

Fatal Acute Pancreatitis Associated with Reactive AA Amyloidosis in Rheumatoid Arthritis with End-stage Renal Disease: A Report of Three Cases

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Abstract

We report three cases of fatal pancreatitis associated with systemic AA amyloidosis in rheumatoid arthritis (RA). All of the patients showed end-stage renal failure, and hemodialysis was introduced during the course of treatment. Autopsy was performed on two of the three patients, and this revealed amyloid deposition on the vascular walls in the pancreas. It was strongly suggested that the acute pancreatitis in all three patients was attributable to deposition of amyloid in vascular and pancreatic tissues. Acute pancreatitis is considered to be a rare complication of end-stage amyloidosis associated with RA, and is frequently fatal. It is important to treat RA patients intensively to avoid such deposition of amyloid.

Key words: AA amyloidosis, pancreatitis, rheumatoid arthritis

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Introduction

Recently, it has become apparent that rheumatoid arthritis (RA) is not only an inflammatory disease affecting multiple joints but also a cause of systemic organ dysfunction due to persistent systemic inflammation; this dysfunction may increase the risk of organ failure and death in affected patients (1-4). Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of RA that arises from chronic, systemic and long-lasting inflammation, with elevated levels of serum AA (SAA) protein (5-7). The frequency of amyloidosis in RA has been reported to vary from 5% to 13.3% in cases confirmed by biopsy and from 14% to 26% in cases confirmed by autopsy (8, 9). In addition, we have previously reported 71 patients with reactive amyloidosis (7.1%) from a cohort of 1,006 RA patients (10). In reactive amyloidosis, gastrointestinal symptoms, renal insufficiency and proteinuria are commonly observed, whereas hepatobiliary and/or pancreatic symptoms

are relatively rare. Acute pancreatitis is usually mild with minimal organ dysfunction, but in about 20% of affected patients the disease becomes severe and is associated with complications and a high risk of mortality (11, 12). Almost all patients with amyloidosis have subclinical organ damage due to amyloid deposition, and in those with pancreatitis, the risk of death is higher. Here we present three cases of fatal acute pancreatitis, two of which were investigated at autopsy, focusing on the pathogenesis.

Case Report

Case 1

A 55-year-old woman with a 19-year history of RA was admitted to our satellite hospital with mild epigastralgia in January 2006. Her family history showed no consanguinity or collagen diseases. Initially she was treated with bucilamine, but this was soon switched to salazosulfapyridine. Her RA disease was temporarily inactive, but later became

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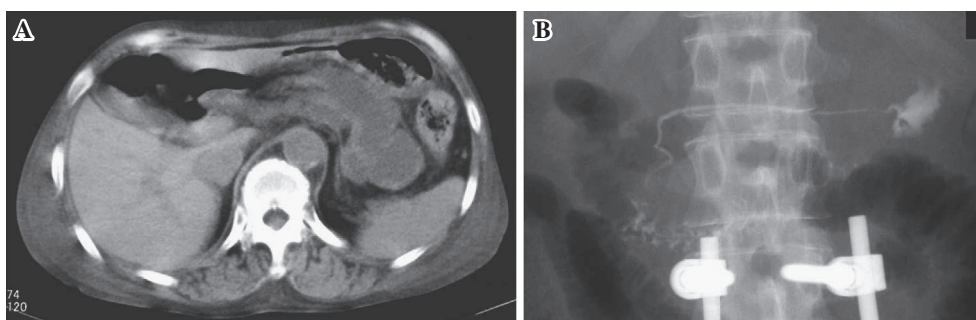


Figure 1. Abdominal CT shows narrowing and enlargement of the main pancreatic duct (1A). Endoscopic nasopancreatic drainage (ENBD) was attempted in case 1, but this was unsuccessful because of widespread narrowing of the pancreatic main duct (1B).

active, and hematuria and urinary protein were detected in January 1999. She was treated with posterior lumbar interbody fusion for lumbar spondylolisthesis in February 2005. Thereafter, her renal function deteriorated and the serum creatinine level was elevated at more than 3 mg/dL in April 2005. She was diagnosed as having reactive AA amyloidosis by gastric biopsy in July 2005. Prednisolone was added to her treatment, but her disease remained mostly active, with a C-reactive protein (CRP) level of 3.3-4.4 mg/dL and intractable arthritis. Her pretibial edema gradually increased in December and she was admitted to hospital because of epigastric pain in mid-January 2006.

