

Two Cases of Gastric and Esophageal Amyloidosis

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Amyloidosis is characterized by extracellular deposition of insoluble protein fibrils that stain with Congo red and appear apple green under polarized light. Resistant to proteolytic degradation, amyloid replaces and destroys normal tissue in vital organs such as the heart, kidneys, and gastrointestinal tract and can lead to early and sudden death. Amyloidosis is usually observed in a systemic form, though 10–20% of cases are localized. We report two cases of upper gastrointestinal amyloidosis that were localized.

Case #1

An 80-year-old man with multiple medical problems, including recent coronary artery bypass graft, stroke, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, carotid artery stenosis, chronic renal failure, anemia, chronic lymphocytic leukemia, and asymptomatic cholelithiasis, was admitted to a rehabilitation unit after coronary artery bypass graft surgery. His hospital course was complicated by anemia and hemoccult-positive stool. Esophagogastroduodenoscopy (EGD) showed gastritis, and colonoscopy revealed polyps, with biopsies from the colon confirming tubular and tubulovillous adenomas. Biopsies from the stomach revealed vascular amyloid deposition and mild chronic gastritis without activity. A Congo red stain was positive for amyloid in the vascular walls of the stomach but not the colon (Figure 1). Light microscopy using hematoxylin and eosin stain revealed vascular amyloid deposition in the stomach (Figure 2). Urine analysis did not reveal

proteinuria. Serum protein electrophoresis, urine protein electrophoresis, rheumatoid factor, antinuclear antibodies, and erythrocyte sedimentation rate were all normal. Several months later, the patient died from respiratory

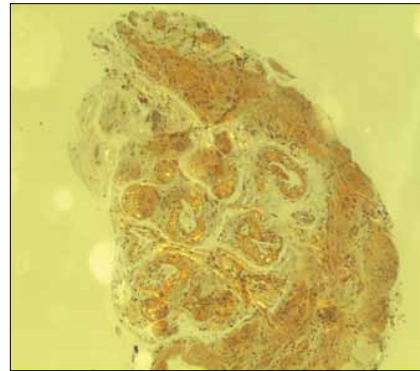


Figure 1. Gastric vascular amyloid deposition. Polarized light microscopic image with Congo red stain showing minimal apple-green birefringence, which is typical of amyloid.

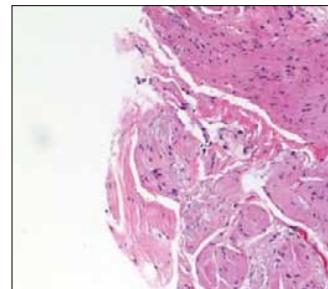


Figure 2. A light microscopic image using hematoxylin and eosin stain showing vascular amyloid deposition in the stomach.

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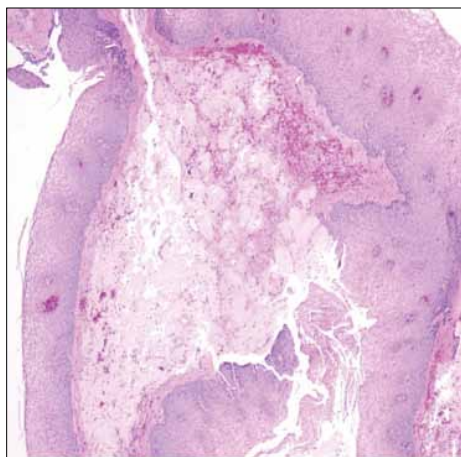


Figure 3. A light microscopic image using hematoxylin and eosin stain showing amyloid deposition in the distal esophagus.

