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A rare case of multifocal osteonecrosis of the femur in a heart transplant patient

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Abstract
Case: A 58-year-old male was reviewed for bilateral hip pain 3 years post cardiac transplant, complicated by episodes of acute rejection, steroid induced diabetes, and cytomegalovirus hepatitis. He was diagnosed with bilateral femoral head osteonecrosis with subchondral collapse and underwent staged cementless bilateral total hip arthroplasties. He re-presented with progressive right knee pain. Investigations revealed femoral diaphyseal osteonecrosis and a rare intra-articular bicondylar distal femur extension without evidence of collapse. To date, this has been monitored and conservatively managed.
Conclusion: Osteonecrosis in long term cardiac transplant survivors is a cause of significant morbidity, with the potential for progressive, multifocal lesions.

Keywords: Osteonecrosis, avascular necrosis, bone infarct, cardiac transplant, total hip arthroplasty

Introduction
Osteonecrosis is generic term referring to the ischaemic death of the constituents of bone. Historically the term Avascular Necrosis (AVN) was typically reserved for subchondral (epiphyseal) osteonecrosis and bone infarct for medullary (diaphyseal) involvement. The common pathophysiological pathway involves coagulation of the intra-osseus microcirculation which eventually leads to necrotic cell death. Periarticular lesions may result in subchondral fractures and collapse, with advanced disease requiring operative intervention. Common causes of osteonecrosis include corticosteroids, excessive alcohol intake, trauma and embolic events [1, 2].
Heart transplantation rates and long-term survivorship have increased globally over the past decade due to improvements in operative techniques, donor-recipient matching and immunosuppressive therapies [3-5]. The increase in survivorship, has seen a corresponding increase in case reports of osteonecrosis in long term heart transplant survivors [6-8]. We report a rare instance of bilateral polyfocal femoral osteonecrosis in a heart transplant patient with involvement of the femoral head, shaft and distal femoral condyles.
This case report was produced in accordance with the SCARE criteria [9]. A search of 3 electronic databases from their dates of inception to March 2022 was conducted to identify potentially relevant studies for the literature review using a comprehensive set of search terms and MeSH terms (Medline (Ovid), Embase (Ovid) and Pubmed).

Case report
A 58-year-old male was reviewed at our facility in 2018 for bilateral hip pain. His past medical history was significant for myocardial infarction with cardiogenic shock in 2014. This led to severe ischaemic cardiomyopathy, and he was bridged to a cardiac transplant in 2017. His post-operative course was complicated by 3 episodes of acute rejection, steroid induced diabetes, and cytomegalovirus (CMV) hepatitis. His immunosuppressive therapy included Prednisone, Tacrolimus and Mycophenolate, with pulse dosing of prednisolone up to 300mg/day during the rejection episodes.
He initially presented in 2020 with bilateral activity limiting groin pain radiating to the buttocks and had difficulty with activities of daily living like wearing socks, shoes and getting into cars. He had a strong element of night pain and poor relief from strong opioid analgesia. Examination revealed painful irritable hips with no overt arthritic change on XRs. Subsequent Magnetic Resonance Imaging (MRI) confirmed subchondral collapse with a crescent sign and significant bone marrow oedema around the femoral heads (Figure 1).

