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A Rare Case of Ascites due to Peritoneal Amyloidosis

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Statistical Analysis C
Data Interpretation D
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Patient: Male, 65
Final Diagnosis: Peritoneal amyloidosis
Symptoms: Anasarca • Dyspnea • Orthopnea
Medication: —
Clinical Procedure: Paracentesis and peritoneal biopsy
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: The clinical manifestations of amyloidosis depend on the type of insoluble protein as well as the location of amyloid deposits in tissues or organs. In the gastrointestinal tract, the small intestine is the most common site of amyloid deposits, whereas peritoneal involvement and ascites are rare.

Case Report: We report on a case of ascites due to peritoneal amyloidosis. A 65-year-old patient was admitted to our institution due to anasarca and pulmonary congestion, mimicking heart failure. We started the patient on diuretics and vasodilators. Despite improvement in pulmonary congestion and peripheral edema, his ascites was not reduced. Echocardiogram revealed restrictive cardiomyopathy and a speckle-tracking pattern suggestive of cardiac amyloidosis. Subcutaneous and peritoneal biopsies revealed amyloidosis.

Conclusions: Amyloidosis is rare in the peritoneum and is usually asymptomatic. Ascites occurs in only 20% of patients with peritoneal amyloidosis. We searched PubMed using "ascites" and "amyloidosis" and identified only eight case reports of amyloidosis with ascites. Physicians should be particularly careful in heart failure and anasarca cases when ascites is disproportional or not responsive to diuretic treatment. To date, there is no specific treatment for peritoneal amyloidosis.

MeSH Keywords: Amyloidosis • Ascites • Heart Failure • Peritoneal Diseases

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/898357

Background

Amyloidosis is a rare systemic disease that occurs via extracellular deposition of insoluble protein (amyloid) in healthy tissues or organs, leading to their dysfunction [1]. Amyloid is identified on histologic sections using Congo red dye, which displays the classical green birefringence when observed under polarized light. However, many authors have demonstrated that examining Congo red stained sections under fluorescent light can have a superior sensitivity, especially in the presence of small quantities of amyloid [2,3].

Differences in amyloid fibril structure leads to classification of amyloidosis into various subtypes. The most common subtypes are amyloid light chain (AL), also called primary amyloidosis and is related to cell dyscrasia; protein amyloid A (AA) amyloidosis, also called secondary amyloidosis and is related to chronic inflammatory diseases, and beta 2 microglobulin [4]. The most commonly affected tissues are the heart, kidney, and gastrointestinal tract [5]. Clinical manifestations depend on the type of insoluble protein as well as the tissue or organ location of the protein deposit. In the gastrointestinal tract, the small intestine is the most common site of amyloid deposits, whereas peritoneal involvement and ascites are rare [4]. We report on the case of a patient with primary amyloidosis, who had amyloid deposits in the peritoneum, myocardium and subcutaneous tissue, and massive ascites.

Case Report

A 65-year-old male patient was admitted to our institution due to anasarca, dyspnea and orthopnea, mimicking heart failure. He had a history of hypertension, diabetes mellitus, atrial fibrillation, and chronic kidney disease. Moreover, his medical record showed hospitalization for heart failure in the last year. During his current admission, his blood pressure was 168/84 mmHg, heart rate was 49 beats per minute, respiratory rate was 26 breaths per minute, and axillary temperature was 36°C. There was marked jugular vein distension, diminished vesicular murmur at the right lung base, and crackles at the left lung base. Abdominal distention due to massive ascites and symmetrical lower leg edema were noticeable. Laboratory analysis showed microcytic and hypochromic anemia, reduced estimated glomerular filtration rate, and polyclonal profile in serum protein electrophoresis (Table 1). Resting electrocardiogram showed sinus rhythm, atrioventricular first-degree block (PR interval was 320 ms) and prolonged QRS interval duration (150 ms) due to bifascicular block (right bundle branch block and left anterior fascicular block).

The patient was started on vasodilators and loop diuretics. Lower leg edema improved thereafter but ascites did not. Transthoracic echocardiography strain rate analysis showed reduced systolic function as well as diastolic dysfunction. The presence of greater impairment of basal longitudinal strain than in the apical segments was a clue to amyloidosis (Figure 1). Diagnostic paracentesis presented serum albumin gradient of 0.2. Abdomen and pelvis computed tomography (CT) showed ascites and peritoneal thickening; liver, spleen, and kidney aspects were normal.

Table 1. Laboratorial parameters.

