Eponychial lesions following bilateral upper extremity vascular composite allotransplantation: a case report

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ABSTRACT

Vascularized composite allotransplantation represents a useful addition to reconstructive options available to the plastic surgeon. Though the procedure provides beneficial functional outcomes, there remain complications, often associated with the immunosuppression necessary to maintain an allograft. We report a case of eponychial fold lesions following successful bilateral upper extremity allotransplantation.

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Introduction

Vascularized composite allotransplantation (VCA) provides a reconstructive option for the recovery of function and appearance in patients who have suffered limb loss. The field of VCA continues to expand. Research has shown favourable outcomes related not only to allograft success and functional improvement, but also to psychosocial benefits [1,2]. However, VCA is also associated with complications, often stemming from the chronic immunosuppression necessary to prevent allograft rejection. Immunosuppressed patients are at a greater risk for developing infections, including human papillomavirus (HPV), due to their inability to mount an appropriate immune response [3]. In this report, we present a complication of HPV-related eponychial fold lesions following bilateral upper extremity transplantation. Healthcare providers should be familiar with this complication and the difference in its clinical presentation and necessary management compared to more commonly seen rejections.

Case report

A 42-year-old male underwent amputation of all four extremities in January 2012 secondary to septic shock due to Streptococcus pyogenes with subsequent limb gangrene. The patient was referred to the Brigham and Women’s Hospital Plastic Surgery Service for consideration of upper extremity allotransplantation. In October 2014, a suitable match was identified and the patient underwent bilateral upper extremity VCAs. The family of the donor denied any social behaviour of increased risk, and all standard serology assessment, including nucleic acid testing, was negative for viral infection, except for EBV-IgG [4]. Induction of immunosuppression included thymoglobulin 1.5 mg/kg. The surgery was without immediate clinical complications, although due to an early finding of donor-specific antibody (DSA) he was treated with plasmapheresis prior to discharge. He was discharged on tacrolimus (goal 8–10 ng/mL), mycophenolate sodium 720 mg twice daily, and prednisone 10 mg daily.

The patient presented for routine evaluation in December 2016. A minor rash was noted on the forearms and a biopsy demonstrated Banff grade II acute rejection. This was treated with a transient increase of oral prednisone and tacrolimus with both clinical and histological improvement.

In February 2017, he was evaluated for worsening cutaneous erythema and roughening of the eponychia...
of the right thumb and index finger, most notable on the thumb (Figure 1). Initially, the eponychial inflammation was severe, involving all digits, and was associated with ragged cuticles and an increased capillary density. Due to suspicion that the worsening eponychial inflammation may have been an early sign of recurrent rejection or that an ongoing underlying inflammatory process may have precipitated this rejection episode, a biopsy was performed (Figure 2). Histology of the biopsy revealed verrucoid keratosis with warty features consistent with verruca plana. As the biopsy results did not support a diagnosis of rejection, the patient was managed with cryotherapy of the lesions.

Subsequent observation showed resolution of skin changes within several weeks. The patient continues with routine outpatient evaluation and has had intermittent episodes of repeated cryotherapy over the past year with near complete resolution of the lesions.

**Discussion**

VCA represents a unique reconstructive treatment for patients who have lost a limb. Despite the overall functional and psychosocial advantages of the procedure, it is not without complications. A major issue for VCA recipients is transplant rejection, which can result in transplant failure. In order to manage the risk of rejection, recipients of VCAs continue lifelong immunosuppression, which is associated with its own complications. We present a case of HPV-related eponychial fold lesions following bilateral upper extremity VCA.

Due to the possible catastrophic effects of severe transplant rejection, providers caring for VCA patients must be vigilant in identifying the early stages of rejection in order to treat this at its early, reversible stages. In contrast to solid-organ transplant, one advantage of VCA is that rejection can be visually monitored through evaluation of its dermatologic changes [5], although we are still learning about the acute and sub-acute changes to the skin and deeper tissues. Clinical suspicion of acute rejection is based on physical examination of the skin; which can have multiple appearances, from a fine petechial rash, to a

![Hyperkeratosis](image1)

**Figure 1.** Right thumb showing worsening cutaneous erythema and roughening of the eponychia.

![Biopsy prepared with haematoxylin and eosin stain (20× magnification).](image2)

**Figure 2.** Biopsy prepared with haematoxylin and eosin stain (20× magnification).
maculopapular rash, to diffuse erythema. Dermatologic findings are highly variable and the severity of skin involvement does not always correlate with histologic findings.

