A Rare Case of Secondary Systemic Amyloidosis in a Young Patient with Crohn's Disease: A Case Report

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Abstract

Amyloidosis in Crohn's disease is rare and an unexpected and late problem. We describe the case of a 28-year-old man with Crohn's disease who did not receive active treatment. The patient was admitted to the hospital with symptoms of acute glomerulonephritis. Swelling of the upper and lower extremities and facial pastosities were also observed. Amyloidosis was suspected based on echocardiography findings. The biopsy was taken during colonoileoscopy. According to the results of histological examination, homogeneous eosinophilic masses were observed to stain red-brown when stained with Congo Red, indicating amyloidosis. The patient's condition gradually deteriorated and the disease ended in death. No autopsy was performed. Further amyloid typing revealed AA amyloidosis. The lack of adequate therapy is probably the reason for the development of such a rare extraintestinal manifestation of Crohn's disease as secondary systemic amyloidosis (AA amyloidosis). A delay in the diagnosis of amyloidosis may adversely affect the prognosis of patients.

Keywords: Case Report; AA-Amyloidosis; Secondary Systemic Amyloidosis; Inflammatory Bowel Disease; Crohn's Disease

Introduction

AA-amyloidosis is a rare serious complication that often occurs as a result of some chronic inflammation.[1] Amyloid deposits in AA amyloidosis consist mainly of serum amyloid A protein, which is synthesized by hepatocytes in response to transcriptional incentives of various proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha.[2,3] Other cytokines may also be associated with amyloidogenesis. IL-10 is an immunoregulatory cytokine,[4] and its elevation is significantly associated with amyloid deposition.[5]

Neutrophil to lymphocyte ratio (NLR) is a reliable marker of polymorphonuclear leukocytes (PMNL).[6] This indicator may be useful in predicting the development of amyloidosis.[7] Transforming growth factor-β1 (TGF-β1) is the most important regulator of immune homeostasis.[8] Increased expression of TGF-beta1 can initiate or promote amyloidogenesis.[9]

Some indices of the general blood test may indicate possible amyloidosis. For example, low mean platelet volume and high red cell distribution width can be observed in amyloidosis.[10-12]

Inflammatory bowel disease (IBD) can be a cause of amyloid deposition.[1,13] Amyloidosis in Crohn's disease (CD) can be either a late or early complication. The activity of the underlying disease is an important factor in the development and progression of secondary amyloidosis.[1,13]

AA amyloidosis is six times less common than AL amyloidosis, so the condition is often not diagnosed in a timely manner.[14] This complication usually develops gradually and is detected unexpectedly during the course of the patient's illness, so there is not enough time to collect all the necessary data to make a correct diagnosis.

We present a clinical observation of a patient with CD who has an extraintestinal manifestation such as secondary systemic amyloidosis. We conducted this study in compliance with the principles of the Declaration of Helsinki. Publication of this case report was approved by the Institutional Review Board of S.S. Yudin City Hospital (Protocol #7, October 4, 2023).

Case Report

A 28-year-old man was admitted to the hospital with complaints of weakness, marked edema, thirst. The patient had been suffering from CD for several years. Since 2015, the patient has experienced diarrhea almost every day, sometimes with blood. He was not actively treated. Notably, azotemia without urinary syndrome was noted in 2021. In August 2022, the patient noted the onset of lower extremity swelling, thirst and dry mouth. On September 9, abdominal pain and diarrhea appeared. Three days later the patient lost consciousness.

On admission, the patient's condition was severe. Skin color is pale pink, skin moisture is increased, cyanosis is absent. Facial pastosity and pale peripheral edema of the upper and lower extremities are noteworthy (Figure 1A). In addition, a bruise-hematoma type of bleeding in the neck, axillary areas, and lumbar region is detected (Figure 1B, C). Blood pressure 159/104 mmHg. Urination by catheter, macrohematuria, oligoanuria.

Figure 1: Objective examination of the patient. (A) Peripheral edema of the lower extremities. (B) Bruise-hematoma type of bleeding in axillary areas. (C) Bruise-hematoma type of bleeding in the lumbar region.

Clinical blood analysis revealed anemia, thrombocytopenia, leukocytosis, eosinophilia, lymphocytopenia, absolute monocytosis. In the biochemical analysis of blood, creatinine and urea levels are increased, the levels of total protein and albumin are reduced. There is an increase in the level of C-reactive protein (Table 1). IgG antibodies to Coronavirus (SARS-CoV-2) were detected. In the general urinalysis: proteinuria >3 g/l, leukocyturia - 125.0 /µl, hematuria - 200.0 /µl. Daily urinalysis showed proteinuria >3 g/day.

