CASE REPORT

Progressive multifocal leukoencephalopathy (PML) in a patient with lymphoma treated with rituximab: A case report and literature review

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Summary Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of a latent JC polyoma virus. The first cases of PML were described 50 years ago in patients with lymphoma. PML typically occurs in immunocompromised individuals, particularly those infected with HIV. We present a 52-year-old male with lymphoma who was treated with R-CHOP (R: Rituximab; C: Cyclophosphamide; H: Doxorubicin; O: Vincristine; P: Prednisone). After six cycles of therapy, the patients developed tonic–clonic seizure. MRI of the brain showed multiple brain lesions. The pathology of a brain biopsy was diagnostic for PML. We review radiographic and histopathological features of the disease. The literature on PML and its association with immunosuppressant agents is reviewed, and the impact of rituximab and other biological agents in the setting is highlighted.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the JC polyomavirus. JC virus infects oligodendroglial cells almost exclusively in
immunocompromised patients, including those with AIDS, lymphoproliferative disorders, and those who had chemotherapy. The occurrence of PML in relation to the use of monoclonal antibodies, such as natalizumab and rituximab, has been reported [1]. The treatment of diffuse cell lymphoma was modified in the last decade. Currently, a combination of anti-CD20 monoclonal antibody (rituximab) and cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) chemotherapy is recommended [2]. The use of R-CHOP has been associated with development of PML [2]. The exact risk of PML after monoclonal antibody use was quantified in relation to natalizumab. It was estimated that the overall risk is approximately 1.66 per 1000 patients with multiple sclerosis treated with natalizumab [3]. The exact risk of PML in patients with lymphoma treated with R-CHOP is not known. In this study, we describe a patient with nodal lymphoma who developed PML after R-CHOP and presented with salient features of the disease.

Case presentation

The patient was a 55-year-old man who first presented with a complaint of cough, fever, and a 4-kg weight loss over eight months’ duration. Physical examination was significant for right axillary lymphadenopathy. A CT scan showed hepatic and splenic lesions and multiple abdominal lymphadenopathies. The patient underwent bone marrow and right axillary lymph node biopsies. The pathology showed diffuse large B-cell lymphoma with bone marrow involvement (stage IV-B). He received R-CHOP. The patient had significant clinical improvement on R-CHOP but developed prolonged neutropenia which required several hospital admissions, despite the use of granulocyte colony stimulating factors. Following additional review, the pathological diagnosis was revised to nodular lymphocyte predominant Hodgkin’s lymphoma; however, the patient was continued on the same regimen. After four cycles of R-CHOP, he had excellent clinical and radiological response to the treatment. The fifth cycle was delayed, as the patient did not appear for the therapy until the following month, when the treatment was resumed. After completing six cycles, a positron emission tomography (PET)-scan showed several small lymph nodes in the mediastinum and in the lung hilar areas with very low Standardized Uptake Values (SUV) of 2.1 of unknown significance. A month later, he was admitted with seizure activity. A CT scan of the brain followed by an MRI showed multiple brain lesions (Figs. 1 and 2). The MRI of the brain showed multifocal cortical and subcortical periventricular lesions with no edema and enhancement. A similar lesion was noted in the brainstem. He was initially started on anti-bacterial and antifungal treatment. A brain biopsy was performed with a pathological diagnosis of progressive multifocal leukoencephalopathy (Fig. 3). During his stay, he became unresponsive and bedridden. He had percutaneous endoscopic gastrostomy (PEG) tube

Figure 1 MRI of the brain showing multifocal cortical and subcortical periventricular lesions with no edema and no enhancement.

Figure 2 MRI of the brain showing multifocal cortical and subcortical periventricular lesions with no edema and no enhancement.
insertion. Mefloquine was not used due to G6PD deficiency.

**Histopathology of the Brain Biopsy**

The biopsy was composed of white matter which showed dense macrophage infiltration associated with myelin loss. The presence of demyelination was confirmed by the stains for LFB/PAS and neurofilament, which highlight the loss of myelin with relative axonal preservation, as is typical of demyelination. In the background, there was evidence of bizarre astrocytes with large hyperchromatic nuclei, as well as more typical viral inclusions characterized by chromatin margination. These inclusions were well-highlighted by the in-situ hybridization studies for John Cunningham (JC) virus. On CD3 and CD20 stains, a moderate number of CD3 positive T-lymphocytes were present.