Skin biopsies with histologic examination are a routine method for assessment of VCA rejection. The most common findings seen on pathology in acute rejection are a superficial dermal perivascular infiltrate composed mostly of lymphocytes and epidermal changes consisting of keratinocyte necrosis, basal cell vacuolization, spongiosis, and acanthosis [6]. The Banff working classification for evaluation of VCA rejection was developed in 2007 and is the current standard for diagnosing acute rejection in VCA recipients. It classifies rejection into five grades (0–IV) of increasing severity [7]. As the number of VCAs increases, there are more pathological changes observed that have not been accounted for by the Banff classification. These include graft vasculopathy, dermal sclerosis, epidermal and adnexal atrophy, and capillary thromboses in the skin [6]. The Banff classification is undergoing refinement to include new findings.

Our patient presented with slightly raised erythematous lesions of the eponychial folds which, in this case, are an atypical presentation of verruca plana given the absence of thrombosed capillaries. Given the patient’s recent episode of Grade II acute rejection, there was suspicion that the worsening eponychial inflammation may have been an early sign of recurrent rejection, so a biopsy with histologic examination was performed. While the dermatologic manifestations were non-specific and could have been compatible with mild allograft rejection, the biopsy results were consistent with verruca plana and the patient was managed accordingly.

Verruca plana, commonly known as flat warts, are most commonly caused by HPV types 2, 3, and 10 [8]. Most individuals are exposed to these viruses in childhood and develop immunity that suppresses the formation of active warts. Ongoing research suggests much of this local immunity is mediated by long-lived skin resident T cells. It is likely that this patient’s transplanted arms were previously colonised and protected by donor-derived resident memory T cells. Although the kinetics of turnover are not yet established, it appears that recipient-derived T cells migrate into the transplanted tissues and destroy the donor resident immune cells. As a result, there is a window of time where the protective T cells are not present and the recipient’s immune system is heavily suppressed, allowing unmasking of conditions for which both the donor and recipient had prior immunity. In this case it is most likely that the donor had prior exposure to HPV but his immune system had kept it in check until the arms were transplanted. Given that the patient was treated with a transient increase of oral prednisone and tacrolimus two months prior to his presentation with HPV-related lesions for an episode of acute rejection, it is possible that the increase in immunosuppression facilitated the manifestation of HPV at that time. We typically keep immunosuppression at the lowest safe dose while also being mindful of rejection (in this case tacrolimus level 8–10 ng/mL), and have not been able to significantly reduce it further. While those with healthy immune systems can eventually clear an HPV infection, the immunosuppressed are not typically able to resolve HPV lesions. Other dermatoses which mimic acute rejection in these patients include tinea versicolour, rosacea, molluscum contagiosum and contact dermatitis.

While correlated with cancer in the immunocompetent population as well, HPV infection in the immunosuppressed is associated with an even higher rate of malignancy. Persistent infection of keratinocytes with HPV has been identified in 40% of cutaneous squamous cell carcinomas (SCCs) in immunocompetent people and in 80% of solid organ transplant patients [9]. In addition to a 65- to 100-fold increase in SCC compared to immunocompetent individuals, organ transplant recipients also have a higher rate of HPV detection in biopsies of their SCC lesions [10]. Preventative vaccination is the most recommended strategy to decrease the burden of HPV-related disease.

Topical imiquimod is a treatment for verruca plana and may be used in the treatment of warts in solid organ transplantation [3], but its safety in VCA has not been established, and theoretically risks immunostimulation in the transplanted allograft. Appropriate treatment for HPV-related skin lesions in this patient population involves cryotherapy and/or observation. Cryotherapy is associated with a variety of adverse effects, including pain, erythema, discoloration, haemorrhagic blistering, recurrence and nail damage [11]. Compared to the risk of immunostimulation with imiquimod, the risks of cryotherapy are less serious and can be more easily prevented. If cryotherapy is chosen, it should be performed judiciously, and potentially less aggressively on multiple occasions, by an experienced clinician to avoid injury to the nail germinal matrix and/or triggering of an immune response.

It is important for clinicians to consider HPV-related lesions as a possible diagnosis when encountering dermatologic changes in VCA recipients. This allows appropriate, directed treatment, and often, the minimisation of immunosuppression.
Disclosure statement
No potential conflict of interest was reported by the author(s).

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