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Bilateral Avascular Necrosis of the Femoral Head in Renal Transplant Recipient: A Case Report

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Abstract

Osteoarticular complications are common after renal transplantation. The complications may result from the bone condition prior to transplantation or the iatrogenic effects of the treatments administered. These complications lead to significant morbidity and mortality, in addition to chronic pain and functional impairment. We report the clinical case of bilateral avascular necrosis (AVN) of the femoral head in a kidney transplant recipient. **Clinical Case:** 53-year-old male with a history of chronic hypertension. He underwent chronic hemodialysis for 12 months and was treated with Entecavir for chronic hepatitis B. The patient received a kidney transplant from a non-related living donor. Induction therapy included Thymoglobulin along with tapered corticosteroids, reaching a dose of 5 mg/day after 3 months, Mycophenolate mofetil (2 g/day), and Tacrolimus adjusted based on residual levels. There was good recovery of renal graft function. After six months, the patient reported bilateral hip pain and functional impairment of both lower limbs. Pelvic X-rays showed signs suggestive of bilateral AVN of the femoral heads. The diagnosis was confirmed by MRI. The patient underwent right hip drilling and total left hip replacement (THR). A right THR was performed a year later. **Conclusion:** AVN constitutes a frequent cause of morbidity and mortality after RT. The pathophysiology of osteonecrosis remains complex and multifactorial. We emphasize the importance of conducting a thorough assessment of bone health in patients both before and after RT.

Keywords

Avascular Necrosis, Femoral Head, Osteoarticular Complications, Renal Transplant

1. Introduction

Renal transplantation (RT) is the treatment of choice for end-stage chronic kidney disease allowing patients to maintain a good quality of life. Osteoarticular complications are common long-term complications after RT leading to significant morbidity and mortality. Osteonecrosis of the femoral head is a progressive condition caused by various factors such as trauma or steroid use [1]. It is also associated with blood dyscrasias, metabolic and coagulation disorders [2].

Approximately 20,000 new cases of osteonecrosis are diagnosed each year in the United States and 5000 - 7000 in Germany [3] [4]. The prevalence of AVN is higher among solid organ transplant patients than in the general population. Some studies report a prevalence reaching up to 20% among transplant patients [5].

The only definitive treatment is total hip arthroplasty, although numerous treatments including disphosphonates and core decompression are used to delay the progression.

We present a clinical case involving bilateral avascular necrosis (AVN) of the femoral head in a kidney transplant recipient. We obtained the patient's consent before sharing their case.

2. Observation

Our patient is a 53-year-old male with a history of chronic hypertension managed with a calcium channel blocker. He underwent chronic hemodialysis for 12 months due to vascular nephropathy and was treated with Entecavir for chronic hepatitis B.

The patient received a kidney transplant from a non-related living donor (his wife). Induction therapy included Thymoglobulin along with tapered corticosteroids, reaching a dose of 5 mg/day after 3 months, Mycophenolate mofetil (2 g/day), and Tacrolimus adjusted based on residual levels. There was good recovery of renal graft function.

After six months, the patient reported bilateral hip pain and functional impairment of both lower limbs. Clinical examination revealed bilateral spontaneous hip pain, predominantly on the right side. A mild functional impairment of the lower limbs was noted.

No signs of localized redness, warmth, or swelling were reported. The body mass index (BMI) was 28 kg/m^2 indicating overweight.

Anti-phospholipid antibodies (APL) were negative. The phosphocalcic assessment revealed: calcium level at 93 mg/l, phosphorus level at 33 mg/l, and PTH 1 - 84 at 230 pg/ml. Vitamin D was at 10 ng/ml, requiring supplementation with cholecalciferol. Metabolic assessment showed: hypertriglyceridemia (4.8 g/L) and hypercholesterolemia (2.5 g/L). Glycated hemoglobin was at 6.3%.

Pelvic X-rays are presented in **Figure 1**. They showed significant coxarthrosis with evidence of subchondral geode images and superior-internally joint space narrowing. Additionally, signs suggestive of osteonecrosis with areas of osteos-

clerosis were observed. Pelvic MRI confirmed bilateral osteonecrosis of the femoral heads (Figure 2).