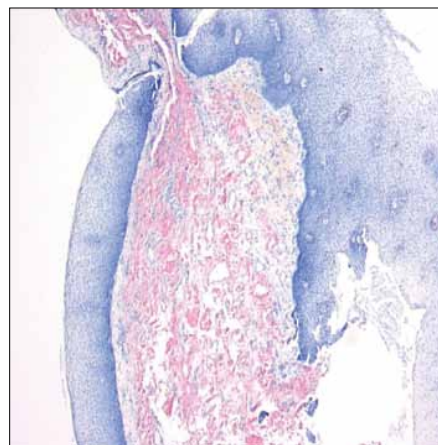


Figure 4. A light microscopic image using Congo red stain showing amyloid deposition in the distal esophagus.

failure due to congestive heart failure and pneumonia. An autopsy was not performed.

Case #2

A 70-year-old white man with a past medical history of hypertension, diverticulitis of the colon with colectomy, cholecystectomy, lumbar herniated disc repair, and appendectomy presented to us with an episode of hematemesis that occurred after a sudden onset of severe epigastric pain and retching. After this episode of hematemesis, the patient developed dysphagia and odynophagia. He denied any history of smoking or alcohol use, and his medications included daily low-dose aspirin. Physical examination revealed telangiectasias over the face and healed surgical scars on the abdomen. Laboratory work-up included normal urinalysis, normal complete blood count (except for a hemoglobin level of 11.7 g/dL), and a normal complete metabolic profile (except for a calcium level of 7.9 mg/dL and a creatinine level of 1.47 mg/dL).

EGD revealed a submucosal hematoma extending from 25 cm to 43 cm from the incisors leading to compression of half of the esophagus. Esophageal biopsies showed only necrotic and inflamed squamous epithelium. Computed tomography scan without contrast was initially performed, as his creatinine level was high, and revealed a fluid-filled dilated esophagus at the mid and inferior portions of the thorax. Repeat EGD demonstrated ulcerated squamous mucosa with marked acute inflammation. Biopsies from the stomach revealed focal intestinal metaplasia without dysplasia, and histology of the biopsy specimens from the esophagus revealed

extracellular deposition of amorphous protein material consistent with amyloid (Figure 3). Congo red stain of the esophageal biopsy specimen was strongly positive, indicating extensive amyloid deposition (Figure 4). Nothing in the history, physical examination, or laboratory results suggested secondary amyloidosis. The patient tolerated feeding after the hematoma resolved and was discharged home. Six weeks after discharge, the patient was doing well.

Discussion

There are six types of amyloidosis. The first type, or primary amyloidosis (AL), is associated with monoclonal light chains and multiple myeloma in 15% of patients.¹ The second type is secondary amyloidosis (AA), which is due to deposition of serum amyloid protein, an acute phase protein produced in the liver in response to inflammatory, infectious, or neoplastic diseases.² Examples of these diseases include rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, tuberculosis, osteomyelitis, bronchiectasis, and several reported cases of systemic lupus erythematosus overlapping with progressive systemic sclerosis and AIDS.^{3,4} The third type of amyloidosis is β_2 -microglobulin amyloid, which is a major complication of long-term renal replacement therapy that affects most patients treated for more than 15 years.^{5,6} β_2 -microglobulin is excreted by the kidneys; in renal failure, it is deposited in different organs. The fourth type of amyloidosis is hereditary—a rare type of amyloidosis that can present with hepatic involvement. These patients have elevated alkaline phosphatase and gamma glutamyl trans-

peptidase levels and may require liver transplantation later in life.⁷ The most common form of hereditary amyloidosis is caused by a mutant transthyretin protein that results in familial amyloidotic polyneuropathy.⁸⁻¹⁰ The fifth type is senile amyloidosis, which is found in elderly individuals.¹¹ The sixth type is localized amyloidosis, which has previously been reported in the stomach and esophagus.^{12,13}

