Fever associated with severe dialysis-related amyloidosis

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Abstract Dialysis-related amyloidosis (DRA) is one of the most important complications in patients on long-term hemodialysis (HD). DRA often affects the osteoarticular system; however, little is known about the role of β_2 -microglobulin in the induction of fever in HD patients. We report a 64-year-old woman on long-term (24 years) HD who developed polyarthralgia and intermittent fever. Infectious diseases, connective tissue diseases, and malignant neoplasm were ruled out. Computed tomography and magnetic resonance imaging showed swelling of the soft tissues around bilateral shoulder and hip joints, suggestive of amyloid deposits. Gallium scintigraphy showed abnormal uptake in the vicinity of several large joints. It was presumed that the fever was related to the amyloid joint deposits, and the patient was treated with prednisolone and β_2 -microglobulin adsorption therapy. The treatment resulted in the resolution of fever, relief of arthralgia, and normalization of several inflammatory cytokines and C-reactive protein. The findings suggest that massive DRA could cause systemic inflammatory response in patients on long-term HD.

Keywords Dialysis-related amyloidosis ·
 β_2 -Microglobulin · Long-term hemodialysis ·
Systemic inflammatory response

Abbreviations

AGE	Advanced glycation end product
β_2 M	β_2 -Microglobulin
CRP	C-reactive protein
DRA	Dialysis-related amyloidosis
HD	Hemodialysis
PSL	Prednisolone

Introduction

Dialysis-related amyloidosis (DRA) is a serious complication in patients on long-term hemodialysis (HD). Its clinical and radiological manifestations include chronic arthralgia, carpal tunnel syndrome, diffuse destructive arthropathy, spondyloarthropathy, and bone cysts [1]. The most distinctive histological feature of DRA is the deposition of amyloid fibrils in the affected joints, especially in periarticular bones.

Although several biochemical and immunohistological studies have demonstrated that β_2 -microglobulin (β_2 M) is a major constituent of amyloid fibrils in DRA [2–5], the pathological role of β_2 M remains poorly understood. Miyata et al. [6, 7] have reported that advanced glycation end product (AGE)- β_2 M may function as a pathogenic factor responsible for induction of the inflammatory response that ultimately leads to joint/bone destruction in DRA. However, only some reports have documented β_2 M-based induction of the systemic inflammatory response in patients on long-term HD [8, 9]. In this report, we describe a patient on long-term HD who developed severe DRA and recurrent fever with arthralgia. Corticosteroids therapy and β_2 M adsorption therapy resulted in successful amelioration of the arthralgia and high fever.

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Case report

A 64-year-old woman with chronic renal failure probably due to glomerulonephritis had been on maintenance HD for 24 years since 1983. She had undergone two surgeries for bilateral carpal tunnel syndrome with dialysis-related amyloid deposition 12 years previously. She had also undergone several operations for left hip osteoarthritis, trigger fingers, and recurrent right carpal tunnel syndrome due to DRA. In December 2005, she visited the Department of Orthopedics for polyarthralgia and intermittent fever. She was diagnosed with pseudogout and prescribed 10 mg/day prednisolone (PSL). The symptoms improved and PSL was reduced to 2.5 mg/day. In July 2007, she had recurrent fever above 38 °C and was admitted to our hospital.

On admission, arthralgia and swelling of the right hip joint were noted. Her arterial blood pressure was 140/72 mmHg and body temperature was 38.2 °C. Clinical examination showed neither abnormal respiratory sound nor lymph node swelling. Laboratory tests showed leukocyte count $9.63 \times 10^9/L$, neutrophils 85.5 %, hemoglobin 99 g/L, platelet count $270 \times 10^9/L$, total protein 70 g/L, and lactate dehydrogenase 183 U/L. High serum levels of β_2M (17.0 mg/L) and C-reactive protein (CRP) (67.8 mg/L) were identified. Serological tests were normal, including rheumatoid factor, anti-nuclear antibody, IgG, and serum complement levels. Thyroid function was also normal. Plain X-ray of the right hip showed a well-defined cystic lesion in the femoral neck and a fragile fracture in the femoral head.

