

Gastrointestinal amyloidosis occurring in three different patterns: Case series

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Abstract

Systemic amyloidosis is a rare disease characterized by extracellular accumulation of amyloid protein in one or more organs. In patients with systemic amyloidosis, the most frequently affected organs are kidney and heart, followed by the nervous system, soft tissues, and lungs. Small bowel and liver involvement are also frequent in systemic amyloidosis. Gastrointestinal (GI) findings are common, and the degree of organ involvement determines the symptoms. Patients usually have nonspecific findings such as abdominal pain, nausea, diarrhea, and dysphagia, which may delay the appropriate diagnosis. Liver involvement occurs in the majority of patients, but the symptoms typically do not happen unless a marked hepatic amyloid deposition occurs. Diagnosis is by tissue biopsy. Treatment and prognosis depend on the underlying disease. GI system involvement is a sign of poor prognosis. In this case series, five patients who were diagnosed with gastrointestinal system amyloidosis in our clinic are presented.

Keywords: Amyloidosis; Gastrointestinal System; Liver; Cholestasis; Diarrhea.

INTRODUCTION

Systemic amyloidosis is a rare disease characterized by extracellular accumulation of amyloid protein in one or more organs (1). In patients with systemic amyloidosis, the most frequently affected organs are kidney and heart, followed by the nervous system, soft tissues, and lungs (2). Small bowel and liver involvement are also frequent in systemic amyloidosis (3). Protein accumulation is mostly seen in the mucosa, submucosal connective tissue, muscularis propria, and blood vessel walls (2). This accumulation causes some symptoms by disturbing both the structure and function of the affected organs. Although the presentation of systemic amyloidosis is different and depends on the degree of organ involvement, common clinical manifestations of gastrointestinal (GI) amyloidosis are weight loss, bleeding, gastroesophageal reflux, constipation, diarrhea and abdominal pain (2).

This study aimed to review the gastrointestinal system amyloidosis by presenting patients with cholestasis, chronic diarrhea and ascites due to gastrointestinal system (GIS) amyloidosis.

CASE REPORT

Case 1

A 54-year-old male patient was admitted to the outpatient clinic with complaints of weakness, weight loss and yellowing of the skin. There was no pathologic finding except jaundice.

Laboratory investigations: creatinine 1.5 mg / dL, total protein 5.0 mg / dL, albumin 1.9 g / dL, total bilirubin 5 mg / dL, direct bilirubin 3.9 mg / dL, AST 63 U / L, ALP 711 IU / L, GGT 1901 U / L and sedimentation measured 56 mm (Table 1). Liver parenchyma was slightly rough and heterogeneous, and lobes were lobulated in abdominal ultrasound. In the ERCP, choledochus was normal, and intrahepatic bile ducts were seen to be rickety. It was attempted to elucidate the etiology of chronic liver disease in the patient; Elisa, autoimmune hepatitis panel, and p-anca results were negative. Liver biopsy was consistent with amyloidosis. Serum Amyloid A positivity was found in the biopsy taken from the rectum for amyloid type (Figure 1 A-B-C). Familial Mediterranean fever (FMF) gene analysis result was normal. Rheumatologic diseases were excluded in rheumatologic examination and tests. Chest

Received: 08.02.2019 Accepted: 06.03.2019 Available online: 26.03.2019

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X-ray and tuberculin skin test performed for tuberculosis were normal. The reason for secondary amyloidosis could not be explained. Approximately two months after the onset of symptoms, the patient died due to sepsis.

Case 2

A 65-year-old male patient presented to the outpatient clinic with complaints of loss of appetite and weight loss. In the history of the patient, it was learned that he developed anorexia for the last three months and developed a weight loss of approximately 15 kg. No pathological finding was found in PE.

Laboratory investigations: Hgb 12 g / dL, CRP 5 mg / dL, total protein 4.8 mg / dL, albumin 1.5 g / dL, total bilirubin 2.8 mg / dL, direct bilirubin 2.3 mg / dL, AST 66 U / L, ALT 68 U / L, ALP 526 U / L, GGT 621 U / L were measured (Table 1). Abdominal ultrasound showed heterogeneous liver parenchyma and a mild lobule with contours. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, and choledochus and intrahepatic bile ducts were normal. Liver biopsy was performed to investigate the etiology of chronic liver disease and to assess the status of fibrosis. Amyloid positivity was found in the liver biopsy. Serum IgG levels were 1.5 times higher than normal levels. Serum Amyloid AL was positive in the biopsies taken from the patient's colon and rectum (Figure 1 D-E).