On physical examination, her blood pressure was 160/80 mmHg with a regular heartbeat of 110 bpm and a temperature of 37.5°C. Pulse oximetry showed an O₂ saturation of 95%. Cardiac, lung and abdominal examination revealed no abnormalities. Marked bilateral pretibial edema was observed and her condition was considered to be anasarca. On neurological examination, no abnormalities were evident. There was symmetric polyarthritis in the proximal interphalangeal and metacarpophalangeal joints of the hand, wrist, and ankle. Left knee arthritis was also observed. Laboratory studies revealed a leukocyte count (WBC) of 17,100 per mm³, a red blood cell count (RBC) of 233×10⁴ per mm³, a hematocrit (Ht) of 21.4%, hemoglobin (Hb) 7.2 g/dL, platelet count (Plt) 27.6×10⁴ per mm³, and a CRP level of 18.13 mg/dL. Electrolytes were normal with a total protein level of 5.3 g/dL and hypoalbuminemia (2.8 g/dL). The blood urea nitrogen concentration (BUN) was 72 mg/dL, and the serum creatinine (Cr) level was 5.8 mg/dL. Urinalysis showed a urinary protein excretion of 0.5 g/day, but no hematuria. The RF level was 5.6 IU/mL (normal <10 IU/mL). The patient's blood tests revealed the following values: alanine transaminase (ALT) 16 IU/L, aspartate aminotransferase (AST) 15 IU/L, alkaline phosphatase (ALP) 355 IU/L, lactate dehydrogenase (LDH) 294 IU/L, glutamyl transaminase (γ-GTP) 59 IU/L, total bilirubin 0.6 mg/dL, total cholesterol 191 mg/dL, triglyceride 126 mg/dL, HDL cholesterol 49 mg/dL and bicarbonate 19.8 mEq/L (reference range: 23-32 mEq/L). Additionally, the amylase (Amy) level (273 IU/L) was slightly elevated. The serum IgG4 level was within normal limits. Computed tomography (CT) of the

chest and abdomen demonstrated bilateral pleural effusion, pericardial effusion, ascites, and fluid retention around the pancreas, suggestive of pancreatitis. The patient's epigastric pain was mild on admission, but gradually worsened. She was considered to be in the end stage of renal failure, and hemodialysis (HD) was started 4 days after admission, together with both 20 mg of prednisolone daily and antibiotics of imipenem/cilastatin (IPM/CS). Additionally, camostat mesilate and nafamostat mesilate were started for treatment of the pancreatitis. Repeated blood tests showed elevation of the ALP and CRP levels to 1714 IU/mL and 16.0 mg/dL, respectively. Repeat abdominal CT demonstrated narrowing and enlargement of the main pancreatic duct (Fig. 1A). Endoscopic nasopancreatic drainage (ENBD) was attempted, but this proved impossible because of the widespread narrowing of the main pancreatic duct (Fig. 1B). Gradually, HD became difficult to perform because of hypotension. In early February, cerebral infarction suddenly developed and the patient died three days later.

Case 2

A 67-year-old woman with a 17-year history of RA was admitted to our satellite hospital with dyspnea in late September 2003. Her family history showed neither consanguinity nor collagen diseases. Her RA had been treated with non-steroidal anti-inflammatory drugs alone, and she had been coming to the hospital as an outpatient for 17 years since disease onset. She was admitted to hospital in 2001 for treatment of a *Mycobacterium avium* lung infection. Renal insufficiency was pointed out at that time, and this gradually progressed. Pretibial edema gradually worsened in September 2002.

