

Disseminated amyloidosis presenting with right proximal femur pathological fracture in a haemodialysis end-stage renal failure patient

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Osteoarticular amyloidosis can be one of the musculoskeletal system manifestations related to dialysis. We share our experience in dealing with a case of disseminated haemodialysis-associated amyloidosis in a 74-year-old end-stage renal failure patient. This patient suffered from a serious complication, namely an unprovoked pathological fracture at the basal neck region of the right femur. Polyarticular cystic and lytic lesions over the contralateral proximal femur, bilateral proximal humerus and the right lunate were noted on further imaging. In view of extensive amyloidotic infiltration into the proximal femur as well as the acetabulum, a cemented total hip arthroplasty operation was performed for pain relief and restoration of function. The radiological investigations, diagnostic challenges, operative as well as histopathological findings are discussed. This disease should be considered in the differential diagnosis of pathological juxta-articular fracture in patients undergoing haemodialysis.

Introduction

Osteoarticular amyloidosis is a well-known complication of dialysis, in which the normally soluble beta-2 microglobulin accumulates in extracellular tissue 40 to 50 times higher than normal concentrations and forms insoluble fibrils.¹ The serum beta-2 microglobulin level in haemodialysis patients is noted to be significantly elevated with a range of 40 to 90 mg/L as compared with 1 to 3 mg/L in normal subjects.^{2,3} The amyloid depositions are found in the peri-articular tissue, synovium and bone, and give rise to cystic lesions in the osseous and articular regions.⁴ The number and size of the cysts increase with the duration of dialysis.⁵ The clinical manifestations of osteoarticular amyloidosis seemed to be dependent on the duration of haemodialysis, typically appearing 6 to 8 years from commencement.^{6,7} This phenomenon was first brought to attention in the wrist, where it manifested as carpal tunnel syndrome with small cystic lesions involving the carpus.⁸ The spectrum of manifestations extend to more serious complications such as destructive spondyloarthropathy⁹ and pathological fractures.¹ Huax et al¹⁰ first described the clinical features of pathological fracture in haemodialysis patients with amyloid deposition in the area of fracture on histological examination in 1985. Since then, most of the reported pathological fractures associated with amyloidosis were usually around the femoral head and neck region,¹¹ whereas in others they manifested as amyloid bone cysts with impending femoral neck fracture.^{12,13} For the treatment of established pathological fractures, hemiarthroplasty¹⁴ and bipolar femoral head replacement¹¹ have been reported. For impending pathological fracture, prophylactic internal fixation with autogenous iliac bone grafting has been performed.¹² For large femoral neck cysts, management has involved prophylactic curettage and autogenous iliac crest bone grafts.¹³

Key words

Arthroplasty, replacement; Amyloidosis;
Hip fractures; Kidney failure, chronic;
Renal dialysis

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Case report

A 74-year-old man, with known polycystic kidney disease and end-stage renal failure, presented with a 2-week history of progressive right hip and thigh pain in December 2010. He had undergone continuous ambulatory peritoneal dialysis (CAPD) since 1997, but in 2006 he was switched to haemodialysis due to multiple episodes of CAPD peritonitis. Haemodialysis with dialyser FX 8 (Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany) bicarbonate, and ultrapure dialysate was conducted 3 times per week.

Clinical examination revealed a shortened and externally rotated right lower limb. Active flexion and the range of movement in general were markedly limited by the hip pain. The hip was particularly painful on axial loading and rocking.

