CASE REPORT

Symptomatic involvement of the stomach and duodenum as initial presentation of AL amyloidosis

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SUMMARY

Primary systemic or amyloid light chain (AL) amyloidosis is a multisystem disorder with myriad presentations. Although it can involve the upper gastrointestinal tract in 8% of cases, symptomatic involvement is exceedingly rare. We chronicle here a case of postprandial epigastric pain associated with AL amyloidosis involving the stomach and duodenum. Pathological examination of endoscopic biopsy using Congo red staining confirmed the diagnosis. In order to establish the underlying aetiology of AL amyloidosis, the patient underwent extensive workup. Eventually, she was diagnosed with multiple myeloma based on the standard set of investigations. This paper underscores the importance of clinical suspicion of amyloidosis in patients presenting with non-specific gastrointestinal symptoms and highlights the role of endoscopic biopsy to confirm the amyloid deposition. Since gastrointestinal amyloidosis is a disease with a poor prognosis, early diagnosis and treatment are particularly warranted.

BACKGROUND

Systemic amyloidosis is a group of complex disorders characterised by the extracellular deposition of non-branching fibrils, ultimately leading to isolated or multiorgan dysfunction. Gastrointestinal (GI) involvement in amyloidosis varies depending on the subtype of the disease.^{1–5} Amyloid A (AA) amyloidosis affects GI tract in 60% of patients whereas 1%–8% of patients with amyloid light chain (AL) amyloidosis have GI infiltration.^{6–7} Although GI vascular involvement has been observed frequently, interstitial GI tract disease with concomitant symptoms and biopsy evidence is rare. In symptomatic patients with GI involvement, prompt endoscopy with biopsy facilitates early detection as histopathological evidence of AL amyloidosis is necessary for diagnosis. The common clinical presentations include oesophageal reflux, constipation, nausea and abdominal pain. Other notable symptoms are diarrhoea, weight loss and early satiety.^{8–12} GI amyloid deposits detected by endoscopic biopsy occur frequently in the duodenum followed by the stomach, colon, rectum and oesophagus.^{13–14} However, the data on amyloidosis localised to the digestive tract are still limited to case reports and small series of patients.^{15–16}

Herein, we describe the case of a female who presented with postprandial abdominal pain. Endoscopic biopsy helped to establish the diagnosis of AL amyloidosis and subsequently, multiple myeloma

was confirmed as the underlying aetiology. Additionally, this paper outlines our current understanding of the epidemiology of and risk factors for AL amyloidosis with GI involvement, the pathophysiology of this disorder and currently available approaches to diagnosis and management.

CASE PRESENTATION

A 56-year-old woman hailing from the Caribbean was referred to the gastroenterology office for evaluation of a several-week history of progressive postprandial epigastric abdominal pain. She reported accompanying early satiety, nausea, vomiting and 40-pound weight loss. She denied dysphagia, odynophagia, melena, haematochezia and use of non-steroidal anti-inflammatory drugs or steroids. Medical history was significant for long-standing hypertension, along with a recent diagnosis of heart failure and paroxysmal atrial flutter. She did not smoke, consume alcohol or use any illicit substances. She had not undergone an upper endoscopy or gastric emptying study in the past. Her family history was negative for cancer. At presentation, the patient was haemodynamically stable. Abdominal examination ruled out hepatosplenomegaly, tenderness or shifting dullness. The remaining examination demonstrated mild conjunctival pallor. No cervical or supraclavicular lymphadenopathy was appreciated.

