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ORIGINAL COMMUNICATION

Immune checkpoint inhibitors for progressive multifocal leukoencephalopathy: a new gold standard?

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Abstract

Objectives Progressive multifocal leukoencephalopathy (PML) is a very rare and opportunistic encephalitis caused by JC polyomavirus that is linked to profound immunosuppression and is usually fatal unless immune function can be restored. Immune checkpoint inhibitors (ICI) are monoclonal antibodies (mAbs) that block either CTLA-4 or PD-1 inhibitor receptors, thus enhancing antiviral T-cell activity. Successful treatment of PML by ICI has recently generated some enthusiasm in case reports/small series of patients. However, the initial enthusiasm was mitigated by some individual case reports that did not show any benefit. More data are thus warranted about efficacy of immune checkpoint inhibitors in the specific context of PML.

Methods and results We report here the outcomes of six PML patients treated by ICI between 2017 and 2019. Underlying causes of immunosuppression consisted in hematologic malignancies ($n=4$), primary immune deficiency ($n=1$) and use of immunosuppressive therapies for myasthenia gravis ($n=1$). Three patients were alive with a mean follow-up of 21 months (14–33) after first ICI infusion, including one patient with frank clinical response, one with stabilization, and one with initial worsening and further stabilization of PML. The three other patients rapidly died from PML.

Conclusions Our data suggest that ICI may be effective for PML treatment but were less impressive than the ones previously reported. Larger studies are thus warranted to confirm this efficacy and to identify the predictive factors of response.

Keywords Progressive multifocal leukoencephalopathy · JCV · Immunosuppression · Immune checkpoint inhibitor · PD-1

Introduction

Progressive multifocal leukoencephalopathy (PML) is an aggressive, opportunistic encephalitis caused by JC polyomavirus (JCV) and responsible for a progressive demyelination of the central nervous system. PML is linked to a profound suppression of cell-mediated immunity related to an underlying disease and/or to immunosuppressive/modulatory therapies. Incidence and prognosis of PML are highly variable according to the underlying disease and the degree of immunodepression [1]. PML is usually fatal unless the immune function can be restored. Currently, reconstitution of the immune system is the only available treatment strategy, but greatly depends on the underlying cause of immunosuppression and thus constitutes an unachievable goal in many circumstances.

The use of immune checkpoint inhibitors (ICI) has recently generated some enthusiasm in case reports/small cohorts of PML patients [2–4]. ICI are monoclonal antibodies (mAbs) that block either cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death-1 (PD-1) inhibitor receptors, thus enhancing tumoral and antiviral T-cell activity [5]. In the first publication, ICI were administered to eight adults with PML including two HIV patients, four with hematological malignancies, and two with idiopathic lymphopenia [2]. Among them, neurological status improved or stabilized in five patients and was associated with reduction

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in JC viral load in the cerebral spinal fluid (CSF). Among the three other patients, two experienced a frank clinical worsening and one no significant change in clinical status and CSF JC viral load. The initial enthusiasm was however mitigated by new reports that did not show any benefit [6], notably for renal transplant recipients [7]. We report here six additional cases of PML treated with ICI in our institution.

Patients and methods

Between December 2017 and December 2019, six patients with a diagnosis of PML were treated by either pembrolizumab or nivolumab, according to drug availability, at Pitié-Salpêtrière Hospital, a tertiary care center located in Paris, France. PML diagnosis followed the American Academy of Neurology consensus [8]. All patients provided written informed consent to receive off-label treatment with pembrolizumab or nivolumab. Details regarding treatment modalities, quantification of JCV and different lymphocyte subpopulations, and evaluation of response are provided in Supplemental Materials and Methods. The case of #Patient 1 has been previously published as case report [3].

