Central Nervous System Involvement in Mantle Cell Lymphoma Presenting Magnetic Resonance Imaging Features of Mild Encephalitis/Encephalopathy with a Reversible Splenial Lesion

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Abstract:
Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) has not been described in lymphoma patients. A 65-year-old man with refractory mantle cell lymphoma (MCL) presented typical MRI features of MERS. The patient’s cerebrospinal fluid contained an increased number of reactive T-cells; a small number of MCL cells were detected by IGH-PCR. His symptoms and the splenial lesion resolved in response to ibrutinib treatment, although the patient eventually died of progressive MCL with overt leptomeningeal disease. We suggest that central nervous system involvement in MCL can present clinicoradiological features of MERS and that ibrutinib could be a choice of treatment.

Key words: mantle cell lymphoma, mild encephalitis/encephalopathy with reversible splenial lesion, polymerase chain reaction


Introduction

Approximately 5% patients with mantle cell lymphoma (MCL) have central nervous system (CNS) involvement, mostly presenting as leptomeningeal disease (1). Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is a rare clinicoradiological entity characterized by a reversible lesion in the corpus callosum, which occasionally involves the symmetrical white matter, as revealed by magnetic resonance imaging (MRI) (2). MERS is predominantly caused by viral infections, and it is less frequently associated with antiepileptic medication withdrawal, high-altitude exposure, and metabolic disturbances (2-4). From a clinical viewpoint, patients with MERS present with mild CNS symptoms, such as consciousness disturbance, seizures, and headache and achieve spontaneous recovery within a month. We herein report a case of secondary CNS involvement in MCL presenting MRI features of MERS at the time of the onset of neurological symptoms.

Case Report

A 65-year-old man presented with a 2-week history of paraphasia and action tremor. Nine years earlier, he was diagnosed with MCL and was treated with five lines of systemic chemoimmunotherapy for multiple relapses of MCL. In the fifth remission under chemoimmunotherapy, computed tomography showed that the mesenteric lymph nodes were less than 3 cm in the long axis diameter. A physical examination revealed conduction aphasia, right oculomotor palsy-related upper eyelid ptosis, exotropia, and mydriasis. MRI revealed an isolated ovoid lesion in the central portion of the splenium of the corpus callosum, characterized by hyperintensity on diffusion-weighted images (DWI) and low apparent diffusion coefficient (ADC) values (Fig. 1A, B). An analysis of the cerebrospinal fluid (CSF) revealed a cell count of 229 cells/μL (mostly mononuclear cells) and an increased protein level (312 mg/dL; reference range, 15-50 mg/dL). Lymphoma cells were not detected by cytology or
flow cytometry. Most CSF-infiltrating cells were immunophenotypically CD3+ mature T lymphocytes, expressing either CD8+ (58%) or CD4+ (21%). There were few CD20+ B cells (<1%), and immunoglobulin light chain restrictions were not detected. Polymerase chain reaction (PCR)-amplified fragments using immunoglobulin heavy chain (IGH) gene consensus primer sets (FR1-, FR2- and FR3-JH) (5) consistently revealed monoclonal IGH gene rearrangement (Fig. 1C), indicating CNS involvement in MCL. IGH-PCR did not detect rearrangement in the peripheral blood leukocytes, which excluded the possibility of sample contamination by traumatic tap. A detailed investiga-
tion that included staining, cultures and PCR assays revealed no evidence of infection in the CSF. The patient was started on ibrutinib, which has high blood-brain barrier penetration. The 2-week follow-up MRI showed resolution of the splenial lesion, with modest improvements in the neurological symptoms.

Two months later, MRI showed a new lesion in the temporal lobe (long-axis diameter: 3 cm), which was also characterized by hyperintensity on DWI and low ADC values (Fig. 2). The CSF contained a large number of cells with morphological features of MCL (1,440 cells/μL). Flow cytometry revealed that most infiltrating cells (approximately 90%) expressed the CD5+CD19+CD20+CD23− MCL immunophenotype with lambda light chain restriction. IGH-PCR also detected monoclonal IGH gene rearrangement. The sizes of rearrangement bands were identical to those seen in the CSF obtained at the time of the onset of neurological symptoms. The patient died of progressive disease 1 month later.

**Discussion**

In this report, we presented a case of MERS in a patient with evidence of secondary CNS involvement in MCL. CSF involvement in MCL was only diagnosed by IGH-PCR in the setting of negative cytology and flow cytometry results. We therefore recommend performing PCR to detect monoclonal IGH gene rearrangement in the CSF, because it has higher sensitivity than cytology and flow cytometry in samples with dense inflammatory lymphocyte infiltration.

It is unclear whether the splenial lesion was formed because of direct lymphoma involvement or an inflammatory response to the lymphoma. Although the pathophysiological mechanism of MERS is unknown, it has been hypothesized that an autoimmune response causes reversible intramyelinic edema and inflammation in the splenium (6, 7). On the other hand, MERS-defining MRI features, including hyperintensity on DWI and low ADC values have also been described in CNS lymphomas (8). In addition, ibrutinib has shown clinical antineoplastic activity against secondary CNS lymphomas, providing progression-free survival of approximately 10 months (9), and anti-inflammatory properties in patients with chronic graft-versus-host disease and coronavirus disease 2019 (10, 11). We therefore hypothesize that a subsided splenial lesion could form either by direct lymphoma involvement or secondarily through the influx of in-
Inflammatory T-cells. In either case, ibrutinib could be an option for MCL patients with possible CNS lesions.

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

Compliance with ethical standards

Written informed consent was obtained from the patient for the publication of this case report.

References


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