CASE REPORT

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Progressive multifocal leukoencephalopathy after immunochemotherapy: a case report highlighting pembrolizumab limitations

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ABSTRACT

A 55-year-old woman with stage IV follicular lymphoma developed progressive multifocal leukoencephalopathy (PML) during rituximab maintenance therapy following bendamustine-rituximab induction. Although pembrolizumab administration was initiated for suspected PML, her neurological status deteriorated, ultimately leading to death. This case highlights the limited therapeutic response to pembrolizumab in profoundly immunocompromised patients, highlighting the need for timely diagnosis, immunovirological assessment, and individualized innovative management approaches for PML.

Keywords: Case reports; Immune checkpoint inhibitors; Immunosuppression therapy; Immunotherapy; Leukoencephalopathy, progressive multifocal

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare, often fatal, demyelinating disease caused by reactivation of the John Cunningham virus (JCV) in immunocompromised patients. Originally observed in human immunodeficiency virus (HIV)-infected individuals, PML has now increasingly emerged in non-HIV populations receiving prolonged immunosuppressive therapies, particularly those involving monoclonal antibodies such as rituximab [1].

Rituximab, an anti-CD20 monoclonal antibody, induces prolonged B-cell depletion, impairing immune surveillance and facilitating JCV reactivation [1,2]. Combination therapy with bendamustine further amplifies immunosuppression through significant T-cell depletion, thereby increasing the risk of PML [3]. Definitive treatments for PML have not yet been established. How-

ever, immune checkpoint inhibitors, such as pembrolizumab, which target the programmed cell death-1 (PD-1) pathway, have shown variable therapeutic potential [4-6].

This case report describes a patient with follicular lymphoma who developed rituximab-associated PML that was unresponsive to pembrolizumab, highlighting the key considerations and challenges in managing this fatal complication.

CASE REPORT

A 55-year-old woman was diagnosed with stage IV follicular lymphoma initially presenting with extensive lymphadenopathy involving multiple regions, including the cervical, axillary, mediastinal, pulmonary hilar, retroperitoneal, and femoroinguinal lymph nodes, accompanied by marked hepatosplenomegaly and diffuse bone marrow infiltration. She received six cycles of bendamustine-rituximab (BR) chemotherapy, which resulted in a complete metabolic response, as confirmed by positron emission tomography–computed tomography. Rituximab maintenance therapy was initiated approximately 2 months post-BR regimen at a dose of 375 mg/m^2 every 8 weeks.

One month into rituximab maintenance therapy, the patient developed a sudden onset of visual disturbances, particularly narrowing of the visual fields predominantly affecting the right side, along with progressive difficulty in reading, counting, and paraphasic speech errors. The gait and writing skills were unaffected.

Brain magnetic resonance imaging (MRI) revealed asymmetric confluent hyperintensity on T2-weighted sequences in both the parietal and left temporo-occipital white matter, with evident U-fiber involvement. Multiple small punctate T2-hyperintense foci were also noted within the lesions, consistent with the so-called 'Milky Way' sign (Fig. 1A). Diffusion-weighted imaging demonstrated a peripheral rim with restricted diffusion at the margin of the right parietal lesion, indicating an advancing edge of demyelination (Fig. 1B). Overall, the findings were most consistent with PML (Fig. 1). On the 15-day follow-up, MRI revealed interval progression with further lesion extension and increased swelling without contrast enhancement (images not shown).

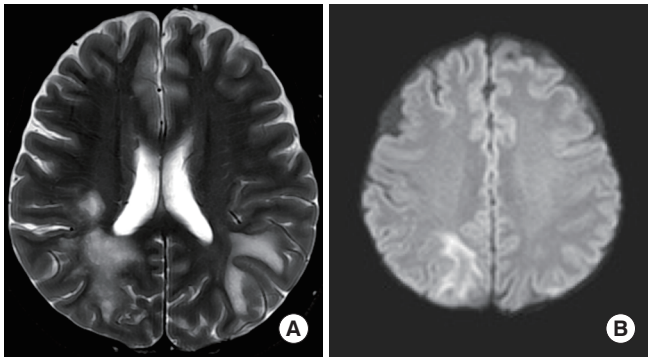

Fig. 1. Magnetic resonance imaging images of progressive multifocal leukoencephalopathy. (A) Axial T2-weighted magnetic resonance image shows asymmetrical, confluent hyperintense lesions in the bilateral parietal white matter, involving the subcortical U fibers. Multiple punctate high-signal foci within the lesion suggest the 'Milky Way' sign. (B) Axial diffusion-weighted image demonstrates diffusion restriction along the peripheral margin of the right parietal lesion, corresponding to the leading edge.

Comprehensive analysis of the cerebrospinal fluid (CSF) ruled out malignancy, bacterial infection, or inflammation. However, polymerase chain reaction (PCR) detected JCV DNA in both the CSF and peripheral blood, confirming the diagnosis of PML due to JCV reactivation [1]. Given the rapid clinical deterioration and delays in definitive diagnostic confirmation, pembrolizumab therapy was initiated at a dose of 2 mg/kg every 4 weeks, approximately 6.5 weeks after symptom onset.