Parameter	Admission	30 days later
Hemoglobin (g/L)	88	99
Leukocytes (cells/mm^3)	7,800	6,300
Platelets (plats/mm^3)	415,000	188,000
Creatinine (µmol/L)	295	229
Sodium (mmol/L)	138	132
Potassium (mmol/L)	4.6	4.3
Chloride (mmol/L)	104	100
Magnesium (mmol/L)	0.98	0.94
Total serum protein (g/L)	63.1	59.3
Albumin (g/L)	19.5	19.3
AST (IU/L)	45	36
ALT (IU/L)	19	13
ALP (IU/L)	234	191

ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Subcutaneous tissue biopsy of the left iliac fossa was performed. Laparoscopy with liver and peritoneal biopsies was also performed. During surgery, 10 liters of ascitic fluid were drained. Peritoneal liquid looked foamy and brownish. No specific macroscopic lesions in the peritoneal cavity were seen. The samples were fixed in 10% neutral buffered formalin and processed in paraffin following standard methods. Hematoxylin-eosin slides were examined, and 5-µm thick sections were also stained by Congo red dye and examined under fluorescence microscopy with a Zeiss microscope using the blue excitation filter for fluorescein isothiocyanate. Amyloid was detected in the peritoneal sample, stained a characteristic bright red-orange (Figure 2). There was a small nodule in the subcutaneous sample (15 mm) that revealed steatonecrosis and giant cell reaction. Amyloid was detected not only in the interstitium but also in the giant cells cytoplasm. No amyloid was detected in the liver sample. Immunohistochemical stains were performed using the antibodies kappa and lambda light chains immunoglobulins that showed non-specific background immunostaining result. Bone marrow biopsy was normal.

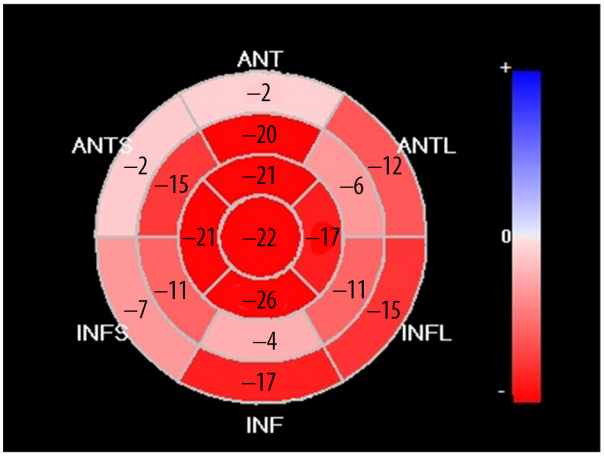

Figure 1. Bull's eye display of segmental peak-systolic longitudinal strain showing greater impairment of basal segments than apical ones. ANT – anterior; ANTL – anterolateral; ANTS – anteroseptal; INF – inferior; INFL – inferolateral; INFS – inferoseptal.

The patient's symptoms improved with diuretics and repeated therapeutic paracentesis. The patient was discharge to follow-up care at our outpatient clinic. Lower leg edema and ascites were still present, but of much lower intensity. In addition, he still complained of effort dyspnea and was able to carry out only home activities, such as eating and bathing. The patient was prescribed furosemide, hydralazine, nitrate, digoxin, and long-acting insulin. However, a few months after discharge, the patient was admitted again to our hospital with pneumonia and died of severe sepsis.

Discussion

We present the case of a patient with amyloidosis and a rare clinical manifestation of ascites with primary peritoneal involvement. Anasarca with prominent ascites has diverse etiologies, such as heart failure, cirrhosis, and nephrotic syndrome. In our case, lack of response to conventional treatment for