At the present admission, physical examination showed a blood pressure of 168/90 mmHg with a regular heartbeat of 66 bpm, and a temperature of 37.2°C. Cardiac and abdominal examination revealed no abnormalities. Coarse crackles were audible in the bilateral lung fields. Marked facial and bilateral pretibial edema was evident. Neurological examination revealed no abnormalities. There was symmetric polyarthritis in the proximal interphalangeal and metacarpophalangeal joints of the hand, wrist, and ankle. Left knee arthritis was also observed. Pulse oximetry showed an O₂ satura-

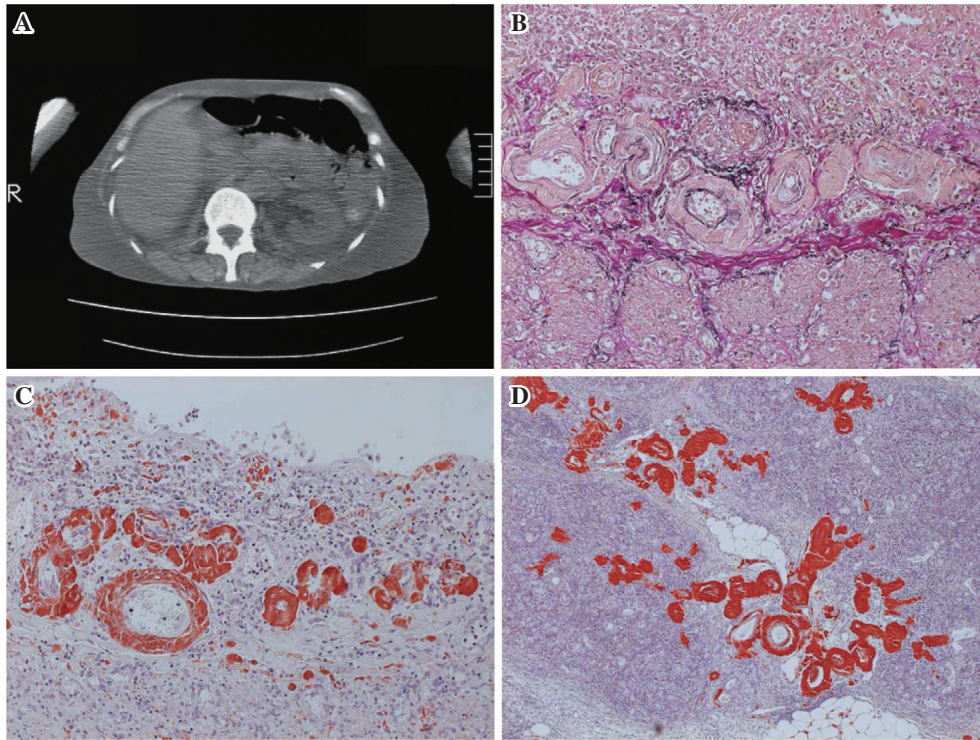


Figure 2. Abdominal CT shows ascites, but no pancreatic stone or dilatation of the main pancreatic duct is evident (A). Elastic van Gieson staining reveals stenosis of small vessels in the small intestine. Amyloid deposits are observed in the lumina of vessels (B). There are many amyloid deposits in the small intestine (C) (Congo red stain) and small vessels in the pancreas (D) (Congo-red stain).

tion of 96% under continuous supply of 1 L/min oxygen by nasal tube.

Laboratory studies revealed a WBC of $12,200$ per mm^3 , RBC 265×10^4 per mm^3 , Ht 27.0%, Hb 8.5 g/dL, Plt 24.4×10^4 per mm^3 , and CRP 18.0 mg/dL. Electrolytes were normal with a total protein level of 7.0 g/dL and hypoalbuminemia at 2.8 g/dL. The BUN concentration was 10.2 mg/dL, and Cr was 2.7 mg/dL. Urinalysis showed a urinary protein excretion level of 0.1 g/day, and no hematuria. The RF level was 139.0 IU/mL (normal <10 IU/mL). The results of blood tests were as follows: ALT 91 IU/L, AST 41 IU/L, LDH 311 IU/L, and total bilirubin (TB) 1.6 mg/dL. Additionally, the Amy level (245 IU/L) was slightly elevated. The serum C3 concentration was 39.0 mg/dL, C4 was 9.0 mg/dL, and CH50 was 8.0 U/mL. Creatinine clearance (Ccr) was 1.8 mL/min per 1.73 m^2 . An antinuclear antibody (ANA) test gave a negative result, and the patient was also negative for SS-A, SS-B, Sm, dsDNA, RNP, Scl-70, proteinase 3, myeloperoxidase antineutrophil cytoplasmic autoantibodies (ANCA), and cryoglobulin. Furosemide and dopamine were started, but her clinical response was poor. Continuous hemodiafiltration (CHDF) was also started, the Amy increased to 1000 IU/mL. Abdominal echography showed swelling of the pancreas. Abdominal CT demonstrated ascites, but neither pancreatic stone nor dilatation of the main pancreatic duct was evident (Fig. 2A). The patient had no abdominal pain. Acute pancreatitis was diagnosed and she was started on 5 mg of prednisolone daily, nafamostat mesi-

