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Use of Pembrolizumab in HIV-Associated Progressive Multifocal Leukoencephalopathy: A Four-Case Series

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Abstract

Background: *Progressive multifocal leukoencephalopathy (PML) caused by JC virus (JCV) remains a severe opportunistic infection in people with advanced HIV infection. Combined antiretroviral therapy (cART) is the cornerstone of management, but prognosis remains poor in many cases and effective adjunctive therapies are lacking. Programmed death-1 (PD-1) blockade with pembrolizumab has emerged as a potential strategy to restore antiviral immune responses.*

Methods: *We conducted a retrospective case series of four adults with HIV-associated PML treated with pembrolizumab under compassionate use between January 2023 and May 2025 at a tertiary hospital in Spain. Diagnosis was established by compatible neurological and radiological findings together with detection of JCV-DNA in cerebrospinal fluid (CSF) by polymerase chain reaction. All patients received pembrolizumab (2 mg/kg every 3 weeks for at least one cycle) combined with bictegravir/emtricitabine/tenofovir alafenamide. Clinical, virological, immunological and safety data were collected.*

Results: *Four patients were included, three men and one woman, with a median age of 43 years (interquartile range [IQR] 25–56). Median baseline CD4+ T-cell count was 142 cells/μL (IQR 9–390), median plasma HIV viral load was 5.5 × 10^5 copies/mL, and median baseline NIHSS score was 3 (IQR 2–7). After pembrolizumab initiation, all patients showed neurological improvement, virological response, or both. Two patients experienced early neurological improvement, with NIHSS decreasing from 4 to 2 and from 3 to 1. In the other two patients, CSF JCV-PCR decreased from 5 × 10^5 copies/mL to undetectable and from 1 × 10^6 to 150 copies/mL, respectively, accompanied by parallel neurological improvement. Median CD4+ T-cell increase during early follow-up was +35 cells/μL (IQR 20–60). Treatment was well tolerated. No immune-related adverse events, infusion reactions, or vascular complications were observed. One patient developed a transient low-grade fever that resolved spontaneously without treatment interruption.*

Conclusions: *In this small case series, pembrolizumab combined with cART was feasible and well tolerated in*

patients with HIV-associated PML and was associated with virological and neurological improvement. These findings support further evaluation of PD-1 blockade as adjunctive therapy in selected cases of HIV-associated PML.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by reactivation of JC virus (JCV) in the setting of cellular immunosuppression. Although its incidence has declined after the widespread implementation of combined antiretroviral therapy (cART), it remains a life-threatening opportunistic infection in people with advanced HIV infection, often associated with substantial neurological disability and poor outcomes. The current cornerstone of treatment in HIV-associated PML is immune restoration through effective antiretroviral therapy. However, this strategy is not always sufficient, and no specific antiviral treatment has consistently demonstrated benefit. In particular, adjunctive agents such as cidofovir have failed to show clear efficacy and are not supported by robust evidence as standard treatment [1-3].

Interest has therefore shifted toward immunomodulatory strategies. PD-1 is an inhibitory immune checkpoint involved in T-cell exhaustion during chronic viral infection. In HIV infection, increased PD-1 expression on virus-specific T cells has been associated with functional impairment and disease progression [4,5]. Blockade of the PD-1 pathway may therefore enhance antiviral cellular immunity and improve JCV control in PML. Pembrolizumab, a monoclonal antibody targeting PD-1, has emerged as a potential adjunctive therapy, although evidence remains limited and is mainly based on case reports and small series [1-3]. We describe a retrospective four-case series of HIV-associated PML treated with pembrolizumab under compassionate use, focusing on clinical evolution, virological response and short-term safety.

Materials and Methods

Study Design and Setting

We performed a retrospective observational case series at Hospital Universitario Virgen de las Nieves, Granada, Spain. The study included consecutive adult patients with HIV-associated PML who received pembrolizumab under compassionate use between January 2023 and May 2025.

Case Definition

The diagnosis of PML was established on the basis of compatible neurological manifestations, suggestive neuroimaging findings, and detection of JCV-DNA in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR).

Treatment

All patients received pembrolizumab at a dose of 2 mg/kg every 3 weeks for at least one cycle. In all cases, pembrolizumab was administered in combination with cART, specifically bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy). No patient received cidofovir or other adjunctive antiviral therapy directed against JCV, given the lack of evidence supporting their efficacy in HIV-associated PML [1].