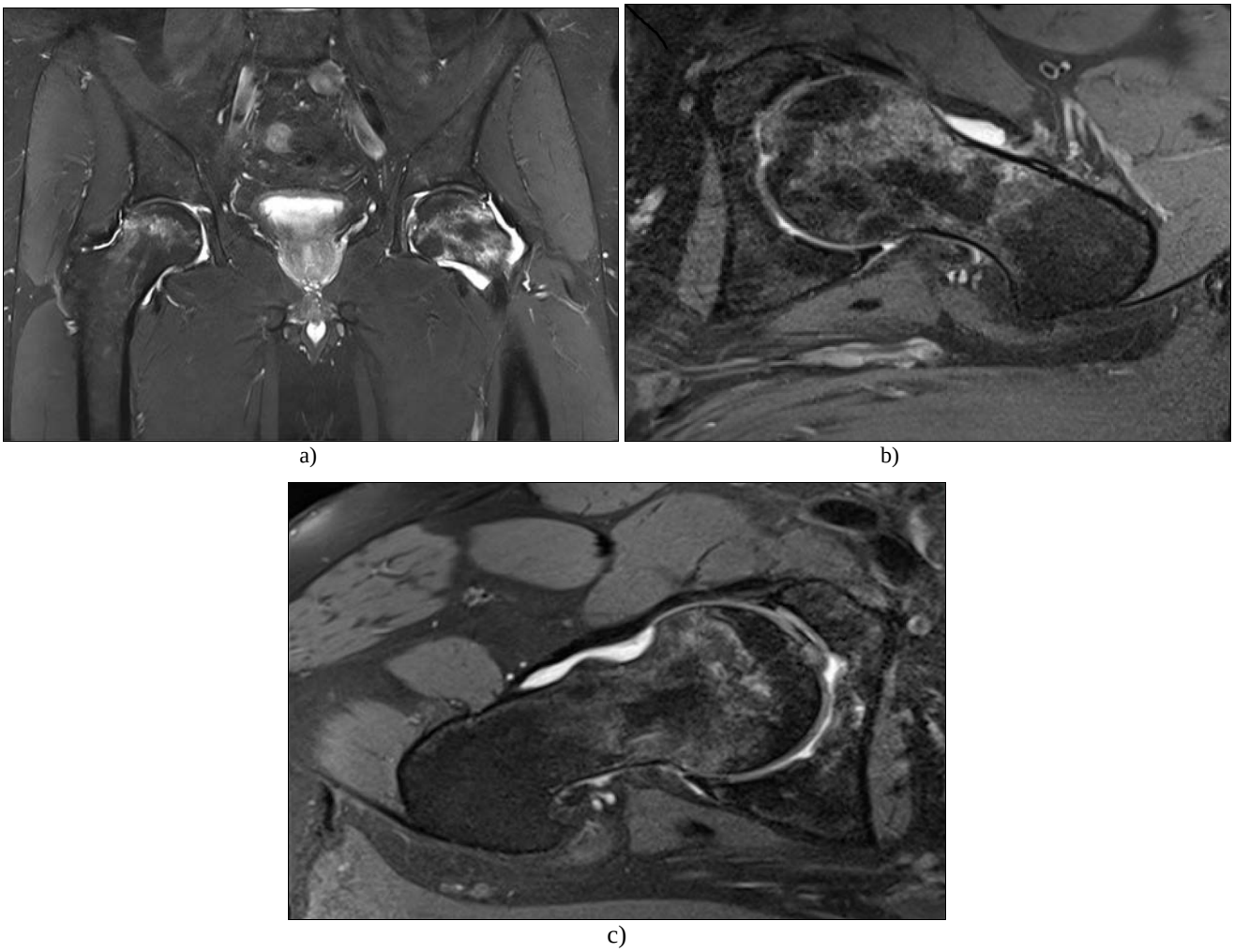
He underwent uncomplicated, staged cementless bilateral total hip arthroplasties with the more symptomatic right side treated first (Figure 2). Intraoperative examination of the resected femoral heads showed subchondral fractures with separation of the cartilage and attached subchondral bone from the underlying area of necrosis (Figure 3).

The patient reported significant relief from the groin pain and was able to resume activities of daily living. On review in 2021, he complained of mild bilateral mid anterior thigh pain with a start-up element. Bone scans confirmed increased activity at the stem tips in both femurs and this was attributed to a bone implant elasticity mismatch and managed conservatively (Figure 4).

He re-presented in 2022 with a 6-month history of progressive right distal femur and lateral knee pain. The pain was distinct from his previous mid-thigh pain. It was exacerbated by weight bearing, walking on incline and he was unable to squat. Examination revealed an antalgic gait with new reliance on walking aids with preserved range of motion in the knee.

Subsequent X-Rays were again unremarkable, but MRI demonstrated a well circumscribed diaphyseal lesion with a classic “smoke up the chimney” appearance and a rare intra-articular bicondylar extension without evidence of collapse (Figure 5).

The decision was made to manage this conservatively with restricted weight bearing and in conjunction with the patient’s treating Endocrinologist he was commenced on Denosumab. At 6-month follow up in September 2022, his right knee pain has now settled, though his left knee has begun causing significant discomfort. This will be investigated with an MRI study to assess for the presence of AVN in the left knee.



a) b)

c)

Fig 1: T2-weighted coronal (a) and axial (b & c) MRI slices of the pelvis and both femoral heads demonstrating AVN.

