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CASE REPORT

Avascular necrosis of the humeral head following bilateral upper extremity vascular composite allotransplantation: a case report

Jacob Rinkinen[a], David Molway[a], Matthew Carty[a], George S. M. Dyer[b], Bohdan Pomahac[a], Anil Chandraker[c] and Simon G. Talbot[a]

[a]Division of Plastic Surgery, Brigham and Women's Hospital, Boston, MA, USA; [b]Department of Orthopaedic Surgery, Brigham and Women's Hospital, Boston, MA, USA; [c]Division of Transplant Surgery, Brigham and Women's Hospital, Boston, MA, USA

ABSTRACT

Vascularised composite allotransplantation (VCA) represents an exciting and emerging field in plastic and reconstructive surgery. Despite the generally good functional and psychosocial outcomes, multiple complications can be associated with the procedure. The authors describe a case of avascular necrosis of the humeral head following successful upper extremity VCA.

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Introduction

Vascularised composite allotransplantation (VCA) offers reconstructive surgeons the option to restore both form and function following debilitating injuries. Since the first successful unilateral hand transplant in Lyon, France, in 1998 [1], more than 70 patients have undergone successful extremity VCA across 13 countries [2,3]. In general, good success rates have been observed with respect to transplant survival, functional metrics, subjective recovery, and psychological and social acceptance [4–8]. However, despite these results, VCA confers significant risks resulting from the need for lifelong immunosuppression and the potential need for chronic steroid use. In this report, we present a complication of avascular necrosis (AVN) of the humeral head following bilateral upper extremity transplantation, including aetiology, pathophysiology and our treatment algorithm. Given the expanding number of VCAs, reconstructive surgeons should be aware of this potential complication.

Case report

Our patient is a 40-year-old male who underwent amputation of all four extremities in January 2012 (right below knee, left above knee, right below elbow and left above elbow) secondary to septic shock and subsequent disseminated intravascular coagulation (DIC). The patient was referred to the Brigham and Women's Hospital Plastic Surgery Service for consideration of upper extremity allotransplantation in 2013. On presentation, he was noted to have regained significant strength in bilateral upper and lower extremities. He continued to be wheelchair-bound; however, he was using upper extremity prostheses an average of 3–4 hours a day. He underwent extensive but routine screening prior to being listed for allotransplantation [9]. Once a suitable match was found, the patient was taken to the operating room in December 2014. No intraoperative complications were encountered (Figure 1). Following the operation, the patient was given an induction bolus of 500 mg intravenous methylprednisolone, followed by oral prednisone 100 mg twice a day tapered by 20 mg daily until reaching a dose of 20 mg daily. The 20 mg daily dose was continued for 7 days in the hospital, prior to the patient being discharged on 10 mg daily. Maintenance immunosuppression included tacrolimus (goal 10–12 ng/mL), mycophenolate mofetil (500 mg twice daily) and prednisone (10 mg daily).

The postoperative course was notable for two positive donor-specific antibodies (DSA) requiring

CONTACT Simon G. Talbot sgtalbot@partners.org Division of Plastic Surgery, Brigham and Women's Hospital Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

Figure 1. Postoperative follow-up demonstrating successful vascularised composite allotransplantation to bilateral arms.

plasmapheresis and intravenous immunoglobulin (IVIG) on postoperative days (POD) 1 and 3. Additionally, by POD7, the patient was noted to have four positive DSA (three new and one prior) requiring three additional rounds of plasmapheresis and IVIG. Skin biopsies were performed and found to be negative for rejection. His ongoing immediate postoperative course was unremarkable. He began occupational therapy immediately and performed range of motion exercises daily, beginning full weight bearing at two months postoperative.

At 11 and 12 months postoperative, the patient endorsed a mild erythematous, epidermal rash with skin biopsies demonstrating grade I/II allograft rejection. This was treated with 250 mg intravenous methylprednisolone for three 3 days.

