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CASE REPORT

만성담낭염으로 발현되고 류마티스성 다발성 근육통으로 오진된 아밀로이드증 1예

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A Case of Amyloidosis Presenting as Chronic Cholecystitis, Misdiagnosed as Polymyalgia Rheumatica

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Amyloidosis is a rare disease defined by extracellular deposits of amorphous fibrillar proteins, derived from aggregations of misfolded proteins. Localization of amyloidosis in the gallbladder is uncommon; only eight cases have been reported. We describe a case of amyloidosis diagnosed by cholecystectomy, which possibly also affected the liver and kidney. The patient was misdiagnosed with polymyalgia rheumatica, but after a cholecystectomy to treat chronic cholecystitis, we ultimately diagnosed him with amyloidosis. We review amyloidosis with gallbladder involvement in the literature. **(Korean J Gastroenterol 2016;68:49-53)**

Key Words: Amyloidosis; Gallbladder; Cholecystitis

INTRODUCTION

Amyloidosis is a rare disease caused by extracellular deposits of amorphous fibrillar proteins, derived from aggregations of misfolded proteins.[1] In systemic amyloidosis, amyloid is deposited in the viscera, blood vessel walls, and connective tissues. Systemic amyloidosis is usually fatal and is the cause of about 1 per 1,000 deaths in developed countries.[2] Amyloid fibers are deposited in tissues such as the brain, kidney, or heart, and the symptoms depend on the organs affected.[3] Typically, amyloidosis does not reach the canaliculi or acini of the peribiliary glands and affects only the epithelium of the intrahepatic bile ducts.[4] Amyloidosis in the gallbladder (GB) is very rare; only eight cases have been reported. We report a case of amyloidosis involving the GB.

CASE REPORT

A 69-year-old man with a history of pulmonary tuberculosis was experiencing poor oral intake, general myalgia, and weight loss of 5 kg over four months. When he visited a local hospital because of dizziness extending over a week, he was treated with aspirin under the impression of a transient ischemic attack. He was referred to our hospital because of generalized myalgia and positive rheumatoid factor. He had bilateral shoulder and hip pain. His erythrocyte sedimentation rate (ESR) was elevated to 86 mm/hour (reference range, 0-20 mm/hour). He was treated with an oral cortico-

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steroid (15 mg/day prednisolone equivalent) under the impression of polymyalgia rheumatica, according to the European League Against Rheumatism collaborative initiative/American College of Rheumatology classification criteria (age ≥50 years, bilateral shoulder ache, and abnormal CRP level or ESR).[5] After three months of treatment, he was admitted because of persistent symptoms, including poor oral intake. On physical examination, direct tenderness in the left chest and right upper quadrant of the abdomen was found. A complete blood count showed a white blood cell count of 7,700/mm^3 (neutrophils, 80.7%), hemoglobin concentration of 12.1 g/dL, and platelet count of 212×10^3/mm^3. The total protein level was 6.0 g/dL (reference range, 6.0-8.5 g/dL), and the albumin level was 3.1 g/dL (reference range, 3.5-5.3 g/dL). The total bilirubin level was in the normal range (0.9 mg/dL); the alkaline phosphatase level was 246 U/L (reference range, 20-120 U/L); the aspartate transaminase level was 55 U/L (reference range, 5-40 U/L); and the alanine transaminase level was 45 U/L (reference range, 8-41 U/L). The prothrombin time was 13.4 seconds (INR 1.28), and the activated partial thromboplastin time was 32 seconds. Blood urea nitrogen and creatinine levels were within normal ranges. The ESR was elevated to 68 mm/hour, and the CRP level was 0.31 mg/dL. The serum concentration of rheumatoid factor was 20.2 U/mL (reference range, 0.00-14.00 U/mL) and the anti-cyclic citrullinated peptide antibody level was 0.2 U/mL (reference range, 0.00-5.00 U/mL). The patient's serum calcium level was 8.6 mg/dL. Urinalysis showed proteinuria (1.33 g/day), so we performed serum protein electrophoresis to evaluate the cause of proteinuria. This revealed a monoclonal band in the gamma region, and the M protein level was elevated (1.02 g/dL), although it did not exceed 3 g/dL. The patient did not show any characteristics of target organ damage related to a plasma cell disorder, so we diagnosed monoclonal gammopathy of undetermined significance (MGUS). Chest CT performed to evaluate his chest wall pain at the time of admission showed focal GB wall thickening at the fundus (Fig. 1). Abdominal ultrasound showed diffuse mild GB wall thickening, suggesting chronic cholecystitis with no definite visible mass in the GB (Fig. 2). No hepatosplenomegaly was seen on abdominal ultrasonography. Chronic cholecystitis was considered because the patient had right upper quadrant abdominal pain, and a laparoscopic cholecystectomy was performed on the 12th day of admission. The pathology showed chronic cholecystitis with multifocal deposition of eosinophilic amorphous material in the vascular wall and stroma (Fig. 3), and polarized light microscopy of Congo red stained tissue showed apple-green birefringence (Fig. 4). Amyloidosis was confirmed pathologically. One month later, the patient's serum creatinine level was elevated to 1.39 mg/dL and persistent proteinuria was seen. Given the persistent proteinuria and elevated serum creatinine, we considered the deterioration in the patient's renal function to indicate progressive systemic amyloidosis, although it was not confirmed histologically. The patient did not have a history of viral hepatitis or heavy alcohol consumption, but liver cirrhosis had developed. We presumed the involvement of amyloidosis in his liver. Despite conservative care, the patient died of liver