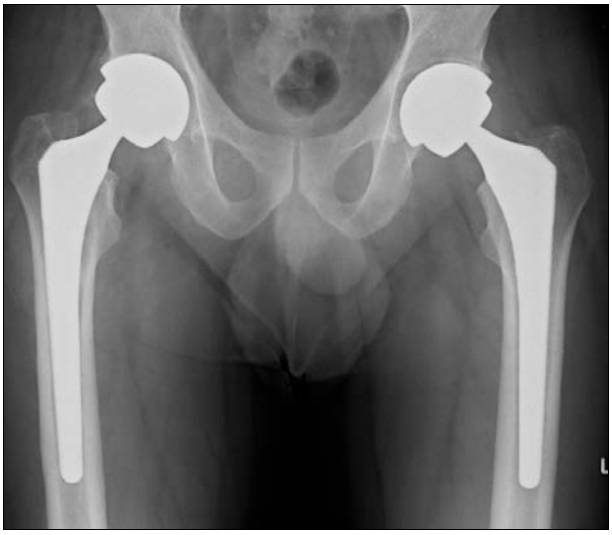


Fig 2: Post-operative anteroposterior X-Ray following bilateral staged hip arthroplasties

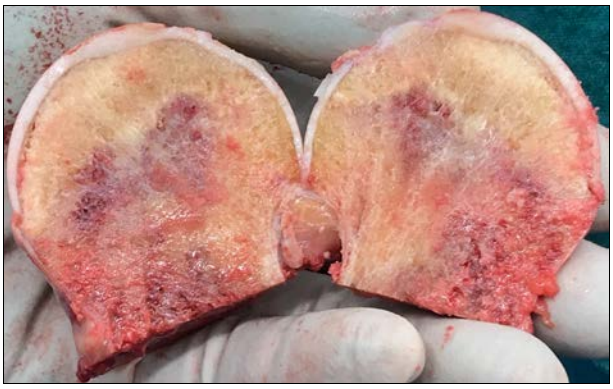
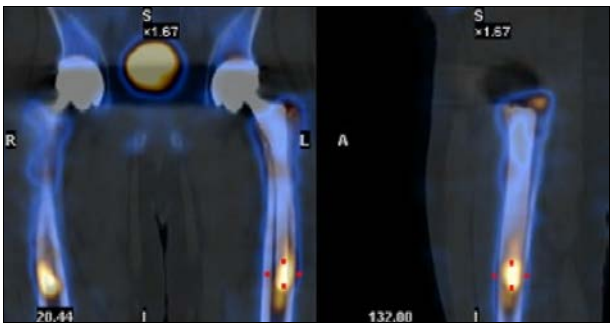
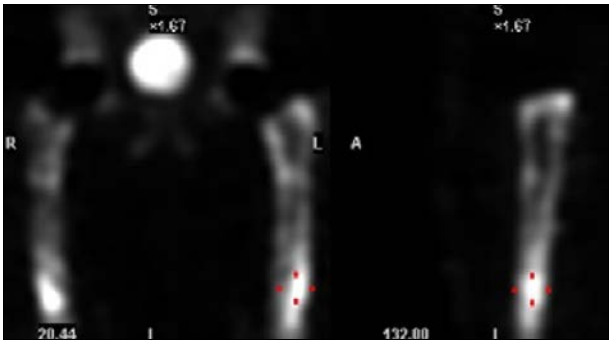


Fig 3: Intraoperative clinical photograph of the excised right femoral head sawed in the sagittal plane. Demonstrates an area of subchondral fracture which was dynamically unstable, overlying necrotic bone



a)

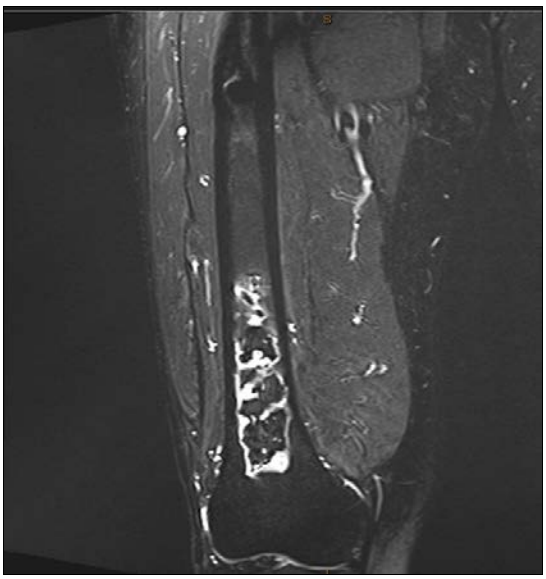


b)

Fig 4: Bone scan demonstrating increased uptake at the distal tip of bilateral stems

a)

b)



c)

Fig 5: T2-weighted MRI slices of the knee in coronal (a) and sagittal (b) planes demonstrating AVN of both medial and lateral condyles without subchondral collapse. T2-weight coronal slice of the diaphysis demonstrating ‘smoke up the chimney’ AVN

Discussion

Continued improvements in transplant medicine and surgery have led to an increased number of long-term cardiac transplant survivors [3, 4]. As this cohort continues to grow, it can be expected that the number of AVN cases requiring specialist Orthopaedic management will also increase. There are currently 35 cases of AVN post cardiac transplant described in the literature, with the onset of symptoms typically occurring 6 months to 5 years following transplantation (Table 1) [6, 8, 10-16]. Amongst this cohort, all cases described have occurred in the femoral heads, with one case of AVN in the femoral condyles. The incidence of AVN among large cardiac transplant cohorts has been shown to be 3-7% [6-8].

