CASE STUDY

Clearance of JC polyomavirus from cerebrospinal fluid following treatment with interleukin-2 and pembrolizumab in an individual with progressive multifocal leukoencephalopathy and no underlying immune deficiency syndrome

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A 71-year-old Caucasian man presented with dysarthria and fluctuating hypoesthesia of the right upper limb in early 2019. Brain magnetic resonance imaging (MRI) demonstrated T2/fluid attenuated inversion recovery hyperintense lesions in the left parietal cortical grey matter and adjacent white matter compatible with embolic stroke of undetermined source. Eight weeks later, symptoms had further progressed with loss of adequate communication, disturbance of fine motor skills, ataxia and neuropsychiatric symptoms. Widespread disease on brain MRI and the detection of JC polyomavirus (JCPyV) DNA from cerebrospinal fluid (CSF) confirmed the diagnosis of progressive multifocal leukoencephalopathy (PML) [1]. Bone marrow biopsy revealed normal findings, and no underlying cause of reduced immunocompetence was identified. Despite rehabilitation, treatment with mirtazapine and two cycles of interleukin-2 (IL-2) (1 mio IE/m² sc once per day for 7 days) administered 2 weeks apart [2], symptoms and MRI lesions further progressed, with complete immobility and severe dysphagia. Nine weeks after definite PML diagnosis and 4 weeks after the last IL-2 dose, a total of three cycles of monthly infusions of pembrolizumab were applied. At the initiation of the third cycle of pembrolizumab, cognitive performance and fine motor skills had temporarily improved, and the patient had regained the ability to walk a few steps with assistance. On MRI, no increase in lesion load and no signs of an immune reconstitution inflammatory syndrome were noted. JCPyV DNA, after a decline that started already following the IL-2 therapy, was no longer detected in CSF, collectively suggesting PML remission (Fig. 1). Enzyme-linked immunosorbent assays revealed increasing JCPyV-specific antibody titers in blood and CSF ($AI_{JCPyV} > 1.5$ [3]). A pembrolizumab effect was indicated by reduced programmed cell death protein 1 (PD-1) expression on peripheral $CD4^+$ and $CD8^+$ T cells after the treatment. Also, during the disease course of PML and following pembrolizumab treatment, proportions of innate immune cells (CD56dimCD16-cytotoxic NK cells, $CD14^+$ CD16 classical and CD14dim $CD16^+$ non-classical monocytes and $CD11^+$ dendritic cells) and pro-inflammatory cytokines and chemokine increased (Appendix S1, Table S1). Four weeks following the last infusion with pembrolizumab, aspiration pneumonia was suspected, and the patient received intravenous piperacillin/tazobactam 4/0.5 g three times per day for 7 days with temporary relief of symptoms. No causative bacteria were detected from blood cultures. Six weeks post-pembrolizumab treatment, respiratory distress occurred again, and the general clinical condition further deteriorated. The patient and his legal custodians decided not to receive further hospital care, upon considering the severe and persistent disability, and the patient died shortly thereafter. As an autopsy was not performed, alternative causes of respiratory distress, such as autoimmune pneumonitis that might occur as an adverse event of pembrolizumab therapy, could not be ruled out.

To date, no JCPyV-directed therapy for PML is available, and management is restricted to attempts at restoring immune functions in patients with an underlying immunosuppressive condition. Here, we report

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on clinical, imaging and immunological findings in a patient with PML treated with IL-2 and pembrolizumab. This patient substantially differs from the 12 previously published cases treated with pembrolizumab for PML, as in the latter underlying immune deficiency of variable cause, such as AIDS, hematological malignancies or T-cell and/or antibody deficiency syndromes, could be identified [4–6]. Our patient presented with no underlying immune deficiency syndrome, and no detectable disease or medication that would predispose for PML. Only higher age was an unmodifiable, potential risk factor for developing PML. We identified increased levels of anti-JCPyV-specific antibodies, pro-inflammatory cytokines, and an expansion of cells of the innate immune system probably reflecting anti-JCPyV-directed immune reconstitution, but possibly also connected to an increased risk of immune-related complications. Despite PML remission, as confirmed by CSF and imaging findings as well as clinical improvement, the unfortunate fatal disease course illustrates the complexity of both the disease itself and the checkpoint inhibitor therapy. We conclude that systematic studies that assess the benefits and risks of PD-1-blocker therapy in PML are needed. Checkpoint inhibitors, possibly in conjunction with IL-2 therapy, may facilitate viral clearance through activation of JCPyV-directed $CD4^+$ and $CD8^+$ T cells. Normal T-cell counts, as shown here, or T-cell functional tests that indicate the ability to sufficiently mount an