late, ulinastatin, citicoline sodium, and IPM/CS antibiotics. The pancreatitis gradually improved, with a normal range of amylase, Cr 2.6 mg/dL and CRP 1.5 mg/dL on October 5th. However, sudden abdominal pain developed on December 10th. Abdominal CT revealed free air in the abdomen, and a diagnosis of small-intestinal perforation was made. However, because of the generally poor condition of the patient, surgery was not possible, and she died in mid-December. Autopsy revealed reactive AA amyloidosis with RA and amyloid deposits in all organs, and but mainly in small arteries. It was found that the ileum had perforated due to arterial occlusion induced by amyloid deposition (Fig. 2B, 2C). Additionally, there were many amyloid deposits in the small vessels of the pancreas (Fig. 2D).

Case 3

A 50-year-old woman was admitted to our hospital for treatment of pancreatitis from our satellite hospital in January 2006. Her family history showed neither consanguinity nor collagen diseases. She had been diagnosed as having RA at the age of 22 years, and had undergone bilateral total hip and bilateral total knee arthroplasty at the ages of 28 and 32 years, respectively. In 1991 she had undergone renal biopsy because of proteinuria, and had been diagnosed as having reactive amyloidosis as a result of renal biopsy. Her renal function had then gradually deteriorated. Constipation and epigastric discomfort appeared in December 2005, and she was admitted to our satellite hospital due to general fa-