Data Collection

Clinical records were reviewed to obtain demographic, clinical, laboratory, radiological and therapeutic data. Variables collected included age, sex, baseline CD4+ T-cell count, plasma HIV viral load, CSF JCV-PCR (JCV-DNA in CSF was recorded according to the local laboratory reporting system; depending on the assay used, results were expressed as copies/mL or IU/mL), neurological manifestations, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), tolerance to treatment, and

short-term clinical outcome.

Outcomes

The main descriptive outcomes were neurological evolution after pembrolizumab initiation, virological response assessed by changes in CSF JCV-PCR, immunological evolution assessed by CD4+ T-cell count, and safety, including infusion reactions and immune-related adverse events.

Statistical Analysis

Given the very small sample size, only descriptive analysis was performed. Continuous variables are presented as median and interquartile range, and categorical variables as absolute counts.

Results

Four patients were included in the study: three men and one woman. Median age was 43 years (IQR 25–56). At baseline, patients showed advanced immunosuppression, with a median CD4+ T-cell count of 142 cells/µL (IQR 9–390) and a median plasma HIV viral load of 5.5 × 10^5 copies/mL. Neurological impairment at treatment initiation was mild to moderate overall, with a median baseline NIHSS score of 3 (IQR 2–7). All patients received pembrolizumab in combination with bictegravir/emtricitabine/tenofovir alafenamide after diagnosis of HIV-associated PML confirmed by positive CSF JCV-PCR and compatible clinical-radiological findings. Following treatment initiation, all four patients showed a favourable early evolution, expressed as neurological improvement, virological response, or both.

Two patients experienced clear early neurological improvement after pembrolizumab, with NIHSS scores decreasing from 4 to 2 and from 3 to 1, respectively. In the four patients there was a marked decline in CSF JCV viral load. A marked decline in CSF JCV viral load was observed in all four patients. In the remaining case, it decreased from 1 × 10^6 to 150 copies/mL. These virological changes were paralleled by neurological improvement, with NIHSS scores decreasing from 2 to 0 and from 3 to 1, respectively.

Immunological recovery was also observed during early follow-up. Median CD4+ T-cell increase at approximately one month was +35 cells/µL (IQR 20–60). Although follow-up was limited, these findings suggest early immune reconstitution accompanying the observed clinical and virological response.

Treatment was well tolerated in all four cases. No immune-mediated adverse events, infusion reactions, or vascular complications were documented. One patient developed a transient low-grade fever after treatment, which resolved spontaneously and did not require discontinuation of pembrolizumab.

The main clinical and laboratory characteristics of the four patients are summarised in Table 1.

Table 1: Individual Clinical and Laboratory Characteristics of Four HIV-Associated PML Cases Treated with Pembrolizumab

Case	Sex	Age (years)	Baseline CD4+ T-cell count (cells/µL)	Baseline plasma HIV viral load (copies/mL)	Baseline NIHSS	Antiretroviral regimen	CSF JCV-PCR response	Neurological response	Adverse events
1	Male	25	9	4,00,000	4	Bictegravir/ emtricitabine/ tenofovir alafenamide	Undetectable	NIHSS 4→2	None
2	Female	51	390	17,90,000	3	Bictegravir/ emtricitabine/ tenofovir alafenamide	Undetectable	NIHSS 3→1	None

3	Male	35	<50	1,00,00,000	2	Bictegravir/ emtricitabine/ tenofovir alafenamide	5 × 10^5→un-detectable	NIHSS 2→0	None
4	Male	56	142	2,46,000	3	Bictegravir/ emtricitabine/ tenofovir alafenamide	1 × 10^6→150 copies/mL	NIHSS 3→1	Tran-sient low-grade fever

Cohort-level data: median age 43 years (IQR 25–56); median baseline CD4+ T-cell count 142 cells/μL (IQR 9–390); median baseline plasma HIV viral load 5.5 × 10^5 copies/mL; median baseline NIHSS 3 (IQR 2–7); median CD4+ T-cell increase at 1 month +35 cells/μL (IQR 20–60).

Discussion

In this retrospective four-case series, pembrolizumab administered in combination with cART was feasible and well tolerated in patients with HIV-associated PML, and all patients showed neurological improvement, virological response, or both. Although the sample size is limited, the consistency of these favourable short-term signals supports the hypothesis that PD-1 blockade may contribute to restoration of antiviral immunity in selected cases [1].