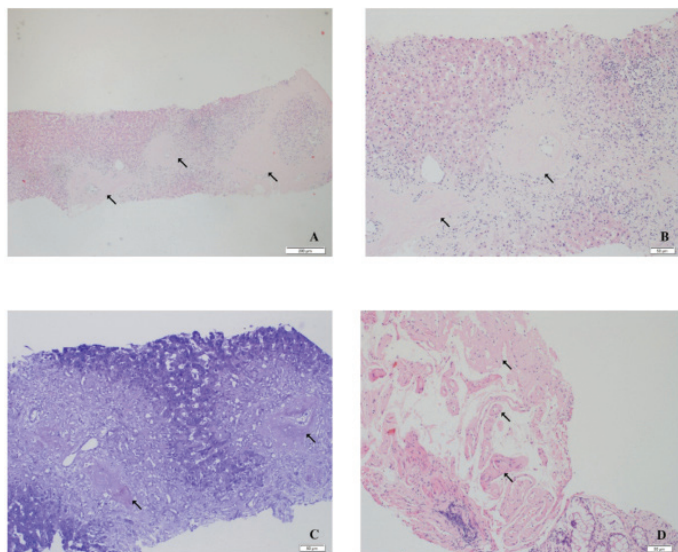


Figure 1. (A-B). Periportal and centrilobular pink, amorphous accumulation in the parenchyma for liver needle biopsy specimen (H&E), (C) The presence of amyloid with crystal violet, (D) Pink, amorphous accumulation in submucosal vessel walls (H&E), (E) The presence of amyloid with crystal violet(arrows)

Bone marrow biopsy revealed plasma cell dyscrasias. The patient was transferred to the hematology clinic. The patient died three months after the diagnosis of amyloidosis.

Case 3

A 54-year-old male patient was admitted to the outpatient clinic with complaints of diarrhea and weight loss of 20 kilograms (kg). There was no known disease or drug use in his history. Physical examination (PE); his general condition was moderate-bad, cachectic, and bilateral + 2 pretibial edema was present.

Laboratory investigations: Hgb 10.9 g / dL, creatinine 1.62 mg / dL, total protein 5.8 mg / dL, albumin 2.4 g / dL were found (Table 1). Gaita microscopy was normal, and stool cultures were negative. Endoscopy and colonoscopy were performed to explain the etiology of chronic diarrhea, and both were considered normal. Amyloid positivity was detected in all biopsies taken from the patient's duodenum, terminal ileum, transverse colon and rectum (Figure 2 A-B). Serum amyloid A was positive and serum amyloid AL was negative. Abdominal computed tomography revealed hepatomegaly. The patient's amyloidosis primer could not be disclosed, and the patient died due to cardiac insufficiency in a short time.

Table 1. The first laboratory values when admitted according to patients

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
Hb (gr/dl)	10.9	12	14.3	13.5	11.7
ESR (mm/h)	23	39	56	57	33
Crea (mg/dl)	1.6	0.7	1.5	0.5	0.4
AST (U/L)	18	66	63	93	96
ALT (U/L)	16	68	40	193	59
ALP (U/L)	59	526	711	969	604
GGT (U/L)	60	621	1901	1092	380
BLB (mg/dl)	0.3	2.8	5	0.7	1.3
Alb (gr/dl)	2.4	1.5	1.9	0.9	2.8

Hb: Hemoglobin; ESR: Erythrocyte Sedimentation Rate, Crea: Creatinine, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, GGT: Gamma Glutamyl Transpeptidase, BLB: Total Bilirubin, Alb: Albumin

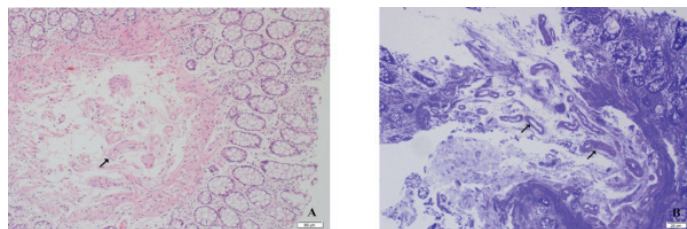


Figure 2 (A-B). Hematoxylin and eosin (H & E) stained biopsy sections of the large intestine revealed a more prominent pink, amorphous, and waxy amyloid deposition of the subepithelial perivascular. An apple green refle was seen in polarized light with Congo Red(arrows)

Case 4

A 46-year-old female was admitted to the outpatient clinic with a complaint of swelling of the abdomen and legs. PE revealed ascites and pretibial edema. The patient was hospitalized for examination.

Laboratory investigations: total protein 7.5 mg / dL, albumin 0.9 g / dL, LDH 2737 U / L, AST 93 U / L, ALT 193 U / L, ALP 969 U / L, GGT 1092 U / L, ascites albumin 0.4 g / dL, ascites total protein was measured as 0.8 mg / dL and serum-ascites albumin gradient was 0.5 (Table 1). +4 urinary proteinuria in the complete urine test and 29 g / day proteinuria was detected in 24-hour urine. Radiological imaging revealed no additional findings except ascites. The current status of the patient was evaluated as nephrotic syndrome. Kidney biopsy was performed to determine the etiology of nephrotic syndrome. AL amyloidosis was detected. Bone marrow biopsy was evaluated as multiple myeloma. Approximately two months after the onset of patient complaints, she died due to sepsis.

Case 5

A 65-year-old female patient with known FMF disease presented to the outpatient clinic with complaints of abdominal pain. Physical examination revealed sensitivity in the right upper quadrant of the abdomen, and amylase and lipase elevation in laboratory tests. The patient was hospitalized with a diagnosis of acute pancreatitis.

