Chronic renal failure due to amyloid nephropathy caused by chronic infection after total hip replacement

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Abstract A 75-year-old woman was admitted to our hospital because of proteinuria, pitting edema on the foot, and renal impairment. She had undergone total hip replacement (THR) for femoral neck fracture at the age of 66. Nine years later, she met with an accident during farming and was treated at an emergency hospital for severe general trauma. On the basis of systemic symptoms, she was diagnosed with nephrotic syndrome. Renal biopsy by Congo-red staining and electron microscopy revealed amyloid deposition on glomeruli, interstitium, and interlobar arteries. The amyloid was immunohistochemically identified as AA amyloidosis. The patient eventually required maintenance hemodialysis because of impaired renal function. AA amyloidosis is an unusual complication of intractable inflammation. Chronic infection with abscess occurred around the artificial hip joint following THR and possibly induced secondary amyloidosis. THR is a common and necessary procedure adopted for femoral neck fracture. Orthopedic surgeons should, however, carefully monitor the occurrence of chronic infection after THR because such an infection could lead to renal dysfunction and/or failure via AA amyloidosis in rare cases.

Keywords Secondary AA amyloidosis · Nephrotic syndrome · Persistent infection · End-stage renal failure · Total hip replacement

Introduction

Amyloidosis is a group of disorders in which insoluble protein fibers, known as amyloid proteins, are deposited in the extracellular space in various organs, causing organ dysfunction. Over 25 proteins are currently shown to be associated with amyloidosis [1–3]. Amyloidosis is broadly classified as systemic or localized based on the site of protein deposition, and serious clinical symptoms are characteristic of systemic disease.

In light chain (AL) amyloidosis, light chain immunoglobulins are produced by plasma cells and are deposited on systemic organs such as heart, kidney, liver, digestive organs, and peripheral nerves. In AA amyloidosis, anti-parallel β -pleated sheets composed of small fibers and serum amyloid A (SAA), which is produced by liver cells via stimulation of various cytokines, are formed and deposited on systemic organs [4, 5]. AA amyloidosis is a relatively rare disease, which has been associated with chronic inflammatory diseases, familial Mediterranean fever, and occasional malignancy.

Renal involvement is common in systemic AA amyloidosis and leads to poor outcome; moreover, survival rates are poor because of the deleterious effects of this disorder [6]. A high percentage of renal dysfunction has been found in patients prior to death [7], and early referral to a nephrologist may improve the poor prognosis [8]. Thus, early detection and treatment of prior condition of AA amyloidosis, such as the latent chronic inflammation, is important to prevent poor prognosis. We report a case of an

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elderly woman who developed nephrotic syndrome and was diagnosed with amyloid nephropathy 9 years after total hip replacement for a right femoral neck fracture, and 6 years after serious occupational injury. Although the specific cause of the amyloid nephropathy was difficult to determine, persistent postoperative infection after total hip replacement was thought to play a significant role.

Case report

A 75-year-old woman presented with proteinuria, edema on the lower extremities without exanthema, and renal dysfunction. She had hypertension since 65 years, for which she took telmisartan. She had undergone myomectomy at 44 and total hip replacement (THR) for a right femoral fracture at 66. At the age of 69, she met with a tractor accident during farming, suffered whole-body injuries, and was admitted under critical condition. Three months later, she was discharged after various treatments including skin grafting.

At the age of 75, she developed edema on the lower extremities and proteinuria (3+) and renal impairment (serum creatinine, 1.7 mg/dL). Her local physician transferred her to our hospital for detailed examination. With regard to familial

Table 1 Urinary data of the patient

Urinalysis	
Urine protein	8.9 g/day
Biochemical analysis (Random urine test)	
β2-microglobulin	27800 μg/L
N-Acetyl-β-D-glucosaminidase	18.5 U/L
Urine protein	592 mg/dL
Urine creatinine	69.7 mg/dL
Dipstick test/random urine test	
Protein	3+
Glucose	±
Occult blood	2+
Urobilinogen	Absent
Leukocyte	2+
Epithelial cell	3–4
Bacteria	Few
Bence Jones protein	Absent
Renal function test	
24-h creatinine clearance	16.5 mL/min
Sediment	
Leukocyte (No./HPF)	50–99/HPF
Blood (No./HPF)	50–99/HPF
Epithelial cells	1+
Bacteria	Few