Blood parameters showed normal white cell count of 7.3×10^9 /L, a normal calcium level of 2.55 mmol/L. The phosphate level was 2.59 mmol/L (reference range [RR], 0.82-1.40

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一名正接受血液透析的末期腎衰竭患者出現右股骨骨折的散播性澱粉樣變

骨關節澱粉樣變可以是與透析有關的其中一種肌骨系統症狀。本文報告一名74歲末期腎衰竭患者呈散播性血液透析相關的澱粉樣變。患者出現嚴重的併發，包括右股骨的基底頸部出現原因不明的病理性骨折。放射影像顯示在對側股骨近端、雙側肱骨近端和右月狀骨有多發性溶骨性病變。由於澱粉樣變已廣泛浸潤股骨近端和髌白，我們替病人進行水泥型全髖關節置換手術以舒緩病人痛楚及恢復其關節的活動能力。本文探討此病的放射性檢查、診斷挑戰、手術及病理組織學結果。接受血液透析的病人如果出現關節周圍骨折的情況，便應把骨關節澱粉樣變納入鑒別診斷中。

mmol/L) and the parathyroid hormone level was 34.1 pmol/L (RR, 1.60-6.90 pmol/L), suggestive of secondary hyperparathyroidism. However, the erythrocyte sedimentation rate and C-reactive protein levels were elevated to 123 mm/h (reference level [RL], ≤ 30 mm/h) and 232.3 mg/L (RL, < 9.9 mg/L), respectively. Tumour marker levels were unremarkable. Prostatic specific antigen was 1.2 $\mu\text{g/L}$ (RL, < 4.0 $\mu\text{g/L}$), alpha-fetal protein was 1 $\mu\text{g/L}$ (RL, < 7 $\mu\text{g/L}$) and carcinoembryonic antigen was 3.5 $\mu\text{g/L}$ (RL, < 3.8 $\mu\text{g/L}$ for non-smokers). However, no septic focus was identified.

Pelvis and right hip X-rays revealed a fracture at the basal neck region of the right proximal femur, crossing a large lytic lesion (Fig 1a). The lesion appeared to be lined with a thin sclerotic rim, was well marginated, and had a narrow zone of transition. To achieve better delineation of the fracture pattern, multi-detector computed tomography of the right hip