INVESTIGATIONS

Laboratory testing revealed normocytic, normochromic anaemia (haemoglobin: 79 g/L). Complete metabolic panel was within normal limits (serum calcium: 10.1 g/dL). CT abdomen ordered by the patient's primary care physician demonstrated concentric thickening of the gastric antrum and pylorus (figure 1). There was associated diffuse mesenteric and retroperitoneal fat infiltration with no evidence of abnormalities in the liver or kidney. Moreover, no elevation in serum levels of alkaline phosphatase and creatinine was noted. On dipstick urine analysis, proteinuria was not detected. Due to the symptoms of epigastric abdominal pain, weight loss and significant radiographic findings, an oesophagogastrroduodenoscopy was performed. It showed nodularity extending from the gastric antrum and pylorus up till the second portion of the duodenum (figures 2 and 3). Multiple biopsies were obtained from these areas.

Histopathological examination of the gastric biopsy showed no evidence of atypical cells

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Figure 1 Contrast-enhanced CT abdomen showing gastric wall thickening (arrow).

but there was substantial extracellular matrix deposition (figure 4). Furthermore, biopsy specimen from the duodenum also showed submucosal deposits (figure 5). The Congo red staining was positive for the characteristic apple-green birefringence, confirming the presence of amyloid deposits (figure 6). In order to further assess the underlying aetiology of amyloidosis, we proceeded with serum protein electrophoresis. It revealed elevated serum free kappa light chains (2780 mg/dL), low free lambda light chains (62 mg/dL) and elevated kappa/lambda ratio (44.84). Bone marrow aspiration was performed to further investigate monoclonal gammopathy. It showed increased cellularity with 30%–60% plasma cells. Echocardiography showed ejection fraction of 37% with sparkling myocardium, suspicious for cardiac amyloidosis. Cardiac magnetic resonance imaging showed changes consistent with infiltrative cardiomyopathy, which was in congruence with systemic amyloidosis.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for diffuse nodularity observed on endoscopic examination of the stomach and duodenum include

Figure 2 Upper endoscopy demonstrating mucosal thickening in the stomach.

Figure 3 Endoscopic appearance of the duodenum demonstrating nodular, thickened folds.

underlying malignancy, hypertrophic gastropathy, infiltrative disorders such as amyloidosis and sarcoidosis, and infections such as tuberculosis. On the basis of histopathological findings, the most likely cause was amyloidosis in this patient. However, due to the associated cardiomyopathy, mild anaemia and hypercalcaemia, there was a concern for monoclonal gammopathy as the underlying aetiology of AL amyloidosis. The diagnosis of multiple myeloma was confirmed based on multisystem involvement with evidence of end-organ damage, an increased kappa free light chains and elevated kappa/lambda ratio with very low serum free lambda light chains, and bone marrow aspiration demonstrating significant plasma cytosis.

TREATMENT

The patient underwent cardioversion for atrial flutter. She remained in sinus rhythm thereafter. The delayed-release metoprolol therapy was continued. Due to tenuous blood pressure and underlying infiltrative cardiomyopathy, addition of ACE inhibitors was not recommended. After the diagnosis of multiple

Figure 4 Biopsy of gastric tissue demonstrating significant stromal soft tissue deposits with no evidence of mucosal atypia (H&E staining; x100).

Figure 5 Photomicrograph of the biopsy of the duodenum showing submucosal deposits (H&E staining; x100).

myeloma, treatment with cyclophosphamide, bortezomib and dexamethasone (CyBorD) was initiated.

OUTCOME AND FOLLOW-UP

One month ago, the patient successfully completed third cycle of CyBorD therapy, without any remarkable adverse events. However, she required hospitalisation for volume overload due to congestive heart failure, necessitating intravenous diuretic therapy. Her tenuous blood pressure precludes maximisation of medical therapy for heart failure. Due to underlying multiple myeloma, she is currently not a candidate for heart transplantation.