HPF high power field

Table 2 Blood work of the patient

Blood count	
White blood cell	8800/mm ³
Red blood cell	256 × 10 ⁴ /mm ³
Hemoglobin	7.2 g/dL
Hematocrit	23.5 %
Mean corpuscular volume	91.8 fL
Mean cell hemoglobin	28.1 pg
Mean corpuscular hemoglobin concentration	30.6 %
Platelet	33.8 × 10 ⁴ /mm ³
Blood sedimentation	1-h value 147 mm/h
Biochemical tests	
Total protein	4.9 g/dL
Albumin	2.3 g/dL
Blood urea nitrogen	33 mg/dL
Creatinine	2.9 mg/dL
Uric acid	6.5 mg/dL
Sodium	143 mEq/L
Potassium	5.1 mEq/L
Chlorine	113 mEq/L
Calcium	7.9 mg/dL
Magnesium	1.9 mg/dL
Phosphorus	3.4 mg/dL
Aspartate-aminotransferase	15 IU/L
Alanine-aminotransferase	10 IU/L
Lactate dehydrogenase	187 IU/L
Alkaline phosphatase	212 IU/L
γ-Glutamyl transpeptidase	20 IU/L
Creatine kinase	121 IU/L
Total cholesterol	170 mg/dL
Triglyceride	127 mg/dL
Iron	16 μg/dL
Unsaturated iron binding capacity	163 μg/dL
Ferritin	165 ng/mL
Amylase	107 IU/L
Fasting blood glucose	80 mg/dL
HbA1c	5.3 %
Arterial blood gas	
pH	7.296
Oxygen partial pressure	95.9 mmHg
Carbon dioxide partial pressure	49.0 mmHg
Bicarbonate ion	23.1 mEq/L
Base excess	−3.3
Immunology	
C-reactive protein	2.31 mg/dL
Immunoglobulin G	1060 mg/dL
Immunoglobulin A	345 mg/dL
Immunoglobulin M	50 mg/dL
Antinuclear antibody	–
dsDNA	7.7 IU/mL

Table 2 continued

Blood count	
Rheumatoid factor	Not tested
C3/C4	97/36 mg/dL
Homolytic complement activity	44.4 CH50/mL
Myeloperoxidase-anti-neutrophil cytoplasmic antibody	–
Cytoplasmic anti-neutrophils	–
Cytoplasmic antibodies	–
Infection	
HBs antigen	–
HCV antibody	–
Parasite eggs	–

hemorrhage. Her height and weight were 158.0 cm and 57.1 kg, respectively. Her vital signs were as follows: body temperature, 36.8 °C; heart rate, 68/min; and blood pressure, 132/80 mmHg. Pitting edema was present in both lower extremities without exanthema. The palpebral conjunctiva was pale and anemic. Blood and urine chemistry results are summarized in Tables 1 and 2. Electrocardiogram revealed normal sinus rhythm with no axis deviation. Plain chest radiograph was normal. The size of the right and left kidney as measured by ultrasonography was 8.9×3.9 and 9.6×4.3 cm, respectively, and the signal intensity of renal parenchyma was increased but morphologically thin. The contrast between renal parenchyma and renal sinus was relatively preserved. Renal biopsy was performed after admission. Light microscopy (Fig. 1) showed 21 glomeruli, of which 17

Fig. 1 Histopathology of the kidney specimen (**a–c**). Periodic acid-Schiff (PAS) staining (**a–b**) and periodic acid methenamine silver (PAM) staining (**c**) were performed. Non-structured amyloid deposits were found in the vessel wall and tubule (**a**), glomerulus (**b–c**) (*red arrowheads*). **d** Congo-red staining (magnification $\times 400$). The sample shows polarization when observed under polarized filter. **e, f** Electron microscopy findings. Amyloid deposits and fibers are seen (*red arrows*)

medical history, her father had suffered from thyroid cancer and cerebral hemorrhage, mother had gastric cancer, 1 sister had thyroid cancer, and 2 sisters had suffered from cerebral

showed large or moderate non-structured substrate deposits. The mesangial cells increasingly grew, and 3 glomeruli showed global and segmental sclerosis.

Fig. 2 Skin-grafted trial area in the right groin. A part of the skin-grafted area develops a granulomatous lesion. Discharge of pus is found

Inflammatory cell infiltration and extensive fibrous hyperplasia were present in the renal interstitium. Non-structure deposits were also found in the renal tubules and interlobular arteries, and fluorescent antibody staining revealed C3 deposits in the glomerular basement membrane, but IgG, IgA and C1q deposits were absent. Congo-red staining confirmed the presence of non-structured substrates. Immunohistochemical staining supported the diagnosis of AA amyloidosis. Electron microscopy revealed amyloid fiber deposits in the glomerulus, interstitial tissue and arterial wall. Amyloid fiber nodules were seen in the glomerulus, suggesting destruction of the basement membrane. She was diagnosed with reactive AA amyloidosis (secondary amyloidosis) based on the aforementioned evidence. Because (chronic) rheumatoid arthritis or tuberculosis was absent, the etiology of secondary amyloidosis was unclear. The patient frequently complained of severe pain in the right femur around the groin, where a fistula had formed (Fig. 2). At this time, CRP level increased to 2.31 mg/dL from 0.01 mg/dL (examined 16 years before) and remained at 2–3 mg/dL thereafter. The patient then consulted the orthopedic hospital where she had undergone THR. Purulent discharge from the right groin indicated infection in the artificial joint, and an abscess surrounding the artificial femoral head was confirmed. Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected from the purulent discharge. The patient received cefditoren pivoxil orally and cephem antibiotics intravenously. The secondary amyloidosis was probably caused by this infection. Nephrotic syndrome was not improved, but serum creatinine levels remained at 1.7 mg/dL before THR. One year after THR, blood urea nitrogen (BUN) and S-Cr levels gradually increased and drastically increased to 67 and 9.0 mg/dL, respectively,

11 months later. Therefore, maintenance hemodialysis was initiated.

