LETTER TO THE EDITORS

Mixed acute kidney allograft rejection after an antiprogrammed cell death protein 1 antibody treatment for lung epidermoid carcinoma

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Dear Editors,

Checkpoint inhibitors as anti-Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) agents are proven effective in metastatic melanoma, non-small-cell lung cancer and renal cell carcinoma [1]. However, their efficacy and safety in solid organ transplant recipients are not defined.

We report an ex-smoker 64-year-old white male who developed an end-stage chronic kidney disease due to acute renal ischemia in 2006. He underwent deceased donor kidney transplantation (KT) in 2009 (HLA-mismatches: A1, B1, DR2, DQ2). Initial immunosuppressive therapies included tacrolimus (FK), mycophenolate mofetil (MMF), and prednisone. He had no history of rejection episode.

A stage 4 lung epidermoid carcinoma was diagnosed 6 years after KT. He received paclitaxel and carboplatin that proved inefficient after two cycles. Thus, nivolumab, an anti-PD-1 antibody, was introduced. The immunosuppressive treatment was reduced with a target for FK trough serum level of 3–5 ng/ml and a MMF

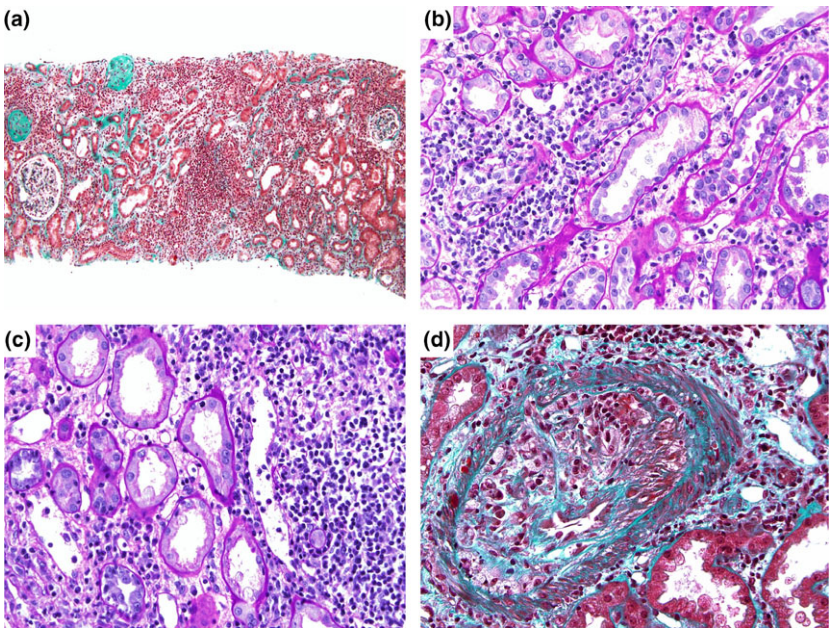

Figure 1 Mixed acute allograft kidney rejection (a). Interstitial infiltration. Trichrome stain, original magnification ×10. (b). Tubulitis. Periodic Acid–Schiff stain, original magnification ×40. (c). Peritubular capillaritis. Periodic Acid–Schiff stain, original magnification ×40. (d). Arteritis. Trichrome stain, original magnification ×40.

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daily dose of 500 mg. After nine nivolumab cycles, he developed an acute kidney injury with a serum creatinine level of 5.7 mg/dl (baseline value: 2.8 mg/dl). No donor-specific antibodies were detected. The kidney allograft biopsy revealed a mixed acute rejection (Banff classification: i2 t2 g0 v2 ptc1 ci0 ct1 cg0 cv3 ah1 C4d0) (Fig. 1).

The patient was treated with pulse methylprednisolone therapy (500 mg daily for 3 days) followed by oral prednisone, associated to an increase of the FK target trough blood level to 6–8 ng/ml and a MMF daily dose of 1000 mg. Serum creatinine level decreased to 3.3 mg/dl.

Due to concomitant progression of the lung epidermoid carcinoma, nivolumab was discontinued and gemcitabine chemotherapy was introduced. The treatment of allograft rejection allowed to avoid dialysis treatment in this palliative situation.

Use of checkpoint inhibitors was reported in six transplant recipients with controversial results highlighting some limitations [2,3]. Firstly, the antagonistic immunosuppressive therapies' mechanisms of action may limit the checkpoint inhibitors' efficacy. A partial response was obtained in four of the six reported patients but associated with immunosuppressive therapies reduction or discontinuation. However, in this case, the lung cancer was not controlled by the anti-PD-1 agent. Secondly, by blocking CTLA-4 and PD-1 to enhance antitumor T-cell immunity, these treatments also enhance alloimmunity and could potentially lead to allograft rejection. Indeed, PD-1 has been reported to be upregulated in human rejecting allografts to suppress alloreactive T-cell responses [4]. Moreover, rejection may also be promoted by the usual concomitant decrease of immunosuppressive therapies in case of cancer diagnosis. No rejection episode occurred in two kidney and two liver transplant recipients treated by an anti-CTLA-4 antibody agent for advanced melanoma. However, two kidney transplant recipients with advanced melanoma developed allograft rejection leading to graft loss after anti-PD-1 antibody treatment following an anti-CTLA-4 antibody treatment.

It is the third acute kidney allograft rejection episode described after anti-PD-1 agents while there is no case of rejection reported with anti-CTLA-4 agents used as monotherapy. Thus, anti-PD-1 agents should be used with caution in transplant recipients because of a substantial risk of rejection and of treatment failure.

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Conflicts of interest

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