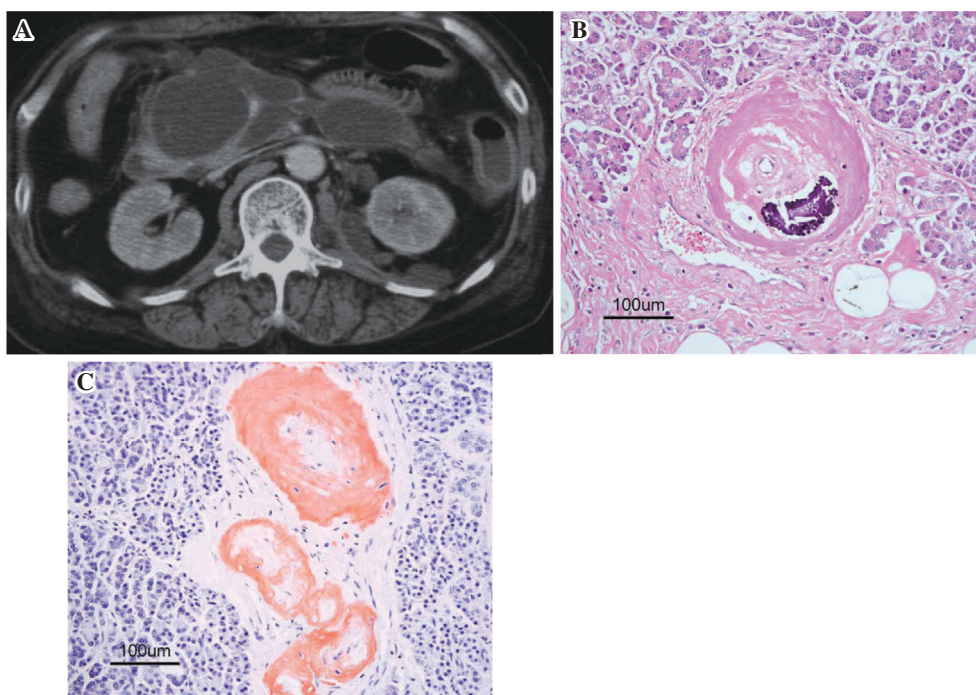


Figure 3. Abdominal CT shows swelling of the pancreas head and multiple pseudopancreatic cysts, and also atrophic kidneys (A). In the pancreas, small vessels are obstructed by calcinosis and amyloid deposits (B) (Hematoxylin and Eosin staining). There are many amyloid deposits in the small vessels of the pancreas (C) (Congo red stain) in case 3.

tigue. Laboratory studies revealed a WBC of 37,500 per mm^3 and a CRP of 21.9 mg/dL. The Amy level (1006 IU/L) was markedly elevated. Abdominal CT revealed swelling of the pancreas head and pseudopancreas cyst, and a diagnosis of acute pancreatitis was made. Her general condition, particularly renal function, deteriorated in spite of intensive treatment. On physical examination, her blood pressure was 112/82 mmHg with a regular heartbeat of 106 bpm and a temperature of 37.6°C. Cardiac and lung examinations revealed no abnormalities. Abdominal examination revealed tenderness in the upper abdomen. No pretibial edema was evident, and there were no neurological abnormalities. There was symmetric polyarthritides in the proximal interphalangeal and metacarpophalangeal joints of the hand, wrist, and ankle, and her bilateral fingers showed mutilans deformity. Laboratory studies revealed a WBC of 39,170 per mm^3 , RBC 265×10^4 per mm^3 , Ht 22.5%, Hb 7.4 g/dL, Plt 37.5×10^4 per mm^3 , and CRP 11.0 mg/dL. Electrolytes were normal, with a total protein level of 5.4 g/dL and hypoalbuminemia (1.5 g/dL). The BUN concentration was 42.0 mg/dL, and the Cr level was 2.2 mg/dL. Urinalysis showed a protein excretion level of 1.0 g/day, but no hematuria. The RF level was 50.2 IU/mL. Blood tests revealed the following values: ALT 37 IU/L, AST 30 IU/L, LDH 367 IU/L, and TB 0.7 mg/dL. Additionally, the Amy level (355 IU/L) was slightly elevated. The serum C3 concentration was 112.6 mg/dL, C4 was 25.1 mg/dL, and CH50 was 43 U/mL. Ccr was 12.7 mL/min per 1.73 m^2 . The levels of trypsin (2112 ng/mL), lipase (130 IU/mL), and DUPAN-2 (440 U/mL) were all elevated. Blood gas analysis was within normal

limits. Abdominal CT revealed swelling of the pancreas head and multiple pseudopancreas cysts, as well as atrophic kidneys (Fig. 3A). She was started on regular HD from mid-February, and administered 15 mg of prednisolone daily, nafamostat mesilate 200 mg daily, and octreotide 100 μg daily, being increased thereafter to 200 mg, as well as of IMP/CS antibiotics. Both the WBC and CRP values gradually improved, together with the abdominal pain. Gradually, HD became difficult to perform because of hypotension, so we switched the patient to CHDF in March. However, hypotension persisted and she died in early April. Autopsy revealed reactive AA amyloidosis with RA and amyloid deposits in all organs, but mainly in the small arteries. The small vessels were obstructed due to calcinosis and amyloid deposits (Fig. 3B), and arterial occlusion in the pancreas due to amyloid deposition was evident (Fig. 3C).