Results

Patients and disease characteristics

Patients' characteristics and clinical courses of the six reported patients are summarized in Table 1. With a median age of 61 years (42–75), our series included two female and four men. Underlying causes of immunosuppression consisted in hematologic malignancies ($n=4$, including #Patient 3 with concomitant HIV infection and #Patients 1/2/4), primary immune deficiency ($n=1$, #Patient 6) and use of immunosuppressive therapies for myasthenia gravis ($n=1$, #Patient 5). At PML diagnosis, the lymphocyte subpopulation cell count showed a profound T-cell lymphopenia which predominated on CD4 T-cell, with respective median of CD3 +, CD4 +, CD8 + counts of 288 (167–632), 129 (53–305) and 102/mm^3 (58–474) (Table 1 and Supplemental Table 1). All patients studied ($n=5$) showed pre-treatment CD8 T-cell activation. The NK-cell count was low in all but one patient (median 95, 13–562/mm^3). Noteworthy, a very profound B-cell lymphopenia was observed in all patients at PML diagnosis (median 1, 0–35/mm^3) (Supplemental Table 1).

The median delay between the onset of neurological signs and PML diagnosis was 1.5 months (0.5–5). All patients presented with progressive neurological signs at PML diagnosis and most of them were severely disabled with a median modified Rankin score of 4 (3–5). The most frequent neurological signs included motor weakness ($n=3$) and visual impairment ($n=2$). All patients had positive JCV PCR in the CSF (median viral load, 393 copies/mL; 154–125,719) except #Patient 2 for whom a cerebral biopsy confirmed PML diagnosis.

Treatment and outcomes

After PML diagnosis, immunosuppressive therapies could have been discontinued or reduced for, respectively, two (#Patients 4 and 5) and one (#Patient 6) patients, while this was not possible in the other three patients. All patients received at least one infusion of ICI (median 3; 1–4) (see administration details in Table 1 and Supplemental Material and Methods) with a median delay since PML diagnosis of 17.5 days (1–30). After ICI treatment, two patients (#Patients 1 and 6) had clinical improvement associated with a decrease in modified Rankin score and reduction or stabilization of the size of PML lesions on MRI (see Table 1 and Figs. 1, 2, 3, 4, 5 and 6). The time to clinical improvement was, respectively, one and four weeks. JC viral load significantly decreased in the CSF for one patient (undetectable after four weeks for #Patient 1) and remained stable for the other one (#Patient 6) (Supplemental Table 3). Only #Patient 1 had prolonged clinical improvement, while ICI had to be discontinued for #Patient 6 due to severe adverse event (see Safety subsection) leading to subsequent rapid PML progression and finally death. #Patient 2 had sustained clinical and radiological stabilization with a follow-up of 16 months since first ICI infusion. #Patient 5 had initial frank clinical worsening, but experienced further clinical and radiological stabilization of PML and is still alive with a follow-up of 14 months. Finally, #Patients 3 and 4 had rapid unfavorable outcome after only one infusion of ICI. On brain MRI (see Figs. 1, 2, 3, 4, 5 and 6), three out of six patients showed an initial improvement of disease activity (#Patients 1, 2 and 5), one a stabilization (#Patient 6) and two a worsening (#Patients 3 and 4). Two patients who showed improvement developed progressive cerebral atrophy (# Patients 1 and 2) and two patients presented a worsening after initial improvement or stabilization (#Patients 5 and 6). It should be noted that none of the patients had complete disappearance of PML lesions.

Safety

Two patients (#Patients 1 and 6) experienced immune-related adverse events, which occurred eight and one weeks after first ICI infusion, respectively. #Patient 1 developed grade 3 myositis, which was confirmed by muscle biopsy and completely resolved after three monthly infusions of intravenous immunoglobulins [3]. #Patient 6, who had a history of digestive tract granulomatosis associated with common variable immune

Table 1 Clinical presentation, complementary exploration, time course of the disease and outcome