Discussion

We report a case of reactive AA amyloidosis (secondary amyloidosis) in which amyloid protein was derived from the acute phase of serum amyloid A protein. This condition is thought to be a consequence of chronic inflammatory disease. After infection, but before initiation of hemodialysis, upper and lower gastrointestinal endoscopy were conducted, but gastrointestinal tract amyloidosis was not found.

The existence of underlying inflammatory disease was initially unknown, and the cause of the secondary amyloidosis could therefore not be determined. However, non-healing wound with pus in the right femur was later discovered, and antibiotic treatment was initiated. However, CRP levels did not improve. Assuming that chronic infection had been persistent after THR, we could have prevented secondary amyloidosis if the source of infection had been identified sooner [9]. In one report, THR was not associated with reduced kidney function [10]. However, another study reported reduction of renal function following artificial joint replacement [11]. A previous report has also suggested that secondary amyloidosis can occur following THR [12]. In our patient, chronic inflammation occurred and probably lasted for a long-time after THR. In addition, antibiotic treatment was frequently interrupted. This situation probably causes secondary amyloidosis. The farming accident may have promoted this condition. AA amyloidosis induces more extensive amyloid deposits on the tubular basement membrane, interstitial tissue, and arteriolar walls of the kidneys and rapidly worsens the prognosis of patients compared to AL amyloidosis [13]. In our case, amyloid deposition on the tubular basement membrane and arteriolar walls of the kidneys was more intense than that previously reported [14]. In addition, immunofluorescence revealed C3 deposition. Thus, membranous type of nephritic syndrome could have coexisted in amyloid fibers and nodules in the glomerulus without causing destruction of the basement membrane because amyloid protein is typically present in the mesangium and peripheral capillary wall at the early stage. If this assumption was true, rapid deterioration of renal function could have occurred.

Systemic diseases have a strong impact on renal function, and therefore early detection of an underlying condition is essential to prevent the deterioration of renal function. A previous report showed that a patient with filariasis—a condition associated with chronic inflammation—receiving antifilarial therapy suffered from reversible

acquired AA-type renal amyloidosis [15]. In a patient with autosomal dominant polycystic kidney disease, recurrent infections from renal or hepatic cysts lasting 30 years induced AA amyloidosis in gastrointestinal tract [16]. In our case, a localized, yet prolonged infection, around the region of the replaced hip, could have led to secondary amyloidosis. In addition, because of the rapid deterioration of renal function in this case, early introduction of hemodialysis was required. Moreover, extensive amyloid deposits on the tubule membranes, interstitial tissue, arteriolar walls, and the glomerulus were thought to significantly contribute to renal function and end-stage renal failure. Furthermore, the patient had a strong familial history of cerebral hemorrhage (father and female siblings) of unclear etiology. While cerebral amyloid angiopathy may have been caused amyloidosis, the amyloid proteins associated with amyloid angiopathy are A β type, which are different from the AA type. Genetic familial amyloidosis can be ruled out in the case of our patient, because it is usually a localized lesion mostly occurring in the eyes and peripheral nerves, and this pattern of involvement was not found in our patient [17–20].

Thus, the prolonged infection in the THR lesion may have caused AA-type renal amyloidosis in our patient.

THR is effective, widely accepted, and one of the most successful orthopedic procedures for femoral neck fracture. THR can relieve pain and improve function, activity of daily life (ADL), and quality of life. Therefore, THR is used for treatment of femoral neck fracture across age groups from very young [21] to older patients [22]. However, inflammation due to infection in the artificial joints is a significant potential complication. Infection is reported to be a frequent cause of surgical failure after joint replacement surgery, and THR revision surgery is required in 7–16 % of cases to treat the infection [23]. Several studies indicate that obesity [24] and superficial and deep infections [25] cause infection after THR. Prolonged inflammation after orthopedic surgery can cause secondary amyloidosis, which may in turn result in end-stage renal failure. Therefore, we think that the association between THR and development of secondary amyloidosis leading to renal failure is a novel finding, and nephrologists should monitor the general condition of the patients after receiving THR, such as increase in body weight, minor signs of infection, etc. Simultaneously, orthopedic surgeons should monitor patients for the development of chronic infection and secondary amyloidosis during THR follow-up.

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Conflict of interest None.

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