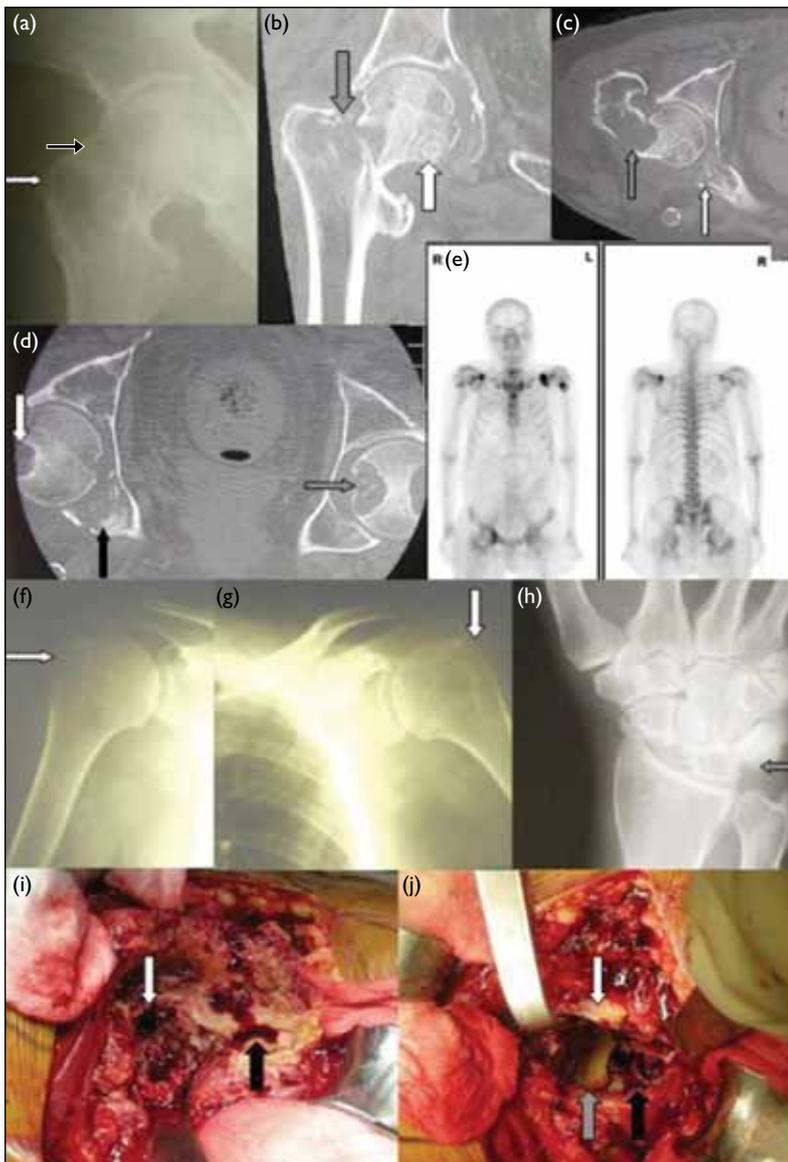


FIG 1. (a) An anteroposterior (AP) X-ray of the right hip shows a large well-demarcated radiolucent lesion with a thin sclerotic rim (white arrow) and a pathological fracture at the basal neck region (black arrow). (b) A coronal computed tomography (CT) of the right hip shows clearly that the fracture plane crosses the centre of the cystic-lytic bone lesion (grey arrow) with another mixed lytic-sclerotic lesion at the inferior femoral head region (white arrow). (c) An axial CT scan of the right hip shows extensive erosion to the acetabular rim (white arrow) and the large lytic lesion (grey arrow) eroding the basal neck region. (d) An axial pelvic CT shows multiple cystic lesions at both femoral heads (white arrow on the right side and grey arrow on the left side) together with acetabular erosion on the right side (black arrow). (e) Technetium-99m methylene diphosphonate bone scan (anterior and posterior views on the left and right side, respectively) predominantly shows abnormal uptake at both hips and shoulders, in which the uptakes at gleno-humeral region may represent additional peri-articular soft tissue uptake of amyloidosis deposition sparing the axial skeleton (ring-like uptake in central abdomen, corresponds to a known old fluid collection on previous contrast CT). (f) An AP X-ray of the right shoulder shows a radiolucent lesion (white arrow) at the greater tuberosity region. (g) Smaller radiolucent lesions (white arrow) are noted on the AP X-ray of the left shoulder. (h) An X-ray of the right wrist shows a small lytic lesion at the medial aspect of the right lunate bone (grey arrow). (i) At surgery, erosion of the right femoral neck (white arrow) with extensive lining of grey- and tan-coloured fibrous-like tissues was noted. (j) Viewing from the labrum (white arrow) superiorly, the superior aspect of the acetabulum (grey arrow) was intact but the inferior acetabulum has already been eroded (black arrow)

joint was performed, and showed multiple expansive cystic-lytic lesions of various sizes in both proximal femora and the right acetabulum (Figs 1b-d). Skeletal survey of this patient also showed multiple similar radiolucent lesions in both humeral heads (Figs 1f-g) and the right lunate bone (Fig 1h). The upper endplate of the fifth lumbar vertebra was eroded. However, there were no fractures identified in these regions. Since there was a pathological fracture through a large lytic lesion in the femoral neck and additional lytic lesions at other sites, our main concern was to exclude metastatic bone disease. Whole-body bone Technetium-99m methylene diphosphonate (^{99m}Tc-MDP) coupled scintigraphy was arranged for further workup.

Unexpectedly, the abnormal MDP-bone uptakes were only located in both hips and both shoulders. The remainder of the axial skeleton was not affected. There was a mild increase in both proximal femora, the right acetabulum, and around both shoulders (including the proximal humerus on both sides) [Fig 1e]. The classical features of hyperparathyroidism (metabolic super-scan, increased skull bone uptake) were absent which made association with brown tumours less likely. In the absence of scattered axial skeletal involvement, multiple lytic metastases and multiple myeloma were considered unlikely. In the context of end-stage renal failure with long-term haemodialysis, the possibility of amyloidosis was considered since this entity commonly affects large joints such as hips and shoulders. Testing for raised serum beta-2 microglobulin level was not available in our hospital.