Table 1: Patient's laboratory findings on admission.

Variable	Value	Reference values
	Complete blood count	
Hb (g/L)	89	120-140
RBC (10^12/L)	2.93	3.70-4.90

Ht (%)	27.2	34.7-47
WBC (10^9/L)	18	4.0-9.0
#NEUT (10^9/L)	12.96	1.8-6.6
%NEUT	72	44.0-72.0
#EOS (10^9/L)	4.14	0.04-0.58
%EOS	23	0.5-5.0
#LYMP (10^9/L)	1.62	1.26-3.2
%LYMP	9	19.0-45.0
#MONO (10^9/L)	1.39	0.09-1.01
%MONO	7.7	3.0-11.0
PLT (10^9/L)	109	180-320
MPV (fl)	7	8-11
%RDW	14	11,5 - 14,5
	Biochemistry	
ALT (U/L)	3.4	0.0-40.0
AST (U/L)	17.9	0.0-40.0
Creatinine (mqmol/L)	757.2	53.0-106.0
Urea (mmol/L)	25.2	2.5-7.4
Total bilirubin (mqmol/L)	14.8	3.0-20.5
Fe (mqmol/L)	8.1	8.1-28.3
Glucose (mmol/L)	4.5	3.9-6.0
Total protein (g/L)	33.8	64.0-82.0
Albumin (U/L)	18.9	34.0-50.0
K (mmol/L)	4.82	3.5-5.10
Na (mmol/L)	130	135-145
Procalcitonin (mqg/L)	>0.5	0.00-0.50
CRP (mg/L)	116.37	0.00-5.00
	Coagulogram	
INR	1.72	0.8-1.3
Prothrombin time (sec)	20.6	12.0-17.0
aPTT (sec)	39.1	23.0-35.0

RBC, red blood count; Hb, hemoglobin; RBC, red blood cell count; Ht, hematocrit; WBC, white blood cell count ; #NEUT, absolute count of neutrophils; %NEUT, percent of neutrophils; #EOS, absolute count of eosinophils; %EOS, percent of eosinophils; #LYMP, absolute count of lymphocytes; %LYMP, percent of lymphocytes; #MONO, absolute count of monocytes; %MONO, percent of monocytes; PLT, platelet count; MPV, mean platelet volume; RDW, Red cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fe, iron; K, potassium; Na, Sodium; CRP, C-reactive protein; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

On admission electrocardiography: sinus tachycardia, incomplete right bundle branch blockade, myocardial changes in the lateral wall of left ventricle (LV). Computed tomography of the chest organs: polisegmental areas of "frosted glass" with single foci of consolidation in the right lung. The heart is dilated, signs of hydropericardium and ascites. Ultrasound examination revealed: echo signs of free fluid in the abdominal cavity; diffuse changes in renal parenchyma.

Colonoileoscopy revealed that during the proximal 15 cm the mucosa was completely scarified. The mucosa in the preserved areas is pastous, vulnerable, with multiple submucosal hemorrhages. The described changes correspond to the picture of a severe course of CD.

Echocardiography from the same day revealed aortic wall thickening, slight decrease in global contractility of LV myocardium, marked hypertrophy of LV myocardium, left atrial enlargement, as well as initial signs of mild mitral stenosis. LV ejection fraction is 50%. When performing the study, myocardial "granularity" was noticed.

A repeat colonoyleoscopy was performed. The mucosa of the examined parts of the sigmoid colon was scarified, with deep ulcers. The conclusion was made: "CD, negative dynamics". During the study a biopsy

of the rectal mucosa was taken: edema of rectal mucosa, diffuse weakly expressed lymphoplasmocytic infiltration, gland atrophy and deposits of homogeneous eosinophilic cell-free masses in the subepithelial layer and around the glands were found. When staining with Congo Red, staining of homogeneous eosinophilic masses in red-brown color was observed, which indicated amyloidosis (Fig. 2).