DISCUSSION

Amyloidosis is a broad term used for a group of uncommon disorders that cause structural and functional organ dysfunction with anomalous extracellular deposition of abnormally-folded peptide derivatives.¹ These amyloid deposits are composed of insoluble fibrils that are generated as a result of abnormal conformational changes in the soluble protein subunits and

their combinations in antiparallel beta-pleated sheets.² Amyloidosis is a disease that can present with systemic or localised organ involvement. Primary and secondary amyloidosis are the more frequently encountered systemic subtypes. Primary or AL amyloidosis mostly occurs as a stand-alone disorder or in association with multiple myeloma, with the deposited fibrils composed of immunoglobulin light-chain subunits. Secondary or AA amyloidosis results from chronic inflammatory processes that increase the levels of acute-phase reactant, serum amyloid A (SAA), with the deposited fibrils comprising SAA subunits. Furthermore, dialysis-related disease, heritable and senile amyloidosis are other systemic subtypes. We present here a case of multiple myeloma-associated AL amyloidosis with symptomatic stomach and duodenal involvement, which is an extremely rare clinical entity.³

The epidemiology of amyloidosis is incompletely assessed owing to rarity of the condition, the wide spectrum of aetiologies and varied clinical presentation. In addition to that, genetic polymorphism encoding amyloid precursors as well as prevalence of aetiologies such as local infections and autoimmune disorders that predispose to chronic inflammation vary in different regions in the world. Therefore, these factors potentially confound the assessment of global incidence. According to one estimate, the annual incidence of amyloidosis in the USA is approximately 2200 cases.⁴ However, symptomatic amyloidosis involving GI tract is a rare, diverse and a difficult condition.⁵ In a case series of 769 patients with biopsy-proven AL amyloidosis, GI disease was noted in 8% while symptomatic stomach involvement was present in only 1% of the cases.⁶ In secondary amyloidosis, about 60% of the patients can demonstrate GI involvement.^{7,8} Systemic AL amyloidosis was observed as the most common cause of GI amyloidosis with 50 of the 76 biopsy-proven cases having immunoglobulin light chains.⁹ It has been reported that 98% of the patients with amyloidosis will have subclinical GI disease and 50% of the patients with GI involvement will have symptomatic disease.¹⁰ However, symptomatic AL amyloidosis with subsequent biopsy evidence, as in the present case, has been documented only in a handful of case reports thus far.

The clinical presentation of GI amyloidosis is mostly dominated by abdominal pain, heartburn, weight loss, malabsorption, GI bleed, reflux, diarrhoea and/or vomiting.^{11,12} In patients with hepatic involvement, jaundice, anorexia and/or steatorrhoea have also been reported. In a retrospective study specifically conducted on patients with AL amyloidosis with GI involvement, a median delay of 7 months was observed in the diagnosis.¹³ The most frequent clinical presentation was weight loss (median: 7 kg), which was followed by diarrhoea.^{13,14} In prior research, it is a well-established clinical fact that the deposition of extracellular amyloid causes organ dysfunction, resulting in signs and symptoms of the disease. In patients with GI involvement, the development of the clinical features is explained variably. Diarrhoea and malabsorption are observed in AA amyloidosis due to the frequent mucosal infiltration observed in these patients. GI obstruction, heartburn and bleeding are more common in AL amyloidosis owing to the involvement of muscularis mucosa in this subtype.¹⁵ Although relatively less frequent, gastroparesis may occur in both subtypes secondary to neuromuscular infiltration and dysfunctional intestinal contractility.

In patients with primary amyloidosis involving GI tract, white-light or chromoendoscopy features can be deceptive and non-specific.¹⁶ The findings in the stomach can easily mimic gastric malignancy, rugal thickening, gastritis, ulcers and/or erosions.^{17–19} In a study of 30 participants with small intestinal amyloidosis, endoscopic features like thickening of the valvulae

Figure 6 Histopathological analysis of gastric specimen showing apple-green birefringence consistent with amyloid deposits (Congo red staining; x10).

conniventes and polypoid mucosal protrusions were associated with AL amyloidosis ($P<0.001$) whereas fine-granular appearance, erosions and mucosal friability were the more dominant findings in AA cases ($P<0.001$).²⁰ However, it is considerably difficult to establish the diagnosis of GI amyloidosis on endoscopy alone as several studies showed no clear correlation between endoscopic features and the disease.^{21 22}

