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Case Report

Light chain (AL) amyloidosis following gastrointestinal symptoms that involve multiple organs: a case report

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Abstract

Light chain (AL) amyloidosis is a complex and rare disease characterized by low incidence and diverse clinical manifestations. At the time of diagnosis, most patients exhibit involvement of multiple organs or tissues, leading to severe illness and a poor prognosis. Therefore, early diagnosis, active treatment, and a comprehensive assessment of the disease hold paramount importance. The initial presentation of this rare condition often manifests as gastrointestinal symptoms, posing challenges in clinical identification and differential diagnosis. In this case report, we describe a 70-year-old man with AL amyloidosis, initially misdiagnosed as irritable bowel syndrome and colon polyps. Subsequently, he experienced a series of complications including renal function impairment, pulmonary nodule, pleural effusion, mediastinal lymph node enlargement, spleen enlargement, reduction of white blood cells, red blood cells and platelets, and small intestinal obstruction. Despite multiple pulmonary nodule biopsy and lymph node biopsy, as well as concurrent splenectomy and partial resection of the small intestine, a clear diagnosis remained elusive. Before admission, diarrhea was aggravated, accompanied by emaciation and fatigue. Following the completion of serum immunofixed protein electrophoresis, renal biopsy, bone marrow and rectal biopsy, a conclusive diagnosis of AL amyloidosis involving multiple organs (Mayo 2012 revision stage III) was finally confirmed after a 12-year period. Treatment with proteasome inhibitors, immunomodulators, and glucocorticoids was recommended. The patient underwent methylprednisolone treatment and was discharged after symptom

improvement. However, eight months into the follow-up, the patient succumbed to multiple organ failure. The repeated misdiagnoses over the past 12 years were attributed to limited perspectives among some specialists who did not conduct a systematic and detailed medical history analysis or comprehensive physical examinations. Additionally, they did not strictly follow the principle of "monism" in diagnosis. On the contrary, early diagnosis and active treatment of the disease are of great significance to improve the prognosis.

INTRODUCTION

AL amyloidosis has been recognized as a group of diseases due to the production of monoclonal immunoglobulin light chain or light chain fragments by plasma cells in the bone marrow, in which amyloid deposition is associated with tissue and organ damage in the patients. AL amyloidosis features a low incidence and complex clinical manifestations that result in a high rate of misdiagnosis. The digestive tract symptoms reported in this disease are rare and difficult to diagnose. In this context, we report a case of AL amyloidosis that involved multiple organs with the onset of digestive tract symptoms, which mainly present as chronic diarrhea and colonic polyps.

CLINICAL CASE

A 70-year-old man was admitted to the Department of Gastroenterology of our hospital on November 3, 2021, complaining of recurrent abdominal pain and diarrhea persisting for more than 12 years, with worsening symptoms in the past year. At the beginning of November 2009, the patient presented with abdominal distending pain without obvious inducement. He described intermittent middle and lower abdominal pain that did not radiate to the waist. Additionally, he had been experiencing low-volume diarrhea (2-3 stools/d) with no blood in the stools and no nausea or vomiting.

The patient was initially treated in a subordinate hospital S. Laboratory analysis reported proteinuria and colonoscopy showed chronic colitis with colon polyps. In September 2012, he was hospitalized in a superior hospital G due to persistent cough. A contrast-enhanced chest CT at this hospital revealed nodules measuring 13 mm in the upper lobe of the right lung, along with bilateral pleural effusion. The pathological report demonstrated no cancer on a smear (mediastinal lymph node biopsy fluid) or on the print (mediastinal lymph node biopsy). No alveolar cavities were observed in certain lung tissue (right lung biopsy tissue). Fibrous tissue hyperplasia was observed in the alveolar septum, accompanied by chronic inflammatory cell infiltration. Immunohistochemistry results showed positive staining for CD3 (+), CD20 (+), CD34 (+), CK (+), TTF1 (+), Ki67 (+ ≤ 10%), and Congo red staining (weak positive). Bone marrow aspiration showed no obvious abnormalities.

In 2013, this patient underwent a splenectomy for spleen enlargement and thrombocytopenia at the hospital S. In 2014, the patient underwent partial resection of the small intestine resection for intestinal obstruction. In the past year, the patient reported abdominal pain and recurrent diarrhea (7-10 stools per day, small volume, no blood) with dizziness and weakness in the limbs.

The patient was admitted to another superior hospital X in March 2021. A colonoscopy showed rectal polyps and sigmoid erosions. Sigmoid pathology showed chronic inflammation of the mucosa. Rectal pathology showed adenomatous polyps. Chest, abdominal, and pelvic contrast-enhanced CT showed a mass in the anterior upper lobe of the right lung (15 × 14 mm) with multiple lymph node enlargements in the mediastinum, abdominal cavity, and retroperitoneum.

