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【 CASE REPORT 】

Therapeutic Experience of Progressive Multifocal Leukoencephalopathy Development during Ofatumumab Therapy for Chronic Lymphocytic Leukemia

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Abstract:
A 79-year-old man experienced cognitive impairment and visual field defects during ofatumumab therapy for chronic lymphocytic leukemia refractory to combination chemotherapy. Magnetic resonance imaging revealed T1-weighted low-intensity and T2-weighted high-intensity lesions with patchy gadolinium enhancement in the subcortical white matter. A diagnosis of progressive multifocal leukoencephalopathy was made after the detection of John Cunningham virus (JCV) DNA in his cerebrospinal fluid (CSF). Following plasma exchange and the administration of mirtazapine and mefloquine, the JCV DNA levels in the CSF decreased. However, the patient died 55 days after treatment was initiated. Ofatumumab treatment appears to be associated with the development of progressive multifocal leukoencephalopathy.

Key words: progressive multifocal leukoencephalopathy, ofatumumab, chronic lymphocytic leukemia

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and severe demyelinating disease of the brain caused by reactivation of John Cunningham virus (JCV) in patients with human immunodeficiency virus (HIV) or people who have received monoclonal antibody therapy (1). Recently, PML has been associated with monoclonal antibody therapies, such as rituximab or natalizumab therapy (2). Many clinical trials and studies of other monoclonal antibodies, such as alemtuzumab, ofatumumab, and ocrelizumab, are seeking to expand the indications of these treatments from oncology to neurology. Therefore, neurologists are encountering monoclonal antibody products increasingly frequently and should be aware of potential severe adverse reactions to these therapies.

Ofatumumab has been approved for the treatment of chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab and for the extended treatment of recurrent or progressive CLL. A previous study also investigated its efficacy as a treatment for relapsing multiple sclerosis after changing the dosage from 2,000 mg weekly intravenous injection for CLL to 20 mg subcutaneous injection every 4 weeks (3). PML associated with ofatumumab therapy has rarely been documented in the literature (4), and its treatment has not been reported.

We herein report a case of PML associated with ofatumumab use and its treatment with multiple therapies.

Case Report

A 75-year-old man diagnosed with CLL was treated with 6 courses of combination chemotherapy consisting of fludarabine, cyclophosphamide, and rituximab in 2015. Because hemolytic anemia, which is one of the symptoms of CLL,

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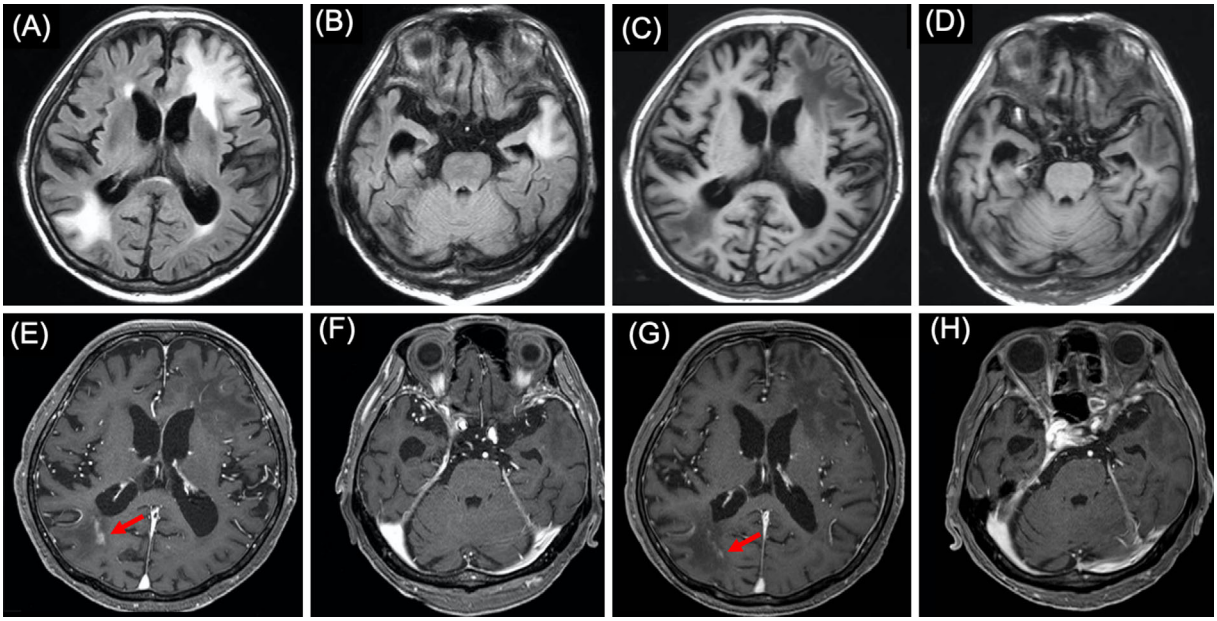

Figure. **Brain magnetic resonance images showing subcortical white matter lesions of the right parietal lobe and the left frontotemporal lobe. Axial (A, B) T2-weighted fluid attenuated inversion recovery, (C, D) T1-weighted, and (E, F) gadolinium-enhanced T1-weighted images of the brain at admission. Arrows show T1-hypointense lesions with patchy gadolinium enhancement. (G, H) Axial gadolinium-enhanced T1-weighted images of the brain at 14 days after treatment.**

was not improved despite treatment, the patient received ibrutinib therapy from October 2016 to February 2017 and steroid therapy from January to March 2017. Steroids were administered orally from January to April 2017, and no immunosuppressive drugs, including steroids, were used thereafter. He experienced apathy and forgetfulness after ofatumumab was administered from March to September 2017. Subsequently, he was admitted to our hospital in November 2017 because of the appearance of visual field defects on the left side.

