Skeletal Radiology (2019) 48:301–306
https://doi.org/10.1007/s00256-018-3009-2

CASE REPORT

Progression of dialysis-related amyloidoma towards pathologic fracture

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Received: 10 May 2018 / Revised: 12 June 2018 / Accepted: 14 June 2018 / Published online: 26 June 2018

Abstract
Amyloidosis is the extracellular deposition of amyloid protein fibrils, and this condition may be hereditary or acquired. Patients undergoing long-term hemodialysis are particularly at risk for developing acquired amyloidosis. A rare form of amyloidosis is an amyloidoma or amyloid tumor, which occurs when amyloid focally deposits in a section of the musculoskeletal system, most commonly in the osteoarticular system. Here, we present a case of a hemodialysis-related amyloidoma of the left femoral neck in an 80-year-old woman with end-stage renal disease on hemodialysis for 8 years. The purpose of this report is to provide an account of the unique clinical, imaging, and histopathologic manifestation of a dialysis-related amyloidoma that progressively enlarges over a 2-year period. This report also highlights some prophylactic measures that may reduce the risk of developing an associated pathologic fracture.

Keywords Amyloidoma · Pathologic fracture · Dialysis

Introduction

Hemodialysis-related amyloidosis is a unique form of acquired amyloidosis resulting from the reduced excretion of amyloid proteins. This type of amyloidosis typically occurs in patients with a history of long-term hemodialysis and is known to have a predilection for the osteoarticular system. This subtype of amyloidosis has clinical manifestations like erosive and destructive osteoarthropathies, destructive spondyloarthropathy most commonly affecting the cervical spine, carpal tunnel syndrome, and lytic bone lesions (i.e., amyloidomas) [1, 2]. Dialysis-related amyloidoma (DRA) has been recorded to have a tendency to localize in the proximal femur and its incidence is noted to increase with the extent of hemodialysis and the patient's age [3]. The primary protein involved in DRA is ß2-Microglobulin (ß2M), which produces the characteristic apple-green birefringence on polarized light following Congo red staining [4] of amyloid. As such, the definitive diagnosis of DRA involves obtaining a biopsy and histopathologic analysis of the sample. The diagnosis of DRA through clinical, imaging and histopathologic evidence is important for delineating these benign lesions from malignancy as well as for patient counseling that can help to reduce DRA-associated morbidity. We present a case of DRA of the left femoral neck in an 80-year-old woman, which exhibited size progression over nearly a 2-year period and subsequently developed a pathologic fracture. We also highlight the importance of careful monitoring of DRAs, serial assessment for pathologic risk fracture and prophylactic methods to reduce DRA progression towards pathologic fracture.

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Case report

Clinical history at first presentation

An 80-year-old woman with history of type 2 diabetes, end-stage renal disease (ESRD) and 8 years of hemodialysis presented to our hospital with left flank pain for 1 month. The

resulting workup was non-specific and also included an abdominal CT scan.

Imaging

On hip and abdominal CT imaging, a left femoral neck bone lesion measuring 1.2 × 1.1 cm was incidentally found (Fig. 1a) in addition to the primary finding of nonspecific mild thickening of the distal ileum and cecum in the right lower quadrant. The benign-appearing lesion had a sclerotic margin with slight focal cortical erosion anteriorly. No fractures or dislocations were noted.

Clinical history at second presentation

One year later, the patient presented with left hip pain resulting in inability to walk for the previous 5 days. The patient lived at home under the care of her granddaughter who denied any recent falls or trauma to the area of pain. Notable laboratory data included normal serum calcium, phosphate, and parathyroid hormone levels, as well as a polyclonal serum hypergammaglobulinemia without a clonal spike (not shown).