The regulation of the patient's bacterial flora was not effective, leading to his hospitalization at hospital S in April 2021. Subsequently, the patient underwent a gastroscopy, which showed gastric retention and non-atrophic gastritis. Colonoscopy showed a sigmoid polyp EMR and pathology showed a tubular adenoma. Color thyroid ultrasonography showed a goiter with hypoechoic nodules in the right lobe of the thyroid (T-radS3 class) and cervical lymph node enlargement. The treatment of a colon polyp EMR, regulation of flora, and protection of the intestinal mucosa proved to be ineffective.

In June 2022, the patient was hospitalized at the hospital H. Contrast-enhanced CT of the chest, abdomen, and pelvis showed a mass in the anterior upper lobe of the right lung (12 × 15 mm) with lymph node enlargement in the mediastinum. A small amount of effusion was observed in the abdominal and pelvic cavities, along with gallstones. Changes in the bilateral adrenal glands and hyperplasia of the spleen were not observed. Electrocardiogram showed sinus rhythm with first-degree heart block, left axis deviation, and high anterochronous transposition. I, II, and avF presented QS wave changes. Proteinuria was identified through urinary analysis. Liver function tests revealed a total protein level of 33.2 g/L and an albumin level of 33.2 g/L. Routine blood analysis showed a red blood cell count of $3.33 × 10^{12}$ /L, hemoglobin at 103 g/L, and a platelet count of $292 × 10^{12}$ /L. Then, the patient came to our hospital for further diagnosis and treatment. Specifically, the patient had experienced a weight loss of 15 kg in the past year.

Physical examination

The patient's blood pressure fluctuated between 80-70 and 50-40 mmHg. Signs of chronic emaciation and anemia were evident. The patient exhibited yellowing of the skin, along with a rash and hemorrhage. Physical indications included hypertrophy of the tongue, enlarged superficial lymph nodes, pale palpebral conjunctiva, and thick double lung auscultation breathing. The heart rate was measured at 74 beats per minute. Moreover, there was a surgical scar with pigmentation on the abdominal wall, accompanied by abdominal tenderness. Notably, no rebound pain or muscle tension was observed. The patient was negative for Murphy's sign with no palpation under the liver ribs, no ascites, and no percussion pain in both of the kidneys. Bowel sounds were active, occurring at a rate of 6-8 times/min, and pigmentation with slight edema was observed in both lower limbs.

Laboratory and auxiliary examinations

The results of blood routine and laboratory biochemical examination are shown in Table 1. Additionally, the blood fat analysis showed a total cholesterol level of 2.03 mmol/L and a complement C3 of 59.30 mg/dL. All other analytes were normal (including electrolytes, blood glucose, myocardial enzymes, serum procalcitonin, gastrin-releasing peptide precursor, serum gastrin, immunoglobulin G4, serum protein electrophoresis, immunofixationelectrophoresis, serum adrenocorticotropic hormone, total prostate-specific antigen, blood Epstein-Barr virus, and serum vascular endothelial growth factor).

The following blood results were collected: (auto-antibody determination: antinuclear antibody detection titer 1: 80, positive for antinuclear antibodies, anti-SSA, anti-SSB, anti-mitochondrial Type 2 IgG, anti-double-stranded DNA antibody, anti-nucleosome antibody, anti-Sm antibody, anti-cardiolipin antibody IgG, anti-U1nrNP antibody, anti-ScL-70 antibody, anti-J0-1 antibody, anti-histone antibody, anti-centromeric antibody, anti-PM-Scl antibody, anti-ribosomal P protein antibody, and anti-proliferating cell nuclear antigen).

Chest and abdominal contrast-enhanced CT revealed the following conditions: (1) IgG4-associated pancreatitis (Type I) with multiple involvements extending into the external pancreas (thyroid, lung, adrenal, jejunum, lymph nodes, and portal hepatis), mediastinum, and abdominal fluid; (2) gallstones; (3) cirrhosis with multiple microcysts in the liver and kidneys; (4) Postoperative changes in the spleen observed in the lumbar and vertebral PVP.

