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Letter to the Editor

CMV disease and colitis in a kidney transplanted patient under pembrolizumab

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Dear Editor,

Transplant recipients have a significantly higher risk for developing melanoma than the general population [1]. Immune checkpoint inhibitors (ICIs) have recently proved efficacy for the treatment of metastatic melanoma by increasing progression-free and overall survival [2]. However, their efficacy and toxicity profiles are not well described in the transplant recipient population, systematically excluded from clinical trials. Indeed, allograft rejection is a most feared adverse effect in transplanted patients [3], and programmed death 1 (PD-1) blockade in solid organ transplantation (SOT) may even be associated with a higher risk of rejection than cytotoxic T-lymphocyte–associated antigen (CTLA-4) inhibitors.

The case reported here raised several difficulties: a paradox between antitumoural response at 6 months with no allograft rejection and inefficient anti-cytomegalovirus (CMV) response to control CMV disease and colitis leading to treatment interruption, tumoural relapse and death.

A 70-year-old man was diagnosed in July 2017 with a 12-mm thick and ulcerated temporal melanoma (pT4b), B-RAF wildtype, 10 years after the first kidney transplantation for polycystic kidney disease. He had a history of primary CMV infection early after prophylaxis withdrawal (CMV serostatus donor, positive/recipient, negative) and then asymptomatic low-level CMV viraemia (<3 Log UI/mL) persistence. Melanoma staging found concomitant homolateral parotid gland adenopathy, bilateral lung and cerebellum extension with normal lactate dehydrogenase levels (stage M1d(0) as per the American Joint Committee on Cancer melanoma classification, 8th edition). Eastern Cooperative Oncology Group performance status was at 1. Neutrophil-to-lymphocyte ratio was elevated at 6.4. Anti–PD-1 therapy (pembrolizumab) was started on

Abbreviations: B-RAF, B-raf protooncogene; CMV, Cytomegalovirus; CTLA-4, Cytotoxic T-Lymphocyte–Associated Antigen 4; ICI, Immune Checkpoint Inhibitor; INF-γ, Interferon-γ; PD-1, Programmed Death 1; PD-L, Programmed Death Ligand; SOT, Solid Organ Transplantation; TNF-α, Tumor Necrosis Factor-α.

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September 2017. Immunosuppression was reduced concomitantly: cyclosporine was stopped, mycophenolic acid was decreased to 750 mg twice a day and steroids were increased to 1 mg/kg/day for cerebellum perilesional oedema. Radiotherapy was cancelled because of cerebellum metastasis reduction after one infusion. In December 2017, at the time of the fourth infusion, the evaluation showed regression of cerebellum metastasis, parotid gland and pulmonary lesions. At the same time, frequent diarrhoea >10/day appeared, despite strong steroid therapy, with severe hydroelectrolytic disorders (Common Terminology Criteria for Adverse Events grade IV), resistant to symptomatic treatment and low fibre diet. The first hypothesis was immune-related colitis leading to treatment disruption and high-dose steroids maintenance at 1 mg/kg/day. Lymphopenia worsened to 240/mm3, and thrombopenia, haemolytic anaemia and neutropenia appeared. CMV disease was confirmed by blood CMV viral load at 4.8 Log (67200 UI/L), despite 3 months of reduced immunosuppression. Colonoscopy showed severe pancolitis. Colic biopsies showed fibroedematous mucous membrane remodelling, insufficient inflammation for an autoimmune colitis diagnosis. Immunohistochemistry proved CMV invasion. Steroids reduction to 10 mg/day, treatment with IV ganciclovir and then valganciclovir resulted in a slow decrease of viral load to undetectable within a month. In a context of transient kidney dysfunction, a kidney biopsy showed no sign of rejection. Diarrhoea disappeared and reoccurred 3 weeks after immunotherapy resumption in April 2018, concomitant with increasing viral load from negative to 3.5 Log (3800 UI/L). Three months after immunotherapy interruption, the patient died in June 2018 because of a pulmonary tumoural progression.

The use of ICIs has been reported in the literature in 31 SOT recipients so far. No severe CMV disease has been described in this context. In this observation, difficulty stood in CMV disease management and establishment of CMV implication in digestive disorders. ICIs are associated with immune-related adverse events, including diarrhoea [4,5]. CMV can be involved in inflammatory bowel diseases. CMV reactivation has recently been associated with therapy-refractory immune-related colitis in non-transplanted patients under ICIs [5–7]. The implication of CMV in inflamed bowel remains unclear and may be, in some cases, an epiphenomenon in a context of underlying inflammation. However, in our case, CMV as a common bystander was not considered because plasmatic viral load increased concomitantly with cytopenia, and diarrhoea occurred despite high doses of steroids.

Programmed death ligand PD-L1/PD-1 pathway has an inhibitory effect on alloreactive T cell–mediated responses in transplant recipients. In this case, a CMV disease was documented, despite potential increase of effector T-cell activation under anti–PD-1 therapy. CMV replication may have been facilitated by immunodeficiency. Specific CD8+ T cells have an essential role in the control of CMV replication in kidney transplant recipients. After transplantation with a CMV-seropositive donor, CMV-seronegative recipients have higher expansion of CD8+ T cells than CMV-seropositive recipients [8]. The incapacity of expanding the CMV-specific cell compartment may be due to exhaustion processes, but this remains a matter of debate. CMV-specific T-cells may be functionally impaired, especially in old patients [9] or transplanted patients. In CMV-viraemic transplant recipients, a significantly higher proportion of CMV-specific CD4+ T cells has been characterised as PD-1 positive, compared with non-viremic patients [10]. Those cells showed phenotypical and functional signs of T cell exhaustion with various stages of impairment, varying levels of PD-1 and interferon-γ expression, and loss of interleukin-2 production, leading to impaired viral control. Blockade of PD-1 signalling in this study led to an increased CMV-specific T cell proliferation.

Lymphocytes exhaustion induced by chronic viral load, preexisting immunosuppression and lymphopenia lead to ineffective immune response against CMV replication. Despite the fact that CMV disease may have been facilitated by inflammation processes, loss of viral control under ICIs is still uncommon.

To conclude, our patient developed antitumoural immune response under pembrolizumab without graft rejection. In parallel, his immune system showed inability to fight against CMV reactivation, despite reduction of immunosuppression. This prevented the pursuit of successful immunotherapy. The potential benefits of immune checkpoint blockade in the SOT population at higher risk of malignancy should drive studies to identify which patient would develop antitumoural response without impairing graft outcome. CMV reactivation may be prevented by viral prophylaxis in patient at high risk of reactivation, having in mind lymphocytes exhaustion in patients with chronic asymptomatic excretion.

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Conflict of interest statement

None declared.

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