Initially, the patient underwent right hip drilling and total left hip replacement (THR). The post-operative radiograph is presented in Figure 3. The aim was to opt for conservative treatment on the right side, where the lesions were deemed less severe. A significant clinical improvement was observed on the left side. However, due to the persistence of pain and functional impairment on the right side, a right THR was performed a year later (Figure 4).

The patient's progress was marked by regression and then disappearance of pain and limping. Six months after the surgical procedure, the patient had regained mobility and autonomy. At 1 year of follow-up, he was completely autonomous and reported no symptoms.

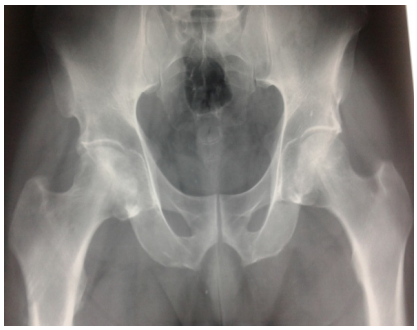

Figure 1. Pelvic radiograph (anteroposterior view) showing signs of osteonecrosis with a focus on osteocondensation of the femoral head.

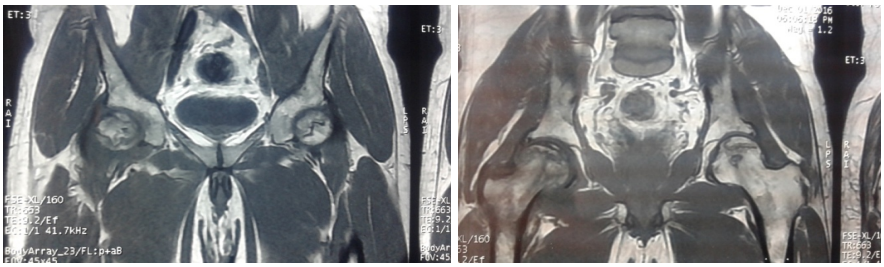

Figure 2. MRI of the pelvis showing bilateral osteonecrosis of both femoral heads with demarcation lines.

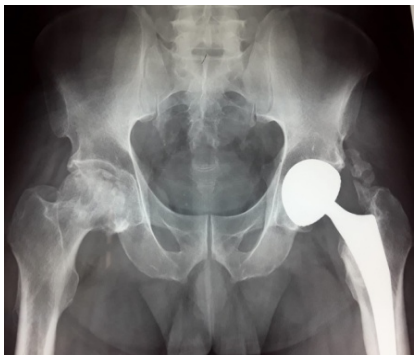

Figure 3. Total hip replacement of the left hip.

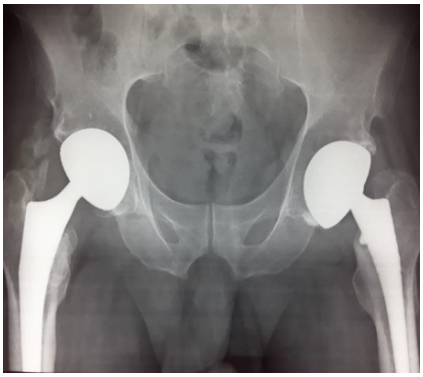

Figure 4. Total hip replacement of both hips.

3. Discussion

After RT, bone and joint complications are common and represent a significant cause of morbidity and mortality. A decrease in bone mineral density (BMD) has been noted 12 to 18 months after transplantation. Long-term, stabilization of BMD has been observed between the 3rd and 5th years [6]. Among the most frequently encountered mineral and bone disorders in transplant recipients are osteoporosis and avascular necrosis (AVN).

AVN refers to the death of all tissue components of the bone (hematopoietic marrow and mineralized tissue), and the persistence of an uninhabited bone framework. The pathophysiology of non-traumatic AVN is complex. It involves reduced bone vascularization, oxidative stress, endothelial and adipose cell dysfunction, increased intra-osseous pressure, and disturbances in apoptosis and coagulation mechanisms [7].