Table 1. The tested parameters of the patient

| Laboratory examinations	Parameter	Value	Unit	Reference value
Blood routine	Lymphocyte number	1.56	10^9/L	0.8-4.0
	Lymphocyte percentage	21.6	%	17-48
	Red blood cell count	2.59	10^{12}/L	3.5-5.5
	Hemoglobin	86	g/L	120-160
	Average volume of red blood cells	94.6	fL	80-97
	Average hemoglobin	33.2	pg	26.5-33.5
	Platelet	217	10^9/L	100-300
Biochemical data	Total protein	50.2	g/L	60-80
	Albumin	29.6	g/L	35-55
	Globulin	20.6	g/L	20-30
	Urea nitrogen	12.8	mmol/L	7-20
	Urinary microalbumin	1817.5	mg/L	4.28-18.14
	Angiotensin II (decubitus)	77.42	pg/mL	28.2-52.2
	Renin activity (decubitus)	2.09	pg/mL	0.32-1.84
	β2 microglobulin	5.66	mg/L	0-0.65
Other results	Hypersensitive troponin-I	131.28	pg/mL	< 26
	B-type cerebral natriuretic peptide	1232.5	pg/mL	< 100
	Blood immunoglobulin light chain Lambda	2.14	g/L	0.9-2.1
	Blood immunoglobulin light chain Kappa	3.4	g/L	1.7-3.7
	Urine light chain Lambda	35.3	mg/L	≤ 5.35
	Urine light chain Kappa	44.8	mg/L	≤ 15.2
	Bence-Jones protein	-	/	-

An epigastric plain scan and magnetic resonance cholangiopancreatography detected the following issues: (1) Pancreatitis, cholangitis (intrahepatic bile duct), edema in the convergence area and mesentery, retroperitoneal fibrosis with multiple enlarged retroperitoneal lymph nodes and abdominal fluid; (2) Inflammatory nodules in the lower segment of the right posterior lobe of the liver; (3) gallstones and cholecystitis; (4) Changes after splenectomy; (5) Thickening of the ventricular septum and bilateral pleural effusion.

Colonoscopy [Figure 1A and B]: Light chain amyloidosis of the rectum. Rectal pathology [Figure 2A-C] showed chronic inflammation of the mucosa with amyloidosis (Congo red staining positive). Immunohistochemistry for CD38 showed scattered positive plasma cells and the kappa/lambda ratio was 3:1.

Color Doppler ultrasonography showed dilatation of the two chambers of the heart and aortic sclerosis with thickening of the ventricular septum and the posterior wall of the left ventricle (17 mm) [Figure 3A and B]. Mild regurgitation in the pulmonary and mitral valves was observed. Moderate regurgitation in the tricuspid valve with reduced left ventricular compliance was also noted. However, normal systolic function was recorded. Renal biopsy [Figure 4A-F] identified amyloidosis, which was consistent with nephropathy. Immunofluorescence results showed the expression of lambda light chain restriction, indicative of AL amyloidosis nephropathy. Positive staining was evident for Congo red (+) and lambda (3+) kappa (+), while staining for IgG4 was negative.
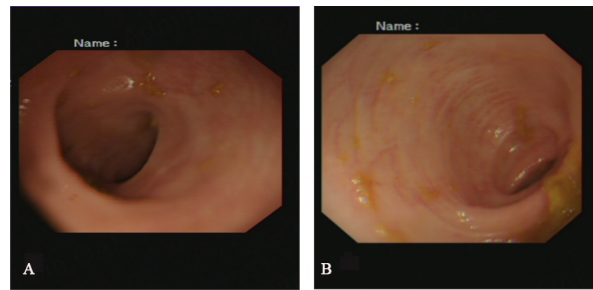
Figure 1. Results of the colonoscopy. (A) rectal mucosa was smooth, vascular network was blurred, and no erosion, bleeding and nodular hyperplasia were found; (B) the lower sigmoid colon was smooth, vascular network was blurred, and no erosion, bleeding and nodular hyperplasia were found.
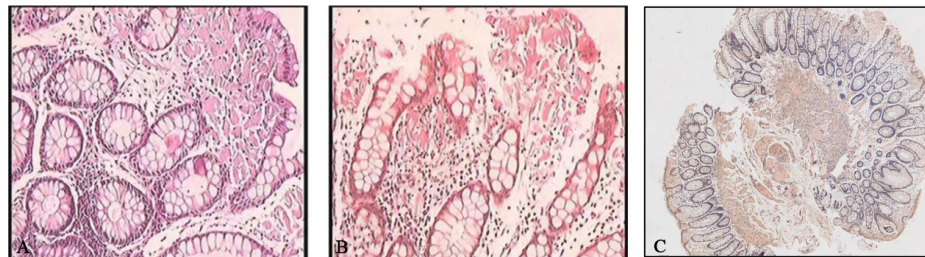
Figure 2. Pathology and immunohistochemistry. (A) chronic inflammation of mucosa with amyloidosis; (B) immunohistochemistry: CD38 showed scattered positive plasma cells, with a Kappa/Lambda ratio of about 3:1; (C) Congo red staining positive.
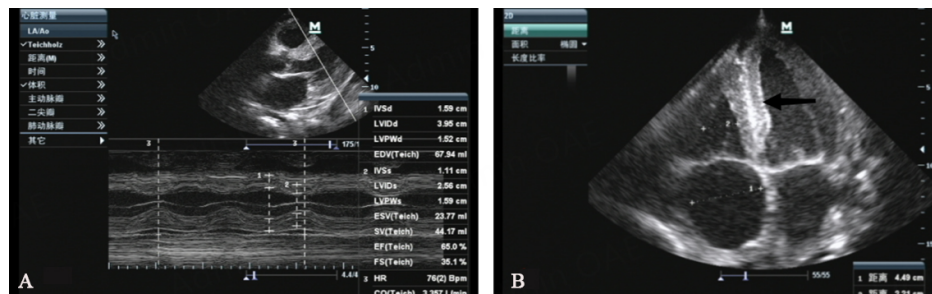

