Transplant International

Transplant International ISSN 0934-0874

CASE REPORT

Allograft vasculopathy after allogeneic vascularized knee transplantation

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Keywords
allograft rejection, chronic rejection, composite tissue allograft, composite tissue transplantation, graft fibrosis, graft vessel disease, hand transplant.

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Received: 27 July 2010
Revision requested: 23 August 2010
Accepted: 20 September 2010
Published online: 20 October 2010

doi:10.1111/j.1432-2277.2010.01178.x

Summary

Composite tissue allotransplantation represents a new discipline in reconstructive surgery. Over the past 10 years, we have performed six human vascularized allogeneic knee transplantations. All of these grafts have been lost within the first 56 months. A histomorphologic assessment of the latest case resulted in the detection of diffuse concentric fibrous intimal thickening and occlusion of graft vessels. Findings are comparable with cardiac allograft vasculopathy. The lack of adequate tools for monitoring graft rejection might have allowed multiple untreated episodes of acute rejection, triggering myointimal proliferation and occlusion of graft vessels. Graft vasculopathy represents an obstacle to long-term vascularized bone and joint allograft survival, and adequate tools for monitoring need to be developed.

Introduction

Over the past decade, more than 150 composite tissue allotransplantations have been performed for reconstruction of tissue defects after devastating injuries [1]. These include over 50 hand and eight partial face transplantations [2,3]. Our group performed three allogeneic vascularized femoral diaphyses [4] and six vascularized knee joint transplantations [5,6]. This represents the only series of such transplants to date.

The indication for grafting was the orthopedic reconstruction of a severely injured leg with extended bone and cartilage loss, destruction of the extensor mechanism and skin/soft tissue defects [7]. The procedure was never thought as an alternative to total knee arthroplasty (TKA) in case of osteoarthritis.

The first five knee allografts were lost within 36 months after transplantation [7]. One transplant was lost because of an infection with *Enterococcus faecium* at 6 weeks after transplantation. Histopathology showed an acute infection with infiltration of polymorphonuclear leukocytes, soft tissue necrosis and bone sequesters, but no signs of vasculopathy.

The remaining four grafts survived for 14–36 months. In one case, the patient discontinued the immunosuppressive medication at 36 months after surgery and subsequently lost the allograft as a result of progressive rejection. All four patients presented with instability and impaired range of motion (ROM) of the knee joint. Histopathology of those cases showed necrosis of the bone and articular cartilage (Fig. 1). There was not enough vital tissue left for histopathologic assessment of the graft vessels.

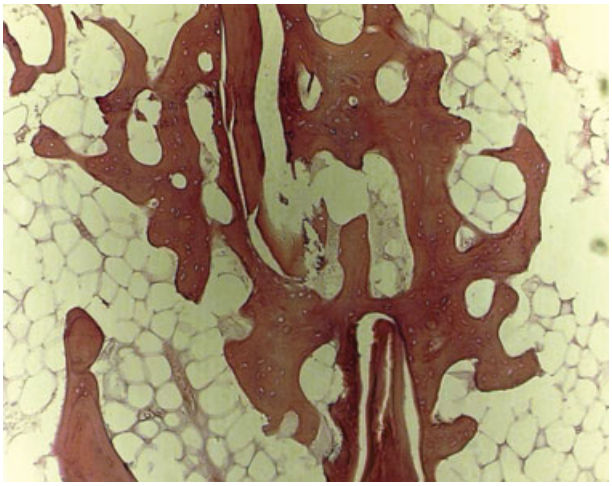

Figure 1 Bone biopsy of a patient presenting with graft dysfunction 2 years after transplantation. Necrotic bone with void osteocyte lacuna, H&E stain.

While acute rejection (AR) was thought to be the cause for graft loss in those patients, we herein present evidence that repetitive AR has resulted in myointimal proliferation of graft vessels and ultimately luminal occlusion. This might have caused ischemia, necrosis and loss of the transplant.