Reactive oxygen species (ROS) play a crucial role in osteoclast function by modulating receptor activator of nuclear factor-kappa B ligand (RANKL)-induced signaling. ROS also cause vascular and osteoblastic damage involved in the pathogenesis of AVN [8].

Studies suggest that corticosteroids lead to a decrease in the expression of antioxidant enzymes and induce oxidative stress. This could contribute to osteoclast hyperactivity and, consequently, the progression of osteonecrosis. Also, corticosteroids tend to decrease osteoblasts proliferation impairing their ability to repair and replace necrotic lesions [9].

Furthermore, glucocorticoids promote adipogenesis by inducing the differentiation of preadipocytes and mesenchymal stem cells into mature adipocytes [10]. Systemic hyperlipidemia promotes the formation of deposits in the vascular sinuses, thereby reducing blood flow [11]. As a result, the bone marrow becomes composed of adipocytes at the expense of hematopoietic cells. This leads to an increase in intraosseous pressure. This pressure compresses the venous sinuses and causes intravascular coagulation, impairing blood flow and resulting in ischemia [10]. The vessels supplying the epiphysis are located within the enclosed chamber of the femoral head. Increased pressure in this area leads to vascular compression, ischemia, and ultimately necrosis of the marrow and bone

[10]. Prolonged and high-dose steroid use is considered the main cause of non-traumatic AVN [8]. A meta-analysis has shown that the risk of developing AVN is 10-fold higher in patients on high-dose corticosteroid therapy and 2-fold higher when the cumulative dose of corticosteroids exceeds 10 g [12]. In our patient, the cumulative dose of corticosteroids administered is 1.37 g. Mont *et al.* support that patients treated with corticosteroid doses > 40 mg/day are at higher risk of osteonecrosis. An increase of 3.6% in the incidence of osteonecrosis is noted for every 10 mg increase in the dose [13]. Saito *et al.* demonstrated a significant dose-response relation between the development of osteonecrosis and the total dose of corticosteroids administered within the first 2 weeks after kidney transplantation [14].

The ARCO (Association Research Circulation Osseous classification) classification criteria for corticosteroid-associated femoral head osteonecrosis include the following: 1) a history of corticosteroid use > 2 g of prednisolone or equivalent over a period of 3 months; 2) a diagnosis made within 2 years following corticosteroid use; and 3) the absence of other risk factors besides corticosteroids [15].

Our patient meets only one of these three criteria since the diagnosis of AVN was made within 6 months following corticosteroid administration. The total dose did not exceed 2 g. The patient had other risk factors: overweight, male sex, and dyslipidemia.

A recent study revealed that the incidence of symptomatic osteonecrosis decreased from 20% to less than 5% with the introduction of ciclosporin and a decrease in steroid use [16]. Basiliximab, an anti-CD25, does not directly reduce the incidence of osteonecrosis but acts by reducing the cumulative dose of corticosteroids [17]. For maintenance immunosuppressive treatment, ciclosporin appears to be more frequently associated with osteonecrosis than tacrolimus. Schachtner and Otto consider the use of ciclosporin as an independent risk factor of AVN, with a rate of 8.0% compared to 2.7% at 10 years ($p < 0.01$). Male sex is also considered an independent risk factor of AVN [18].

A genetic implication could explain why only certain patients under systemic glucocorticoids develop the disease. Polymorphisms in genes involved in corticosteroid metabolism may influence the risk of developing osteonecrosis. This is the case with the ATP-binding cassette subfamily B member 1 (ABCB1) gene [7]. Mononucleotide polymorphism of plasminogen activator inhibitor-1 (PAI-1) has also been associated with an increased risk of steroid-induced osteonecrosis [19]. The Japanese study by Higushi *et al.* regarding AVN risk factors implicated HLA incompatibility, particularly HLA II [20]. Immunologically, our patient shared 2 identities with the kidney donor concerning HLA II (DQ03 and DQ06).

