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CASE REPORT

Amyloid Arthropathy — a Cause of an Asymptomatic Hip Mass

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ABSTRACT

Dialysis-related β-2-microglobulin amyloidosis is a well-recognised complication of long-term haemodialysis. The joints are preferentially affected. Most patients with amyloid arthropathy are asymptomatic, with the first symptom usually presenting as a highly morbid complication such as pathological fracture. Radiological findings precede clinical findings, therefore, greater awareness of amyloid as a cause of joint abnormality in patients undergoing haemodialysis will promote earlier radiological diagnosis and prevent further unnecessary investigations. Conventional imaging, including bone scan, is non-specific and non-sensitive. However, indium-labelled β-2-microglobulin scans offer the prospect of better detection rates in the future. This report is of a patient with asymptomatic amyloid arthropathy of the hip joint, which is intended to heighten awareness of this condition.

Key Words: *Amyloid; beta 2-Microglobulin; Joint diseases; Renal dialysis*

INTRODUCTION

Dialysis-related amyloidosis is a well-recognised complication of long-term haemodialysis. Amyloid, derived from β-2-microglobulin (β2M), an insoluble circulatory proteinaceous material not filtered by standard haemodialysis membranes, is preferentially deposited in the cartilage, capsule, and synovium of the joints over the viscera, progressing to the adjacent bones. Most patients with amyloid arthropathy (AA) are asymptomatic. Clinical manifestations, which occur in a small number of patients, include periarticular swelling/soft tissue mass, joint pain, bone cyst formation, pathological fracture, and carpel tunnel syndrome. These manifestations can cause considerable morbidity and do not present until late in the disease process. Importantly, radiological findings always precede clinical symptoms. This report is of a patient with asymptomatic AA of the hip joint, which is intended to heighten awareness of amyloid as a cause of non-calcified joint masses among patients undergoing haemodialysis, to highlight the poor sensitivity and specificity of conventional imaging in the detection of amyloid, and to promote earlier radiological diagnosis and better patient care through prevention of complications.

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CASE REPORT

A 62-year-old man with a 25-year history of haemodialysis for end-stage adult polycystic kidney disease and a recent episode of acute diverticulitis presented in 2004 with a fever of 38.0°C. Initial investigations revealed a

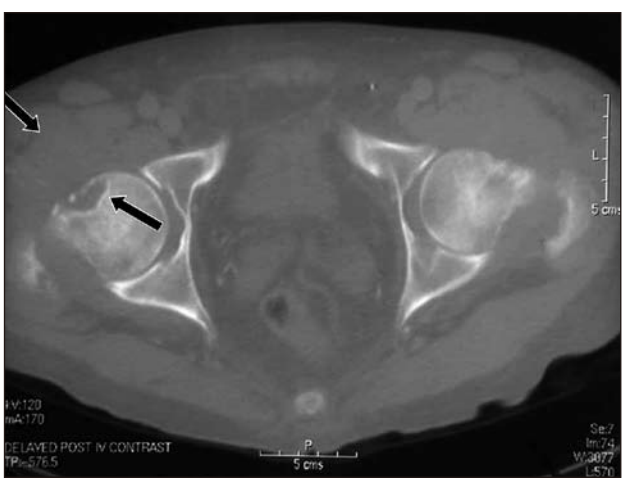

Figure 1. Abdominal computed tomography showing an incidental large heterogenous non-calcified soft tissue mass involving and extending anteriorly from the right femoral head and neck (arrows).

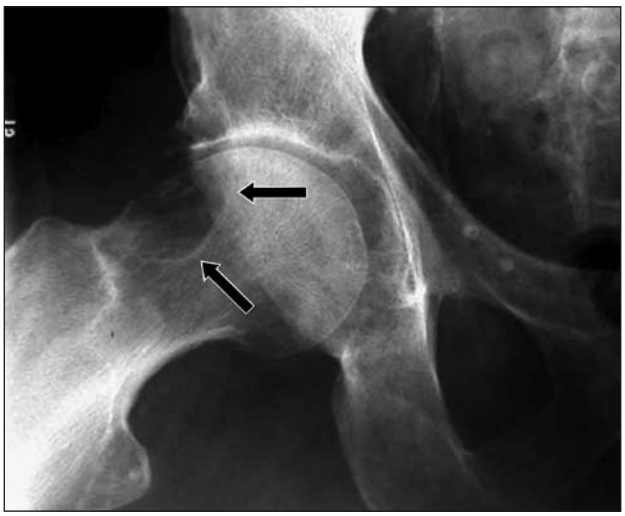

Figure 2. Plain radiograph of the right hip showing the presence of a lytic lesion in the right femoral head and neck, demonstrating a well-defined medial sclerotic margin (arrows).

normal white blood cell count of 4 x 10^9/L but elevated C-reactive protein of 150 mg/L. Physical examination was unremarkable.