Discussion

Reactive amyloidosis carries a high risk of organ failure and death (13). It is a serious systemic disease that can appear against a background of chronic inflammation, and it can lead to an increase in the levels of acute-phase proteins. The proteolytic cleavage products of these proteins, such as SAA, are insoluble fibrinoid proteins that can be deposited in the kidneys, heart, or gastrointestinal (GI) tract. Chronic renal failure due to amyloidosis is an important cause of death in patients with RA (14-16). Despite the lack of available treatment for elimination of amyloid deposits, an alternative approach would be a form of therapy that can reduce

the supply of amyloid fibril precursor proteins, thereby improving organ function (17). The present three patients showed end-stage renal failure, which necessitated HD during the course of treatment. Renal failure in these patients was the result of amyloid deposition in the glomeruli, tubules, and vessels. These deposits were detected not only in the kidney but also in systemic vessels. In general, the pancreas is rarely involved in any type of amyloidosis (18). One report has indicated that gallstones (GS) are frequently detectable in patients with RA by abdominal ultrasonography (US) (19). Our patients had acute pancreatitis but no findings suggestive of GS on abdominal CT and US. Two of them (Cases 1 and 2) did not have severe abdominal pain at the onset of acute pancreatitis. Generally, these patients with RA were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and steroid, and this might have decreased the pain associated with acute pancreatitis. The common causes of acute pancreatitis are excessive alcohol intake and cholelithiasis (20). However, neither appeared to be etiologically relevant in our patients. Two possibilities can be considered for the mechanism of pathogenesis: an autoimmune mechanism or an amyloidosis-related effect. Autoimmune pancreatitis is characterized by diffuse swelling of the pancreas with irregular stenosis of the main pancreatic duct, associated with hyper- γ -globulinemia and auto-antibodies, and a favorable response to corticosteroid therapy (21-24). This is sometimes associated with autoimmune disorders such as Sjögren's syndrome or IgG4-related disease (25-27). In the present patients, this autoimmune mechanism appeared unlikely, because acute pancreatitis developed during treatment with prednisolone and there were no characteristic features on abdominal CT. Despite their long history of RA, none of our patients were positive for autoantibodies that would suggest any association with Sjögren's syndrome or IgG4-related disease. With regard to an amyloidosis-related mechanism, there are several defense mechanisms against pancreatitis in the pancreatic duct, including the duodenal major papilla (27, 28). Case reports of systemic AL and AA amyloidosis have indicated that amyloidoma around the duodenal papilla disturbs pancreatic secretion and induces recurrent acute pancreatitis (29, 32). Although no amyloidoma-like lesions were detectable by abdominal CT in our patients, AA amyloid was present in the gastrointestinal tissue in all three. Amyloidosis was proved at autopsy in Case 2. All three patients might have had dysfunction of the duodenal papilla due to amyloid deposition, and might have developed bacterial infection and/or secretory disturbance in the pancreatic duct, leading to acute pancreatitis. As another possible amyloidosis-related mechanism, circulatory disturbance, has recently been speculated to cause acute pancreatitis (31, 32), and two of our patients (Cases 2 and 3) showed amyloid deposition on the vascular walls of the pancreas at autopsy. No autopsy was performed in Case 1, but her renal condition was end-stage, and it is considered that amyloid was deposited in her vascular wall of not only in the kidney but also in the pancreas vessel walls. It was speculated that

our three cases showed that the impairment of microcirculation of the pancreatic vasculature reduces the blood perfusion and causes more rapid deterioration, compared to the natural course of acute pancreatitis and this vascular damage aggravated the microcirculation of other amyloid deposited organs. Recently, in AA amyloidosis, we have shown that treatment of RA with biologics can reduce the extent of amyloid deposits in gastroduodenal biopsy specimens (33). This treatment may reduce amyloid deposits in the vascular walls or ameliorate dysfunction of the duodenal papilla. It is well known that if patients have been started on HD, the prognosis is poor in those with amyloidosis associated with RA (34). Biologics may reduce the number of amyloidosis patients who require HD. If amyloid deposits are removed from tissues by such treatment, it may become possible to reduce the incidence of acute pancreatitis caused by reactive amyloidosis.

We conclude that the acute pancreatitis in all three of the present patients was very likely due to deposition of amyloid in vascular and pancreatic tissues, similar to that observed in the kidneys and gastrointestinal tract. Acute pancreatitis is considered to be a rare complication of end-stage amyloidosis associated with RA. Acute pancreatitis can be fatal in amyloidosis patients with end-stage renal failure associated with RA. It is therefore important to treat RA patients intensively to avoid deposition of amyloid.

The authors state that they have no Conflict of Interest (COI).

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