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Baseline characteristics						
Age (years)/sex	49/F	73/M	52/M	75/M	71/M	42/F
Past medical history	AML	DLBCL	HIV (HAART), T-cell lymphoma	Follicular lymphoma	Myasthenia gravis	CVID, digestive tract granulomatosis
Previous treatments	Allo-HSCT	–	CHOEP, auto-HSCT	R-CHOP, bendamustine, lenalidomide	Corticosteroids, azathioprine, mycophenolate mofetil, rituximab	Corticosteroids
Clinical features at diagnosis						
Delay between the onset of neurological symptoms and PML diagnosis (months)	1.5	2.5	0.5	1.5	0.5	5
PML symptoms	Left homonymous lateral hemianopia, left upper-limb motor deficit	Left hemiplegia	Intracranial hypertension with vomiting, cerebellar symptoms, dysarthria	Cognitive disorders, left homonymous lateral hemianopia, left hemi hypoesthesia	Dysexecutive syndrome, aphasia (mutism), right hemiplegia (upper limb > lower limb)	Left hemiparesis, tremor
Modified Rankin score (range, 0–6)	3	4	5	4	3	4
Complementary exploration at diagnosis						
Lymphocytes cell count						
T CD3/CD4/CD8 (/mm^3)	173/89/81	181/53/116	632/164/474	167/106/58	500/152/333	395/305/89
CD4/CD8 ratio ($N = 1.4–3.8$)	1.09	0.45	0.34	1.82	0.45	3.42
B-cell ($N = 115–522$/mm^3)	1	35	14	0	1	1
NK-cell (N = 129–449/mm^3	92	13	99	257	562	21
Cerebrospinal fluid						
Cellularity (/mm^3)	2	2	2	8	69	0
Protein level (g/L)	0.2	0.2	0.5	0.6	0.5	0.3
Glucose level (mmol/L)	3.5	5.5	3.3	3.7	3.4	2.9
JCV PCR (copies/mL)	+ (154)	–[b]	+ (457)	+ (125,719)	+ (110,686)	+ (329)
Brain MRI results[a]	Lesions in right parieto-occipital regions	Lesions in right posterior frontal regions	Bilateral and multiple lesions in frontal and parietal regions	Lesions in right frontal, temporal, parietal and occipital regions	Lesions in right parietal and occipital regions and in left anterior frontal regions	Lesions in right frontal and occipital regions
Brain biopsy	NP	+	NP	NP	NP	NP

Table 1 (continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
ICI treatment						
Substance	Nivolumab	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab	Nivolumab
Delay between diagnosis and ICI administration (days)	30	15	21	14	12	1
Dosage	1 mg/kg for the first 2 infusions and then 3 mg/kg for the last infusion, every 2 weeks	3 mg/kg every 2 weeks	3 mg/kg	2 mg/kg	2 mg/kg, every 4 weeks	3 mg/kg[c]
Number of infusions	3	3	1	1	4	2[c]
Adverse events	Yes (myositis)	No	NA	No	No	Yes (colitis, hepatitis)
Outcome						
Follow-up after first infusion of ICI (months)	33	16	0.1	2	14	3
Death (cause)	No	No	Yes (PML)	Yes (PML)	No	Yes (PML)
Clinical response	Partial	Stabilization	NA	Progression	Progression	Partial
Modified Rankin score (range, 0–6) at last follow-up	2	4	6	6	4	6
Virological response in the CSF (PCR negativation)	Yes	ND	NA	ND	No (stable)	No (stable)
Radiological response on brain MRI	Reduction of disease activity followed by progressive atrophy	Reduction of disease activity followed by progressive atrophy	NA	Worsening	Reduction of disease activity followed at distance by worsening	Initial stabilization followed by worsening

AML acute myeloid leukemia, *CD* cluster of differentiation, *CHOEP* cyclophosphamide-hydroxyadriamycine-vincristin-etoposide-prednisone, *CHOP* cyclophosphamide-hydroxyadriamycine-vincristin-prednisone, *CSF* cerebrospinal fluid, *CVID* common variable immune deficiency, *F* female, *FLAIR* fluid-attenuated inversion recovery, *DLBCL* diffuse large B-cell lymphoma, *HIV* human immunodeficiency virus, *HSCT* hematopoietic stem cell transplantation, *ICI* immune checkpoint inhibitor, *ICU* intensive care unit, *JCV* John Cunningham virus, *M* male, *NA* not applicable, *ND* not determined, *NP* not performed, *PML* progressive multifocal leukoencephalopathy, *PCR* polymerase chain reaction, *R-CHOP* rituximab-CHOP