Figure 3. Echocardiographic examination results. (A-B) Atrial dilatation, aortic sclerosis, ventricular septum and posterior wall of left ventricle thickened about 17 mm, pulmonary valve mild regurgitation, mitral valve mild regurgitation, tricuspid valve moderate regurgitation, left ventricular compliance decreased, systolic function measured normal.

Bone marrow flow cytometry showed that 2.07% of the plasma cells exhibited monoclonal hyperplasia, with a karyotype 46, XY (20). Subsequent bone marrow FISH using a 1q21 amplification probe yielded negative results. Additionally, tests using deletion probes for RB1, D13S319, and p53 were negative, as was the IGH separation probe. Multiple lesions indicative of peripheral neuropathy were observed.

Following a multidisciplinary team (MDT) consultation, a diagnosis of primary systemic light-chain amyloidosis with multi-organ involvement (Mayo 2012 revision stage III) was established, prompting the patient's transfer to the Department of Hematologic Oncology for further treatment. Given the patient's advanced age and compromised health, treatment involved a combination of proteasome inhibitors, immunomodulators, and glucocorticoids.
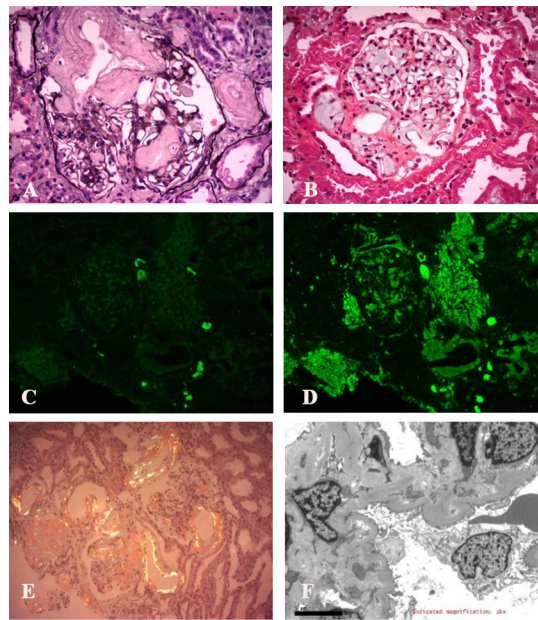
Figure 4. Pathology and immunohistochemistry. (A-B) the mesangial area of the glomerulus is enlarged and the nodular changes are seen with HE staining (× 400); (C-D) A: Light chain lambda and kappa deposits in glomeruli and arteriole (× 400); (E) Polarized light microscopy shows apple green refracting in glomeruli positive for Congo red staining (× 400); (F) Electron microscopy shows slender, disordered amyloid fibril deposition.

DISCUSSION

AL amyloidosis is a group of diseases where amyloid deposits cause damage to tissues and organs, yet the pathogenesis remains unknown. The incidence of AL amyloidosis is low and typically affects individuals between in 53-56 years old, with males constituting about 55% of the affected population[1]. However, in China, large-sample epidemiological data about AL amyloidosis patients are currently lacking. Domestic studies have reported an incidence of 0.03%, while foreign studies have indicated an incidence of 0.08%-0.8%, highlighting the rarity of this disease in clinical settings.

In cases of AL amyloidosis, the involvement of the digestive system most frequently occurs in the stomach and small intestine, leading to symptoms such as abdominal discomfort, diarrhea, malabsorption, and gastrointestinal bleeding. Approximately 8% of cases experience gastrointestinal changes such as dyspepsia, obstruction, and constipation. Liver involvement is characterized by hepatomegaly and elevated levels of alkaline phosphatase. Moreover, other organs including the kidneys and heart, and physiological systems such as blood and nervous system are also affected in these patients.