Imaging

Initially, a radiograph of the left hip was obtained. On the radiograph, a lucent lesion is observed at the superolateral aspect of the left femoral neck junction (Fig. 2). On CT imaging, this 1.6 × 1.3-cm lucent lesion was visualized in the same location with no apparent fractures or malalignment (Fig. 1b). Comparison with a previous CT scan from about 1 year prior demonstrated a slight increase in size of the lesion. On MRI, the lobulated erosive lesion appeared hypointense on T1- and T2-weighted imaging with cortical destruction but with well-defined borders and no soft tissue component (Fig. 3). Based on the imaging findings, the differential diagnosis included brown tumor and amyloidosis. A malignant lesion was less likely given the patient's history, presentation, and the lesion's characteristics on imaging. At this time, orthopedic oncology physicians recommended follow-up with repeat imaging in 3–4 months.

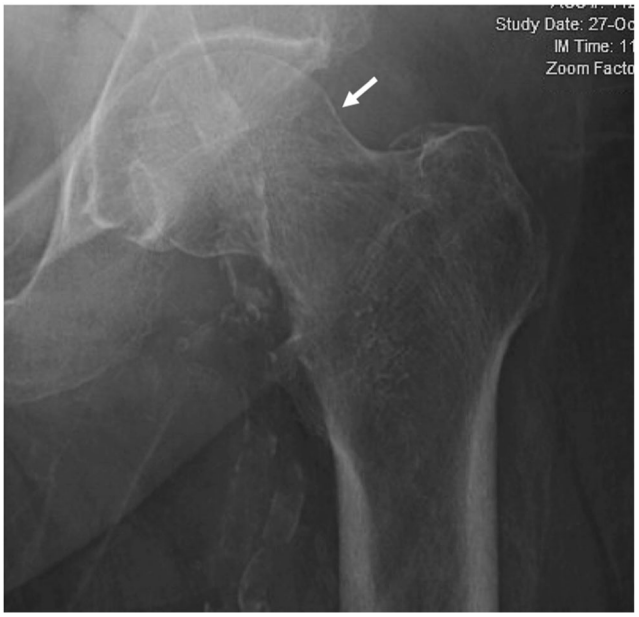

Fig. 2 AP radiograph of the left hip on the patient's second presentation. A lucent lesion (*arrow*) is seen on the superolateral aspect of the left femoral head-neck junction. Additional findings include evidence of diffuse osteopenia and extensive arterial calcifications. The Mirels' score was calculated to be 10 at this time

Clinical history at time of fracture

Two years after the initial presentation, the patient returned with an acute worsening of her left hip pain without any precipitating fall or trauma. Prior to this acute presentation, the patient had increasing difficulty with mobility.

Imaging

On hip and pelvic radiographs, a lucent line in the femoral neck suggestive of a pathologic fracture was seen. On CT, a nondisplaced fracture of the left femoral neck was found traversing the femoral neck lesion. Comparison with previous

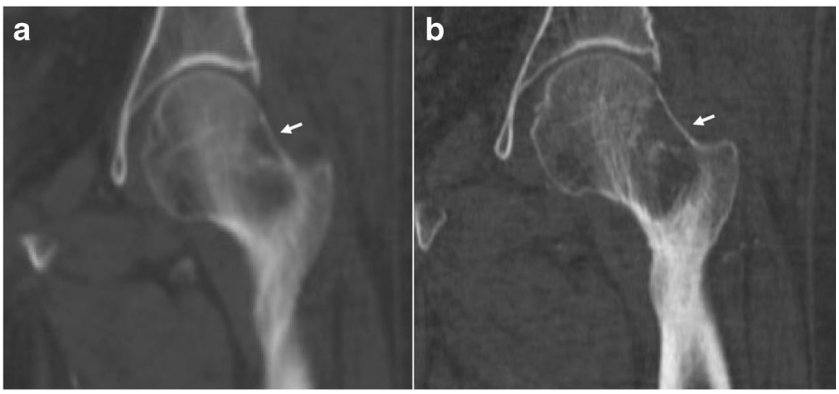

Fig. 1 An 80-year-old woman with left flank pain at initial presentation. A coronal CT reformation of the left femoral head and neck showing a lucent lesion (*arrow*) at **a** initial presentation and **b** 1 year later (*arrow*). An increase in lesion size from 1.2 × 1.1 cm to 1.6 × 1.3 cm can be observed

