AA-amyloidosis in Autosomal Dominant Polycystic Kidney Disease Caused by Chronic Cyst Infections Lasting for 30 years

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Abstract

We herein report the case of a 66-year-old Japanese woman who was admitted to our hospital due to diarrhea and malaise. She had been diagnosed with autosomal dominant polycystic kidney disease (ADPKD) at 35 years of age and had suffered from recurrent cyst infections since that time. Antibiotic therapy combined with hepatic cyst drainage and cyst sclerosing therapy led to transient improvements each time. At 66 years of age, watery diarrhea occurred. The patient’s serum albumin level declined to 1.8 g/dL, and her C-reactive protein level was 4.5 mg/dL. An endoscopic biopsy of the descending colon revealed amorphous deposits in the small arteries and tissues of the submucosal layer. The deposits were positive for Congo Red staining and amyloid A staining. Therefore, AA-amyloidosis was diagnosed. An endoscopic biopsy of the stomach and duodenum also showed AA-amyloid deposits. If an ADPKD patient with a long history of cyst infection develops diarrhea and malaise, AA-amyloidosis should be considered as a possible complication.

Key words: hemodialysis, amyloidosis, ADPKD, infection

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder (1). Cyst infection is a major complication for patients with ADPKD and is the second most common cause of death in this population (2). If cyst infections become resistant to oral or intravenous antibiotics, percutaneous aspiration of infected renal or hepatic cysts and drainage can be performed, as well as sclerosing therapy (3), nephrectomy, partial hepatectomy or transcatheter arterial embolization (TAE) (4) of the renal artery.

We encountered an ADPKD patient in whom diarrhea and malaise developed following a chronic hepatic cyst infection that became resistant to these therapies. An endoscopic biopsy disclosed AA-amyloidosis of the gastroduodenal region and colon.

Amyloidosis that arises secondarily to chronic inflammatory conditions is now called amyloid A amyloidosis (AA-amyloidosis) because a major component of the protein deposits is a cleaved product of the acute phase serum protein amyloid A (5). Although chronic infections such as tuberculosis are known to cause AA-amyloidosis, chronic cyst infections associated with ADPKD have rarely been reported as a cause of AA-amyloidosis (6). We herein report an association between chronic hepatic cyst infections and AA-amyloidosis in a patient with ADPKD.
A 66-year-old Japanese woman was admitted to our hospital due to diarrhea and malaise. She had been diagnosed with ADPKD after an investigation of flank pain when she was 35 years old. Since then, she had suffered from recurrent cyst infections. Intravenous antibiotics were effective each time; however, the level of C-reactive protein remained relatively high even when she did not have any symptoms. Hemodialysis was started at 54 years of age due to deterioration of the patient’s renal function. At 61 years of age, TAE was performed on the bilateral renal arteries to reduce the volume of the kidneys with 36 platinum microcoils according to the published method (7). At 63 years of age, TAE was also performed to treat cystic regions of the left and anterior right hepatic lobes (Fig. 1) using platinum microcoils according to the previously reported method (8). At 65 years of age, the patient suffered from right flank pain and a low-grade fever (37.5°C) that were resistant to the administration of intravenous antibiotics. Laboratory tests revealed that the white blood cell count was 7,100/μL and the C-reactive protein level was 2.0 mg/dL. Percutaneous aspiration of cyst fluid was performed under ultrasound guidance in an abnormal cyst that was located in the right lobe of the liver, and minocycline was injected into the cyst as a sclerosing agent. A culture of the cyst fluid was sterile, and no pathogenic organisms were detected, most likely due to the continuous administration of antibiotics. Although the patient’s fever subsided one week after she underwent cyst drainage, the level of C-reactive protein persisted at 2.4 mg/dL. Six months after the first drainage procedure, the fever and flank pain recurred. The patient hesitated to accept this option. She died of a cyst infection that was refractory to antibiotics 12 months after receiving the diagnosis of AA amyloidosis.

**Histologic findings of the gastrointestinal tract**

An endoscopic biopsy of the descending colon as well as the stomach and duodenum was performed to evaluate the patient’s diarrhea and malnutrition. The specimen of the descending colon revealed amorphous deposits in the small arteries and tissues of the submucosal layer (Fig. 2a). These deposits were positive for Congo Red staining and showed apple-green birefringence under polarizing light (Fig. 2b) and amyloid A staining (Fig. 2c); however, they were negative for kappa chain, lambda chain, β2 microglobulin and prealbumin. Accordingly, amyloid A amyloidosis (AA amyloidosis) was diagnosed. An endoscopic biopsy of the stomach and duodenum also showed AA amyloid deposits in the small arteries and tissues of the submucosa (Fig. 3a-3c). No left ventricular hypertrophy was observed on echocardiography, and the wall motion was normal.