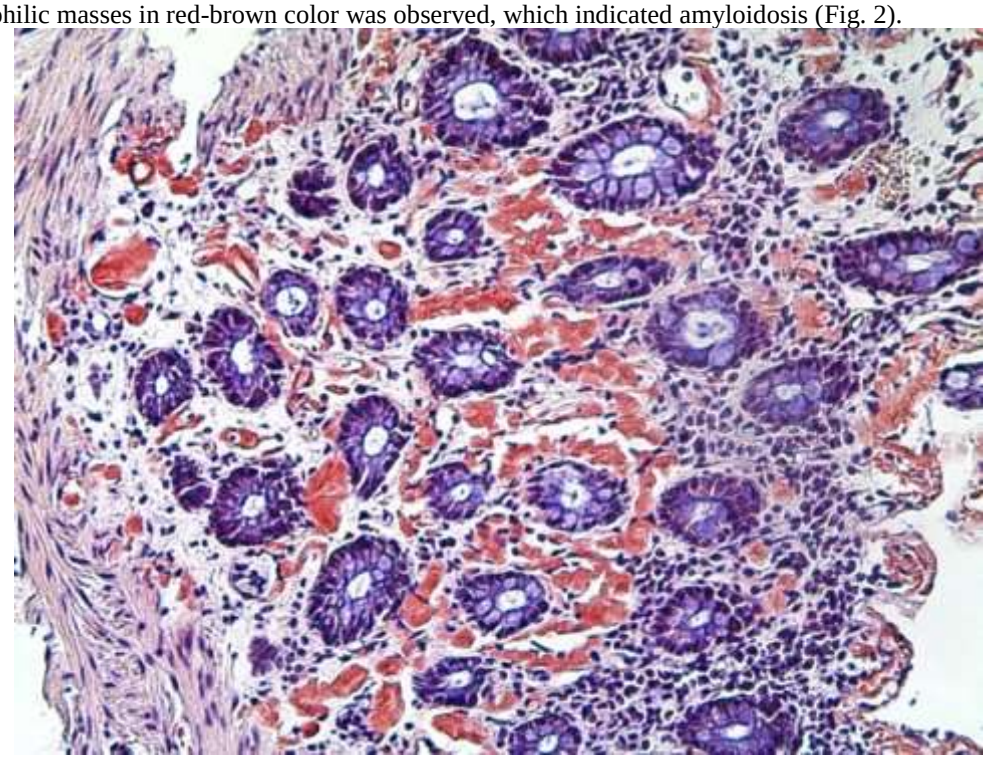

Figure 2: Histologic image of biopsy material of colon mucosa, Congo Red staining. Staining of homogeneous eosinophilic masses in red-brown color (CRx200).

Due to a severe attack of CD, he was treated with prednisolone 2 mg/kg/day and sulfasalazine 1500 mg 4 times daily. Due to the presence of leukocytosis, positive procalcitonin test, infiltration in the lungs, meropenem treatment was performed. Antihypertensive therapy with amlodipine. Renal replacement therapy was started. Metoprolol 25 mg 2 times a day was prescribed due to the revealed changes on echocardiography.

The severity of the patient's condition was conditioned by mixed nephrotic syndrome. Persistent inflammatory syndrome was most likely associated with a severe attack of CD and accession of urinary tract infection and pneumonia. Despite antibacterial treatment, multiple foci of consolidation and "frosted glass" type infiltration in both lungs with negative dynamics were detected on computed tomography images of the chest organs polysegmentally. Antibacterial and antifungal treatment was carried out (polymyxin 100 mg 2 times a day, tigecycline 100 mg 1 times a day intravenously, biseptol 9560 mg 2 times a day intravenously).

Due to the severe condition and increasing signs of acute respiratory failure, tracheal intubation was performed and artificial ventilation was started. The patient fell into coma. The condition worsened due to cytotoxic brain edema, dislocation syndrome. A few days later after ineffective cardiopulmonary resuscitation, the patient died. No autopsy of the body was performed due to the relatives' statement.

After the patient's death, typing of amyloid detected in biopsy specimens of the colonic mucosa was performed. Immunofluorescence study using antibodies to Kappa and Lambda light chains yielded negative results (Fig. 3A, B). Immunohistochemical examination of the samples by immunoperoxidase immunoassay using antibodies to the A component of amyloid revealed marked expression in areas of amyloid deposition (Fig. 3C). AA amyloidosis was confirmed.

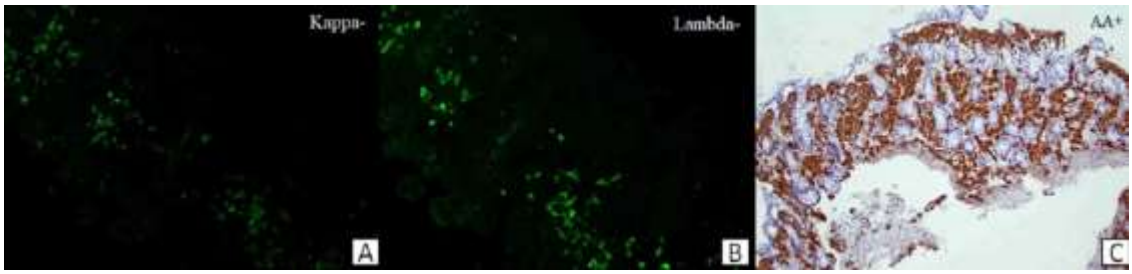

Figure 3: Amyloid typing. (A) Immunofluorescence study using antibodies to Kappa light chains yielded a negative result. (B) - Immunofluorescence study using antibodies to Lambda light chains yielded a negative result. (C) - Immunohistochemical examination of specimens by immunoperoxidase immunoassay using antibodies to the A component of amyloid revealed marked expression in areas of amyloid deposition (x100).