Whilst the pathogenesis of AVN in cardiac transplantation remains incompletely understood, it is hypothesized that the high doses of corticosteroids used in immunosuppression play a major role [1, 17]. Proposed theories include corticosteroid induced adipose hypertrophy, fat embolism, hypertension and atherosclerosis [17-19]. However, both Bradbury *et al.* and Lieberman *et al.* showed no relationship between the peak or cumulative dose of Prednisone received and the development of AVN in cardiac transplant patients [7, 20]. Thus, Lieberman *et al.* hypothesised there is likely an underlying predisposition in these patients. Nonetheless, reduced corticosteroid dosage post renal transplantation has been shown to reduce AVN [21] and prophylactic anti-resorptive therapy may also play an important role in preventing AVN [22, 23]. Finally, our patient suffered CMV hepatitis, another commonly quoted risk factor for AVN, though the literature on this topic is sparse [24].

There are major challenges in the peri-operative period for arthroplasty following cardiac transplant. The optimal management of these patients requires a multi-disciplinary team approach. In the peri-operative period these patients are at significant risk for medical and surgical complications, and it is vital that the patient has an appropriate anaesthetic work-up with involvement of their transplant physician. Apart from the anaesthetic risk, several intraoperative challenges face the arthroplasty surgeon. Early results of cemented total hip arthroplasty in AVN were poor, with high rates of loosening, sepsis and revision [25-27]. Modern porous coated cementless femoral prosthesis and improved cement techniques have demonstrated marked improvements in clinical and radiological results, with current evidence supporting both cemented and cementless approaches to hip arthroplasty in AVN [28]. However, in patients with significant cardiovascular disease or transplant, we would advocate for cementless approach to avoid risk of bone cement implantation syndrome [29] in these patients with poor functional reserve. Furthermore, the potential progression of the femoral diaphyseal lesion presents a challenge to the arthroplasty surgeon. Diaphyseal osteonecrosis might preclude use of stemmed femoral components which might be helpful if metaphyseal bone involvement necessitated the use of sleeves or cones.

Finally, cardiac transplantation necessitates ongoing immunosuppression with corticosteroids, with dose increments required perioperatively or if rejection episodes occur, raising the risk of infection and further osteonecrosis. Cosic *et al.* showed a complication rate of 76% among an arthroplasty cohort of patients post lung or heart transplant [11]. These included surgical complications such as bleeding, infection and intra-operative fracture, and medical complications such as pulmonary embolus, acute kidney injury and hospital acquired pneumonia. However, other studies have presented post-operative data with promising outcomes and low rates of complications [6, 8, 10, 12, 12-16].

The study is the first to report on the ongoing orthopaedic sequelae in a cardiac transplant patient after an initial proximal AVN episode. To our knowledge this pattern of subsequent diaphyseal bone infarction and distal femoral condyle AVN has never been reported in the literature. We predict that with the increasing life expectancy cardiac transplant patients, the incidence of multifocal AVN will increase.

The current study is inherently limited due to presentation of a single case only. Future studies should aim to analyse medical records from national registry data across all cardiac transplant patients to assess the true incidence and treatments to date for AVN post cardiac transplantation. The excellent length of patient follow-up in this study is a strength which has shed light on the issue of subsequent distant AVN not previously seen in other studies. Our case highlights the importance for close follow-up and surveillance of these patients, with a low threshold for investigating new musculoskeletal pain.

Table 1: Study characteristics AVN following cardiac transplantation [6, 8, 10-16]

Author	Year	Country	Number of patients	Location of AVN	Treatment
Antonopoulos *et al.*	2011	Greece	2	Hip	THA
Burton *et al.*	1978	USA	2	Hip	THA
Cosic *et al.*	2019	Australia	4	Hip	THA
Danzig *et al.*	1976	USA	1	Hip	Non-operative
Graham	2020	USA	1	Knee	Non-operative
Leon *et al.*	2007	Spain	18	Hip	THA
Leonard *et al.*	2012	USA	5	Hip	THA
Kim *et al.*	2010	Korea	1	Hip	THA
Woolf *et al.*	1992	UK	1	Hip	THA

Conflict of Interest
Not available

Financial Support
Not available

Declarations: Written informed consent was obtained from the patient for publication of this case report and accompanying images. All data analysed during this study are included in this published article. The authors have no competing interests to declare.

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