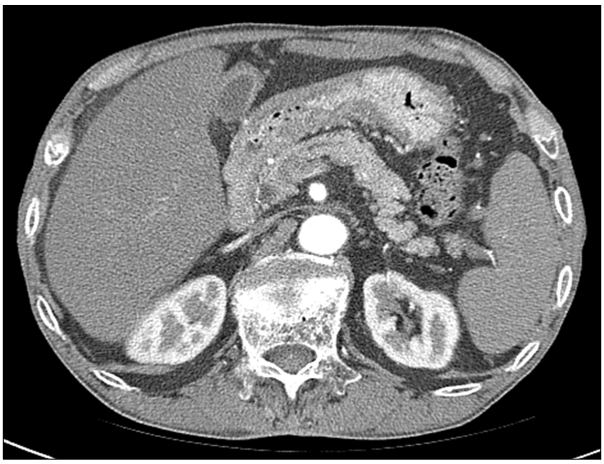

Fig. 1. Chest CT showed gallbladder (GB) wall thickening at the fundus, suggesting chronic cholecystitis, GB cancer, or adenomyomatosis.

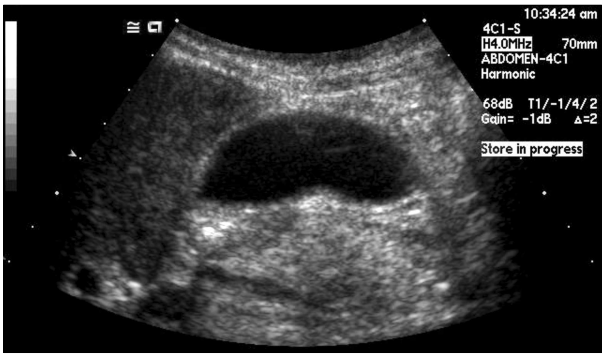

Fig. 2. Abdominal ultrasound showed diffuse mild gallbladder (GB) wall thickening, suggesting chronic cholecystitis with no definite visible mass in the GB.

