Progressive Multifocal Leukoencephalopathy Localized in the Cerebellum and Brainstem Associated with Idiopathic CD4\(^+\) T Lymphocytopenia

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that favors the cerebrum and typically occurs in immunosuppressed patients. We herein report the case of a 66-year-old man with PML, idiopathic CD4\(^+\) T lymphocytopenia (ICL), and chronic renal failure. Cranial magnetic resonance imaging (MRI) showed a crescent-shaped lesion in the left cerebellum, brainstem, and middle cerebellar peduncle. Although the patient did not present with HIV infection, collagen diseases, or tumors, JC virus DNA was detected in the cerebrospinal fluid. Clinicians should consider PML and ICL in the differential diagnosis if the patient develops progressive ataxia and a crescent-shaped cerebellar lesion on MRI.

Key words: brainstem, cerebellum, crescent-shaped, idiopathic CD4\(^+\) T lymphocytopenia, progressive multifocal leukoencephalopathy

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating, rapidly progressive, and fatal disease resulting from JC virus activation. PML typically occurs in immunosuppressed patients and preferentially involves the cerebrum (1). However, cases of cerebellar PML in patients with idiopathic CD4\(^+\) T lymphocytopenia (ICL) or with renal failure have been reported by several groups (2-6). ICL indicates an absolute CD4\(^+\) T lymphocyte count of less than 300 cells/mm\(^3\) or less than 20% of the total T cells on more than one occasion, with no evidence of HIV infection or any other defined immunodeficiency or therapy that is associated with low CD4\(^+\) T cell levels. We herein report the case of a PML patient with ICL and renal failure who presented with a crescent-shaped lesion in the cerebellum and brainstem and a review the pertinent literature for similar cases.

Case Report

A 66-year-old man suffering from progressive gait and speech impairment for the last one and a half months was admitted to our hospital. The patient’s medical history revealed diabetes mellitus of 22 years with Stage IV chronic renal failure and retinopathy and hypertension. A neurological examination revealed saccadic eye movement, lateral gaze-evoked nystagmus, ataxic dysarthria, and ataxia in the left upper and lower extremities; the patient was unable to walk due to ataxia. Laboratory tests showed lymphocytopenia [total count, 555 cells/mm\(^3\); CD4\(^+\) T cell count, 84 (normal range: 441-2,156) cells/mm\(^3\); CD8\(^+\) T cell count, 130 (normal range: 125-1,312) cells/mm\(^3\)], creatinine at 5.88 mg/dL, and HbA1c at 5.4%. Serological tests were negative for collagen diseases, hepatitis virus types B and C, HTLV-1, and HIV. Systemic computed tomography (CT) scanning did not show any tumors or other visible abnormalities. A cerebrospinal fluid (CSF) analysis was normal (cell count:
Figure. Cranial MRI findings of the present case. Cranial MRI showing a crescent-shaped, white matter lesion involving the left cerebellar hemisphere, middle cerebellar peduncle, and brainstem on T2WI (A) and FLAIR (B) images.

Table. ICL-associated PML with Cerebellum/Brainstem Lesion.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Other underlying disease</th>
<th>Lesion distribution</th>
<th>CD4+ (cells/mm³)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>57</td>
<td>male</td>
<td>tuberculosis cervical lymphadenopathy</td>
<td>brainstem, cerebellum</td>
<td>139</td>
<td>methylprednisolone</td>
<td>alive for more than 3 years</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>male</td>
<td>none</td>
<td>middle cerebellar peduncle, cerebellum</td>
<td>80</td>
<td>amantadine</td>
<td>alive for more than 20 months</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>female</td>
<td>biliary cystadenocarcinoma of the liver, hypothyroiditis</td>
<td>middle cerebellar peduncle, brainstem</td>
<td>247</td>
<td>mefloquine</td>
<td>alive for more than 22 months</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>male</td>
<td>dermatomal herpes zoster infection</td>
<td>cerebellum, midbrain, cerebrum</td>
<td>242</td>
<td>mirtazapine</td>
<td>alive for more than 34 months</td>
</tr>
<tr>
<td>Present case</td>
<td>66</td>
<td>male</td>
<td>diabetes mellitus, chronic renal failure</td>
<td>middle cerebellar peduncle, brainstem, cerebellum</td>
<td>84</td>
<td>mefloquine, methylprednisolone</td>
<td>died 3 months after onset</td>
</tr>
</tbody>
</table>

PML: progressive multifocal leukoencephalopathy, ICL: idiopathic CD4+ T lymphocytopenia

Discussion

The presence of rapidly progressing ataxia and the crescent-shaped cerebellar lesion detected by MRI led us to diagnose PML following the detection of JC virus DNA. Our patient, while suffering from chronic renal failure, did not present with any signs or symptoms suggestive of HIV infection, collagen diseases, or tumors; thus, we evaluated the T cell counts, which led to the ICL diagnosis according to low CD4+ T cell levels.

HIV infection, hematopoietic malignancies, collagen diseases and renal failure are major underlying causes of PML, whereas the etiology is unknown in a subset of patients (8, 9). However, in recent years, several cases of PML in patients with ICL in the absence of other underlying diseases have been reported (6, 10). While a study by Gheuens et al. revealed that 13% of non-HIV PML cases also had ICL (8), another study suggested that ICL is underdiagnosed as the cause of PML (9). PML typically occurs in patients...
with cellular immunodeficiency, and the clinical manifestations of PML (e.g., lesion distribution, prognosis) may vary depending on the underlying cause of immunodeficiency. In this case, it is possible that both chronic renal failure and ICL were involved in the development of PML. To the best of our knowledge, cerebellum and brainstem PML associated with both renal failure and ICL has not been reported. According to the literature review, the prognosis in all reported cases, except for our case, was relatively good; thus renal failure may underlie a bad prognosis, as observed in our patient with ICL (Table).

PML lesions in the cerebellum or brainstem typically appear as crescent-shaped, hyperintense areas (11). A “crescent-shaped cerebellar lesion” is a specific finding of PML because it is seen only in patients with PML, and not in patients with multiple sclerosis (12). Cerebellar and brainstem lesions in PML are rare in HIV patients: the incidence is 6.2% (1). However, PML lesions in these anatomical locations are relatively frequent in renal failure (8) and ICL patients, at an incidence of 60% and 20%, respectively (5, 6). Although the precise mechanism of regional preferences in PML is not clear, specific mutations in the JC virus DNA may explain these differences (13).

In conclusion, PML associated with ICL is a rare condition that often presents as a cerebellar lesion. The crescent-shaped lesion is a characteristic finding of cerebellar PML, and ICL should be considered in these patients in the absence of other underlying diseases.

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

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References