Laboratory investigations: total protein 5.6 g / dL, albumin 2.8 g / dL, ALT 59 U / L, AST 96 U / L, ALP 604 U / L, GGT 380 U / L, amylase 666 U / L, lipase 1642 U / L and Hgb 11.7 g / dL were measured (Table 1). Abdominal ultrasound showed normal choledochus and millimeter stones were observed in the gallbladder lumen. The patient's current status was evaluated as biliary pancreatitis. Acute pancreatitis improved in follow-up. Because of the onset of respiratory distress, chest X-ray was performed, and bilateral pleural fluid was observed. Thoracentesis was performed, and the fluid sample was evaluated as transudate. The patient was referred to rheumatology, and a lip biopsy was performed for amyloidosis. AA amyloidosis was detected. Colchicine treatment was started. Approximately three months after the onset of patient complaints, she died due to sepsis.

DISCUSSION

Amyloidosis has several main forms. AL amyloidosis (primary) is caused by the accumulation of protein produced from immunoglobulin light chain fragments of AL amyloid, formed by a plasma cell dyscrasia (4). AA amyloidosis (secondary) is a potential complication of chronic diseases, including continuous or recurrent inflammation, leading to the generation of serum amyloid A (5).

In developed countries, AL is the most common type of systemic amyloidosis, whereas in developing countries AA amyloid is more common. This condition is a result of a higher incidence of chronic infectious diseases such as tuberculosis, leprosy, and osteomyelitis (6). AL amyloidosis was detected in two of our cases, and AA

amyloidosis was found in three of our cases. Multiple myelomas were detected in patients with AL amyloidosis. The causes of chronic infection of secondary amyloidosis patients were investigated, and tuberculosis and other causes were ruled out. One of the three patients with secondary amyloidosis was considered as FMF, and the other two patients died before the underlying disease was found.

GIS amyloidosis is frequently associated with symptoms such as weight loss, diarrhea, abdominal pain, malabsorption, gastro-esophageal reflux and fatal upper and lower GI system bleeding (7). In three of our patients, weight loss was common, but in one case there was diarrhea, while in two cases there was jaundice. One of the remaining two cases had abdominal distension, and the other had abdominal pain.

The most common sites of mucosal infiltration are the second part of the duodenum (100 percent), the stomach and the colorectum (> 90 percent), and the esophagus (approximately 70 percent) (8). In the amyloidosis of AL, the amyloid accumulated in the muscularis mucosa, submucosa and muscularis propria causes polypoid protrusions and thickening of the mucosa. AL amyloidosis is usually characterized by constipation, mechanical obstruction or chronic intestinal pseudo-obstruction. In AA amyloidosis, granular amyloid deposition occurs mainly in the mucosa and results in a fine granular appearance, mucosal fragility, and erosions (9). One of the patients with AL amyloidosis had diarrhea. One of our cases with AA amyloidosis had diarrhea, and one had constipation. The present findings were consistent with the literature data.

Neuropathic symptoms such as nephrotic syndrome, congestive heart failure or orthostatic hypotension occur in about 80% of cases (1). In two patients, hypoalbuminemia induced ascites, pleural fluid, and pretibial edema were observed due to nephrotic syndrome and malabsorption. In two cases, malabsorption related cachexia was present.

Liver amyloidosis is characterized by amyloid deposits present in the liver stroma or liver vascularity. In some cases, hepatocyte damage and biliary drainage disorder may develop due to pressure from the high amyloid accumulation (10). Patients presenting with the complaint of jaundice constitute only a small portion of all GIS amyloidosis presentations. In a review by Kyle et al., comparing 229 cases with clinical features, it was shown that patients presenting with jaundice constitute only 4% of GIS amyloidosis (11). Therefore, the cholestatic amyloidosis that we present is becoming more significant.

The diagnosis typically requires biopsy and special dyes to identify the amyloid infiltration and the specific structure of amyloid protein infiltration (12). Three of five patients had rectum biopsy, one patient had a kidney biopsy, and one patient had a lip biopsy. We found liver involvement in two patients who underwent liver biopsy.

The primary treatment of amyloidosis is the treatment of

the underlying disease, such as malignancy, infection or autoimmune disease, which causes the accumulation of amyloid precursors (13).

Prognosis depends on the underlying etiology of the accumulation of amyloid and also on the degree of organ involvement. AL amyloidosis typically has a worse prognosis because of its association with underlying malignancy. In a prospective follow-up of 137 patients with AL amyloidosis, there was a median survival of 15.8 months for those without GI involvement, while in those with GI involvement it was 7.9 months (14). In a study evaluating 374 AA amyloidosis patients, a mean survival of 133 months was determined. The presence of hepatic amyloidosis in the study has been shown to increase the risk of death 1.9 times (15). All of our patients died approximately two months after the diagnosis.

CONCLUSION

Treatment and prognosis depend on the underlying disease. GI system involvement is a sign of poor prognosis.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports

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