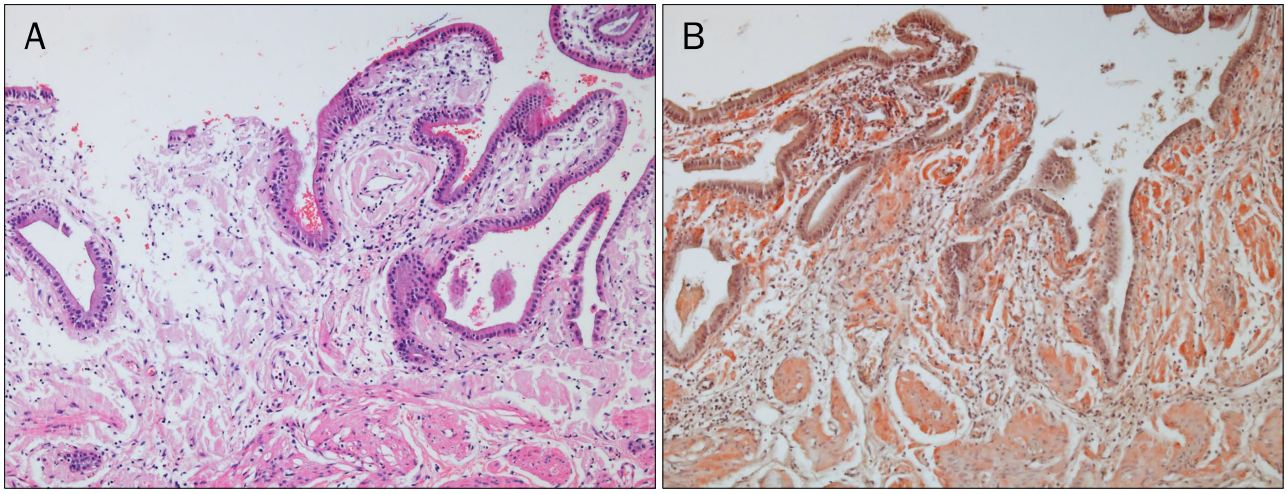

Fig. 3. (A) Postoperative H&E staining of the gallbladder showed chronic cholecystitis with amorphous eosinophilic depositions in the lamina propria mucosa (×40). (B) In Congo red staining of the gallbladder, amyloid depositions were stained in the lamina propria mucosa (×40).

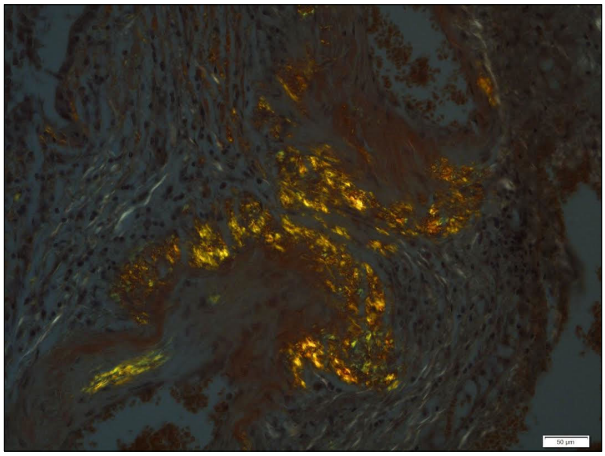

Fig. 4. Apple-green birefringence was demonstrated in polarized light microscopy of Congo red staining (×40).

cirrhosis and its complications.

DISCUSSION

Clinically, amyloidosis is classified as localized or systemic. In localized amyloidosis, amyloid protein is deposited in a localized area, such as the respiratory tract, urogenital tract, skin, or brain.[3] One systemic form of amyloidosis is light-chain (AL) amyloidosis, once called primary amyloidosis. AL amyloidosis accounts for most cases of systemic amyloidosis. Generally, it is related to monoclonal gammopathy and caused by plasma cell disorders, such as multiple myeloma. AL amyloidosis may involve any organ except the brain, and it can be expressed as a neuropathy, congestive heart failure, renal failure, hepatomegaly, splenomegaly, and/or worsening of hepatosplenic function. Amyloid A (AA) amyloidosis, another systemic amyloidosis, was once called secondary amyloidosis. In this disease, AA protein is deposited in organs as a complication of chronic infection or chronic inflammation. AA amyloidosis is associated with rheumatoid arthritis, Crohn's disease, and familial Mediterranean fever. AA amyloidosis often involves the spleen and is typically diagnosed because of hepatomegaly or splenomegaly.[6] In the United States and Europe, AA amyloidosis has become uncommon, occurring in less than 1% of amyloidosis cases, perhaps because of advances in anti-inflammatory and antibiotic treatments. AA amyloidosis is more common in Turkey and the Middle East, where it occurs in association with familial Mediterranean fever.[2]

Familial amyloidosis (AF) is a rare autosomal-dominant disease. The most common form of AF is caused by mutations in the protein transthyretin. Dialysis-associated amyloidosis is caused by the deposition of beta 2-microglobulin protein in patients who undergo dialysis for long periods.