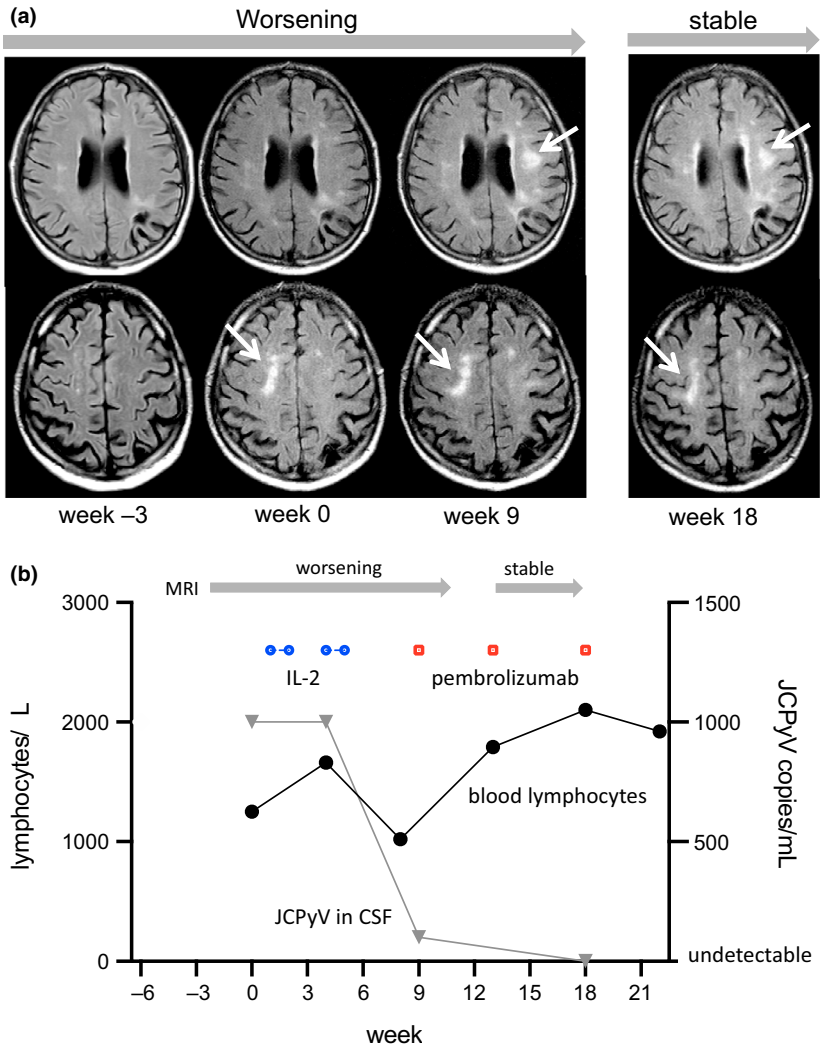

Figure 1 (a) Axial fluid attenuated inversion recovery images demonstrate evolving supratentorial PML lesions associated with the diagnosis of PML at week 0 (time of first positive JCPyV DNA detection from CSF). (b) IL-2 and pembrolizumab treatment, peripheral blood lymphocyte counts and JCPyV viral load in CSF in association with the lesions' evolution of PML based on MRI. [Colour figure can be viewed at wileyonlinelibrary.com]

immune response to JCPyV following PD-1 blockade might be positive predictors for the response to therapy [7].

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Disclosure of conflicts of interest

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Data availability statement

The data that support the findings of this study are available in Appendix S1 of this article.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Method details.

Table S1. Changes in immunological parameters before and after pembrolizumab treatment, relative to diagnosis of PML as confirmed by positive JCPyV PCR from CSF.

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