(Fig. 1a). Chest and abdominal computed tomography scans indicated swollen soft tissues around the bilateral shoulder joints and the bilateral hip joints, suggesting amyloid deposits. Magnetic resonance imaging of the right hip joint showed a low-intensity area, probably due to amyloid deposits on T1- and T2-weighted images, and a high-intensity area due to fluid collection on the T2-STIR image (Fig. 1b).

Percutaneous needle biopsy was taken from the swollen soft tissue around the right hip joint 2 weeks after admission. The Congo red-stained specimens showed amyloid deposits. The culture of fluid collected from around the amyloid deposits in the hip joint was negative for bacteria. Gallium scintigraphy taken to determine the cause of fever showed abnormal uptake in the vicinity of the bilateral shoulder, hip, elbow, knee, wrist, and ankle joints (Fig. 1c). However, no abnormal uptake was detected in the lymph nodes and other internal organs by gallium scintigraphy. Percutaneous tissue biopsy was obtained from the amyloid deposits in the right hip joint 1 month after admission. The specimen showed amyloid deposits inside the soft tissue with mild chronic inflammatory infiltration, though neutrophil infiltration was minimal.

Infectious diseases, connective tissue diseases, and malignant neoplasm were ruled out. We presumed that severe amyloid deposits around the joints caused focal inflammation, which was associated with fever. At day 43 of hospitalization, the patient was treated with 10 mg/day PSL, which was later increased to 20 mg/day. The fever subsided and her CRP level fell to within the normal range (Fig. 2). Normal body

Fig. 1 **a** X-ray of the right hip shows a well-defined cystic lesion in the femoral neck (arrows) and a fragile fracture in the femoral head (arrowheads). **b** T2-STIR magnetic resonance images of the right hip joint shows a low-intensity area (arrow), probably due to amyloid deposits, and a high-intensity area (arrowheads) representing fluid collection. **c** Gallium scintigraphy taken in July 2007 shows abnormal uptake in the bilateral shoulder, hip (arrows), elbow, knee, wrist, and ankle joints. **d** Gallium scintigraphy taken in February 2009 shows similar uptake in the same joints (arrows), with the exception of milder uptake in the right hip joint. **e** Gallium scintigraphy taken in March 2010 shows further diminution of the uptake (arrows)

temperature and CRP were maintained under PSL therapy; however, the patient still experienced pain in the right hip joint associated with the fragile fracture. Thus, she underwent

right total hip arthroplasty at day 93 of hospitalization. After surgery, pain in the hip joint completely disappeared and the body temperature was normalized.

Fig. 2 Clinical course. *PSL* prednisolone, *THA* total hip arthroplasty, *CRP* C-reactive protein, *BT* body temperature

Fig. 3 Histopathological examination of the surgical specimen shows amyloid deposition in the synovial membranes. **a** Hematoxylin and eosin staining shows nodular lesions in the synovium ($\times 40$). **b** Deposition of amyloid is clearly recognized by Congo red staining

($\times 40$). **c** Immunohistochemical examination identifies β_2 M in the synovial connective tissue ($\times 40$). **d** CD68-positive monocytes/macrophages infiltrate the synovial tissue ($\times 40$)

The synovial tissues in the surgical specimen contained amyloid deposition (Fig. 3a, b), and immunohistochemical examination identified large amounts of β_2 M-positive cells (anti- β_2 M antibody; DAKO, Glostrup, Denmark) (Fig. 3c), as well as the presence of amyloid deposition (Fig. 3b). Numerous CD68-positive monocytes/macrophages (anti-CD68 antibody; DAKO) were frequently seen in the synovial tissue of β_2 M-positive lesions (Fig. 3d).