Histopathologic examinations are the gold standard for the diagnosis of amyloidosis, with commonly biopsy sites including the liver, kidney, intestine, and skin. Combining bone marrow biopsy with samples from affected organs can significantly improve diagnostic accuracy. However, performing multiple biopsies is not recommended due to the potential risk of unnecessary bleeding. Echocardiography is often used to screen for myocardial amyloidosis due to its ease of use. For patients with myocardial amyloidosis, cardiac magnetic resonance imaging has become the preferred imaging method. Additionally, blood and urine immune-fixed electrophoresis plus Congo red staining is an important diagnostic method.

The diagnostic criteria for primary systemic amyloidosis[2] include typical clinical manifestations and signs indicating affected organs, monoclonal immunoglobulin in blood and urine, positive Congo red staining in biopsy samples, and the confirmation of amyloid light chain components through immunohistochemistry. Except multiple myeloma, lymphoma, and so on. This patient fulfills the diagnostic criteria for primary systemic light chain amyloidosis.

Currently, effective treatments for AL amyloidosis are lacking, and the main reference treatments are those used in multiple myeloma. Patients with amyloidosis affecting multiple organs or tissues should receive systemic therapy as soon as possible to achieve hematologic and organ remission. Early diagnosis and prompt treatment are crucial for prognosis. A hematologic remission rate of 71% has been reported in amyloidosis treatment using subcutaneous injections of bortezomib/dexamethasone. This treatment exhibits a low rate of peripheral neurotoxic reactions while demonstrating efficacy similar to intravenous administration. Combining lenalidomide, pomalidomide, and other immunomodulators with bortezomib can significantly enhance hematological and organ remission rates in patients. Statistics indicate that 40% of patients died two years after diagnosis[3]; the primary cause of death was either the inability of patients' hearts to tolerate high-intensity chemotherapy[4] or a lack of response to treatment.

Studies have shown that t (11; 14) is a prognostic factor in the treatment of AL amyloidosis with proteasome inhibitors and immunomodulators. Additionally, 1q21 amplification in the bone marrow is recognized as an adverse prognostic factor in the treatment of AL amyloidosis with melphalan/dexamethasone and Daletumab/dexamethasone[5,6]. After 3 months, there was a hematologic complete response in 64% of cases and a partial response in 48%; in comparison, the combined use of bortezomib treatment resulted in response rates of 66% and 55%, respectively[6].

After 6 months, 22% of patients treated with Daletomumab/dexamethasone and 26% of those receiving Daletomumab/dexamethasone/bortezomib experienced cardiac reactions. In a recent study[7], daratumumab (DARA) monotherapy or combined with bortezomib or lenalidomide in the treatment of relapsed/ refractory AL amyloidosis and high bone marrow plasma cells resulted in a complete blood response of 16%, a partial response of 42%, a cardiac response of 29%, and a renal response of 60%. In China, Xianghua and colleagues[5] observed a blood response rate of 84.2% in the treatment of relapsed refractory AL amyloidosis. Both studies demonstrated significant partial responses or better outcomes. These findings suggest that the effectiveness of DARA in the Chinese population mirrors that in European and American populations. Adverse reactions to this drug are infrequent, mostly infusion-related, and typically occur within 2 hours after infusion. Further validation is needed to ascertain the efficacy and safety of DARA in patients with severe organ involvement.

In summary, AL amyloidosis is associated with a range of clinical manifestations and is common in patients with primary light chain type plasma cells. This condition often affects multiple organs, notably the heart and kidneys, and nervous system. Potential treatments for AL amyloidosis include proteasome inhibitors, immune modulators, targeted drugs, and autologous or allogeneic hematopoietic stem cell transplantation.

DECLARATIONS

Author contributions
Contributed to the conception and design of the study: Chen Y, Wang Z, Zhou H
Organized the database: Pi X
Performed the statistical analysis: Yuan S

Wrote the first draft of the manuscript: Tang X
Wrote sections of the manuscript: Liao Y, Wen X
Contributed to the manuscript revision and read, and approved the submitted version: Chen Y, Wang Z, Pi X, Yuan S, Tang X, Liao Y, Wen X, Zhou H

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
This retrospective review of patient data did not require ethical approval inaccordance with local/national guidelines. Written informed consent has beenobtained from the spouse of this deceased patient for publication of this case reportand accompanying images.

Consent for publication
Not applicable.

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