Follow-up time is defined as the interval between the date of first infusion of ICI and of last visit/death

[a]All PML lesions were FLAIR hyperintense and T1 hypointense in MRI

[b]This patient underwent three lumbar punctures and JCV RT-PCR was 3 times negative

[c]The 2 infusions of nivolumab are 2 months apart due to the described immune-related adverse event. In between, the patient was treated with interleukin-7. Considering initial clinical and radiological response after the first infusion of nivolumab and further neurological worsening under interleukin-7, a second infusion of nivolumab was decided despite the adverse event

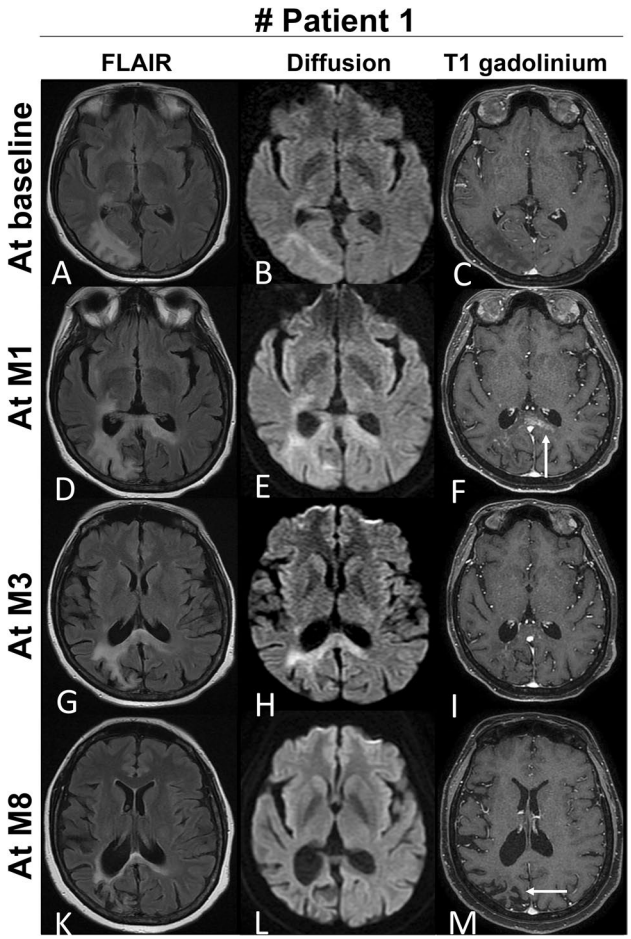

Fig. 1 Baseline and follow-up brain MRIs of the Patient #1: T2 FLAIR (**a**, **d**, **g**, **k**), diffusion weighted (**b**, **e**, **h**, **l**) and T1-post gadolinium (**c**, **f**, **i**, **m**) sequences. T2 FLAIR (**a**) and diffusion (**b**) hyperintense posterior right white matter lesion including subcortical U-fibers without gadolinium enhancement (**c**) is seen on the initial MRI (**a**–**c**). M1 control MRI shows T2 lesion expansion within the splenium of the corpus callosum (**d**, **e**) and a patchy gadolinium enhancement (**f**, arrow) in favor of immune reconstitution inflammatory syndrome. The following MRI reveals disappearance of the gadolinium enhancement and edema reduction. Cortico-subcortical atrophy is to notice (**m**, arrow)