Case report

Recipient characteristics

In January 2000, a 41-year-old Caucasian man presented with an IIIb open femur diaphysal and supracondylar fracture from a motorcycle accident. Postoperative osteomyelitis had developed after open reduction and internal fixation performed at a trauma centre at Bangkok, Thailand. Treatment of infection included multiple surgical debridements, removal of all implants and antibiotic therapy. After recurrence of osteomyelitis in January 2002, the distal femur and knee joint were resected. Subsequently, written consent was obtained for transplantation.

Surgery

Procedural aspects and the surgical technique of vascularized knee transplantation have been described in detail elsewhere [6–8]. In short, after debridement of the recipient's site, the allogeneic knee joint with intact capsule was inserted and fixed by an antegrade femur and a retrograde tibia nail. The graft vessels were anastomosed to the recipient's superficial femoral artery and vein in end-to-side technique. Next, the tendons were reconstructed. Vascularized donor skin (sentinel skin graft, SSG), measuring 8 × 10 cm, was transplanted into the thigh of the recipient as a monitoring tool for rejection [9].

Immunosuppression

Induction therapy was started with antithymocyte globulin (ATG, 4 mg/kg BW i.v.) together with methylprednisolone (250 mg i.v.) for 7 days. Tacrolimus was started at 2 × 5 mg p.o. and then adjusted to achieve target serum trough level of 8–10 ng/ml. Mycophenolate mofetil (MMF) was given at 2 × 1 g p.o. Methylprednisolone was given at a dose of 10 mg p.o. starting on day 8. A surgical site infection at 48 months after transplantation prompted the withdrawal of MMF and steroid treatment and reduction of tacrolimus dose to achieve trough levels of 5–6 ng/ml (Fig. 2).

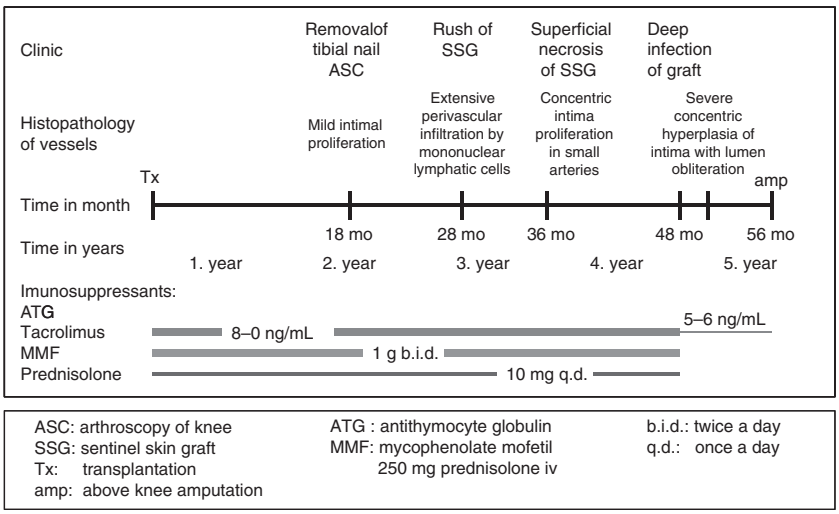

Figure 2 Summary of clinical events, histopathology and immunosuppressive medication.

Follow-up and monitoring

Post-transplant examinations (clinical examinations, laboratory tests, tacrolimus serum level, Duplex-sonography and radiologic assessment) were performed on a regular basis [7]. Follow-up visits at our clinic were scheduled every other month. Tacrolimus serum trough levels were monitored weekly. The patient was educated to self-monitor the SSG and requested to report any changes to the surgical team immediately.

Samples for histology were taken during planned surgeries or whenever rejection was suspected. Protocol biopsies were not performed. All specimens were fixed in formalin, paraffin-embedded and stained with hematoxylin–eosin (H&E), Elastica-van Gieson stain (EvG) and methyl green pyronin stain (MGP).