A neurological examination showed left homonymous hemianopia. Neither muscle weakness nor sensory disturbance were observed. No hyperreflexia was noted, and the plantar response was flexor. His Mini-Mental State Examination score was 3/30. Magnetic resonance imaging (MRI) revealed T1-weighted low-intensity and T2-weighted high-intensity lesions with patchy gadolinium enhancement in the subcortical white matter of the right parietal lobe and the left frontotemporal lobe, without evidence of mass effect (Figure). The serum IgG levels were 100 mg/dL, and the lymphocyte count was 803/μL before the initiation of ofatumumab therapy; these values changed to 198 mg/dL and 745/μL, respectively, on admission. A cerebrospinal fluid (CSF) analysis indicated pleocytosis (87/μL, mononuclear cells 99%) and an increase in the protein level (282 mg/dL). JCV DNA was detected in the CSF using real-time polymerase chain reaction (PCR) (8.57×10^6 copies/mL), leading to a diagnosis of PML in November 2017. No brain biopsy was performed.

We performed plasma exchange 5 times and administered mirtazapine (15 mg/day) and mefloquine (275 mg/day for 3 days, then 275 mg weekly), a regimen approved by the institutional ethics board of the hospital. After these therapies, the JCV DNA level in the CSF decreased to 0.99×10^6 copies/mL. Follow-up MRI showed that the lesions had not expanded further and that the enhanced lesions observed with gadolinium had slightly faded. However, despite these treatments, the patient's cognitive impairment and homonymous hemianopia were not improved, although he presented with no new neurological symptoms. While continuing these oral treatments, the patient died of bacterial infection in an immunocompromised state with CLL 55 days after treatment was initiated.

Discussion

PML is a disease induced by cell-mediated immune deficiency. Both genetic mutations of JCV and the robustness of the host cellular immune response have been implicated in the onset of PML. Whether PML is induced by the reactivation of JCV that is dormant in the brain or by the proliferation of dormant PML-type JCV in the peripheral blood that is then transferred to the brain remains controversial (1). Nevertheless, the reactivation of JCV is thought to be involved in the hypothesis that the decline in cell-mediated immunity caused by the decrease in cytotoxic T-lymphocytes leads to uncontrollable JCV proliferation.

The etiology of PML associated with ofatumumab is unknown, but the anti-CD20 monoclonal antibody rituximab, which is similar to ofatumumab, is known to be one of the main causes of PML. Rituximab may be responsible for the decrease in B-lymphocytes in cerebral perivascular spaces

associated with PML, resulting in decreased antigen presentation to T-lymphocytes. Subsequently, the cellular immune response is altered (5), and recruitment of the mature B-lymphocyte population after B-lymphocyte depletion by rituximab therapy may contribute to the expansion of pre-B-lymphocytes harboring latent JCV (2). The T-lymphocyte cytokine profile was altered in immune thrombocytopenic purpura patients who responded to rituximab, indicating that the T-lymphocyte activity can change after B-lymphocyte depletion (6). Ofatumumab may therefore carry a low risk of causing PML (7), but a similar action to rituximab may occur with ofatumumab.

In addition to HIV patients, people with hematological malignancies can also develop PML. Indeed, PML was first described as a complication of CLL and Hodgkin's lymphoma (8), and the incidence of PML is as high as 0.52% in CLL patients. CLL treatment requires multiple immunosuppressive therapies, including fludarabine, which itself causes PML. The high incidence of PML in CLL patients may be related to the cumulative effects of previous CLL treatments, including fludarabine.

Monoclonal antibody-related PML requires discontinuation of the suspected drug, especially for natalizumab-associated PML, for which patients empirically receive plasma exchange (9). However, it was recently reported that plasmapheresis in natalizumab-associated PML did not improve the survival or clinical outcome (10). Whether or not to perform plasma exchange in PML associated with monoclonal antibodies should therefore be decided after careful consideration. Some single case reports have shown that certain treatments, including mefloquine and mirtazapine, improved the symptoms and MRI findings of PML. In those cases, the JCV DNA levels in the CSF tended to be low or undetectable compared with refractory cases (11, 12, 13). While we noted no improvement in the life expectancy in the present case, the removal of ofatumumab and application of mefloquine and mirtazapine significantly improved the JCV DNA levels, suggesting that these treatments may help control the disease activity.

Whether or not patients without CLL who receive ofatumumab treatment will develop PML is unclear, as ofatumumab has only been approved for the treatment of multiple sclerosis. When the indications for ofatumumab are expanded in the future, physicians should be alert for the development of ofatumumab-related PML.

The authors state that they have no Conflict of Interest (COI).

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