PML remains one of the most devastating opportunistic infections in advanced HIV infection. The fundamental therapeutic principle is immune restoration through effective antiretroviral therapy, but outcomes remain heterogeneous and neurological sequelae are common. No adjunctive antiviral treatment has demonstrated consistent efficacy [1]. In this context, pembrolizumab represents a biologically plausible strategy because it may reverse T-cell exhaustion and enhance JCV-specific immune control. This rationale is supported by previous studies on PD-1 biology in HIV infection. Increased PD-1 expression on HIV-specific T cells has been associated with functional impairment, disease progression, and CD8+ T-cell exhaustion [4,5]. These observations provide a mechanistic basis for the use of PD-1 blockade in HIV-associated opportunistic infections with defective cellular immunity.

Clinical evidence on pembrolizumab in PML remains limited but is increasing. Available case series and observational reports suggest that immune checkpoint inhibition may induce neurological and virological improvement in selected patients, although responses are heterogeneous and patient selection remains uncertain [1-3]. Our findings are aligned with this emerging literature and contribute additional data specifically in HIV-associated PML treated with a homogeneous antiretroviral backbone. An important point in our series is that all patients received bictegravir/emtricitabine/tenofovir alafenamide. This provides therapeutic consistency but also limits attribution of benefit exclusively to pembrolizumab, since cART remains the cornerstone of management and likely played a major role in immune recovery. Therefore, our data should be interpreted as supportive of pembrolizumab as an adjunctive, not standalone, strategy.

No patient in our series received cidofovir. This decision reflects the absence of convincing evidence for its benefit in HIV-associated PML and current clinical practice, where its use has become exceptional. In contrast, pembrolizumab was considered in a setting of severe disease, limited alternatives, and a plausible immunopathogenic target.

The safety profile in our cohort was acceptable. No severe immune-related toxicities were observed, and only one transient febrile episode occurred. This is clinically relevant because the use of immune checkpoint inhibitors in patients with advanced HIV infection and opportunistic disease may raise concern regarding excessive inflammation, paradoxical worsening, or poor tolerance. Our study has important limitations. The retrospective and uncontrolled design precludes causal inference. The sample size is very small, and follow-up was short. Functional outcomes beyond the early phase, radiological evolution, survival, and long-term safety could not be adequately

assessed. In addition, detailed immunological monitoring beyond routine clinical practice was not available.

Despite these limitations, this report adds to the still limited evidence supporting PD-1 blockade in HIV-associated PML. Prospective multicentre studies are needed to better define the efficacy, optimal timing, number of cycles, patient selection criteria, and safety profile of pembrolizumab in this setting3.

Conclusion

In this retrospective four-case series, pembrolizumab combined with cART was feasible, well tolerated, and associated with early virological and neurological improvement in patients with HIV-associated PML. Although the small sample size and observational design prevent definitive conclusions, these findings support further investigation of PD-1 blockade as adjunctive therapy in selected patients with this severe opportunistic infection.

Declarations

Ethics approval and consent to participate. This retrospective descriptive study was based on anonymised clinical data obtained during routine care. Ethical approval and informed consent requirements were handled according to local institutional regulations.

Consent for Publication

All data were anonymised and no directly identifiable patient information is included in this manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Boumaza X, Bonneau B, Roos-Weil D, Pinnetti C, Rauer S, et al. (2023) Immunotherapy for PML Study Group. Progressive multifocal leukoencephalopathy treated by immune checkpoint inhibitors. Ann Neurol 93: 257-270.
2. Cortese I, Muranski P, Enose-Akahata Y, Ha SK, Smith B, et al. (2019) Pembrolizumab treatment for progressive multifocal leukoencephalopathy. N Engl J Med 380: 1597-1605.
3. Hoang E, Bartlett NL, Goyal G (2020) PD-1 blockade in progressive multifocal leukoencephalopathy: a case series and literature review. Neurology 95: e1137-e1145.
4. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, et al. (2006) PD-1 expression on HIV-specific T cells is associated with functional impairment and disease progression. Nature 443: 350-354.
5. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, et al. (2006) Upregulation of PD-1 on HIV-specific CD8+ T cells leads to exhaustion. Nat Med 12: 1198-1202.