In March 2016, the patient presented to the plastic surgery clinic with vague flu-like symptoms and musculoskeletal pain overlying his right deltoid. He denied fevers or chills, and no erythema, induration or loss in range of motion of the shoulder was noted. Laboratory testing was significant for a leucocytosis to 15,000 white blood cells per microliter. He underwent a shoulder plain film which was concerning for avascular necrosis of the right humeral head. He subsequently underwent further characterisation with MRI, demonstrating a subchondral bone marrow signal abnormality of the humeral head with collapse superiorly and proximal to the supraspinatus footprint, consistent with avascular necrosis of the humeral head (Figure 2). The dimensions of the lesion were 47 mm in diameter and 9 mm in depth, encompassing almost the entire articular surface. Definitive treatment of such a large lesion in the humeral head typically requires resurfacing hemiarthroplasty, as this is too large for an osteochondral transplant or other osteoplasty. This option was discussed at length in the office, and the patient decided his symptoms were not currently severe enough to warrant such a significant procedure. The patient continues to be followed conservatively by plastic surgery and orthopaedic surgery as an outpatient with ongoing physical and occupational therapy.

Discussion

Vascularised composite allotransplantation offers reconstructive surgeons another option for patients who have suffered debilitating limb loss. With the increasing number of VCAs performed worldwide, a growing number of complications are being seen. The complications most commonly documented with VCA include acute rejection, opportunistic infections, hypertension, hyperglycaemia and renal impairment. Rarer, but notable, complications include the need for reoperation, acute limb ischaemia requiring reamputation, avascular necrosis of the hip resulting in bilateral replacement, end-stage renal disease and death [1,10]. We present a case of unilateral AVN of the humeral head following bilateral upper extremity VCA.

The aetiology of non-traumatic AVN is multifactorial with the most commonly reported cause being corticosteroid therapy [10–13]. Other risk factors include haemoglobinopathies, alcohol abuse, vasculitis, hyperlipidaemia, hypercoagulable state, pancreatitis and radiation injury [13]. The first case of AVN following corticosteroid therapy was documented in 1957 [14]. Since then, the number of reported cases has risen exponentially with increasing use of corticosteroids in treating numerous conditions. AVN most often coincides with chronic administration of corticosteroids; however, multiple reports in the literature have described AVN following high, short-term doses. For example, case reports have included humeral head AVN following a 1-week course of corticosteroids following an inflammatory arthritis exacerbation [15], bilateral shoulder and unilateral hip AVN following a 15-day steroid course consisting of 9 days of methylprednisolone and 6 days of prednisone (total dose of 1.75g) during treatment of septic shock [16], and bilateral hip AVN following unilateral hand transplant complicated by five episodes of acute rejection requiring

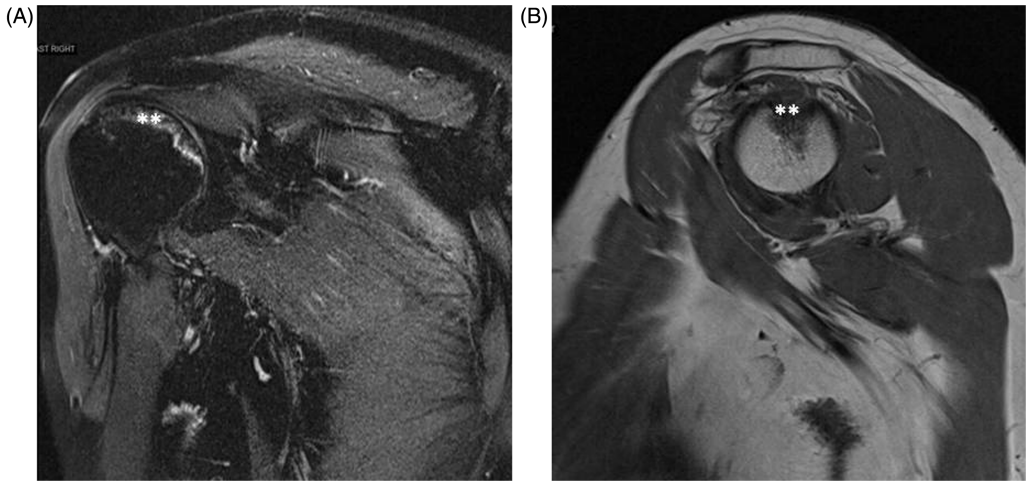

Figure 2. MRI showing region of avascular necrosis of humeral head (**refers to location in depiction). (A) Coronal and (B) axial.

Table 1. Humeral head avascular necrosis staging.