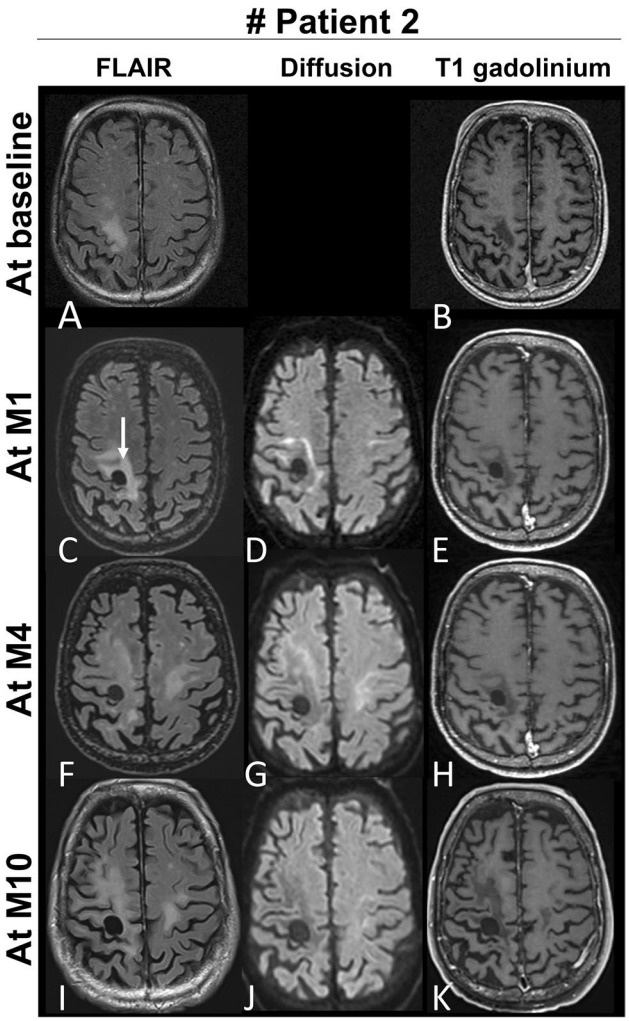

Fig. 2 Baseline and follow-up brain MRIs of the Patient #2: T2 FLAIR (**a**, **c**, **f**, **i**), diffusion weighted (**d**, **g**, **j**) and T1-post gadolinium (**b**, **e**, **h**, **k**) sequences. Progressive expansion of the T2 hyperintensity and diffusion hyperintensities within both semi-oval centers white matter on the M1 MRI. Late follow-up MRI (**i**–**k**) shows a diffusion hyperintensity reduction with a noticeable right fronto-parietal atrophy. Of note, the central cavitation is due to the brain biopsy (**c**, arrow)

deficiency, experienced severe grade 4 extensive colitis and hepatitis that required intensive care unit hospitalization, ICI discontinuation and re-introduction of corticosteroids.

Discussion

Our series of six PML cases treated by ICI constitutes the second largest series to date that interrogated the efficacy of ICI in PML. While our study has some limitations precluding definitive conclusions and comparisons with other publications, which included missing data regarding evolution of JC viral load in CSF, quantification and evolution of PD1-expressing T cells in blood and CSF, and exploration of T-cell JCV-specific activity, several points can nevertheless be highlighted. PML cases occurred in a classical setting of immunodepression dominated by hematological malignancies and related therapies. PML diagnoses and ICI initiation were performed in a reasonable time period after the onset of neurological symptoms (Table 1). All patients were progressive at initiation of ICI and severely disabled. Results were less impressive than the ones previously reported by Cortese et al. [2], but still compared favorably with poor outcomes usually described in PML that are almost invariably fatal, notably in patients with hematological malignancies [9]. In our series of six patients, three were alive with a mean