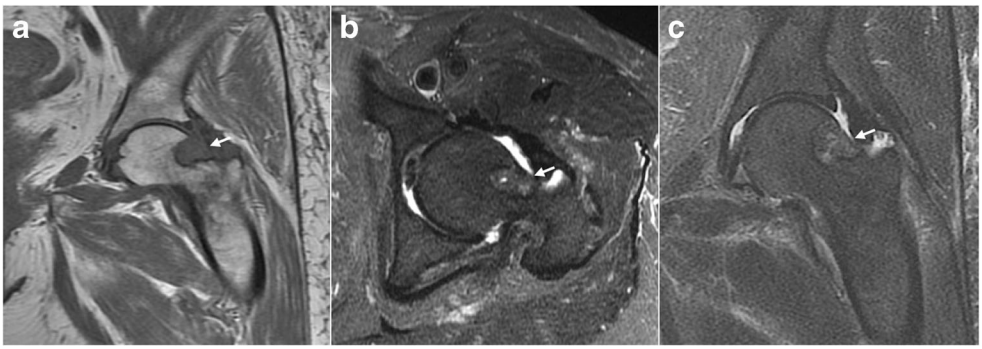

Fig. 3 MRI of the left hip obtained 1 year later after the initial presentation. **a** Coronal T1-weighted image showing a hypointense, well-defined 1.6 × 1.3 cm lesion (*arrow*) in the femoral neck region. **b** Axial fat-saturated T2-weighted image showing the lesion (*arrow*) with mostly low signal intensity. **c** Coronal STIR sequence also mostly shows a low signal intensity lesion (*arrow*) with slight heterogeneity but well-defined margins

CT images revealed a more discernible trend in size progression over nearly a 2-year period, with the latest measurement of approximately 2.0 × 1.5 cm (Fig. 4). Given a preoperative diagnosis of a pathologic left femoral neck fracture, the patient underwent a left hip hemiarthroplasty (Fig. 5).

Surgical pathology

The specimen consisted of a proximal femoral head and neck (4.6 × 4.4 × 4.3 cm) containing a firm white rubbery 1.8 × 1.1 × 1.0-cm lesion with irregular borders abutting the distal resection margin (Fig. 6). Routine hematoxylin and eosin stained sections of the lesion demonstrated densely eosinophilic proteinaceous debris, hemorrhage, and rare bland spindle cells within the intramedullary mass (Fig. 7a). A Congo Red stain was positive in the proteinaceous material, producing apple-green birefringence under polarized light were observed (Fig. 7b, c). The presence of ß2M amyloid was confirmed with immunohistochemistry (Fig. 7d). Immunohistochemistry for kappa- and lambda-light chain and transthyretin were negative (not shown).

Discussion

To the best of our knowledge, this is the first report that provides the size progression of a DRA on imaging over a 2-year period leading up to a pathologic fracture. Moreover, even though lytic lesions are frequent radiographic findings in patients with hemodialysis-related amyloidosis, very few of these lesions actually undergo biopsy and are histopathologically confirmed [1]. On radiographs, a typical DRA will appear as a lucency with sclerotic margins within the cortical or medullary bone. This lucency will vary in size and may present with cortical destruction. The differential diagnoses for a juxta-articular lesion in a patient with a history of hemodialysis should include DRA or a brown tumor from secondary hyperparathyroidism. CT will provide a better image for evaluating the extent of bony involvement, which can help guide a subsequent percutaneous biopsy. Moreover, MRI can be helpful in the diagnosis of DRA, which will tend to appear as a lesion with low intensity on T1-weighted imaging. However, on T2-weighted imaging, DRA lesions may present with signal intensities that can vary from hypointense to hyperintense in fluid sensitive images [5]. In one case series, it was found

