Bilateral femoral capital avascular necrosis in a renal transplant recipient on tacrolimus-based immunosuppression

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Introduction

Avascular osteonecrosis (AVN) of the femoral head is one of the most common skeletal complications of kidney transplantation [1,2]. Factors governing its prevalence, risk factors and therapy remain controversial, even four decades after the initial description. It is generally accepted that corticosteroids play a crucial role in the pathogenesis. Prevalence of this complication decreased following the introduction of cyclosporin [1,3], but the effect of more recently introduced immunosuppressive agents is not so well documented. Here we report a 22-year-old patient who developed bilateral femoral head AVN 3.5 months after kidney transplantation, despite being on tacrolimus.

Case

A 22-year-old male presented to our Institute for kidney transplantation in January 2004. He was first detected to have chronic kidney disease due to IgA nephropathy at another health facility in September 1999 and started on antihypertensives, phosphate binders, active vitamin D3 and iron. Prednisolone was given in a dose of 100 mg every other day between March and June 2001. Renal function deteriorated and he started haemodialysis in December 2003.

The pre-transplant investigations revealed a serum creatinine of 14.3 mg/dl, albumin 4.3 g/l, fasting blood sugar 104 mg/dl, calcium 8.7 mg/dl, phosphates 4.8 mg/dl and intact parathyroid hormone (iPTH) 236 pg/ml. He underwent transplantation on March 26, 2004. The donor was his one haplotype-matched elder brother. He was immunosuppressed with tacrolimus, azathioprine and prednisolone. Tacrolimus dose was adjusted to maintain trough levels between 10 and 15 ng/ml in the first 3 months, 8–12 ng/ml between 3 and 6 months and 5–10 ng/ml thereafter. Prednisolone was started at 0.5 mg/kg/day, and tapered at a rate of 5 mg/month to a maintenance dose of 7.5 mg/day. Serum creatinine levels remained between 1 and 1.2 mg/dl, and he did not experience any rejection episode. His investigations in July 2004 showed a serum creatinine of 1.1 mg/dl, albumin 4.5 g/dl, fasting blood sugar 96 mg/dl, calcium 9.1 mg, phosphates 3.9 mg/dl, uric acid 6.2 mg/dl, total cholesterol 183 mg/dl and triglyceride 138 mg/dl. He remained well until the second week of August 2004, when he started having pain in both hip joints (right > left) while walking. Examination revealed painful abduction and flexion of both hips, and tenderness over the right hip joint. There was no warmth or swelling over the joints. Plain X-ray of hip joints was normal. However, a magnetic resonance imaging (MRI) scan revealed areas of altered signal intensity in bilateral femoral heads and the intertrochanteric region which were hypointense on T2 and inversion recovery sequence. There was typical subarticular involvement suggestive of AVN (Figure 1). Single photon emission computed tomography (SPECT) of the hip region was performed with 20 mCi of Tc99m MDP. Two focal areas of photon-penia surrounded by a peripheral rim of increased tracer uptake suggestive of AVN were seen in the femoral head region on both sides. Lumbar bone mineral density measured by quantitative CT scan showed a t-score of −3.1 and z-score of −3.5. The iPTH level was 54 pg/ml. He was started on alendronate, calcium and vitamin D, and underwent core decompression of the right hip in October 2004. Biopsy revealed dead as well as viable osteopenic bone fragments and marrow spaces showing extensive haemorrhage. Post-operatively, there was significant
reduction in pain in the right hip. He was able to walk without crutches 1 month after the surgery, and 6 months later he is able to walk freely with >90% reduction in pain, albeit with a noticeably waddling gait. Repeat MRI showed a few foci of revascularization, but was otherwise largely unchanged (Figure 1D).

Discussion

AVN is the most disabling musculoskeletal complication of transplantation and adversely affects the quality of life. The prevalence figures vary (5–40%) in different studies [1–5], which are retrospective and had variable screening protocols and follow-up durations.

The unusual features of this case were: (i) development of bilateral femoral head AVN relatively early after transplant in a 22-year-old male; (ii) appearance of this complication despite being on tacrolimus and a small dose of steroids; and (iii) the discrepancy between the plain radiograph and MRIs. None of the risk factors typically associated with this complication [1–5], such as long duration of transplant, female sex, advanced age, use of high dosage of steroids and multiple rejection episodes, was present in this case. The mean time of onset of joint symptoms in post-transplant AVN is 18 months, but can range from 1 to 120 months. Radiological features become apparent 1–12 months after the onset of symptoms [4].