Our case had systemic amyloidosis demonstrated by cholecystectomy that probably also affected the liver and kidney. Therefore, we diagnosed MGUS based on the monoclonal gammopathy. The amyloidosis in this case can be categorized as AL amyloidosis.

Amyloidosis affects the epithelium of the intrahepatic bile ducts without actually reaching the canaliculi and acini of the peribiliary glands. In experimental models of amyloidosis, the presence of amyloid localized to the GB has not been

Table 1. Cases with Gallbladder Localization of Amyloidosis in the Literature

Author (year)	Sex/age (yr)	Symptoms	Treatment	Other localization of amyloidosis
Arista-Nasr et al. (1993)[7]	M/80	Asthenia, fever, weight loss, melena, diarrhea	- (autopsy finding)	Intestinal tract
Remy et al. (1995)[4]	M/60	Right upper quadrant pain, fever	Laparoscopic cholecystectomy	Liver
Shimizu et al. (1996)[8]	F/54	Peripheral nerve and autonomic dysfunction, renal failure	- (autopsy finding)	Peripheral and autonomic nervous system, heart, blood vessels, kidney, bladder, intestinal tract, submandibular glands, tongue, spleen, pancreas, thyroid, lung, liver, adrenal gland
Casassus-Builhe et al. (2000)[9]	F/76	Dyspepsia	-	Liver, salivary glands, heart, intestinal tract, kidney
Kim et al. (2003)[10]	M/63	Right upper quadrant pain	Cholecystectomy	Kidney
Kwon et al. (2007)[12]	F/63	Incidental finding on abdominal US	Laparoscopic cholecystectomy	Duodenum
Denève et al. (2008)[11]	M/42	Right upper quadrant pain, fever, vomiting	Cholecystectomy	Intestinal tract, kidney, heart
Tirotta and Durante (2011)[1]	M/74	Asthenia, abdominal pain	Cholecystectomy	Heart, bone marrow

observed. Amyloidosis of the GB diagnosed after cholecystectomy is very rare; only eight cases have been reported. Their characteristics are summarized in Table 1. In the first case, amyloidosis involvement of the GB was found at autopsy in a patient with diffuse small lymphoplasmacytic lymphoma of the gastrointestinal tract, associated with massive intestinal amyloidosis.[7] A case of secondary amyloidosis in the liver and GB was reported in a patient with pancreatic cancer.[4] A case of familial amyloidotic polyneuropathy with autopsy findings showing GB involvement and systemic amyloidosis in the GB, liver, salivary gland, heart, gut, and kidney was reported.[8,9] In one case each, GB amyloidosis presented with acute suppurative cholecystitis, mimicking GB cancer, and severe acute hemorrhagic cholecystitis.[10-12] The final reported case was a patient with multiple myeloma with amyloidosis of the GB, heart, and bone marrow.[1]

Chronic cholecystitis is usually caused by repeated cystic duct obstruction by GB stones. In some cases, however, cholelithiasis is not observed, and these cases are thought to be caused by bile stasis and dysfunction of the sphincter of Oddi.[13] Although the pathogenesis of chronic acalculous cholecystitis due to amyloidosis is unclear, it is likely to involve motility dysfunction of the GB, resulting from the neuromuscular infiltration of amyloid.[14]

The rarity and variable spectrum of the disease often cause missed or delayed diagnosis. The diagnosis and treatment of amyloidosis remain a clinical challenge. In this case, the patient was diagnosed with polymyalgia rheumatica, based on old age, bilateral shoulder and hip pain, and an elevated ESR. Despite treatment, the patient was admitted because of worsening symptoms. After further evaluation, we diagnosed amyloidosis, rather than polymyalgia rheumatica. Polymyalgia rheumatica has multiple differential diagnoses, does not have definite diagnostic criteria, and commonly follows a benign course.[15] The patient presented with poor oral intake and loss of weight for several months; amyloidosis was mistaken for polymyalgia rheumatica because of the non-specificity of its presentation.

Due to the low incidence and broad clinical manifestations of amyloidosis, suspicion and diagnosis of this disease are difficult. In this report, we describe a rare case diagnosed following laparoscopic cholecystectomy and reviewed a few similar cases.

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