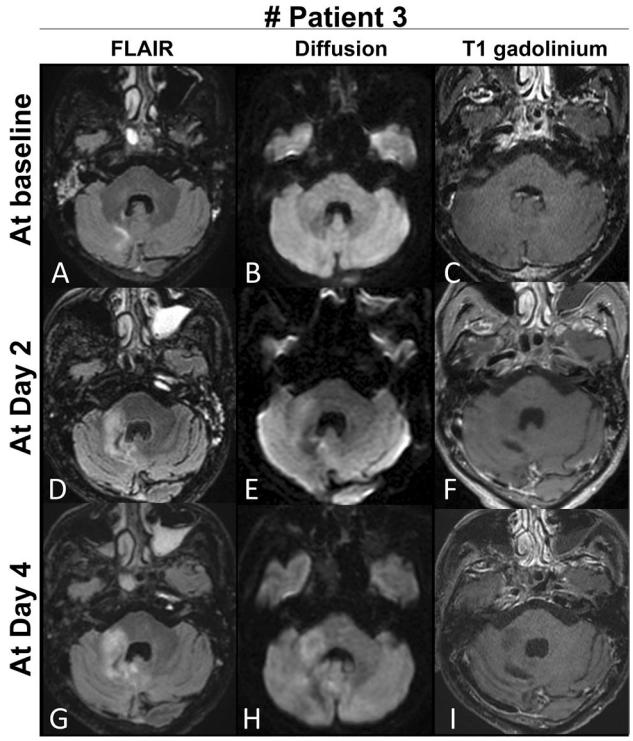

Fig. 3 Baseline and follow-up brain MRIs of the Patient #3: T2 FLAIR (**a**, **d**, **g**), diffusion weighted (**b**, **e**, **h**) and T1-post gadolinium (**c**, **f**, **i**) sequences. Right cerebellar T2 FLAIR and diffusion hyperintensity expands rapidly towards the right peduncle on the follow-up MRI images (**d**–**i**). No gadolinium enhancement is noticeable

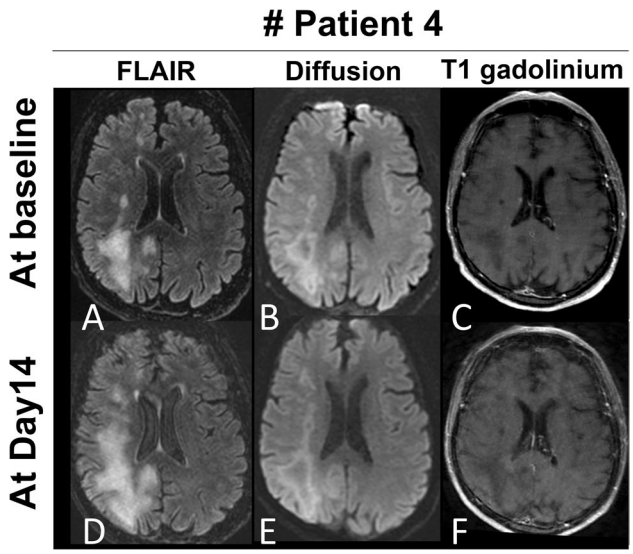

Fig. 4 Baseline and follow-up brain MRIs of the Patient #4: T2 FLAIR (**a**, **d**), diffusion weighted (**b**, **e**) and T1-post gadolinium (**c**, **e**) sequences. There is an extension of the T2 FLAIR hyperintensity without gadolinium enhancement within the right hemisphere