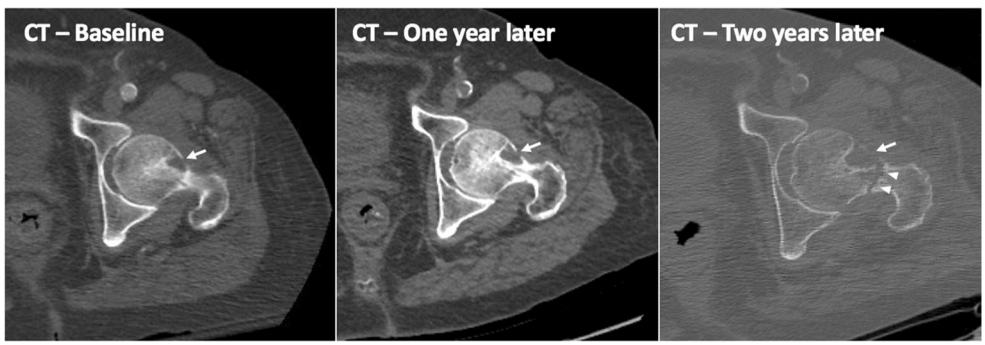

Fig. 4 Axial CT images of the hip lesion exhibiting significant size progression over a 2-year period and eventually developing a pathologic fracture (left to right). An increase in size can be observed from the first image [1.2 × 1.1 cm] (*left*) to subsequent images [1.6 × 1.3 cm, 2.0 × 1.5 cm] (*middle right*). The lesion appears largest 2 years later when a non-displaced fracture of the left femoral hip has found near the lesion (*right*)

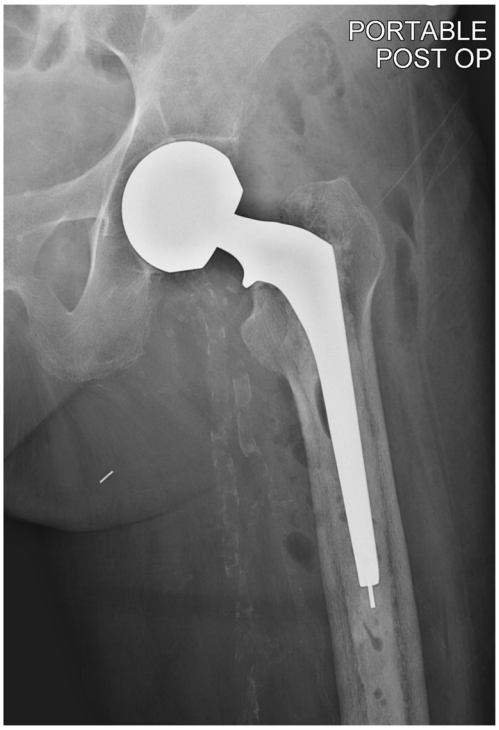

Fig. 5 AP radiograph of the left hip following a successful hemiarthroplasty

that approximately 53% of identified DRAs exhibited increased T2 signal intensity while the remaining 47% exhibited low to mixed T2 signal intensity [6]. This variability in T2 signal intensity may be due to a combination of fluid collection and amyloid deposits within the lesion. While biopsy is almost always required for a definitive diagnosis, clinical history and imaging findings can be used to assess for the possibility of a DRA.

In the healthy kidney, ß2M amyloid is a low molecular weight protein that is normally filtered, reabsorbed, and broken down in the proximal tubule. In the setting of chronic kidney disease requiring long-term hemodialysis, serum ß2M amyloid can become significantly elevated. This is mainly due to the suboptimal filtration and removal of these amyloid proteins by conventional hemodialysis membranes [7]. Amyloidosis related to long-term hemodialysis is unique in that it involves ß2M amyloid deposition and predominantly affects the osteoarticular system, which may be partly explained by ß2M amyloid's affinity for type I and II collagen [8]. Dialysis-related amyloidosis commonly involves sites like the wrists, shoulders, spine, and knees. Clinical manifestations include carpal-tunnel syndrome, destructive osteoarthropathies, and focal lesions known as amyloidomas. DRAs have a predilection for juxta-articular bones, specifically the proximal femur; one case series suggests that up to 70% of DRAs preferentially affects the proximal femur [1].