Stage	Radiographic	MRI	Clinical
I	Normal	Low-signal bands	Normal
II	Mottled, sclerotic bone	Uniform loss of signal	Normal
III	Crescent sign	Crescent sign	Pain with activity
IV	Extensive collapse	Effusion	Pain with activity
V	Glenoid degenerative changes	Extensive collapse, glenoid change	Pain at rest

pulse steroids [10]. Moreover, the time between steroid administration and symptom presentation often ranged between 6 and 24 months [10,17]. Similar to these reports, our patient developed symptoms 15 months following initial induction steroid dosing and two subsequent pulse steroid courses (consisting of 250 mg methylprednisolone for three days for each course) for rejection episodes. There are multiple theories describing the pathogenesis of corticosteroid-induced AVN. Two major theories have been postulated involving changes in fat metabolism at either the level of the liver or bone. The first theory suggests that an increased volume of intraosseous fat leads to ischaemia and elevated intraosseous pressure resulting in AVN [11,18]. The second theory involves metabolic changes in the liver; with corticosteroid administration causing an increase in circulating lipids resulting in micro-emboli migration to subchondral vessels and associated focal osteocyte necrosis [18]. Given these findings, patients on chronic or high-dose systemic steroids should be monitored closely for metabolic changes, more specifically lipophilic variation which may place patients at a higher risk for developing AVN.

Review of the literature regarding postoperative complications following solid organ transplantation demonstrates an overall low incidence of AVN. Cardiac transplant patients were shown to have a 3% incidence of symptomatic AVN in the hip and knee (5 patients with femoral head and 1 patella) [19]. Similarly, large database searches (27,772 patients) of individuals who underwent renal transplantation showed a less than 4% incidence of AVN [20]. Patients who underwent orthotopic liver transplantation developed osteonecrosis of the hip 2% of the time following transplantation [21]. Among these studies, there was no association noted between steroid dose and the development of AVN. The femoral head was shown to be the most common location of AVN among all solid organ transplant recipients. More specifically, one reported case of bilateral femoral head osteonecrosis has been reported following a unilateral hand VCA [10]. To our knowledge, no cases of humeral osteonecrosis following upper extremity transplantation have been reported.

Of additional interest is the association in case reports, and in our patient, of sepsis and corticosteroid administration being associated with AVN. It may be that our patient's relative ischaemia at the time of sepsis was a 'first hit' and steroid administration a 'second hit' resulting in enough ischaemia to cause AVN. Retrospective review of pre-operative plain films shows mild sclerotic change over a limited area, which hints at this process beginning prior to steroid induction, but likely worsened by steroids and weight bearing with transplanted limbs.

Clinical presentations often vary between patients. Presentation is often with vague shoulder pain

associated with movement. Patients may describe worsening shoulder pain at night leading to difficulty sleeping, painful clicking or symptoms preventing normal work. Physical exam is often notable for local tenderness over affected joints with preservation of passive and active range of motion until late-stage disease. Full assessment of all joints is imperative due to the increased risk of multiple joint involvement. Laboratory tests should rule out other aetiologies of symptoms, especially infection, and include a complete blood count, C-reactive protein or erythrocyte sedimentation rate, and other specific serology to rule out rheumatoid arthritis and other inflammatory conditions. Next imaging should be obtained including plain radiographs and MRI for staging (Table 1) if high clinical suspicion for AVN. Once a lesion has been identified, contralateral radiographs of other susceptible joints may be obtained to help identify subclinical disease.

Treatment varies by severity of symptoms and stage of humeral head AVN. Non-operative treatment should focus on minimising risk factors such as tobacco and alcohol use and focus on judicious dosing and duration of corticosteroids. However, in transplant patients, the risk of developing rejection must be strongly weighed against progression of AVN. Furthermore, for patients experiencing mild symptoms with stage I or II disease, physical therapy to preserve shoulder motion, activity restrictions to minimise overhead adduction and non-steroidal anti-inflammatory medications for discomfort help to stabilise disease progression and provide mild symptomatic relief [13]. Once patients reach stage III or higher, they often benefit from surgical intervention including core decompression, hemiarthroplasty or total shoulder arthroplasty [11,15].

We present the first reported case of unilateral AVN of the humerus following bilateral upper extremity VCA. It is important for clinicians to understand the risks associated with such procedures to ensure adequate informed consent, pre-operative planning and surveillance following surgery. The postoperative complications associated with steroids demonstrate the need for future research to address corticosteroid-induced side effects, improve immunosuppression options and create modalities to ameliorate these outcomes.

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