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The challenge of dermatopathological diagnosis of composite tissue allograft rejection: a review

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ABSTRACT

Advances in immunosuppressive treatments and microsurgical techniques have rendered allotransplantation of composite tissues (i.e. heterogeneous, non-organ tissues) possible in humans. Most of these allografts (hands, face and abdominal wall) contain skin that may be the target of rejection, the diagnosis of which relies mainly on clinicopathological monitoring of the skin. Rejection of allografted skin manifests with changes that are characteristic but not very specific. Although composite tissue allografts are still in their infancy, they have opened a new era in the field of transplantation surgery and pathology, so that (dermato) pathologists may occasionally be faced with the challenge of diagnosing skin rejection of a composite tissue allograft. The diagnostic difficulties that may be encountered in the pathological evaluation of skin in this setting are discussed in this review.

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Article Text

Advances in immunosuppressive treatments and microsurgical techniques have rendered allotransplantation of composite tissues (i.e. heterogeneous, non-organ tissues containing skin, muscles, bones, tendons and nerves) possible in humans. Such composite tissue allografts (CTA) include vascularized tendon, nerves, veins, muscle, femur, knee, larynx, intestine and abdominal wall, tongue, penis and hands.[1] The gold standard of these CTA are hand allografts (HHA), by virtue of the complexity of the tissues (including skin) composing them. Following the first modern-era human hand transplantation performed in our hospital in 1998,[2,3] 27 additional patients have received single or bilateral HHA worldwide.[4] In November 2005, the first (partial) human face allotransplantation (HFA) was performed in Amiens, France,[5] followed by similar cases in China and Paris. These skin-containing CTA often undergo (temporary) episodes of rejection, namely in the first weeks or months post graft. The diagnosis of rejection in CTA relies mainly on clinicopathological examination of the skin, because up till now no reliable serologic or cellular markers have been found to correlate with rejection in this particular setting, in contrast to vital organs (such as the kidney or liver) where biological parameters (such as serum creatinine or hepatic enzymes) reflect rather reliably the level of organ function. On the other hand, the impact of pathological rejection in the skin or other tissues contained in the CTA on graft function and outcome is not yet precisely known, but it may be expected to be less compared with allografts of vital organs such as the kidney, liver and heart.

Rejection of the skin contained in a CTA (or in the sentinel skin from the donor grafted onto a non-exposed area of the recipient's own skin allowing biopsies to be taken from it without harming the CTA) manifests clinically with erythematous macules that may progress, if left untreated, to infiltrated scaly violaceous lichenoid papules covering the whole surface of the allograft.[6] The pathological changes seen in the skin during episodes of CTA rejection vary according to the severity of the process; although characteristic, they are not specific of rejection and may mimic several inflammatory dermatoses. We discuss here the problems of pathological differential diagnosis that may be encountered in the evaluation of skin undergoing rejection in CTA, and provide some clues to avoid the pitfalls. Our experience is based on the study of over 100 biopsies obtained from the allografted skin of seven patients with single or bilateral HHA performed in Lyon (n = 4) and Milan (n = 3) from 1998 to 2007, and 45 skin and oral mucosa biopsies from the first HFA performed in Amiens and followed regularly in our hospital. Detailed clinical, surgical and therapeutic data regarding these patients can be found elsewhere.[2–11] The skin biopsies obtained spanned a wide spectrum of clinical changes, ranging from clinically normal skin (absence of visible changes) to severe, nearly experimental-type rejection that

occurred in the first HHA after the immunosuppressive treatment was discontinued because of patient non-compliance.[7]

Pathological skin changes in CTA rejection

In the late 70s–early 80s, experimental works studied the rejection mechanisms of vascularized human skin allografted on volunteers who were not receiving immunosuppressive treatment. These studies showed that skin rejection manifested pathologically with predominantly vascular changes in the dermis, including ischemia and infarction.[12] These vascular changes were associated with a cellular infiltrate made primarily of T cells (CD4 and CD8-positive cells in a ratio of 1.5 : 1 to 3 : 1).[13] This infiltrate formed perivascular cuffs and penetrated the epidermis, leading to dyskeratosis of epidermal and adnexal keratinocytes.[12]

Present-day CTA differ from this model in several respects: firstly, the skin grafted is associated with other tissues, a fact that may render it less antigenic (by virtue of as yet poorly-known mechanisms); secondly, an immunosuppressive treatment (both for induction and maintenance) is given to CTA recipients, and is apparently able to prevent, in the majority of cases, the development of (severe) rejection; finally, some CTA recipients also receive injections of donor-derived bone-marrow cells, in an attempt to induce microchimerism that allegedly favors the development of graft tolerance. Compared with the afore-mentioned model of experimental skin allograft rejection, the pathological changes seen in the skin and mucosa during CTA rejection are also predominantly located in the dermis, and consist in an inflammatory infiltrate of varying density, appearing initially as perivascular cuffs or nodules. This consists mainly of CD3+ T-cells of recipient's origin (as evidenced by the expression of recipient's specific HLA-class I antigens) expressing mostly the CD4 and to a lesser extent the CD8 phenotype.[6] About 10–20% of the cells express the phenotype of T-regulatory cells (FoxP3+),[11] but their involvement in favoring allograft tolerance remains so far undefined. TIA-1+ cytotoxic T-cells, CD68+ cells of the histiocytic/macrophage lineage, eosinophils, CD20+ B-cells, plasma cells and mast cells are often admixed to various degrees (Fig. 1A–D). In cases of more severe rejection, the cell infiltrate becomes denser and may form a subepidermal (lichenoid) band hugging the basal cell layer of the epidermis. The epidermis is somewhat less frequently involved, with lymphocyte exocytosis, basal keratinocyte vacuolization, presence of necrotic keratinocytes (usually seen as colloid or cytoid bodies within the lower epidermal layers), spongiosis (that may result in vesicle formation), occasionally hyperkeratosis, hypergranulosis, acanthosis and saw-tooth appearance of the dermal-epidermal junction. The same changes seen in the epidermis can be observed in its adnexa, namely the eccrine sweat glands. The hypodermis may be affected in the most severe cases,

with presence of perivascular inflammatory lymphocytic and eosinophilic infiltrates. These pathological changes taken individually are not specific per se, because they can be observed in a variety of inflammatory, infectious and rarely neoplastic dermatoses. On the basis of the above-mentioned pathological findings, we and others[14–17] have independently proposed pathological scores for assessing the severity of skin CTA rejection, that are remarkably very similar. During the latest 9th Banff allograft pathology meeting held recently in La Coruna (Spain) (June 23–29, 2007), a consensus conference was devoted to CTA and a common score was agreed upon, distinguishing five grades of rejection, ranging from 0 (no rejection) to IV (severe, necrotizing rejection). The issue of pathological differential diagnosis discussed below is based on these five grades of (skin) rejection.