Endoscopic biopsy and appropriate pathological staining are vital for the diagnosis. AL amyloidosis can involve the muscularis mucosa, submucosa or muscularis propria, but these changes may not be confluent. Therefore, in order to increase the diagnostic yield, multiple endoscopic biopsies are recommended from both the upper GI tract and large intestine for detection of AL kappa and AL lambda amyloidosis, respectively.²³ The histopathological analysis of the biopsy specimen with Congo red stain is gold standard for confirmation of the diagnosis. Apple-green birefringence and red staining with Congo red are pathognomonic findings in these cases. Abdominal fat tissue aspirate has specificity of up to 100% and sensitivity of up to 73% in cases of AL amyloidosis.²⁴ Rectal biopsy also has a sensitivity of up to 85%.²⁵ A bone marrow biopsy is necessary to establish the diagnosis of plasma cell dyscrasias when suspecting systemic amyloidosis. Elevated kappa/lambda light chain ratio after electrophoresis measurements and urinary Bence-Jones proteins support the diagnosis of multiple myeloma. It is imperative that the patients with AL amyloidosis who have initial presentations related to GI tract should also undergo screening for cardiac and renal disease.

The standard criteria for best therapy have not yet been established. According to existing data, the tolerability, efficacy and rapid activity of drug regimens are important considerations in regard to the choice of therapy. Treatment of the monoclonal gammopathy is indicated when organ involvement with primary systemic amyloidosis is confirmed.²⁶ A combination therapy with melphalan, dexamethasone and bortezomib has been found to have good biochemical response with a significant improvement in survival in cases with multiple myeloma and related AL amyloidosis.^{27 28} In the present case, we added cyclophosphamide to this regimen. For the management of GI symptoms, supportive management is indicated. It helps to maintain quality of life, delay organ failure and prolong survival as specific therapy requires time to take effect after initiation. In selected patients with irreversible organ damage, solid organ transplantation and/or stem cell transplantation are considered. However, organ transplantation remains contentious because of the multisystem nature of AL amyloidosis and risk of recurrence in the graft.²⁹

The prognosis of AL amyloidosis involving the stomach and duodenum is largely dependent on the underlying aetiology and the nature, number, and extent of the organ involvement. In essence, involvement of the GI tract usually implies extensive disease. In a prospective study of 137 patients, Lim *et al* demonstrated median overall survival duration of 7.95 months in patients with GI involvement compared with 15.84 months in patients without GI involvement.³⁰ Similarly, AL amyloidosis causing GI disease has a poor long-term prognosis (median survival: 4–6 months) when detected at an advanced stage, with cardiac disease, renal dysfunction and infection being the major causes of death. In one series of patients with primary amyloidosis, 51% of deaths occurred due to heart failure whereas renal failure and infection accounted each for 15%.³¹ On the other hand, patients with limited organ involvement can expect a median survival in excess of 5 years with currently available therapy. Hence, the key prognostic factors that affect the

outcome of AL amyloidosis include the presence and severity of cardiac involvement and the presence of concurrent myeloma.

Learning points

- ▶ Gastrointestinal infiltration is common in systemic amyloidosis and it should be suspected in affected patients presenting with non-specific symptoms.
- ▶ A clinical presentation suggestive of amyloidosis must be evaluated by electrophoresis (serum and urine) and immunofixation.
- ▶ While performing histopathological examination of the endoscopic biopsy specimens, amyloid light chain amyloidosis should be considered in the differentials; apple-green birefringence and red staining with Congo red are pathognomonic findings.
- ▶ In these patients, amyloid subtype and extent of involvement determine the therapeutic regimen. However, supportive measures remain the mainstay of treatment for the gastrointestinal symptoms of this disease.

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