

## Chronic Renal Graft Rejection-associated Bullous Pemphigoid: A Cross-reactive Immune Response?

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Rare cases of immune disturbances after solid organ grafting have been described, mainly autoimmune hepatitis, bullous autoimmune skin diseases, and autoimmune cytopenia. We describe here a patient who developed two similar flares of bullous pemphigoid (BP) in a setting of recurrent chronic renal graft rejection.

### CASE REPORT

A 50-year-old man with a background of uraemic haemolytic syndrome received a kidney transplant in October 1996. The immunosuppressive treatment (mycophenolate mophetil) was interrupted in 2002 because of chronic graft rejection, but the graft was not removed. Four months after this interruption, a diffuse inflammatory and bullous skin eruption gradually appeared (Fig. 1) without involvement of mucous membranes. Standard laboratory tests showed a moderate hyper-eosinophilia ( $628/\text{mm}^3$ ). Cutaneous biopsy showed a subepidermal blistering with an eosinophilic infiltrate of upper dermis, and cutaneous direct immunofluorescence (DIF) revealed linear and continuous deposits of C3 (but not of immunoglobulin; Ig) on the dermo-epidermal junction consistent with BP. Immunoblotting (IB) of the patient's serum was positive with antibodies directed to a unique 180 kDa epidermal antigen, confirmed by positive enzyme-linked immunoassay (ELISA) for BPAg2 and contrasting with the absence of anti-BP230 antibody in IB. BP was then considered and the patient

was treated successfully with oral steroids and dapsone (50 mg/day). The graft was later removed according to the hypothesis of cross-reactivity between receiver skin and rejected graft antigens, a decision further supported by scarce reports of similar cases with complete cutaneous clearance after graft removal without any other therapeutic intervention (1–3). Graft removal resulted in complete clinical and immunological remission with disappearance of anti-BPAg2 antibodies. The patient then returned to dialysis until 2005 and subsequently received a second kidney graft. However, chronic rejection recurred 2 years later and the immunosuppressive treatment was gradually reduced over the following months. One month after discontinuation of steroids, skin lesions similar to the previous ones occurred with the same histological and immunological pattern except for the additional presence of antinuclear antibody with a high initial titre (1/2500). Once again, the graft was surgically removed and the cutaneous lesions cleared completely, allowing an early tapering and interruption of steroids with no relapse, while immunological tests again showed rapid disappearance of anti-BPAg2 antibodies in ELISA and a decrease in antinuclear antibodies rates (1/320 vs. 1/2500). Histopathological examination of the removed graft was in favour of chronic rejection with a dominant T lymphocytic infiltrate, whereas DIF was negative.

### DISCUSSION

Chronic graft rejection may be associated with complications involving organs other than the graft itself. More specifically, rare autoimmune complications affecting the host have been described in this setting, including autoimmune hepatitis (4–7), cytopenia (8) and cutaneous disorders (1–3). The pathomechanisms of these infrequent conditions are debatable, but they might be explained by a cross-reactive immune response between graft and self-antigens related to epitope-spreading phenomenon, molecular mimicry or the presence of genuinely common structures (8).

The occurrence of auto-immune bullous disease associated with chronic graft rejection has been reported previously in only 3 patients, all of them recipients of renal grafts (1–3). In all 4 cases including our observation, the clinical, histological and immunological pattern is strikingly similar and consistent with chronic graft rejection-associated BP appearing within some weeks or months after interruption or reduction of immunosuppressive



Fig. 1. Diffuse bullous eruption with tense large bullae and urticarial plaques on the trunk.

treatment as justified by the chronic rejection. In all cases, cutaneous lesions cleared completely, with no recurrence after surgical removal or spontaneous involution of the rejected graft. Accordingly, a direct causative relationship between chronic graft rejection and occurrence of cutaneous auto-immunity appears very likely, based on both conceptual and chronological reasons. This hypothesis is strongly supported by our observation, which features a unique history of two identical BP flares occurring after two successive events of chronic graft rejection, with complete disappearance of cutaneous lesions after graft removal in both cases.

More specifically, it is likely that the auto-immunity targeting the cutaneous basal membrane zone is aetiologically closely related to chronic rejection-related immunological events, since it is selectively active only when the rejected graft is present, either related to a cross-reaction of immune cells or antibodies primarily responsible for the graft rejection itself or to the secondary elicitation of a cross-reacting cellular or humoral response to graft antigens (mainly of the glomerular basal membrane zone) that are unmasked by the progressive destruction of the graft. The development of such an antibody-mediated response is supported by the demonstration of C3 and Ig deposits on the glomerular basal membrane zone in a previous report (3). To fit the clinical events, it might be hypothesized that these antibodies remain harmless as long as the immunosuppressive treatment is operative, but can result in skin lesions when this treatment is reduced or interrupted. Cross-reactivity itself between self (cutaneous basal membrane in this case) and graft antigens might be explained through a phenomenon of molecular mimicry, epitope-spreading or because the same target structure is present both in kidney and the skin with the components of the basal membrane zone of both structures being the most conspicuous candidates. However, it must be pointed out that the only known common antigen between cutaneous and renal basal membrane zone is collagen IV, and not collagen XVII (BPAg2), but the search for anti-collagen IV auto-antibodies is not a routinely performed investigation. However, the occurrence of anti BPAg2 antibodies may be secondarily triggered by the initial cutaneous aggression through a phenomenon of epitope-spreading, which may also explain the apparition of anti-nuclear antibodies during our patient's second flare. This notion of auto-antibodies production triggered by repeated organ transplantations was also suggested by Morelli & Weston in 1999 (9).

Several cases of bullous eruption have also been reported as early signs of chronic graft-versus-host disease after allogeneic bone marrow transplant, but DIF was always negative and the setting is very different, which makes this differential diagnosis quite theoretical.

The occurrence of BP in a context of chronic rejection of a renal graft is a rare condition and the most efficient treatment is probably the removal of the initial source of immune system-stimulating antigens, the chronically rejected graft itself, as illustrated by the rapid favourable outcome and the absence of relapse in the four patients who benefited from this procedure. Accordingly, this complication should be identified rapidly and adequate treatment implemented quickly to spare the patient an inadequate and protracted treatment with steroids and/or immunosuppressive drugs, all the more because progressive epitope-spreading and molecular mimicry may result in progressive immune damages to multiple organ sites.

*The authors declare no conflict of interest.*

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