Results

The surgical procedure and the postoperative course were uneventful and have been reported previously [7,10]. At 18 months, the tibial nail was removed and biopsies of the cartilage, bone and synovia were taken (Fig. 2). Biopsies showed vital tissue without necrosis. In the synovial vessels, a mild proliferation of the intima with infiltration by mononuclear cells was found (Fig. 3). This was interpreted as a mild rejection with no need for treatment.

Erythematous papules on the SSG were noticed by the patient at 28 months. Skin and synovial biopsies of the SSG and the allograft confirmed acute cellular rejection [10]. Treatment with methylprednisolone (250 mg i.v. for 3 days) was initiated and resulted in restitution of normal skin histology. This remained the sole episode of a visible AR on the SSG.

At 36 months after transplantation, a proportion of the SSG became necrotic. Biopsies of the SSG showed superficial skin necrosis. In the deeper layers, concentric intima proliferation in small arteries with luminal occlusion was found. Subsequently, biopsies of the allograft were taken. Synovial and soft tissue samples revealed perivascular mononuclear cell infiltrates, intimal proliferation with mononuclear cell infiltration and concentric subtotal obliteration of small vessels. In some sections, complete occlusion and fibrosis of the surrounding tissue were observed (Fig. 4).

At 50 months, knee function (ROM) decreased from 0-0-90° Flexion to 0-10-40° and an anterior instability developed. In allograft biopsies, articular cartilage and bone necrosis was found. Vessels showed severe concentric hyperplasia of the intima with variable degrees of lumen obliteration (Figs 5 and 6).

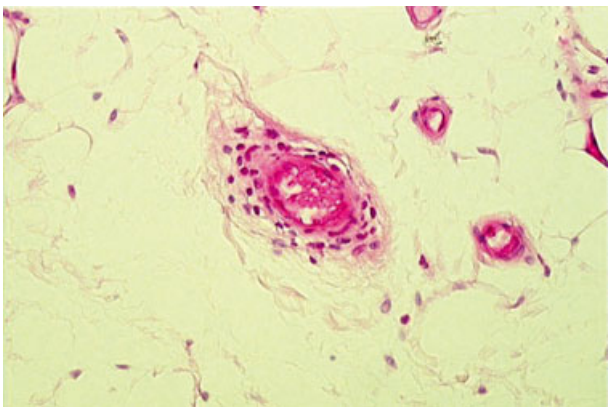

Figure 3 Synovial biopsy 18 months after transplantation: mild proliferation of the intima, H&E stain.

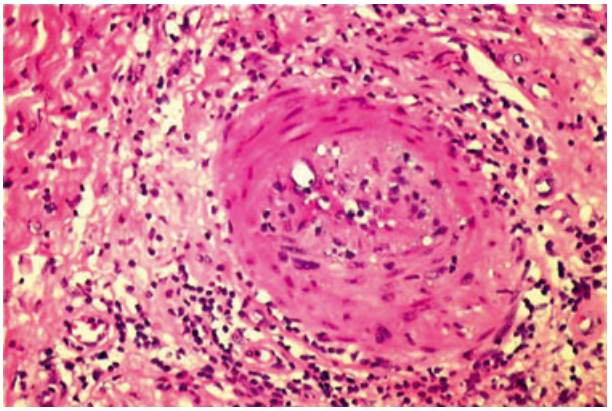

Figure 4 Biopsy of sentinel skin graft (SSG) 36 months after transplantation: concentric narrowing of small arterial vessels by fibrotic proliferation of the intima, H&E stain.

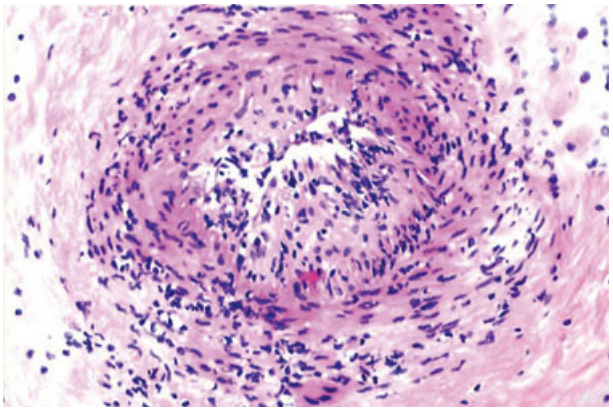

Figure 5 Synovial biopsy 50 months after transplantation: Concentric fibroses of the intima with subtotal occlusion of the lumen, H&E stain.