Abdominal computed tomography (CT) was performed to exclude complications of diverticulitis. A heterogeneous, non-calcified soft tissue mass was incidentally noted in the right femoral head and neck, where there was a 2-cm diameter lytic lesion with overlying cortical breach, but a well-defined medial sclerotic margin (Figure 1). Subsequent plain X-ray confirmed the well-defined medial sclerotic margin (Figure 2). Hydroxymethylene diphosphonate scintigraphic bone scan did not show any increased or decreased radioisotope uptake around the right hip or in the rest of the skeleton. Magnetic resonance imaging (MRI) of the right hip demonstrated that the right femoral head and neck mass was proton-density and T2-hypointense, and extended into the overlying soft tissue with patchy gadolinium enhancement (Figure 3). No additional soft tissue mass or bone lesions were noted. Due to the presence of a cortical breach and large soft tissue component, an aggressive bone lesion such as metastasis or myeloma was considered.

Ultrasound-guided biopsy of the right hip soft tissue mass was subsequently performed. Histology revealed irregular broad bands of Congo red stain–positive fibrous material, which exhibited pale apple green birefringence to light, confirming the diagnosis of β2M AA.

DISCUSSION

The association between AA and β2M deposition was first described in 1985.[1] β2M is an insoluble circulatory proteinaceous material that is not filtered by standard haemodialysis membranes. The exact mechanism of amyloid fibril formation from β2M is unknown.[2] Nearly all patients undergoing haemodialysis for more than 7 years have evidence of β2M deposition.[3] Not all patients with histological amyloid have symptoms.[4,5] The prevalence of AA increases with the duration of haemodialysis and the patients' age at initiation of dialysis, with older patients developing AA faster than younger patients.[6,7]

Early β2M amyloid joint deposition occurs in the cartilage, progressing to involve the capsule and synovium.[8] Amyloid deposition is followed by a secondary inflammatory reaction, increased cytokine expression, and macrophage recruitment. This mechanism is thought to cause increased β2M production, synovial thickening with the creation of an associated inflammatory soft tissue mass, marginal bone erosions in the periarticular

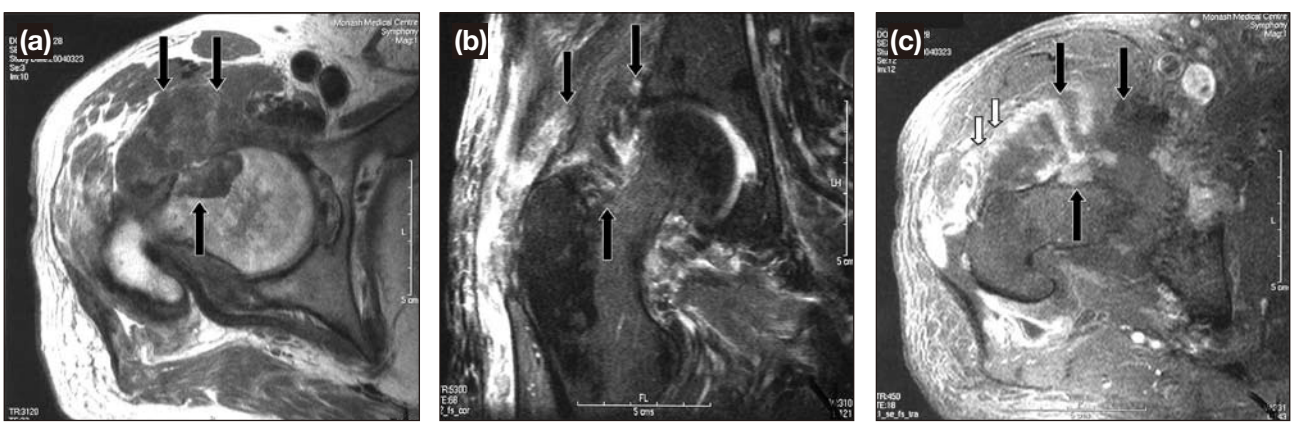

Figure 3. Magnetic resonance imaging. (a) Proton-density–weighted axial image demonstrating a low-signal homogenous soft tissue mass arising from the right femoral head and neck, extending anteriorly (arrows); (b) corresponding axial T2-weighted image demonstrating mixed low to intermediate signal intensity to the soft tissue mass (arrows); and (c) post-gadolinium coronal fat-suppressed T1-weighted sequence showing patchy contrast enhancement of the mass (black arrows), which is indistinguishable from the adjacent iliofemoral ligament (white arrows).