The gastrointestinal tract may be primarily affected or a component of systemic amyloidosis. In a study by James and colleagues of patients with systemic AL amyloidosis of the luminal gastrointestinal tract, gastrointestinal symptoms or signs related to amyloid involvement were noted in 95% of patients. Abdominal pain, change in bowel habits, overt gastrointestinal bleeding, and complaints related to altered motility were the predominant presentations.^{14,15} Gastrointestinal amyloidosis can present as upper gastrointestinal tract bleeding,¹⁶⁻¹⁸ nausea, vomiting,^{19,20} gastric and duodenal ulcers,²¹ diarrhea, malabsorption,²² gastric outlet obstruction,¹⁹ elevated liver enzymes,⁷ peritonitis,²³ gastric and colonic perforation,²⁴⁻²⁶ local amyloid tumor¹² (gastric amyloidoma), and vitamin B12 deficiency.²⁷ Esophageal amyloidosis has variable presentations. It may present in the form of achalasia,²⁸⁻³³ esophageal spasms,³⁴ nonspecific motility disorders,³⁵⁻³⁷ and decreased lower esophageal sphincter pressure.³⁸ These motility disorders occur due to deposition of amyloid in the muscles and nerves innervating the esophagus. There are even reported cases of esophageal perforation secondary to deposition and infiltration of the amyloid in the lower esophagus.³⁹ Rarely, amyloid deposits (amyloidomas) can present as masses in the esophagus.⁴⁰

Radiologic tests such as computed tomography scans or I¹²³-labeled serum amyloid P component scintigraphy^{41,42} and endoscopic findings may be suggestive of amyloidosis; however, a tissue biopsy is necessary for diagnosis. A biopsy can be obtained from the kidney, subcutaneous fat, bone marrow, or gastrointestinal tract. Gastroduodenal biopsy is recommended for screening and diagnosing secondary or systemic amyloidosis. Kuroda and associates included a total of 1,006 rheumatoid arthritis patients in a study.⁴³ Gastroduodenal biopsies found amyloidosis in 71 patients. As amyloid deposits were detected in the specimens from both the stomach and duodenum in 69 patients and only from the duodenum in 2 patients, they concluded that gastroduodenal biopsy in patients with rheumatoid arthritis had a high positive rate for amyloid deposits. In another study by Kobayashi and coworkers, biopsy specimens were obtained from the stomach and the duodenum in 407 patients with rheumatoid arthritis, and gastrointestinal amyloidosis was confirmed in 54 (13.3%) patients.⁴⁴ The study findings suggest that gastroduodenal biopsies may be useful for diagnosing secondary amyloidosis and that

the degree of amyloid deposits appears to be correlated with the clinical manifestations of rheumatoid arthritis. Tada and associates studied 37 patients with amyloidosis involving the gastrointestinal tract.⁴⁵ Endoscopic examinations revealed fine granular appearance more often in AA type amyloidosis, polypoid protrusions mainly in AL type amyloidosis, erosions, ulceration, mucosal friability with the highest frequency in the duodenum, and 1 patient with esophageal ulceration.⁴⁶

Treatment for AL amyloidosis consists of chemotherapy and stem cell transplantation,⁴⁷⁻⁴⁹ whereas treatment for AA amyloidosis consists of controlling the underlying disease, as this step is necessary for resolution of amyloidosis.⁵⁰ There are reports of success with the use of colchicine in inflammatory bowel disease.⁵¹ Surgery may be indicated in patients with gastrointestinal bleeding, perforation, or other severe complications.

Summary

Amyloidosis is a rare disease, and diagnosis requires a high index of suspicion, particularly in the elderly population, patients with chronic inflammatory diseases, hemodialysis patients, and patients with multiple myeloma. Gastrointestinal tract involvement is more common than is generally realized, and gastroduodenal biopsy can be used for diagnosis. Esophageal amyloid deposition is less frequently reported in the literature, and the frequency is unknown. Sufficient involvement of the esophagus to produce symptoms appears to be a very uncommon manifestation.