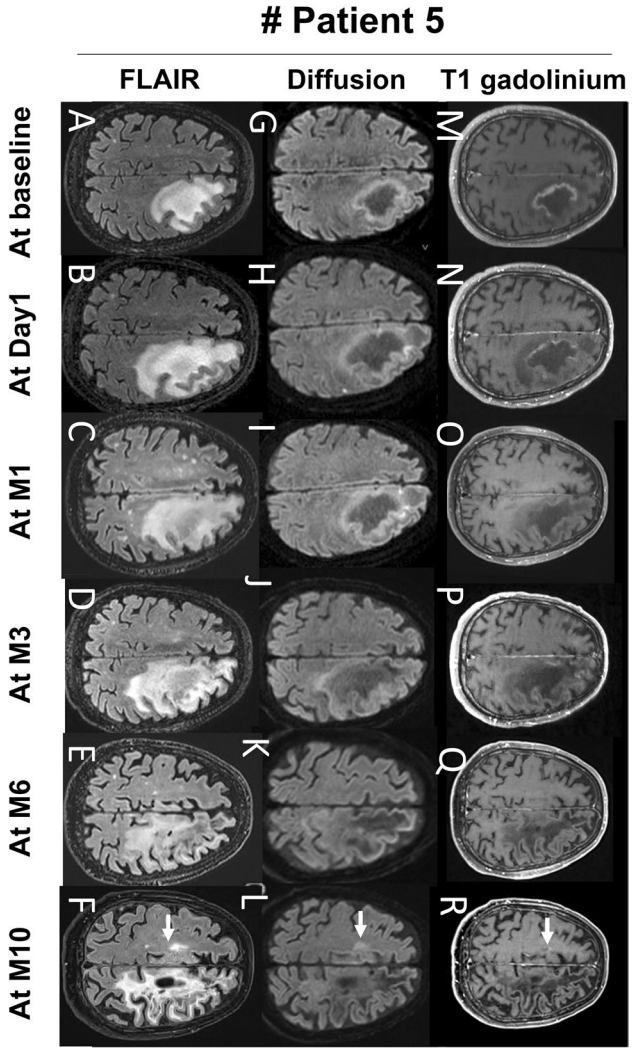

Fig. 5 Baseline and follow-up brain MRIs of the Patient #5: T2 FLAIR (**a**–**f**), diffusion weighted (**g**–**l**) and T1-post gadolinium (**m**–**r**) images. There is a reduction of the peripheral gadolinium enhancement and diffusion hyperintensity within the left frontal lesion at M1. Progressive fading away of the diffusion hyperintensity within leading edge is demonstrated by the following control MRIs. A new gadolinium enhanced lesion is seen at M10 (**f**, **l**, **r** arrows)

follow-up of 21 months (14–33) after first ICI infusion, including one patient with frank clinical response (#Patient 1), one with stabilization (#Patient 2), and one with initial worsening and further stabilization of PML (#Patient 5, for whom the additional potential role of reducing immunosuppressive therapies cannot be definitely ruled out). The three other patients rapidly died from PML.

The safety profile of ICI use in this specific context was acceptable but it should be noted that two patients experienced grade 3 and 4 immune-related adverse events, leading in one case to ICI discontinuation (#Patient 6). Further studies will need to better define risk factors for ICI toxicity in the specific context of PML. Its use should probably be

