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Pembrolizumab Experience in a Patient with Progressive Multifocal Leukoencephalopathy Following Multiple Myeloma Treatment: A Case Report and Literature Review

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ABSTRACT

Introduction: Progressive multifocal leukoencephalopathy (PML) is a progressive demyelinating infection of the central nervous system. PML arises in immunosuppressive conditions or circumstances necessitating immunosuppressive treatment, such as malignancies. Recently, data have been published regarding the use of different immune checkpoint inhibitors (ICIs) for the treatment of PML. However, the extent to which ICIs impact and improve PML in individual patients remains uncertain.

Case: A 68-year-old female patient, diagnosed with multiple myeloma in 2012 and with a history of using various chemotherapeutic agents, presented with dizziness, gait disturbances, and speech difficulties. The patient was diagnosed with PML and started on pembrolizumab treatment. This treatment led to improvements in both clinical symptoms and imaging findings.

Conclusion: Regardless of the underlying cause in PML, the use of ICIs can improve the clinical course of the disease and prolong the patient's lifespan.

Keywords: Multiple myeloma, pembrolizumab, progressive multifocal leukoencephalopathy

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INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a progressive demyelinating infection of the central nervous system caused by the opportunistic John Cunningham virus (JCV) due to systemic immunosuppression (1,2). Progressive multifocal leukoencephalopathy may occur in immunodeficiency states or during treatments for conditions such as malignancies, organ transplants, and autoimmune diseases (1,2). Although multiple myeloma (MM) is the second most common hematological malignancy, the development of PML in patients with MM is quite rare (3). Progressive multifocal leukoencephalopathy development is believed to occur more as a secondary effect of the treatments used for multiple myeloma (MM) rather than as a direct consequence of the disease itself (3).

In recent years, several case reports discussing the efficacy of different checkpoint inhibitors in the treatment of PML have been published (4,5). Pembrolizumab is a humanized IgG4 monoclonal antibody targeting the programmed cell death protein 1 (PD-1) receptor, developed for the treatment of melanoma, solid tumors, and lymphomas (6). The literature reports a few cases of patients who developed PML during MM treatment and were treated with pembrolizumab for this condition. (2,7). This case report will discuss the successful treatment of a 68-year-old patient who developed PML following long-term treatment for MM and was successfully treated with pembrolizumab.

Highlights

- **Pembrolizumab can improve the clinical course in PML.**
- **PML following multiple myeloma treatment is quite rare.**
- **Immune checkpoint inhibitor use may prolong the lifespan of PML patients.**

CASE

A 68-year-old female patient was diagnosed with kappa myeloma in 2012**.** She underwent three cycles of VAD (vincristine, adriamycin, and dexamethasone) before receiving autologous stem cell transplantation five months later. From 2014 to 2020, she was treated with lenalidomide and dexamethasone. After experiencing a relapse in 2021, carfilzomib was added to her regimen. A year later, treatment was switched to pomalidomide due to side effects such as osteoporosis and stress fractures. In February 2023, with increasing IgA and kappa levels, bortezomib was introduced alongside pomalidomide.

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After four cycles of this combination therapy, she began to experience dizziness, gait disturbances, and speech difficulties in May 2023. Neurological examination upon admission revealed severe dysarthria, motor strength of 3/5 in the left upper extremity, difficulty with the heel-to-shin test, as well as ataxia and dysphagia. Brain MRI demonstrated hyperintense demyelinating lesions on T2 and FLAIR-weighted images located in the right perirolandic area, bilateral cerebral hemispheres, adjacent to the dentate nucleus, and at the pons-medulla junction, without diffusion restriction or contrast enhancement.

Lumbar puncture (LP) revealed a cerebrospinal fluid (CSF) protein level of 35 mg/dL (normal range: 15–40 mg/dL) with a normal leukocyte count. Given the MRI findings consistent with PML, a polyomavirus JCV PCR test was performed on the CSF, which returned negative. Initially, the brain lesions were attributed to potential toxic effects of bortezomib and pomalidomide, resulting in the cessation of treatment.