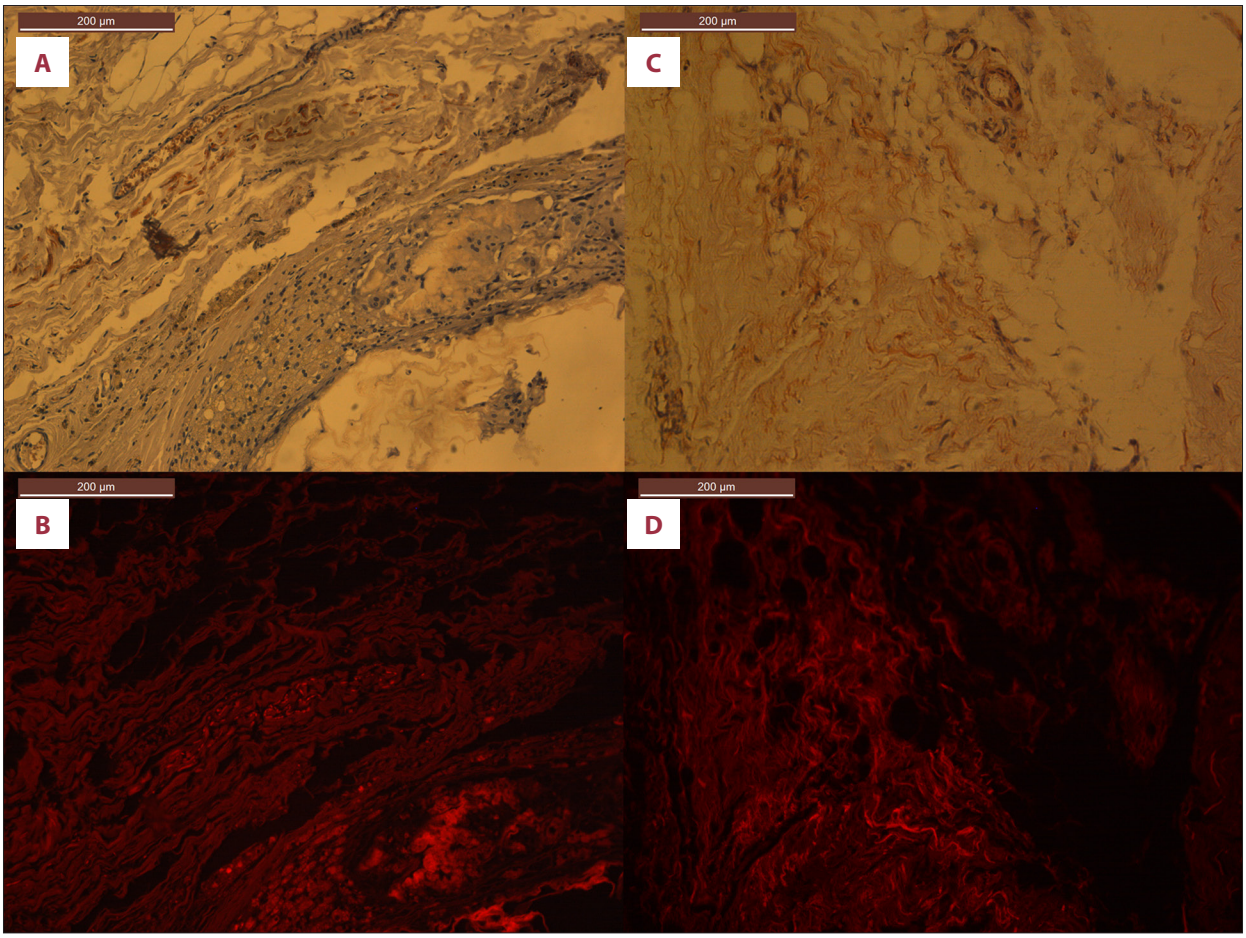

Figure 2. (**A**) Peritoneum: salmon-pink amyloid substance in Congo red stain. Original magnification ×400. (**B**) Peritoneum: red-orange amyloid in perivascular space (Congo red fluorescence, TRITC filter). Original magnification ×400. (**C**) Subcutaneous steatonecrosis and giant cell reaction. Original magnification ×200. (**D**) Subcutaneous amyloid in the cytoplasm of giant cells (Congo red fluorescence, TRITC filter). Original magnification ×400. TRITC, tetramethylrhodamine.

heart failure was the reason for investigating a primary peritoneal disease. Amyloidosis aspect on echocardiography was crucial to guide our investigation and treatment.

Cardiac amyloidosis or amyloid cardiomyopathy occurs in 50% of AL patients but in only 5% of AA patients [6]. Amyloid cardiomyopathy most commonly manifests as heart failure with preserved ejection fraction (restrictive cardiomyopathy), characterized by dyspnea and edema. Angina, pre-syncope, and syncope may occasionally be presenting features. In our patient's previous hospitalization, his symptoms were attributed to hypertensive cardiomyopathy. Echocardiogram was a clue to amyloidosis: increased left ventricular wall thickness with evidence of diastolic dysfunction is the earliest echocardiographic abnormality in amyloidosis. Moreover, in most patients, strain rate imaging shows impairment in long-axis contraction even when the left ventricular ejection fraction is within normal range [7]. The degree of long-axis dysfunction in amyloidosis cardiomyopathy (severe dysfunction in basal segments with preserved contraction in apical segments) is different from other conditions associated with true left ventricular hypertrophy such as hypertrophic cardiomyopathy or aortic stenosis [8,9]. In the present case, there was both systolic and diastolic dysfunction, but basal segments had greater impairment in myocardial contraction than apical ones.