**Clinical course**

Because a close relationship between chronic infection and AA amyloidosis was suggested, conservative therapy with antibiotics and drainage was administered intensively; however, the diarrhea and the high value of C-reactive protein persisted. Surgical resection of the infected hepatic cysts was offered as the next therapeutic option. However, the patient hesitated to accept this option. She died of a cyst infection that was refractory to antibiotics 12 months after receiving the diagnosis of AA amyloidosis.

**Amyloid staining**

The collected tissues were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 4 mm. The deparaffinized sections were stained with hematoxylin and eosin. Some sections were stained with Congo Red (Merck, Tokyo, Japan; 1:500). Positive reactions for Congo Red staining and showed apple-green birefringence under polarizing light (Fig. 2b) and amyloid A staining (Fig. 2c); however, they were negative for kappa chain, lambda chain, β2 microglobulin and prealbumin. Accordingly, amyloid A amyloidosis (AA amyloidosis) was diagnosed. An endoscopic biopsy of the stomach and duodenum also showed AA amyloid deposits in the small arteries and tissues of the submucosa (Fig. 3a-3c). No left ventricular hypertrophy was observed on echocardiography, and the wall motion was normal.
Figure 2. a. An endoscopic biopsy of the descending colon displays amorphous deposits in the small arteries and the tissues of the submucosa. (×200 Hematoxylin and Eosin staining). b. The deposits are positive for Congo Red staining. (×200 Congo red stain). c. The deposits are positive for amyloid A. (×200 Amyloid A stain).

Figure 3. a. An endoscopic biopsy of the stomach and duodenum shows amorphous deposits in the small arteries and tissues of the submucosa. (×200 Hematoxylin and Eosin staining). b. The deposits are positive for Congo red. (×200 Congo red stain). c. The deposits are positive for amyloid A. (×200 Amyloid A stain).

amyloid-P component (Dako; 1:200), kappa-light chain (Dako; 1:100,000), lambda-light chain (Dako; 1:100,000) and prealbumin (transthyretin) (Dako; 1:3,000) and mouse monoclonal antibodies against amyloid A component (Dako;
chains in primary amyloidosis patients and amyloidosis patients, monoclonal immunoglobulin light chains in primary amyloidosis patients and β2 microglobulin in dialysis patients.

The deposits of amyloid originate from serum amyloid A proteins, acute-phase proteins produced in response to inflammation. Therefore, AA amyloidosis occurs in patients with chronic inflammatory diseases such as rheumatoid arthritis (5), juvenile rheumatoid arthritis, inflammatory bowel disease (9), familial Mediterranean fever (10), microscopic polyangitis (11), Castleman’s disease (12), Reiter’s disease (13), Behcet’s disease (14), Whipple disease (15) and multiple sclerosis (16).

Chronic infections can also lead to AA amyloidosis in patients with conditions such as tuberculosis (17), bronchiectasis (9), injectable drug abuse (9) and osteomyelitis (9). However, there has been only one report of AA amyloidosis occurring in an ADPKD patient with a chronic cyst infection. Kamimura et al. reported the case of a 62-year-old Japanese woman who had been receiving hemodialysis for one year (6). The patient had a markedly enlarged polycystic liver and a history of recurrent hepatic cyst infections for 15 years. She died of a hepatic cyst infection; however, no pathogenic organisms were detected, most likely due to the long-term administration of antibiotics. At autopsy, deposits of AA amyloid were seen in the submucosa of the small intestine and tongue, as well as in the small vessels of the myocardium and kidneys.

Our patient had a 30-year history of chronic cyst infections starting at 35 years of age. The inflammation did not subside completely and persisted even after the long-term administration of antibiotics, which might have contributed to the development of AA amyloidosis secondary to chronic infection. We could not determine exactly how chronic cyst infections induce AA amyloidosis. However, deposition in the submucosal layer of the intestines might induce diarrhea, resulting in malaise and weight loss. If an ADPKD patient with a long history of cyst infection was diagnosed as having AA amyloidosis, further intensive therapy with drainage or partial resection of the infected hepatic cysts should be attempted. This will also aid the selection of effective antibiotics by detecting intracytic pathogens, as well as removing the focus of infection. In addition, remission of amyloidosis can be achieved if the cyst infection is completely controlled.

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

References


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