Twenty-seven days after JCV PCR negativity in July 2023, after a single cycle of daratumumab, the patient experienced further neurological decline. A repeat MRI four weeks later showed lesion progression. A second lumbar puncture with JCV PCR returned positive, detecting 3.470 copies/mL, thereby confirming a diagnosis of definite PML (8), and her multiple myeloma treatments were discontinued. Over time, her condition worsened, with increased dysarthria, dysphagia, and left upper extremity plegia. She became unable to stand without assistance, and feeding support was initiated.

Given the co-diagnoses of multiple myeloma and PML, pembrolizumab was considered for treatment with the joint decision of neurology and haematology departments. While awaiting off-label approval for pembrolizumab, mirtazapine was initiated at a dosage of 15 mg per day. Fifteen days after JCV PCR positivity following approval, pembrolizumab (200 mg IV every three weeks) was initiated alongside mirtazapine. Three weeks after the first dose, a repeat lumbar puncture revealed a cerebrospinal fluid (CSF) protein level of 33.8 mg/dL and a JCV PCR level of 583 copies/mL. After the fourth dose of pembrolizumab, the JCV PCR result became negative.

Initial magnetic resonance imaging (MRI) of the brain revealed T2-hyperintense, non-enhancing lesion in the right cerebellar peridentate region and a tiny subcortical lesion in the right frontal lobe. Subsequent MRI scans demonstrated an increase in the size and number of these lesions. Despite initiating treatment with pembrolizumab, disease progression persisted on imaging studies conducted 10 and 74 days later. However, a significant turning point was observed on day 153, marked by the commencement of lesion regression, the regression continued in subsequent follow-up imaging. Importantly, no signs of immune reconstitution inflammatory syndrome (IRIS), typically indicated by contrast enhancement, were detected throughout the pembrolizumab treatment course. While the lesions diminished in size, localized volume loss was observed in the affected area, accompanied by diffuse atrophy in the cerebrum and cerebellum. Furthermore, as the lesions regressed, an accumulation of iron was noted in the dentate nuclei (Figure 1).

The patient's clinical status remained stable for an extended period, with notable improvements after the seventh dose, including enhanced motor strength (4/5) in the left upper extremity and resolution of dysarthria and dysphagia, which allowed for the removal of feeding support. Over the course of one year, the patient received a total of 19 doses of pembrolizumab, resulting in significant clinical improvement, although she still requires assistance for mobilization.

DISCUSSION

This case report describes a patient with multiple myeloma (MM) diagnosed with PML based on clinical evaluations, radiological findings, and the detection of JC virus in CSF. Fifteen days after the diagnosis, she received pembrolizumab, leading to improvements in both neurological examination findings and MRI features. During this treatment, neurological symptoms were limited and CSF JCV load decreased in parallel. Consistent with rare previous reports, our case exhibited a prolonged period of lesion progression after initiating pembrolizumab treatment, which was subsequently followed by regression.

To raise another point of discussion in this case, the only side effect observed in our patient was a herpes zoster infection that occurred after the 13 th dose of pembrolizumab. The zoster infection was quickly controlled with specific treatment. No autoimmune side effects related to ICIs or contrast enhancement on MRI suggesting PML-IRIS were observed during the patient's follow-up at any stage. Although PML-IRIS associated with ICIs is more commonly observed in patients with HIV/AIDS and chronic inflammatory diseases, it can also develop in hematologic malignancies and can be fatal (7). The absence of detectable IRIS could potentially be attributed to the infrequent MRI follow-up intervals, which may have led to a missing of inflammatory activity. However, despite the observed shrinkage of the lesions on the most recent MRI, the nature of the residual signal abnormalities remains uncertain. It is unclear whether these represent gliosis or partially persistent infection. The inherent lack of contrast enhancement typically observed in PML lesions limits its utility as a marker of disease activity. Therefore, we plan to integrate clinical and laboratory findings alongside radiological features to guide treatment discontinuation decisions.

