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The Histocompatibility and Immunogenetics of Hand Transplantation

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Abstract

This short review will be concerned with the literature that has developed connected with the immunogenetic and tissue compatibility aspects of hand transplantation and will also draw on connected work in the more general area of vascularised composite allotransplantation (VCA) which includes face, abdominal wall uterus, and larynx.

Keywords: hand, HLA, antibody, rejection, outcomes

Introduction

The promise of the restoration of form and function following the loss of a limb is the subject of some of the very earliest written accounts of transplantation. The *Sushruta Samhita*, possibly dating to the first millennium BCE, is perhaps the earliest of these and refers to both limb and organ transplantation. The first representation of a limb transplant appears in a 14th century painting by the artist Matteo di Pacino which depicts the 5th century story of Saint Cosmas and Saint Damien who purportedly replaced the diseased leg of a living man with the healthy leg of a deceased man (interestingly of a different race). This historic fascination with the subject therefore predates the modern era of limb transplantation by more than 2500 years. Public interest has also surrounded current programmes with each early case attracting the attention of the popular media and publicity for both the recipient and the teams involved in the transplant.

The UK hand transplant programme is based in Leeds Teaching Hospitals NHS Trust. The first transplant was performed in 2012 and the programme has now delivered ten transplants in six individuals. The experience of the local laboratory in supporting this programme is reported upon elsewhere in this edition of the International Journal of Immunogenetics.

This review discusses the literature that has developed in connection with the immunogenetic and tissue compatibility aspects of hand transplantation and will also draw on related work in the more general area of vascularised composite allotransplantation (VCA) which includes face, abdominal wall, uterus, and larynx.

The immunological considerations for hand transplantation are common with those of any transplant, namely the influence of HLA matching and the relevance of donor HLA specific antibody (DSA) to outcome.

HLA matching

With a published worldwide experience of 113 hand transplants in 76 patients (Aloabi 2017), 38 abdominal wall transplants (Giele 2016), 37 face transplants (Sosin & Rodriguez, 2016), and smaller numbers of uterine (Brännström 2018) and penile (Jonczyk MM 2019) transplants, the dataset is not yet sufficiently large or mature to

make a valid evaluation of the impact of HLA mismatching. The limited opportunity to match HLA prospectively (as a consequence of the small pools of donors and recipients) and need to achieve an acceptable physical match, mean that these data will be slow to accumulate". An international registry (IRHCTT) to collate the growing evidence base has been established (Petruzzo 2010).

There is a significant literature relating to skin allografting which provides a basis from which to work. One of the earliest reports concerns the selection of the optimal kidney donor for a patient in end-stage renal failure using the results of skin grafting from available family donors (Shackman 1966). This, and the following publication of Jonker at al (1979), identified the high immunogenicity of skin, linking this to levels of HLA matching achieved between donor and recipient.

Although the differences reported did not reach statistical significance, the recent review by Bonastre (2012) involving 68 rejection episodes in 28 recipients of hand transplantation performed between 1999 and 2011 identified a link between the number of acute rejection episodes and number of HLA mismatches.

It is certainly tempting to speculate that the phenomenon of 'split rejection' in which the different tissues comprising a VCA reject at different times or are involved in rejection processes to differing extents (Sinha 2013) may be a reflection of their comparative levels of HLA expression. The potential impact of tissue antigen expression level on graft outcome has recently been explored by Carey et al (2019) who comment that, together with knowledge of circulating HLA-specific antibody, the capability to measure the cellular expression of each HLA antigen is important towards assessment of transplant risk.

Within the Leeds programme, there is currently no intention to pursue HLA matching. It does however influence the clinical risk estimate at time of offer and would be prospectively utilised as a deciding factor when two potential recipients would otherwise both match the donor based on crossmatching and physical characteristics. Post-transplant knowledge of the HLA match achieved permits informed interpretation of results of serum screening and significance of these to clinical events.

A large portion of the solid organ donor pool would meet eligibility criteria as VCA donors (Mendenhall 2018). Although not specifically addressed in this paper expansion of the donor population may offer scope to improve HLA matching in the future.

Alloimmunity and rejection

The literature concerning recipient sensitisation to HLA has more recently begun to accumulate and whilst relatively scant, shows, as for solid organ transplantation, that this is an important consideration in VCA.

The case report of Chandraker et al. (2014) concerning management of antibody-mediated rejection in a presensitized recipient of a full-face allotransplant represents the only published report concerning pre-existing sensitisation, reflecting the precautionary approach adopted in VCA programmes. The transplant was performed in the situation of a T and B cell positive pre-transplant crossmatch. Despite significant clinical efforts to overcome the incompatibility via post-transplant plasmapheresis, evidence of rejection with correlating increase in levels of donor HLA specific antibody and C4d deposition in the allograft was found by the fifth post-operative day. This was successfully treated with a regimen including plasmapheresis, eculizumab, alemtuzumab, bortezomib, and steroids. In a follow-up report, Win (2017) details three later episodes of T cell mediated rejection; all resolved following treatment. Expansion of T follicular helper (CD4+, PD1+, CXCR5+) and memory B (CD19+, CD27+) cell populations linked to the increase in DSA during the initial antibody mediated rejection episode.