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Review

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Amyloidosis is defined as the extracellular deposition of insoluble protein fibrils that have characteristic staining properties using Congo red.¹ There are six different types of amyloidosis. Primary amyloidosis (AL) with deposition of light chains is the most common type and is associated with multiple myeloma in 15% of cases.² Secondary amyloidosis (AA) consists of the deposition of serum amyloid A protein, an acute phase reactant produced by the liver in response to infectious, inflammatory, and, less commonly, neoplastic diseases.³ Amyloidosis associated with long-term hemodialysis involves the deposition of β 2-microglobulin, which is normally excreted by the kidneys.⁴ The rare hereditary amyloidosis is most commonly due to variant transthyretin, resulting in familial amyloidotic polyneuropathy. Senile amyloidosis is found in elderly individuals.⁵ Finally, many reports demonstrate amyloidosis localized to the esophagus,⁶ stomach,⁷ small bowel,⁸ and colon.⁹

The cases described by Shatnawei and associates illustrate localized amyloidosis in the stomach and esophagus.¹⁰ The first issue is whether these cases truly represent localized disease. AL amyloidosis is associated with monoclonal light chains, found in 89% of patients by immunoelectrophoresis with immunofixation.² In case #1, serum and urine protein electrophoresis tests were normal, arguing against AL amyloidosis, though a small M spike could be missed by this method. The lack of proteinuria also argues against AL amyloidosis, as it is present in 73–86% of cases.^{2,11} There are no inflammatory, infectious, or malignant diseases to suggest that these cases represent secondary AA amyloidosis. Chronic lymphocytic leukemia in case #1 has not been reported to cause amyloidosis. In addition, the rheumatoid factor is negative in case #1, arguing against the presence of rheumatoid arthritis, which accounts for 48% of

patients with AA amyloidosis.³ The patients treated by Shatnawei and colleagues were not on hemodialysis, and hereditary amyloidosis is rare, though senile amyloidosis is a possibility.

Localized disease is suggested by the absence of amyloidosis in the colon and stomach in cases #1 and #2, respectively. Although amyloidosis can cause a restrictive cardiomyopathy, the congestive heart failure in case #1 is likely due to ischemia, as the patient had undergone coronary artery bypass surgery. It is certainly possible that amyloid deposition may be present in other organs not sampled in these cases. For example, a bone marrow biopsy may reveal amyloidosis and multiple myeloma. To further characterize the type of amyloidosis, immunohistochemical staining could be performed. Overall, it is likely that these cases represent localized disease.

The presenting symptom and sign in case #1 was anemia and hemoccult-positive stool, whereas the symptoms and signs in case #2 were hematemesis, epigastric pain, retching, dysphagia, and odynophagia. All of these presentations have been described in systemic amyloidosis. Bleeding occurs as a presenting symptom in 25–45% of patients with amyloidosis^{1,12} and may be due to ulceration, an infiltrated lesion, ischemia, infarction, or a generalized oozing without a localized site. It is also possible that amyloid infiltration of vessels may interfere with their normal constriction and clot formation after laceration. The finding in case #2 of a hematoma causing compression of the esophagus has not been reported previously.

The diagnosis of amyloidosis was confirmed by Congo red stain in both cases. In case #1, there was minimal green birefringence under polarized light (Figure 1). In both cases, there was amyloid deposition seen with hematoxylin and eosin staining (Figures 2 and 3). Figure 4 shows the typical appearance of amyloidosis by Congo red staining under light microscopy.

Differentiating between AL and AA amyloidosis is important, as the treatment for each type differs. AL amyloidosis is treated with chemotherapy and stem cell transplantation, whereas AA amyloidosis is approached by treating the underlying disease.¹ Here, in Shatnawei's patients, the localized disease was managed.

The true incidence of amyloidosis is unknown, as only symptomatic patients are generally investigated. Gastric involvement, for example, occurs in 12% by autopsy, with only 1% being symptomatic.¹ Any gastrointestinal symptom could be a manifestation of amyloidosis, with investigational studies showing a range of abnormalities. These case reports add to the small number in the literature illustrating localized gastrointestinal amyloidosis.

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