The initial imaging examination is usually a radiograph. However, radiographs may appear normal in the early stages. When the femoral head collapses due to a subchondral fracture, the crescent sign may be observed, which is pa-

thognomonic of the disease [7]. MRI is now considered the most sensitive and specific diagnostic technique. Viable areas show low signal intensity on T1 and higher signal intensity on T2 images. Necrotic areas are hypointense on both T1 and T2. In our patient, the diagnosis of femoral head osteonecrosis was confirmed by MRI. The necrotic area of the head was visualized with hyperintensity on both T1 and T2. The sphericity of the femoral head was preserved.

The size and location of the necrosis are the main determinants of therapeutic management. Various classifications have been developed to characterize the size and location of the necrosis. Currently, the widely used classifications are the Steinberg classification and the Japanese Investigation Committee (JIC) classification [21].

The Steinberg classification system categorizes the extent of involvement into three subsets: mild (<15% of the articular surface or head affected), moderate (15% to 30%), and severe (>30%).

The JIC classification system is based on the T1-weighted image in the mid-sagittal section of the femoral head. Necrotic lesions are classified into four types:

- type A for a lesion < 1/3 medial of the weight-bearing portion;
- type B for a lesion < 2/3 medial of the weight-bearing portion;
- type C1 for a lesion > 2/3 medial of the weight-bearing portion but not extending laterally to the acetabular margin;
- type C2 for a lesion extending laterally to the acetabular margin. The prevalence of collapse is less than 10% for type A, 40% for type B, 80% for type C1, and greater than 90% for type C2 [21]. The risk of collapse depends on the size and location of the necrotic portion. Small lesions rarely tend to collapse. Therefore, the size of the necrotic portion should be evaluated before treating femoral head osteonecrosis (FHO) [22].

To date, enoxaparin, statins, disphosphonates, iloprost, and acetylsalicylic acid have been tested to slow or reverse the progression of the disease. However, none of them have proven efficacy [22].

Surgical decompression (SD) is performed to reduce intraosseous pressure, promote increased blood flow, and stimulate bone genesis. SD has been used in FHO at an early stage with the hypothesis that it could reverse disease progression [23]. Recently, autologous bone marrow concentrate (BMC) injection has been combined with traditional surgical decompression to improve outcomes. Bone grafting aims to provide structural support to reduce intraosseous pressure and prevent collapse in the early stages of FHO. Vascularized bone grafting helps to improve blood supply. It has demonstrated a hip survival rate of 80% at 5 years in pre-collapse lesions with a low rate of total hip arthroplasty [11]. Joint resurfacing involves replacing the articular surface with artificial materials to preserve natural anatomy. Due to material-related complications and potential contribution to osteonecrosis progression, joint resurfacing is no longer used as a treatment for femoral head osteonecrosis [24]. In advanced stages, when the

joint is irreparably damaged, total joint replacement is necessary [7]. Arthroplasty is indicated in cases of advanced disease, continuous disease progression, and persistence of predisposing factors [25].

Total hip replacement (THR) using highly cross-linked polyethylene liners or ceramic-on-ceramic bearings has shown excellent results in short and medium-term follow-up studies. However, long-term results have not yet been revealed [21].

Initially, our patient underwent decompressive drilling of the right hip and total hip replacement of the left hip. The aim was to be as conservative as possible with the right hip, where the lesions were deemed less severe. After 1 year, due to persistent pain and functional impairment of the right lower limb, a total hip replacement of the right hip was performed. One year after the procedure, our patient reported no complications related to the surgery.

4. Conclusion

Osteoarticular complications are common after RT and are often associated with the pre-transplant bone condition or the immunosuppressive treatments used post-transplantation. Among these conditions, AVN constitutes a frequent cause of morbidity and mortality. The pathophysiology of osteonecrosis remains complex and multifactorial. We have reported the case of a kidney transplant recipient who developed bilateral AVN of the femoral head within the first year following RT. The effect of these osteoarticular complications on patients' quality of life and autonomy underscores the importance of conducting a thorough assessment of bone health in patients both before and after RT.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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