regions, formation of subchondral bone cysts, and arthralgic symptoms.[9,10] The number and size of bone cysts increase with the duration of dialysis.[11]

Symptoms develop once amyloid deposition and its associated inflammatory reaction are sufficient to cause nerve or tendon damage. Chronic arthralgias and restricted range of movement usually occur bilaterally, predominantly involving the shoulders, knees, hips, and long bones.[4] Carpel tunnel syndrome, caused by median nerve entrapment by amyloid deposition around the wrist, usually develops after more than 5 years of dialysis.[12] Amyloid spondyloarthropathy, with erosion of the intervertebral discs and adjacent vertebral end plates with bone cyst formation, preferentially affects the lower cervical spine, with occasional involvement seen in the atlanto-axial joint and lumbar spine.[13]

Histologically, biopsy of the affected bone or synovium, followed by routine haematoxylin and eosin staining, reveals homogeneous eosinophilic material. Amyloid deposits are positive for Congo red staining, showing green birefringence of the amyloid fibrils under polarised light, with these being the definitive diagnostic criteria.[14]

Conventional, non-invasive imaging techniques are non-specific and/or non-sensitive. Plain radiograph may show well-defined lytic geode-type bone lesions of variable size, with sclerotic margins seen in the juxta-articular epiphyseal areas,[15] particularly in the proximal femur and humerus.[16] Characteristically, there is an absence of soft tissue calcification or osteophyte formation.[17] The geode-type bone lesions may show progressive enlargement, with a corresponding increase in the risk of pathological fracture, particularly in the femoral neck.[18] The differential diagnosis of geode-type bone lesions includes brown tumours, osteoarthritis, synovial tumours such as pigmented villonodular synovitis, and metastases. The joint space is preserved until late in the course of the disease.[19] Bony expansion, bone deposition, and periosteal reactions do not occur.[20]

CT, with its superior resolution and cross-sectional capability, is better than plain radiography for demonstrating smaller lytic lesions, periarticular erosions, and a constant sclerotic lesion rim.[21] Associated soft tissue masses related to amyloid deposition, giving an aggressive appearance, can also be seen.

MRI is superior to any other imaging modality in its ability to demonstrate the extent of soft tissue masses in and around joints, as well as bone marrow lesions.[22] Amyloid deposits exhibit long T1 and short T2 relaxation times. Signal intensity of intraosseous and soft tissue lesions is therefore uniformly low on T1-weighted images, while the signal intensity on T2-weighted imaging is heterogenous, ranging from low to intermediate T2 signal intensity; this is probably related to a combination of low T2 signal amyloid and T2 hyperintense fluid within the lesion.[11] Gadolinium-diethylene-triamine-penta-acetic acid enhancement pattern is patchy and variable.

Conventional technetium-labelled diphosphonate bone scan findings are highly non-specific for amyloid.[23-25] Previous studies that have employed such scans have demonstrated lower than expected detection rates of amyloid deposits in patients undergoing long-term haemodialysis.[26] Radioisotope may or may not bind to amyloid deposits or to any area of soft tissue calcification or bone turnover.[23] Attempts to inject radiolabelled serum amyloid P component into patients with β2M amyloidosis as a means of identifying and monitoring disease activity have also been found to be non-specific and insensitive.[27] By contrast, 131-iodine radiolabelled β2M scintigraphy was found to have greater specificity for β2M amyloid detection.[28] This technique has limitations regarding radiation dose (due to the suboptimal, relatively long half life of 131-iodine) and limited resolution (secondary to the heterogeneous radiation emission spectrum of 131-iodine).

Attempts have subsequently been made to label β2M with 111-indium, a material of shorter half life and narrower exclusively γ-ray emission spectrum, following β2M conjugation with chelator diethylene triamine penta-acetic acid. Scintigraphy with this compound was found to offer improved image contrast and increased sensitivity at a comparable dose to conventional bone scan.[29] Indium-labelled recombinant β2M scintigraphy has been demonstrated in a single-centre study to be most sensitive in demonstrating β2M accumulation in patients undergoing long-term haemodialysis.[30] The technique is yet to be proven across larger studies and is currently not in widespread use.

The prevalence of dialysis-related AA will increase with the rise in the number of patients undergoing long-term dialysis and the longer survival time. Conventional bone scans and cross-sectional imaging methods are non-specific and non-sensitive. As pathological and radiological evidence of amyloid precedes clinical symptoms,

awareness of amyloid as a differential diagnosis for asymptomatic non-calcified aggressive-looking soft tissue joint masses among patients undergoing haemodialysis, and knowledge of its imaging characteristics will facilitate earlier diagnosis before serious complications, such as pathological fracture, occur. The use of 111-indium–labelled β2M offers the prospect of reasonable detection sensitivity and specificity in the future.

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