Koutsavlis published the clinical characteristics of patients diagnosed with progressive multifocal leukoencephalopathy (PML) in individuals with multiple myeloma (MM) up to the year 2020 (9). The patients had a median age of 63 (9). Most of these patients (64.7%) unfortunately succumbed rapidly, typically within two months of the PML diagnosis, and very few patients survived (9). Prolonged survival was observed, although it was sometimes associated with irreversible neurological damage, and experimental therapies were implemented (9). These therapies included mefloquine, mirtazapine, cidofovir, citalopram, or various combinations of these agents (9). One case has received successful treatment of allogeneic bone marrow transplantation (BMT) for multiple myeloma (MM), utilizing JC virus-specific donor lymphocytes (10).

Checkpoint inhibitors, particularly those targeting PD-1 and PD-L1, have profoundly changed the natural course of various solid malignancies and have been explored as a therapeutic option in multiple myeloma patients. Preclinical studies, along with early phase 1 and 2 trials, have demonstrated the potential of checkpoint inhibitors in the treatment of multiple myeloma (11–13). Therefore we considered pembrolizumab as an important option for this patient whose other immunosuppressive treatments were limited due to the development of PML. There are very limited number of case reports on this subject in the literature. In a study by Boumaza et al. on the use of immune checkpoint inhibitors (ICIs) in PML, all 38 patients with hematological malignancies who developed PML had received ICIs. Among them, only one had multiple myeloma, although the specific ICI used was not mentioned (7). The authors were contacted via email; it was learned that the myeloma patient received nivolumab, not pembrolizumab. Additionally, Hoeynck et al. published data on six cases of multiple myeloma with PML, of which only three patients received pembrolizumab (2). The time intervals between the diagnoses of MM and PML in the three patients ranged from 2.5 years to 4.8 years (2). Two of these patients received one dose each, while the other received three doses of pembrolizumab (2). The lifespan of one of