Discussion

IBD (CD and ulcerative colitis (UC)) is associated with a variety of extraintestinal manifestations, at least one of which may be present in 36% of patients with IBD. Secondary systemic amyloidosis is a very rare extraintestinal manifestation of CD and UC.[1,15] IBD is among the group of diseases most strongly associated with the development of AA-amyloidosis.[13] Information on the epidemiology of AA-amyloidosis associated with IBD is still very scarce. The frequency in the United States was estimated to be 0.9% in patients with CD and 0.07% in patients with UC.[16] However, recent data indicate that the prevalence of AA-amyloidosis in hospitalized patients with IBD is much lower than previously reported and is similar in patients with CD (0.02%) and in patients with UC (0.02%).[1]

As we know from our patient's history, even a year before the onset of renal symptoms, there was azotemia in the tests, which could indicate some parenchymatous renal damage already at that time. During hospitalization, one of the main reasons for the severity of the condition was kidney damage (in addition to the exacerbation of CD). For example, in a study conducted in Egypt, 24% of patients in the IBD cohort (n=896) developed renal dysfunction during 10 years of follow-up. Nephrotic (37%) or subnephrotic (17%) proteinuria was the most frequent manifestation. One of the most frequent findings on renal biopsy was renal amyloidosis (26%).[17]

Secondary systemic amyloidosis is known to affect multiple organ systems.[14] All studies agree that the kidney is a key target organ in secondary amyloidosis.[18] Proteinuria leading to nephrotic syndrome and renal failure is the earliest and most frequent clinical manifestation that should raise suspicion of AA-amyloidosis in patients with chronic inflammatory conditions. Proteinuria is present in 95% of patients and determines prognosis.[3,19] More than 75% of patients with renal amyloidosis have peripheral edema: this is due to nephrotic syndrome, renal failure, heart failure or a combination of these.[20] Renal replacement therapy or kidney transplantation is often required.[18] There are reports of sickle cell glomerulonephritis in patients with AA-amyloidosis. The authors state that this type of glomerulonephritis can be suspected in these patients if there is a rapid progressive deterioration of renal function.[21] Our patient had peripheral edema several months before hospitalization, and objective examination revealed facial pastosity. The swelling subsequently spread to the point of developing anasarca. According to the data of objective and laboratory studies, it can be concluded that there is a mixed nephrotic syndrome. Despite the absence of a lifetime renal biopsy and the impossibility of pathologic examination, it cannot be excluded that the renal damage in this patient is associated with AA-amyloidosis.

Secondary systemic amyloidosis can also affect the heart. Cardiovascular damage in amyloidosis is polymorphic.[22] Criteria for the diagnosis of amyloid heart disease are defined as LV wall thickening > 12 mm without a history of high systemic blood pressure and at least one of the following features: atrial dilatation, pericardial effusion, and restrictive-type heart failure. In addition, some patients show such a "typical" sign of amyloidosis as granular shiny echogenicity.[22,23] The results of a Japanese single-center study showed that cardiac involvement was a major predictor of adverse outcomes in renal amyloidosis.[24]

In our patient's case, there were no pronounced cardiovascular symptoms, but it was the echocardiographic findings that raised the possibility of amyloidosis.

Amyloidosis of the lower respiratory tract is less common. Diffuse alveolar-septal form of pulmonary amyloidosis may be a consequence of systemic amyloidosis. This condition should be suspected in the absence of positive dynamics and atypical course of certain pulmonologic diseases.[25,26] Duration and character of changes in the lungs of the patient make us think that the cause of these changes is not only pneumonia. Possible pulmonary amyloidosis cannot be excluded in this case.

The patient had been suffering from CD for about 8 years, but had not received adequate therapy all this time. This is probably the reason for the development of such a rare extraintestinal manifestation of CD as secondary systemic amyloidosis (AA-amyloidosis). Although the incidence of amyloidosis in IBD is low, it should still be excluded, especially in patients with prolonged uncontrolled inflammatory activity and in the presence of clinical symptoms of renal failure. Obviously, a delay in the diagnosis of amyloidosis may adversely affect the prognosis of patients with IBD. It is very important to know and remember about this problem and to be vigilant in detecting early signs and symptoms to prevent disease progression and initiate timely adequate treatment

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