De- novo sensitisation occurring post VCA is reported by several authors. Schneeberger (2013) identified appearance of donor HLA specific antibody coincident with cellular rejection in four out of five recipients of upper extremity transplants. An earlier paper from the same authors (2008) implicates poor patient compliance with the prescribed immunosuppressive regimen as a contributory factor to outcome in some cases but also suggests antecedent mechanical injury as a potentially important trigger. In our experience, physical trauma, either directly to the

transplant or remotely, or other processes that induce an inflammatory response such as sun-burn, viral illnesses, and surgery, appear be associated with acute rejection.

The first case report of antibody mediated rejection of a hand transplant resulting from de novo sensitisation was given by Weissenbacher (2013). These authors identified the presence of DSA in a patient nine years after transplantation correlated with the appearance of B cell clusters in the dermis. The patient had been undergoing stepped reduction of immunosuppression and reported a viral infection occurring approximately one month prior to the rejection episode. Prompt treatment with rituximab led to a reduction of DSA levels and resolution of symptoms.

A multicentre study by Berglund and colleagues (2019) identified a high prevalence of DSA in 45 recipients of hand transplant from 15 centres. HLA class 2 mismatch was correlated with antibody development. Cellular rejection occurred ahead of the appearance of DSA in nearly all cases and the development of antibodies correlated significantly with the number of rejection episodes observed per year. The authors suggest that antibody prevalence in the study group is probably underestimated since standardized protocols were not being followed. Importantly, they identify that in most cases rejection was diagnosed prior to alloantibody detection and, on this basis, hypothesize that an ongoing immune response triggers DSA development rather than DSA preceding a cellular process.

The management of highly sensitised VCA patients is a current area of controversy. By far the majority of VCA programmes require a negative crossmatch ahead of transplantation but many of the patients entering these programmes will have had broad exposure to foreign HLA through blood transfusion and, in the case of burns victims, skin grafts. In our own programme the longest waiting recipient had a pregnancy and transfusion related CRF of 75% and was denied transplant opportunities on four separate occasions as a result. Whilst transplantation across antibody barriers was considered, a compatible donor was eventually found, obviating that need. As VCA programmes grow, this situation will arise more frequently and although novel techniques such as limb perfusion (Amin 2018a), protocol developments, and expanding geographic catchment may expand donor

pools, antibody incompatibilities may need to be addressed through desensitisation approaches (Kueckelhaus 2016).

Non-HLA immunity in VCA has been addressed in a limited number of publications. Banasik (2014) identified the presence of anti-angiotensin II type 1 receptor and anti-endothelin receptor antibodies in a hand transplant patient who repeatedly developed acute rejection episodes. Similarly Dwyer (2017) reported a case of refractory rejection in the recipient of a hand transplant in whom anti-angiotensin II type 1 receptor antibody was detected. More recently Kollar (2018) also identified an association of antibody against non-HLA, skin-specific antigens with acute rejection episodes in a clinical series of five face and two hand transplants. It is apparent then that, similar to the situation in solid organ transplantation, non-HLA directed reactivity may contribute to graft pathology and clinical outcome.

Since the tissue carries a large passenger leucocyte population (Amin 2018b) it should not be overlooked that the potential for alloreactive interaction occurs in two vectors in hand transplant. Moreover the donor/recipient origins of dendritic and T cell populations allows for up to four varieties of immunological synapse to occur. A complex immunological environment therefore exists that requires careful consideration and management. This includes potential for HvG, GvH and DTH type reactions that may result in mixed/overlapping clinical presentations. Dermatological conditions may also confound the picture (Kanitakis 2008).

Banff criteria have been established for grading histological rejection in graft skin in VCA (Cendales 2008) and now provide the standard for diagnosing and grading of rejection. These place emphasis on lymphocyte mediated injury, identifying four categories of inflammatory change. The incidence of acute rejection in VCA exceeds 80% (Fischer 2014). Signs of rejection occur more regularly in the early post-transplant period and reduce in frequency over time. Most episodes can be reversed with increased immunosuppression. Criteria for antibody mediated rejection are not included in the current Banff classification. Chronic rejection processes remain poorly described (Morelon 2018).

Future directions

The life-enhancing as opposed to life-prolonging nature of hand transplantation raises an ethical dilemma around the risks associated with the requirement for lifelong, often intensive, immunosuppression. This issue may be addressed by the application of cell based protocols such as those reported by Schneeberger (2013), using a donor bone marrow based approach in a clinical setting, and Waldner (2018) with mesenchymal stem cells in-vitro. These approaches are however subject to further evaluation and will require large randomised trials for their validation. Whilst these are awaited, several case reports of donor skin allograft survival after bone marrow transplant from the same donor can be found in the literature. Although the majority concern HLA-identical donors some involve transplants between haploidentical pairs (Mache 2006). Combined bone marrow and kidney transplants have demonstrated the feasibility and safety of this approach and provided evidence of the development of a tolerant state (Scandling 2015). Whilst the approach remains experimental the potential clinical benefits in the context of hand transplantation are readily apparent.

Clinical outcomes

Hand transplant programmes deliver excellent clinical results with reported graft survival of 90.4% at 1 year and 86.6% at 5 and 10years (Petruzzo 2017). Significantly, IRHCTT data indicates most hand transplant recipients report improved quality of life and satisfaction with outcome (Petruzzo 2017). The commissioning of a UK Hand Transplant programme in Leeds by NHS England identifies that a clear clinical benefit of this approach is acknowledged. It is remarkable that through this programme (and others like it around the world) the earliest imaginings of the possibilities offered by transplantation have now become a reality.

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