With regard to the extensive erosion of the right acetabulum and pathological fracture of right proximal femur in this patient, we performed cemented total hip arthroplasty for symptomatic relief and to restore early mobility. Cementation aimed to fill the acetabular defect and avoid further destruction due to ongoing amyloidosis which may occur following autogenous bone grafting. More importantly, he could immediately bear full weight postoperatively. His condition was optimised by haemodialysis 1 day before the operation. He was put in a right lateral position under general anaesthesia. A standard posterior Southern approach of the right hip was adopted. Upon further exposure, there was friable granulation tissue occupying the fracture plane and basal neck region of proximal femur (Fig 1i). The antero-inferior aspect of the acetabulum was eroded with similar tissue (Fig 1j). The granulation tissue was excised by extensive curettage of the involved regions. After the acetabulum was prepared by reaming, the acetabular defect (involving the inferior part of anterior column extending into the pubic ramus and also acetabular floor) was augmented with gentamicin-loaded cement. A 44-mm Original M.E. Müller

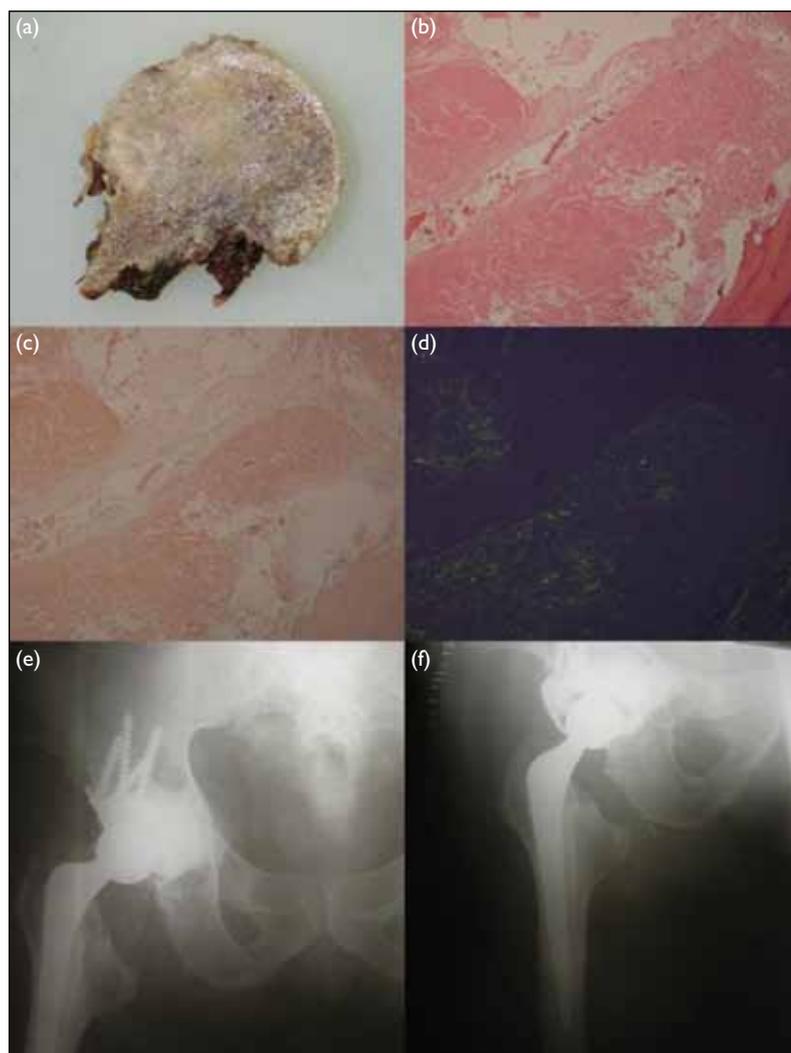


FIG 2. (a) A gross photo of the femoral head. The cut surfaces are greyish with friable tissue near the resection margin. (b) Microscopic examination shows aggregate of amorphous pinkish material (H&E stain, x 100). (c) and (d) Congo red stain under ordinary light, source and polarised light respectively (x 100). Apple-green birefringence under polarised light confirms the presence of amyloid. (e) Coronal and (f) sagittal X-rays of the pelvis shows cemented total hip arthroplasty implant in situ