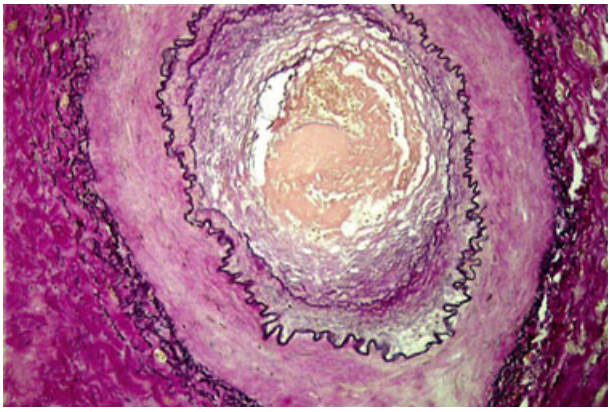

Figure 6 Soft tissue biopsy 50 months after grafting: Hypertrophic intima with an intact internal elastica lamina, Elastica-van Gieson stain.

A deep surgical site infection, descending from the necrotic SSG to the allograft developed. This infection caused by *Pseudomonas aeruginosa* persisted despite therapy with antibiotics, surgical debridement and vacuum-assisted closure therapy (VAC™; Kinetic Concepts Inc., San Antonio, TX, USA). After a detailed discussion of the medical status and the lack of treatment alternatives with the patient, he consented to an above knee amputation, which was performed at 56 months after transplantation.

Discussion

Allograft vasculopathy has not been previously described in human composite tissue transplantation [11]. We here provide a case of vascularized knee allograft loss with evidence that the cause might be myointimal proliferation as a consequence of repetitive/ongoing rejection.

The hand and face transplantations performed in the last decade revealed that the skin of a CTA is not immediately or irreversibly rejected but might serve as a useful monitor tool for such a graft [12]. Acute rejection episodes of the skin occurred in 85% of patients with hand transplants within the first year [13] and were treated successfully with topical treatmentor or steroids, basiliximab, ATG and alemtuzumab [14]. In the first five cases of knee allografts, no episodes of AR had been detected. Without a SSG, the graft could not be adequately monitored, however. In the case described here, an islet of vascularized skin was transplanted with the allograft. With skin biopsies of this SSG, AR was detected and adequately treated [10].

Signs of a progressive vasculopathy became apparent at 36 months after transplantation as described above. Unadkat *et al.* have published recently the findings from an orthotopic hind limb allotransplantation model in rats where multiple AR episodes resulted in the development of myointimal proliferation and morphologic signs for chronic rejection [15]. In this model, repeated AR episodes were treated with CyA and dexamethasone. At postoperative day 90 animals had gone through 19 episodes of AR, and myointimal proliferation associated with concentric luminal occlusion and perivascular fibroses was observed.

We see possible parallels between this trial and the case presented here with similar histologic alterations in vessels and bones. However, as we have only recognized one single AR in our follow-up compared with up to five in the first year after hand allotransplantation, multiple AR might have been missed because of the lack of adequate monitoring tools.

Histopathologic features of composite tissue vasculopathy are morphologically comparable with cardiac allograft vasculopathy after cardiac transplantation [16–18].

In summary, allograft vasculopathy has been observed in this case of vascularized knee transplantation. As treatment options in case of a vasculopathy are very limited, we suggest careful monitoring and immediate treatment of AR episodes. Our clinical knee transplantation program is on halt until better tools to monitor rejection are available and more knowledge about the risks of allograft vasculopathy has been gained.

Authorship

MD: collected and analyzed data and wrote the paper; AN: analyzed data; SS: analyzed data; FW: performed research and collected data; GOH: performed research and designed the study.

Funding

No grants or sponsors/no conflict of interest.

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