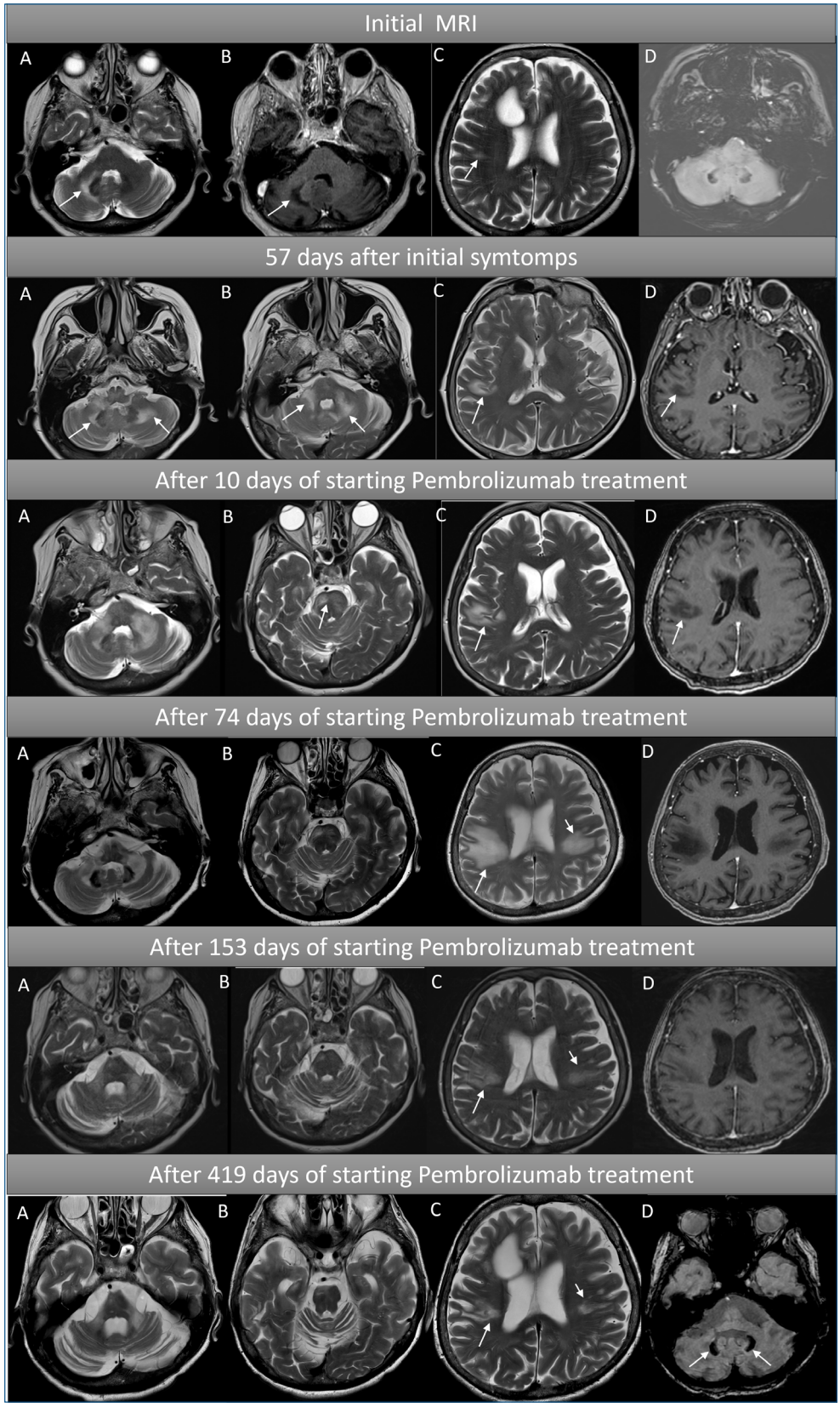

Figure 1. Series of brain MRIs obtained after the onset of neurological symptoms and the initiation of Pemrolizumab treatment. The initial scan, axial T2-weighted and postcontrast T1-weighted images show a lesion with the characteristic "crescent sign" (A, arrow) without contrast enhancement (B, arrow) in the right middle cerebellar peduncle and peridentate area. Additionally, a small subcortical T2 hyperintese non-spesific lesion is observed In the right parietal lobe. Axial susceptibility-weighted imaging (SWI) im-age shows mild paramagnetic accumulation in the dentate nucleus. MRI obtained 57 days after initial neurological symptoms reveals progression both cerebellum-brainstem and right parietal lobe. Fifty-seven days after the onset of neurological symptoms, second row images reveal progression of the both lesions in the cerebellum-brainstem and the right parietal lobe. MRI performed 10 and 74 days after the initiation of Pemrolizumab treatment demonstrate progression without contrast enhancement in pro-gressive multifocal leukoencephalopathy (PML) lesions and a newly developed PML lesion in the left pari-etal lobe 74 days after Pemrolizumab (fourth row, C, arrow). MRI performed on days 153 and 419 after the initiation of Pemrolizumab demonstrates significant regression in PML lesions, cerebral and cerebel-lar atrophy, and prominent paramagnetic substance accumulation in the dentate nuclei (last row, ar-rows).

these patients is unknown, while the ot her two patients died 60 and 75 days after the initiation of pembrolizumab treatment (2).

Including our case, there are now four documented instances in the literature of multiple myeloma patients treated with pembrolizumab. There is no clear data regarding the duration and continuity of pembrolizumab administration in the reported cases. In the literature, the number of doses of pembrolizumab was found to vary, the follow-up duration for patients can range from as short as 60 days to as long as 38 months (1,14).

As a result, the outcomes of pembrolizumab treatment vary among patients, making it difficult to draw definitive conclusions about its efficacy and survival benefits (14). Although survival duration varied, the mean survival at one year follow up for patients with all hematologic malignancies who received ICI is 51.9% (7).

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Informed Consent: Informed Consent:Consent obtained from parent (s)/guardian (s).

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