Ring, CP Titanium (Protasul-Ti) ISO 5832-2 (Zimmer GmbH, Winterthur, Switzerland) was fixed with titanium screws. Thereafter, a 44-mm Original M.E. Müller Low Profile Cup was cemented using a 44/28, UHMW Polyethylene (Sulene-PE) ISO 5834-2, CP Titanium (Protasul-Ti) ISO 5832-2 (Zimmer GmbH). The femoral canal was then prepared. An Exeter V40 cemented hip stem with 37.5 mm Offset No. 0 (Stryker Orthopaedics, Mahwah [NJ], US) femoral prosthesis was fitted using a modern cementing technique. Reduction of the hip was completed with stability confirmed at 90 degrees of flexion and 50 degrees of internal rotation. The wound was closed in layers in an ordinary fashion.

Histobiochemical examination of the excised femoral head and fibrous tissue by haematoxylin-

eosin staining showed an aggregate of amorphous pinkish material. The amorphous pinkish material showed apple-green birefringence under polarised light using the Congo red stain, which confirmed the presence of amyloid (Figs 2a-d). Gram staining of the specimens was negative, while tissue culture yielded no microbial growth.

The patient started full-weight-bearing walking exercises 3 days after the operation upon drain removal. Postoperative X-rays were taken (Figs 2e-f). The left femoral cysts were closely monitored as the patient remained asymptomatic over the left hip. His haemodialysis regimen was switched to high-flux Dialyser FX 60 (Fresenius Medical Care AG & Co. KGaA) with an advanced Fresenius Polysulfone membrane (Helixone; Fresenius Medical Care AG & Co. KGaA) and bicarbonate, ultrapure dialysate 3 times per week each for 4 hours, so as to filter beta-2 microglobulin molecules from the blood circulation more effectively.

Discussion

The differential diagnosis of multiple lytic lesions in bone in patients undergoing haemodialysis includes: multiple myeloma, metastatic disease, cystic change from brown tumours of hyperparathyroidism, subchondral degenerative cysts, infection, or Waldenström's macroglobulinaemia.¹⁴ Besides the characteristic imaging features in characteristic locations, the diagnosis of amyloidosis can only be achieved by histology and immunostaining.¹⁴

The X-ray and computed tomographic (CT) findings of our patient demonstrated the well-delineated, round or oval radiolucencies in the femoral neck region, sometimes referred to as 'the herniation of the femoral neck'.¹⁵ This appearance was thought to be caused by herniation of soft tissues through erosions or perforations on the surface of the femoral neck region from pressure of the overlying capsule.¹⁵ The juxta-articular location of the bone cysts in the proximal femur could reflect a process in which amyloids invade locally from adjacent synovium.¹⁶ The amyloid infiltration is

known to cut off blood supply to the femoral head and neck, causing osteonecrosis first, femoral head subchondral fractures, and subsequently pathological neck fractures.¹⁷ Besides lytic lesions and pathological fractures, other osteoarticular manifestations of amyloid include: osteoporosis, osteonecrosis, peri-articular soft tissue masses, subchondral cysts and erosions, contractures and joint subluxations.⁴ However, whether the pathogenesis of amyloidosis in patients receiving haemodialysis occurs via local or systemic routes remains controversial.^{11,13}

The relatively short 4-year period of haemodialysis in our patient, rapid progression to disseminated osteoarticular amyloid infiltrations over multiple bones, together with pathological fracture of the right proximal femur, all posed an unusual clinical picture. However, retrospective review of a previous CT scan of the abdomen and pelvis (undertaken for sepsis) showed that the disease process had already started in 2007. At that time, smaller-sized cystic-lytic lesions were already present in both femoral heads. Lee et al¹⁴ attributed the rapid development of pathological femoral neck fracture to the greater age of patient at haemodialysis commencement, the long duration of the patient's chronic renal disease despite a short period of haemodialysis, and a newly designed haemodialysis membrane. It was noted that beta-2 microglobulin-derived amyloidosis may occur in elderly patients on dialysis for less than 5 years.²

The osteopenic or osteoporotic bone quality, vulnerable haemodynamic status of patients in end-stage renal failure, and potential impairment in wound healing due to uraemia all pose a collective challenge to successful total joint arthroplasty operation.