The dose of PSL was reduced to 12.5 mg/day and the patient was discharged from the hospital after approximately 5 months of hospitalization. After discharge, she visited the HD clinic regularly three times per week, maintained PSL therapy at 5–12.5 mg/day, and remained free of any fever, with near-normal CRP. In February 2009, she developed intermittent fever with polyarthralgia again when the dose of PSL was 5 mg/day. Adrenal insufficiency was not apparent because her serum cortisol and adrenocorticotrophic hormone (ACTH) levels were normal. Gallium scintigraphy showed abnormal uptake at the bilateral shoulder, hip, elbow, knee, wrist, and ankle joints again (Fig. 1d), though the uptake in the right hip joint was less than before. She underwent HD combined with β_2 M adsorption column (Lixelle[®]; Kaneka Corporation, Osaka, Japan) from March 2009 to reduce her blood β_2 M level. The fever subsided and the patient maintained normal temperature since April 2009. A repeat gallium scintigraphy in March 2010 showed lesser uptake in all joints relative to that observed previously (Fig. 1e).

Discussion

DRA is recognized as a serious complication in patients on long-term HD and results in the development of carpal tunnel syndrome, bone cysts, destructive spondyloarthropathy, and joint pain, with functional disturbances such as limitation of motion [10]. However, there is no information on whether β_2 M induces the systemic inflammatory response in HD patients.

Previous studies have indicated that β_2 M can cause inflammation in certain conditions and that β_2 M deposits are associated with pericapsular and synovial accumulation of macrophages in dialysis patients [5, 11]. Pathologically, these macrophages could worsen bone erosion in these patients. Miyata et al. [7] showed that AGE-modified β_2 M

increased the secretion of TNF- α and IL-1 β from macrophages in vitro. Other studies also suggested that AGE-modified β_2 M was a potential factor in the inflammatory response of monocytes [12–15]. Considered together, these data suggest that β_2 M deposits could initiate an inflammatory response through monocyte/macrophage accumulation. For this reason, we measured serum IL-1 β , IL-6, and TNF- α concentrations in this patient; their respective levels were high at 32 pg/mL (normal range; <10 pg/mL), 11.1 pg/mL (<4.0 pg/mL), and 3.2 pg/mL (0.6–2.8 pg/mL) at the time of intermittent fever in February 2009 (Table 1). The pathological role of these cytokines in the inflammatory process (probably through DRA) was confirmed when fever subsided following PSL therapy and β_2 M adsorption therapy in March 2010; these changes were associated with large reductions in the serum IL-1 β , IL-6, and TNF- α to 13, 2.3, and 3.1 pg/mL, respectively. Gallium scintigraphy also indicated abnormal uptake in the joints in February 2009, in association with amyloid deposition, and such uptake diminished in March 2010 following treatment.

The inflammatory process in this patient might also involve other mediators in addition to IL-1 β , IL-6, and TNF- α . In this regard, the β_2 M column Lixelle[®] has the adsorptive ability of a battery of cytokines, such as IL-1, IL-6, IL-8, and TNF- α [16, 17], which are known to be closely related to the systemic inflammatory response. A recent report showed that Lixelle[®] decreased the serum level of high-sensitivity CRP in HD patients because Lixelle[®] adsorbs a variety of inflammatory cytokines [18]. From these findings, the systemic inflammation in this patient may have been improved by the ability of Lixelle[®] to adsorb inflammatory cytokines.

Fever associated with DRA in HD patients is rare. Some studies have reported the presence of fever in patients with DRA and a 20-year history of HD [8, 9]. Our patient underwent maintenance HD for 24 years since 1983, and she had numerous DRA deposits in several joints. The exact prevalence of complications associated with DRA in patients on long-term HD like this patient needs to be evaluated.

In summary, we described a patient on long-term HD with severe DRA who developed intermittent fever and polyarthralgia. Laboratory and radiological investigations suggested that DRA could be the underlying cause of the systemic inflammatory response. Furthermore, the combination of corticosteroid therapy and β_2 M adsorption therapy seems beneficial and effective against this inflammatory process.

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Conflict of interest All the authors have declared no competing interest.

Table 1 The changes of serum inflammatory cytokines

	IL-1 β (pg/mL)	IL-6 (pg/mL)	TNF- α (pg/mL)
Normal range	<10	<4.0	0.6–2.8
February 2009	32	11.1	3.2
March 2010	13	2.3	3.1

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