While DRA can be clinically silent, they can also present as pain and cause significant morbidity in the form of pathologic fractures. The greatest risk factor associated with the development of DRA is the duration of hemodialysis and renal failure as well as the patient's increasing age [9]. With the improving survival of patients on hemodialysis, the incidence of DRA may also be increasing. Thus, clinicians must be aware of this particular pathology to be able to counsel patients and minimize associated morbidity.

Currently, there is no treatment for DRA. Identified DRA lesions should warrant careful observation through scheduled visits and serial imaging to assess the risk of an impending pathologic fracture. In the presence of a DRA lesion, factors like significant functional pain and sizeable cortical bone destruction (> 50%) can be predictive of a pathologic fracture [10]. Additionally, standardized tools such as Harington's or Mirels' criteria can be utilized to gauge pathologic fracture risk from an identified bone lesion [11, 12]. On the initial presentation, our patient with an incidental, asymptomatic finding of a lytic bone lesion in the peritrochanteric region that was < 1/3 the size of the cortex on the initial CT would have earned a Mirels' score of 7; for a benign lesion, observation would have been clinically recommended. On her second visit, the patient presented with functionally limiting pain. In this instance, the patient's Mirels' score would have been 10,

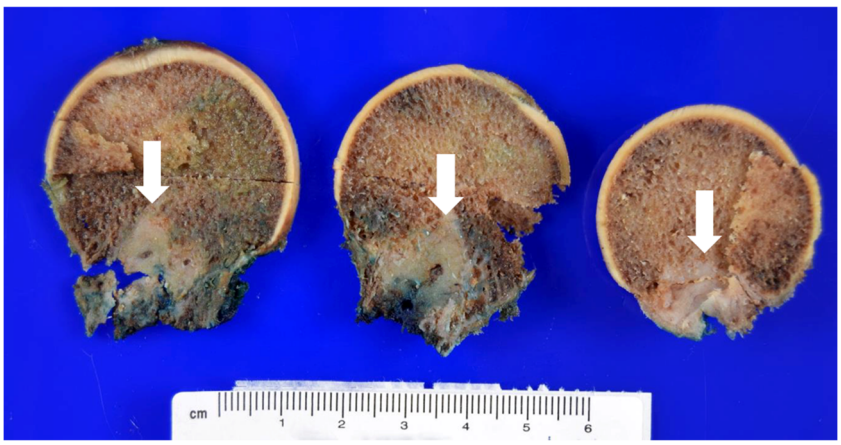

Fig. 6 Cross-sectional slices of the resected femoral head. A firm white rubbery lesion (*arrows*) was grossly identified