Conclusions

The occurrence of osteoarticular amyloidosis in patients receiving long-term haemodialysis enters the differential diagnosis of any bone cyst. Serious complications such as pathological hip fracture can occur as there is a documented propensity of the amyloidosis to involve the proximal femoral regions. This condition is surgically treatable.

References

1. Danesh F, Ho LT. Dialysis-related amyloidosis: history and clinical manifestations. *Semin Dial* 2001;14:80-5.
2. Stein G, Schneider A, Thoss K, et al. Beta 2-microglobulin serum concentration and associated amyloidosis in dialysis patients. *Nephrol Dial Transplant* 1991;6 Suppl 3:57S-61S.
3. Mumtaz A, Anees M, Bilal M, Ibrahim M. Beta-2 microglobulin levels in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2010;21:701-6.
4. Isaacs M, Bansal M, Flombaum CD, Lane J, Smith J. Case report 772. Stress fracture of the hip secondary to renal osteodystrophy and erosion of ischium due to amyloid deposition. *Skeletal Radiol* 1993;22:129-33.
5. Gielen JL, van Holsbeeck MT, Hauglustaine D, et al. Growing bone cysts in long-term hemodialysis. *Skeletal Radiol* 1990;19:43-9.
6. Jadoul M. Dialysis-related amyloidosis: importance of biocompatibility and age. *Nephrol Dial Transplant* 1998;13 Suppl 7:61S-64S.

7. Dember LM, Jaber BL. Dialysis-related amyloidosis: late finding or hidden epidemic? *Semin Dial* 2006;19:105-9.
8. Schwalbe S, Holzhauer M, Schaeffer J, Galanski M, Koch K, Floege J. Beta 2-microglobulin associated amyloidosis: a vanishing complication of long-term hemodialysis? *Kidney Int* 1997;52:1077-83.
9. Naito M, Ogata K, Nakamoto M, Goya T, Sugioka V. Destructive spondylo-arthropathy during long-term haemodialysis. *J Bone Joint Surg Br* 1992;74:686-90.
10. Huaux JP, Noël H, Bastien P, et al. Articular amyloidosis, femoral neck fracture and chronic periodic hemodialysis [in French]. *Rev Rhum Mal Osteoartic* 1985;52:179-82.
11. Tateishi H, Maeda M, Yoh K, Nakano T, Nakano K. Pathologic fracture associated with amyloid deposition in the bone of a chronic hemodialysis patient. A case report. *Clin Orthop Relat Res* 1992;274:300-4.
12. Naito M, Ogata K, Shiota E, Oyama M. Amyloid bone cysts of the femoral neck. Impending fractures treated by curettage and bone grafting. *J Bone Joint Surg Br* 1994;76:922-5.
13. Fukunishi S, Yoh K, Yoshiya S. Bone graft for large bone cysts of the femoral neck in patients on hemodialysis. *Clin Orthop Relat Res* 2007;461:175-9.
14. Lee KS, van Holsbeeck MT, Abbud A. Atypical rapid progression of osteoarticular amyloidosis involving the hip in a patient on hemodialysis using polyacrylonitrile membranes. *Skeletal Radiol* 2010;39:79-83.
15. Pitt MJ, Graham AR, Shipman JH, Burkby W. Herniation pit of the femoral neck. *AJR Am J Roentgenol* 1982;138:1115-21.
16. Goldstein S, Winston E, Chung TJ, Chopra S, Pariser K. Chronic arthropathy in long-term hemodialysis. *Am J Med* 1985;78:82-6.
17. Resnick D. *Diagnosis of bone and joint disorders*. 4th ed. New York: WB Saunders Co; 2002: 2054-8, 2176-83.

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