Despite the initiation of pembrolizumab treatment, her neurological symptoms progressively worsened. She developed marked cognitive decline, with profound memory deficits, impaired language comprehension, and increasingly disorganized speech. Severe abulia and akinetic mutism resulted in extended periods of unresponsiveness and loss of autonomy in basic activities of daily living. Her neurological and clinical conditions continued to deteriorate rapidly, ultimately leading to death approximately 7 weeks after two doses of pembrolizumab.

This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (KBSMC IRB No: 2025-08-061). The requirement for obtaining written informed consent from the patient was waived due to the patient's death in accordance with institutional regulations. This study was conducted in accordance with the principles of the Declaration of Helsinki.

DISCUSSION

Why this patient was high risk in PML development

JCV is primarily controlled by CD4+ and CD8+ T cells [1]. BR chemotherapy produces substantial immunosuppression, particularly a profound depletion of CD4+ T lymphocytes [7]. This depletion creates an environment conducive to opportunistic infections [6,7]. Eventually, prolonged immunodepletion by BR chemotherapy induced JCV reactivation and PML

development.

In a cohort of 57 patients reported by Carson et al. [2], PML developed a median of 5.5 months after the last rituximab dose and was associated with a 90% mortality rate, with a median survival of 2 months after diagnosis. Most cases occurred in the setting of marked lymphocyte depletion. Similarly, our patient with follicular lymphoma, treated with six cycles of BR followed by a single rituximab maintenance dose, developed PML within 1 month [2]. BR therapy can induce prolonged CD4+ lymphocyte depletion and long-term immunological dysfunction, with a median time to CD4+ T-cell recovery of approximately 25 months after treatment [7].

Therapeutic approaches

The therapeutic rationale for pembrolizumab, an anti-PD-1 monoclonal antibody, involves the reactivation of JCV-specific T-cell responses by interrupting immune checkpoints [4]. Although pembrolizumab has shown promising efficacy in some PML cases, responses are inconsistent, particularly among profoundly immunosuppressed individuals [6,8,9]. Evidence from recent clinical reports suggests favorable outcomes when pembrolizumab is administered early in the disease course, and in patients with lower viral loads, preserved CD4+ T-cell responses, or detectable JCV-specific T-cell reactivity [4,5,8]. Conversely, delayed pembrolizumab initiation, profound quantitative T-cell depletion, and qualitative impairment of virus-specific T-cell functionality significantly reduce the likelihood of successful outcomes [5,9].

Factors associated with pembrolizumab failure

In our case, several factors likely contributed to the therapeutic failure. First, profound and prolonged lymphopenia markedly reduced the potential efficacy of immune checkpoint blockade. At the time of pembrolizumab initiation, the absolute lymphocyte count was about 380/μL, with an estimated CD4+ count likely below 200/μL. Prior studies have suggested that merely reducing PD-1 expression using pembrolizumab does not ensure the recovery of virus-specific immune function unless adequate numbers of competent progenitor-exhausted T cells remain [5].

Second, delayed initiation of pembrolizumab approximately 6.5 weeks after symptom onset, may have reduced therapeutic efficacy. Literature suggests a narrow therapeutic window for optimal outcomes, with treatment being more favorable when initiated within weeks rather than months [4,5]. Delayed intervention allows extensive viral replication and neuronal damage, possibly limiting the reversibility of neurological deficits, even if the immunological control of JCV is restored [5,6].

A critical limitation of this study was the absence of comprehensive baseline immunovirological evaluations, including quantitative assessments of the JCV viral load in the CSF, anti-JCV antibody indices, and measurements of JCV-specific T-cell functionality. These parameters can inform therapeutic strategies and indicate the need for adjunctive interventions [10].

Strategies for earlier diagnosis and better management

In immunocompromised patients receiving intensive chemotherapy including anti-CD20 monoclonal antibodies, PML should be promptly considered when new neurological symptoms develop, especially during post-treatment lymphopenia. Early brain MRI with fluid-attenuated inversion recovery and diffusion sequences, as well as quantitative JCV PCR from blood and CSF, are essential for rapid diagnosis. Before immune checkpoint blockade, baseline immunovirological profiling of CD4/CD8 counts and CSF viral loads may guide treatment eligibility. Moreover, close collaboration among the hematology, neurology, and radiology teams is critical to ensure timely diagnosis and coordinated management.

In conclusion, our case highlights the significant therapeutic challenges posed by PML following rituximab-containing chemotherapy regimens and the limited role of pembrolizumab monotherapy in immunocompromised patients. Early identification of high-risk patients, timely initiation of pembrolizumab therapy, and strategic use of adjunctive immunotherapeutic modalities are essential for improving the clinical outcomes in patients with PML.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Drafting the work or revising: DS, YGL.
Final approval of the manuscript: DS, SWC, KHL, DYK, YGL.

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