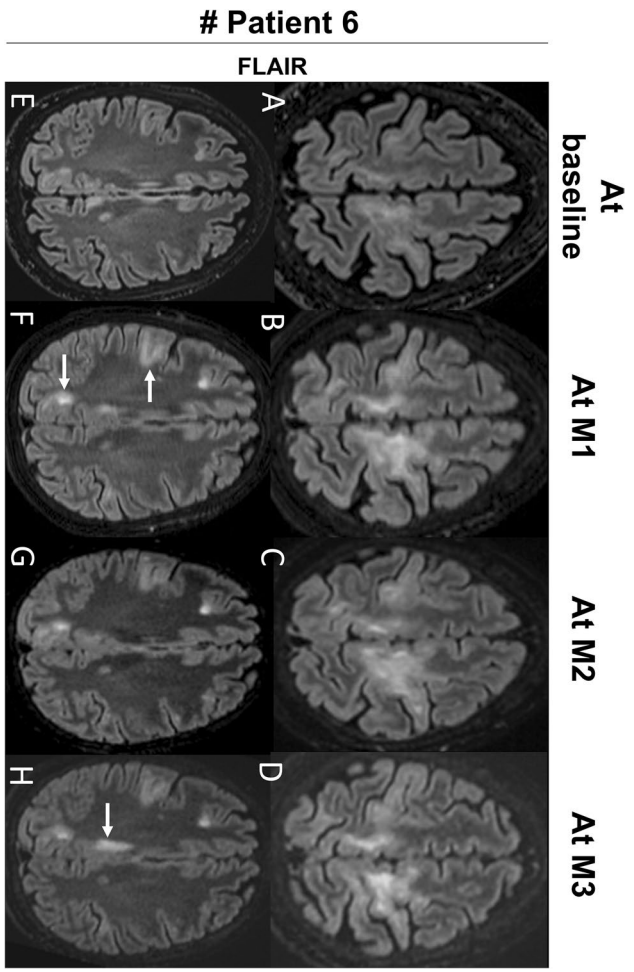

Fig. 6 Baseline and follow-up brain MRIs of the Patient #6: T2 FLAIR initial (**a**, **e**) and follow-up MRI images (**b**–**d**, **f**–**h**) show extensive, bilateral T2 hyperintense white matter lesions becoming more visible at M1 and remaining stable at M2. It is to notice the left cingulate lesion growth at M3 (**h**, arrow)

decided after careful assessment of the expected benefits and risks.

The pathophysiology of PML implicates predominant impaired T-cell immunity and exhaustion. PD-1 is overexpressed on circulating CD4 + and CD8 + T cells of PML patients compared to healthy controls, and frequent in JCV-specific CD8 + cytotoxic T-cells. Contrary to what has been previously reported [2], all patients in our series also harbored a very profound B-cell lymphopenia (Table 1). A role for B-lymphocytes in JCV immune responses is supported by JCV reactivation and PML in patients with congenital disorders of humoral immunity and with respect to the potential imputability of rituximab in some PML cases [10]. The mechanism underlying JCV reactivation in the context of B-cell depletion is probably complex involving both release of JCV in the circulation by pre-B cells that differentiate to repopulate B-cell functions and impaired crosstalk between B- and T-cell immune responses that coordinate antiviral activity.

Finally, although the rate of effectiveness in our case series remains modest, our data confirm that ICI may be effective in some PML patients and compare favorably to previously published outcomes before the use of ICI. Larger prospective studies are warranted to confirm the efficacy and tolerability profile of ICI in PML and to understand which clinical or biological factors are predictive of treatment response.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-021-10414-y.

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Compliance with ethical standards

Conflicts of interest No conflict of interest to declare.

References

1. Kartau M, Verkkoniemi-Ahola A, Paetau A et al (2019) The incidence and predisposing factors of John Cunningham virus-induced progressive multifocal leukoencephalopathy in Southern Finland: a population-based study. Open Forum Infect Dis 6:ofz024
2. Cortese I, Muranski P, Enose-Akahata Y et al (2019) Pembrolizumab treatment for progressive multifocal leukoencephalopathy. N Engl J Med 380:1597–1605
3. Uzunov M, Demeret S, Nguyen-Quoc S et al (2020) Postallogeneic transplantation progressive multifocal leukoencephalopathy successfully treated by nivolumab. Br J Haematol 188:e82–e84
4. Walter O, Treiner E, Bonneville F et al (2019) Treatment of progressive multifocal leukoencephalopathy with nivolumab. N Engl J Med 380:1674–1676
5. Barber DL, Wherry EJ, Masopust D et al (2006) Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 439:682–687
6. Kupper C, Heinrich J, Kamm K, Bucklein V, Rothenfusser S, Straube A (2019) Pembrolizumab for progressive multifocal leukoencephalopathy due to primary immunodeficiency. Neurol Neuroimmunol Neuroinflamm 6:e628
7. Medrano C, Vergez F, Mengelle C, Faguer S, Kamar N, Del Bello A (2019) Effectiveness of immune checkpoint inhibitors in transplant recipients with progressive multifocal leukoencephalopathy. Emerg Infect Dis 25:2145–2147
8. Berger JR, Aksamit AJ, Clifford DB et al (2013) PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology 80:1430–1438

9. Adrianzen Herrera D, Ayyappan S, Jasra S et al (2019) Characteristics and outcomes of progressive multifocal leukoencephalopathy in hematologic malignancies and stem cell transplant—a case series. Leuk Lymphoma 60:395–401

10. Carson KR, Evens AM, Richey EA et al (2009) Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. Blood 113:4834–4840

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