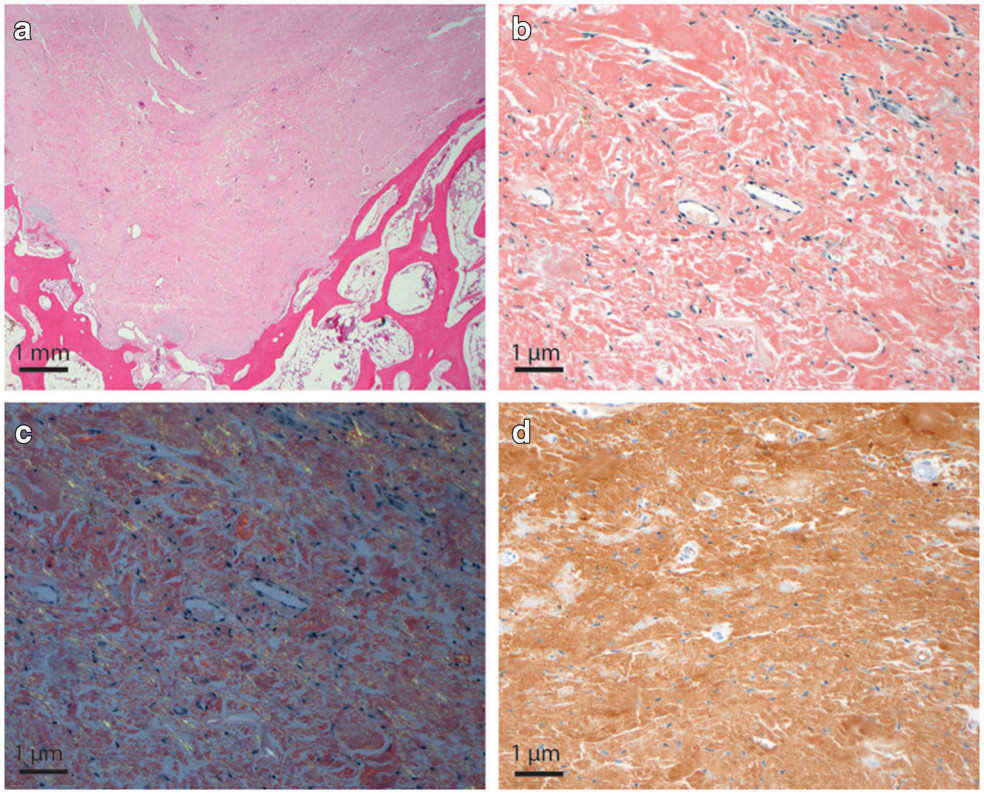

Fig. 7 Histopathology of surgical specimen. **a** Routine H&E-stained section demonstrates dense eosinophilic deposit abutting native lamellar bone (*bottom*). **b** The deposit stains positively with Congo Red. **c** Apple-green birefringence of Congo Red-stained section under polarized light. **d** Immunohistochemistry for ß2M is positive

and prophylactic intervention for the increasing risk of an impending pathologic fracture would have been recommended.

Patients with DRA bone lesions that are deemed high risk for a pathologic fracture should be counseled and considered for a prophylactic fixation, which has a shorter operative time, decreased associated morbidity, and more rapid recovery than fixations occurring after sustained pathological fractures [13]. There are various methods for prophylactic fixation, depending on the affected anatomical location, such as surface plating, medullary nail fixation, hemiarthroplasty, etc. Specifically, for the proximal femur, a prophylactic hemiarthroplasty has been found to have a lower risk of fixation failure, reoperation, or pathologic fracture compared to an intramedullary nail fixation. Performing a prophylactic fixation may be most beneficial when a patient is still ambulatory as pre-operative ambulation has been found to be the strongest predictor of unassisted postoperative ambulation [14].

A potential strategy against the development or progression of DRA is improving ß2M amyloid clearance. This can be achieved by utilizing high-flux dialysis membranes, instead of low-flux membranes, to help preserve residual renal function, reduce ß2M amyloid serum levels and reduce the incidence of DRA [15, 16]. In the case of patients with suspected DRA, such as the one in this report, intervening on modifiable factors such as using high-flux dialysis membranes can potentially halt amyloidoma size progression and subsequently delay or even prevent the resulting pathologic fracture. Other methods to increase ß2M clearance include hemofiltration, immunoadsorption and renal transplantation [17].

Conclusions

Overall, this is the first report that provides information on the size progression of a DRA on imaging and highlights its development towards a pathologic fracture. A DRA should be suspected when a lucent lesion is seen in the osteoarticular system of a long-term hemodialysis patient. Early identification can provide opportunities in risk reduction of associated pathologic fractures through patient counseling, prophylactic fixation, and modifications in hemodialysis treatment.

Compliance with ethical standards

Grants This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number TL1 TR001871. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Conflict of interest The authors have no conflicts of interest regarding this study.

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