to be unlikely given the presentation and laboratory diagnostics. The definitive method for diagnosis remains tissue biopsy.[23,24] The combination of fat pad biopsy and bone marrow biopsy has been shown to have an overall diagnostic sensitivity of 83% in AL amyloid.[36] Congo red staining and typical apple-green birefringence under polarized light remains the gold standard for confirming amyloid deposition and has overall sensitivity of 57–85% and a specificity of 92–100%.[34,35] If positive for amyloid, confirmation of type of amyloid fibril is crucial to guide therapy.[25] The most common methods of fibril typing include immunohistochemistry, immunoelectron microscopy, or liquid chromatography/mass spectrometry.[26] When there is a suspicion of hereditary amyloid (ATTR), gene sequencing must be performed.[19]

The prognosis of AL amyloid depends heavily upon the extent of organ involvement at presentation, the magnitude of involvement of the individual organs, and the hematological response to treatment.[32-35,55] When treated with standard regimens, the expected median survival for patients with AL amyloid is greater than 5 years.[36-41] In contrast, those patients with cardiac involvement have been classically found to have increased morbidity and mortality which appears to directly correlate to cardiac amyloid load (as determined by septal thickness), cardiomyocyte destruction (as determined by baseline troponin levels and ejection fraction), and ProBNP levels.[57] The expected survival in such patients may be as short as 4–6 months.[42-48] It appears that GI involvement has a similarly increased morbidity and mortality. AL amyloid is typically associated with a worse prognosis when compared to AA amyloid, which significantly increased in cases of GI involvement.[50] Multi-organ AL amyloid remains a major clinical challenge with a significant mortality rate within a few months of diagnosis.[41] Typical causes of death include infection, renal failure, heart failure, and hepatic failure.[51]

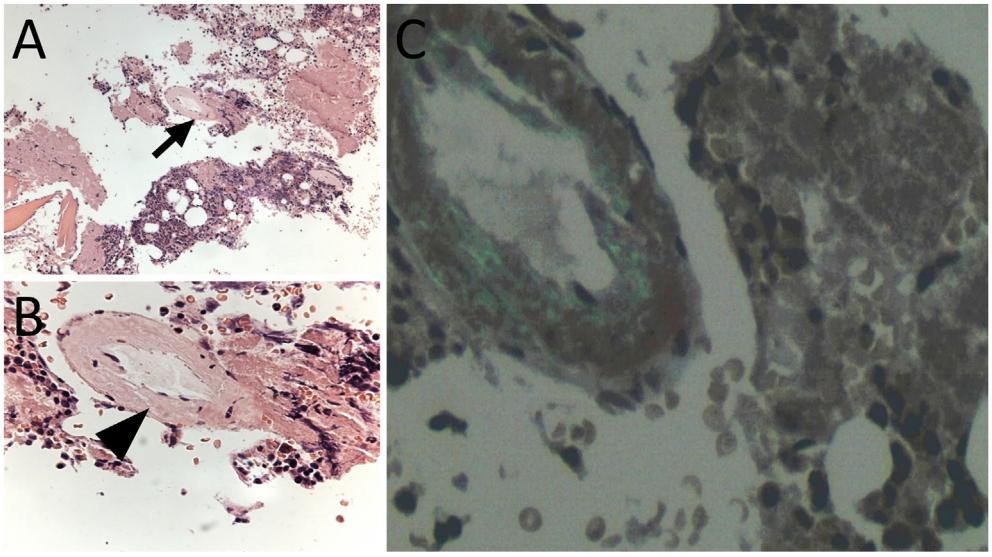

Fig. 3. Bone Marrow Histopathology. (A) H&E staining of bone marrow at 100x magnification demonstrates a vessel (arrow) with wall thickened by pink amorphous material. (B) 200x magnification demonstrates same vessel (arrowhead to thickened wall). (C) Polarized light examination of Congo red stained bone marrow biopsy at 400x magnification demonstrates apple green birefringence in vascular wall consistent with amyloid.

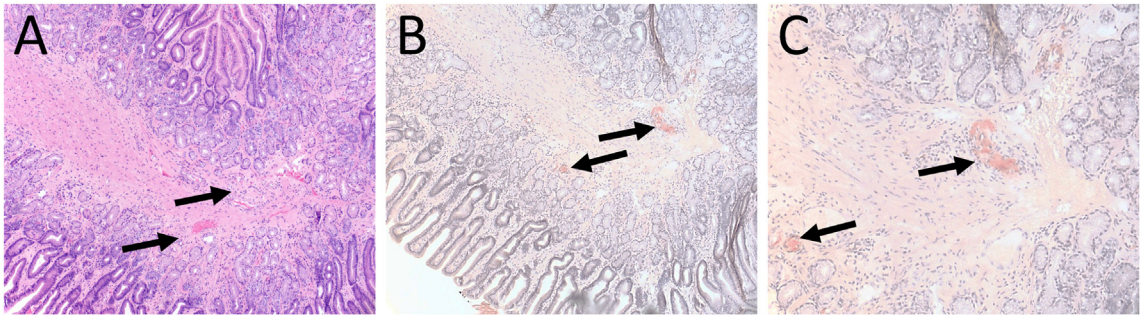

Fig. 4. Gastric Histopathology. (A) H&E staining of the gastric antrum in 100x magnification demonstrates thin layer of eosinophilic amorphous matrix around the submucosal small vessel. (B) Congo red staining of the gastric antrum in 100× magnification demonstrates submucosal perivascular amyloid deposition. (C) Congo red staining of gastric antrum biopsy in 400x magnification demonstrates perivascular orange colored amyloid protein.

To date, no medical therapy is able to reverse the deposited amyloid fibrils and treatment is directed at suppressing the underlying plasma cell dyscrasia[27] or stabilizing the potential amyloidogenic protein. Typical chemotherapeutic regimens include: bortezomib with cyclophosphamide and dexamethasone or melphalan with dexamethasone.[28-31] The addition of daratumumab, a monoclonal antibody to CD38 has been found to have a halting effect on further organ damage and hematologic progression in AL amyloid.[52] Definitive treatment for AL amyloid remains hematopoietic cell transplantation, however greater than 80% of newly diagnosed patients will be ineligible for transplant as they should meet certain criteria to be an appropriate candidate.[39]

4. Conclusion

GI deposition of AL amyloid remains a complex clinical entity with multiple sequelae. Advanced and irreversible organ dysfunction often precedes the diagnosis of gastrointestinal amyloid, which itself has non-specific symptoms. Imaging may show peritoneal involvement with our without GI pathology, with definitive diagnosis based upon detection of serum free light chains, marrow biopsy, and Congo red staining. To date, there are no specific treatment guidelines for GI amyloid.

Conflict of interest

None.

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