It is interesting to speculate on the reasons for the development of AVN in this case. While the exact pathogenesis remains unclear, the most widely accepted factor is thought to be the adverse effect of corticosteroids [1–4]. An association has been shown between mean daily as well as cumulative steroid doses and the likelihood of AVN. Rejection episodes increase the steroid need [1] and consequently the AVN risk. A significant reduction in incidence was found when the average total corticosteroid dose came down from 2.9 to 1.2 g during the first 3 weeks post-transplantation [5]. Other studies [3] have failed to confirm such an association. Other contributory factors include non-traumatic systemic fat embolization, intravascular coagulation, increased intramedullary pressure due to an increase in fat cells, persistent secondary hyperparathyroidism and occlusive arterial disease [2–5]. Our patient did not receive a high dose of steroids after transplant. The mean daily prednisolone dose of 18.3 mg in the first 6 months in this case was far less than the 100 mg proposed by Ibels et al. [4], and he did not require any dose of methyl prednisolone. No study has analysed the effect of pre-transplant steroid intake, a factor that was present in this case. He had received steroids 2.5 years before transplant for his native kidney disease and it could be argued that that treatment contributed to the osteopenia and/or post-transplant AVN. However, there was a long interval between that treatment and transplant, and a cause and effect relationship between the two would be purely speculative. Other factors that contribute to osteopenia in chronic kidney disease include altered endocrine metabolism, chronic metabolic acidosis and secondary hyperparathyroidism. The association between low bone mass and AVN is not well established [6]. There was a rapid reduction in iPTH levels in our case, making it less likely that it played an aetiopathological role. The PTH levels decrease in the first 6 months after transplant, but regression is incomplete in about half the cases [7].

The introduction of cyclosporin was followed by considerable reductions in steroid dosages as well as rejection episodes, with consequent lowering of AVN incidence [1,8]. Tacrolimus is more effective than cyclosporin in preventing acute rejections, and hence
has allowed further curtailment of steroid use. Data on frequency of musculoskeletal complications are sparse, but suggestions are that the frequency is less than that seen in those who receive cyclosporin. In one series [9], AVN was noted in 16% of 32 cyclosporin-treated cases, whereas none out of 32 who received tacrolimus developed this complication. Compared with cyclosporin-treated patients, those receiving tacrolimus exhibit preserved bone mineral density [10], and lower incidence of vertebral fractures. In this case, however, the bone mineral density was reduced. Additional favourable effects of tacrolimus, such as reduced cholesterol and triglyceride levels and anticoagulant effect, might contribute in preserving bone integrity and lowering AVN risk [10]. To the best of our knowledge, this is the first reported case of AVN in a tacrolimus-treated renal transplant recipient.

AVN in organ transplant recipients should be differentiated from a pain syndrome described in those taking a calcineurin inhibitor and/or sirolimus. This syndrome has been typically reported 2–10 months after transplant, involves knees, ankles or feet, and regresses spontaneously [11,12]. MRI shows ill-defined lesions that generate a low signal on T1-weighted and a high signal on T2-weighted sequences with fat saturation. The changes are thought to be due to bone marrow oedema. This diagnosis was considered unlikely in our patient for two reasons: (i) hip joint involvement does not occur with this syndrome; and (ii) the presence of MRI findings typical of AVN. The diagnosis was finally confirmed on biopsy of the tissue obtained at the time of surgery.

Another unusual feature was the demonstration of class D lesions at MRI in a case with a normal plain radiograph of the hips. Such a discrepancy is described at early stages, but is less common with advanced disease. Core decompression provided significant pain relief in this case. The goals of therapy in patients with AVN are pain control and preservation of joint integrity. Asymptomatic patients with early lesions picked up on MRI can be managed with non-surgical measures such as statins, aspirin, vasodilators and weight reduction. Around 6–28% of these will deteriorate [13] and need core decompression with or without bone grafting. Decompression decreases the intra-medullary pressure, facilitates venous drainage and encourages revascularization. Unless performed very early in the course, progression to collapse is seen in 40–80% despite initial symptomatic relief following the decompression [14]. Those with collapsed femoral heads require bone grafting, limited femoral resurfacing or hip arthroplasty.

In conclusion, AVN can develop in renal transplant recipients who receive tacrolimus and low dose steroids, and should be considered in the differential diagnosis of new onset pain. Pre-transplant steroid intake could be an important confounding factor in such cases.

Conflict of interest statement. None declared.

References


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