Although cardiac magnetic resonance has higher sensitivity and specificity than echocardiogram, amyloid kidney disease may limit its use [10]. Myocardial biopsy is the "gold-standard" for cardiac amyloidosis diagnosis. However, typical echocardiographic findings in a patient with amyloidosis diagnosed by other non-myocardial tissue biopsy allows for the diagnosis of cardiac involvement without myocardial biopsy, as in our case. Cardiac magnetic resonance imaging was not done in this case due to chronic kidney disease. Besides heart failure, cardiac amyloidosis can manifest as peripheral vascular disease, autonomic neuropathy with syncope, thromboembolic events, or arrhythmias. In our case, the patient had trifascicular block and sinus bradycardia.

Gastrointestinal deposits in amyloidosis are common in AA amyloidosis subtype (as high as 60% of patients in some series) [11]. On the other hand, these deposits are seen in only 8% of AL patients, and less than 1% have clinical manifestations. In a study involving 2,334 patients with amyloidosis, 3% had amyloid deposition in gastrointestinal tissue. Of these, 80% had systemic amyloidosis and 20% had only gastrointestinal amyloidosis [12]. Most affected sites were: second portion of the duodenum (100%), stomach (90%), colon and rectum (90%), and esophagus (70%) [13]. Liver involvement may be as high as 90% in patients with AL subtype and 60% in patients with AA subtype [14]. Although liver involvement is common, our patient presented no amyloid deposits in the liver. However, there was a pattern of chronic passive congestion on the liver biopsy.

Most patients with liver involvement by amyloidosis are asymptomatic. They are usually identified by imaging studies or liver tests alterations. Previous studies observed that 57% to 83% of patients with liver involvement by amyloidosis had hepatomegaly [15,16]. An increase in alkaline phosphatase is reported as the most common liver test alteration (up to 86% of patients), followed by an increase in aspartate aminotransferase [17]. Our patient was asymptomatic and had normal liver tests. In addition, liver size by CT was also at normal range.

Gastrointestinal amyloidosis may also present as gastrointestinal bleeding in 25% to 45% of patients [18,19]. Bleeding may be due to ischemia, infarction, vascular friability, or mucosal lesions (ulcers, nodularity or polypoid lesions, erosions, submucosal hematomas, and small mucosal hemorrhages). Other clinical manifestations of gastrointestinal amyloidosis are: malabsorption syndrome which can result from mucosal infiltration, pancreatic insufficiency, abnormal growth of bacteria, protein-losing gastroenteropathy, and chronic gastrointestinal dysmotility. In our reported case, there were few gastrointestinal clinical manifestations and none of these complications.

Amyloidosis is very rare in peritoneum and is usually asymptomatic [4]. Ascites occurs in only 20% of patients with peritoneal amyloidosis. We searched PubMed using "ascites" and "amyloidosis" and identified only eight case reports of amyloidosis with ascites [4,5,20–25]. CT findings are often nonspecific. Occasionally, peritoneal amyloidosis mimics peritoneal carcinomatosis, with two different patterns: nodular and diffuse. A nodular pattern presents with mesenteric masses and localized intestinal wall thickening. A diffuse pattern presents as diffuse peritoneal thickening with amorphous or irregular calcifications [4]. Our patient's CT showed slight diffuse peritoneal thickening. This was the reason for surgical biopsy. Our intent was to make a differential diagnosis of amyloidosis, chronic infections, carcinomatosis, and other infiltrative diseases [4].

The gold standard for detecting amyloid deposits is Congo red stain and polarized microscopy. However, this method has limitations: small quantities of amyloid can produce a false-negative result, the rotation of the microscope stage is necessary to visualize obscure areas due to the "shadow of polarization" and darkened room and pupil accommodation are also mandatory. The Congo red dye itself is a fluorochrome, thus it can be examined under fluorescent light. This technique is easier to perform and interpret results, and has a higher sensitivity. Different filters can be used; we used a green excitation filter for tetramethylrhodamine isothiocyanate (TRITC) that reveals amyloid in a red-orange color [2,3,26].

Amyloidosis treatment goal is to reduce the amount of protein that forms amyloid deposits. Treatment is more efficacious in AL than in AA subtypes [4]. Symptomatic treatment with diuretics and repeated therapeutic paracentesis can alleviate heart failure and nephrotic syndrome symptoms. Amyloidosis with multiple organ involvement has poor prognosis and median survival is only nine months [17]. Main causes of death are infections, acute kidney injury, restrictive cardiomyopathy, and ischemic heart disease [27].

Conclusions

Ascites is a rare presentation of amyloidosis. Physicians should be particularly careful in heart failure and anasarca syndrome cases where ascites is disproportional or not responsive to diuretic treatment. CT images can show peritoneal involvement in amyloidosis, but definitive diagnosis is made by positive staining with Congo red dye in biopsy samples, using birefringence in polarized light or fluorescence in fluorescence microscopy. To date, there is no specific treatment for peritoneal amyloidosis.

Conflict of interest

The authors have no conflict of interest.

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