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LETTER TO THE EDITORS

Minimizing immunosuppression as a trigger for a fatal antibody-mediated rejection after lung transplantation

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Dear Sir,

The clinical importance of antibody-mediated rejection (AMR) after lung transplantation (LTx) remains poorly defined [1]. We report here a case of fatal AMR in an LTx recipient with asymptomatic high-level donor-specific antibody (DSA), which was triggered by minimizing immunosuppression.

A 55-year-old patient with lung fibrosis underwent left single-LTx in September 2009. The donor haplotype was HLA-A2, 11; -B35, 60; -DR1, 4; -DQ5, 7, with negative direct CDC cross-match between donor and recipient. Tacrolimus, mycophenolate mofetil (MMF) and prednisone were initiated for maintenance immunosuppression. The postoperative course was uneventful, and the patient was discharged at home on POD29. At day 0, a single antigen flow-beads (SAFB) Luminex–detected antibody anti-DQ7 [mean fluorescence intensity (MFI):3310] was evidenced, directed against donor HLA. This DSA was persistent in the first 3 years post-LTx, with MFI levels above 6000 (Fig. 1a). Intravenous immunoglobulin treatment (IVIg, 2 g/kg monthly for 4 months) was administered at 1 year post-LTx, resulting in transient decrease of MFI levels (Fig. 1a).

At 3 years post-TX, the patient underwent total cystectomy for a bladder cancer, with minimizing of immunosuppression (withdrawal of mycophenolate mofetil and lowering blood trough level targets of tacrolimus from 8–12 to 4–7 ng/ml). Three months later, the patient was hospitalized for rapidly increasing breathlessness. PaO_2 was 52 mmHg, and $PaCO_2$ was 35 mmHg (room air). Forced

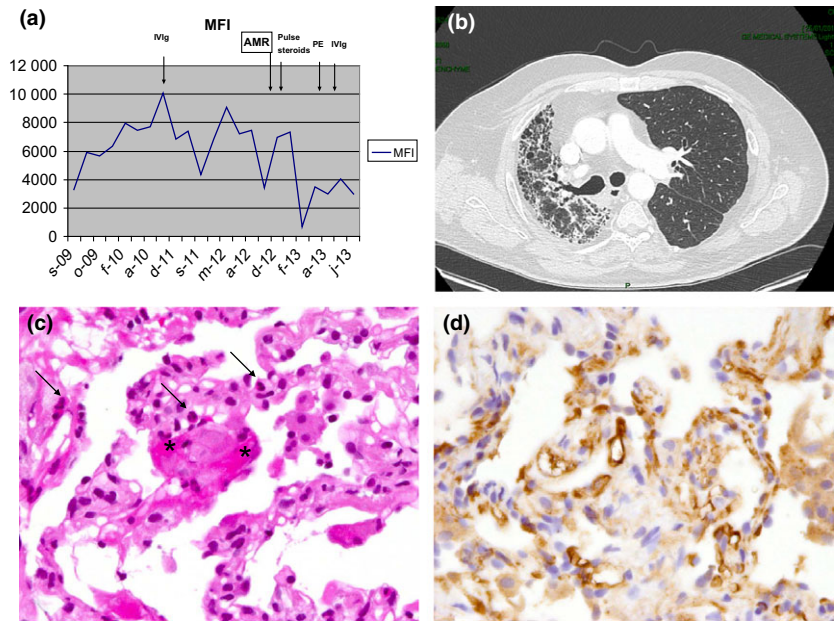

Figure 1 (a) Mean fluorescent intensity (MFI) levels of donor-specific antibodies (DSA) directed against HLA-DQ7, detected by Luminex single-antigen assay by the time after lung transplantation. (b) CT scan showed no noticeable changes of the lung parenchyma in the left graft and the known fibrosis pattern of the right native lung. (c) Histological findings of transbronchial biopsies: capillary injury with neutrophilic margination (arrow), and intra-alveolar fibrin deposition (*) and (HPS, ×40). (d) Intense and diffuse C4d+ staining of the capillary endothelium (x40).

expiratory volume in 1-s was 1.8 l/s (57% of predicted, with a decline of 400 ml). CT scan showed an unchanged left graft and no pulmonary embolism (Fig. 1b). Bronchoalveolar lavage showed no viral, parasitic, mycologic, or bacterial infection. Although TBBx were graded A0B0 [2], boluses of methylprednisolone (15 mg/kg/day for 3 days) were administered, resulting in slight improvement, but persistence of oxygen dependency (3 l/min). Additional histological examination of TBBx showed localized alveolar damage with intra-alveolar fibrin deposition, capillary injury with neutrophilic margination, and intense and diffuse C4d+ staining (Fig. 1c and d). SAFB Luminex assay detected persistent DSA against HLA-DQ7 (Fig. 1a). AMR was ultimately diagnosed and the patient underwent plasma exchange (n = 5), followed by IVIg (2 g/kg monthly for 4 months). Nevertheless, Grade 3 bronchiolitis obliterans syndrome (BOS) developed within 6 months after the AMR occurrence resulting in death of the patient.

This case fulfills all the consensus criteria for AMR in LTx recipients, including histopathologic features, C4d+ immunostaining, circulating DSAs, and allograft dysfunction [2]. The onset of AMR occurred late after transplantation, with a fulminant presentation after 3 years of remarkable functional stability. Pathology revealed pure AMR and was associated with persistent high levels of DSA since the day-0 of LTx, which argues for an isolated humoral process. Such case of late-onset AMR is not well documented in LTx, whereas it is now recognized as a major cause of graft failure in kidney Tx [3]. Only the planned tapering of immunosuppression was identified as a potential trigger of the AMR episode, as reported in kidney Tx [3]. In conclusion, this case suggests a high immunologic risk for AMR when minimizing immunosuppression in stable LTx recipient with asymptomatic high-level DSA, even in the long term.

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Conflict of interests

The authors of this manuscript have no conflict of interests to disclose as described by the *Transplant International Journal.*

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