**Discussion**

In recent years, monoclonal antibodies are becoming the drugs of choice for many rheumatological diseases and inflammatory conditions, such as inflammatory bowel disease and multiple sclerosis. The use of these monoclonal antibodies is associated with several infectious diseases, such as PML [1]. In a study of 30 patients with Crohn’s disease who were prescribed natalizumab, no patient developed PML [4]. In another study of 34 confirmed cases of PML in the setting of autoimmune rheumatic diseases (ARDs), 17 had systemic lupus erythematosus, 10 had rheumatoid arthritis, 4 had vasculitis, and 3 had dermatomyositis [4]. In another study, 15 patients were treated with one or more biologic agents, and 14 received rituximab (RTX). Six received anti-tumor necrosis factor (anti-TNF) therapy, and of those patients, five received an anti-TNF agent prior to RTX [5]. The study concluded that there is a possible relationship between rituximab and PML [5]. Natalizumab was associated with fatal progressive multifocal leukoencephalopathy due to reactivation of JC virus and occurs with greater frequency in patients with previous JC virus infection [6]. None of the 29 patients with Crohn’s Disease who received natalizumab treatment for a median of 7 months (interquartile range, 3–21.5 months) had PML [7].

There was a concern regarding the excretion of JC virus in the urine of patients who received biologic agents. Among 16 such patients

**Figure 3** Brain biopsy. (A–C) Dense macrophage infiltration with bizarre astrocytes featuring large hyperchromatic nuclei and viral inclusions characterized by chromatin margination (hematoxylin and eosin stain. A: 10×, B: 20×, C: 40×). (D) Marked decrease/loss of myelin (neurofilament immunohistochemical stain. 40×). (E) Relatively normal area for comparison (neurofilament immunohistochemical stain. 40×).
Table 1  A summary of PML cases in patients treated with R-CHOP.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Malignancy</th>
<th>Number of R-CHOP cycles prior to diagnosis</th>
<th>MRI findings</th>
<th>CSF PCR for JC virus</th>
<th>Activity of lymphoma at diagnosis of PML</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>M</td>
<td>Diffuse large cell B-lymphoma</td>
<td>8</td>
<td>Multiple demyelination in anterior pontomesencephalon region and the right thalamus</td>
<td>Not done</td>
<td>Remission</td>
<td>[2]</td>
</tr>
<tr>
<td>74</td>
<td>F</td>
<td>Lymphoma</td>
<td>Symptoms started after the third cycle, received additional 3 R-CHOP cycles and diagnosis was after 3 additional Rituximab cycles</td>
<td>Two hyperintense lesions</td>
<td>Negative</td>
<td>Active</td>
<td>[12]</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>Diffuse large cell B-lymphoma</td>
<td>5</td>
<td>Right cerebellum</td>
<td>Positive</td>
<td>Remission</td>
<td>[13]</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Lymphoma</td>
<td>6</td>
<td>Multifocal cortical and subcortical lesions</td>
<td>Not done</td>
<td>Remission</td>
<td>Current case</td>
</tr>
</tbody>
</table>

who were treated with Etanercept (n=8), infliximab (n=4), adalimumab (n=1), multiple anti-TNF agents sequentially (n=2) and Rituximab (n=1), only two (12.5%) patients excreted JC virus in the urine [8]. The significance of such activation was not delineated. In contrast, the risk of PML in multiple sclerosis and natalizumab was correlated with the positive JC serology, prior use of immunosuppressants, and increased duration of natalizumab treatment [9]. In contrast, in HIV positive patients, JC viremia was not predictive of PML [10]. Subclinical reactivation of JC virus was documented in multiple sclerosis patients who were treated with natalizumab [11]. Those patients had an increase in the prevalence of JC virus in the urine from 19% to 63% after 18 months of treatment [11]. However, the risk of PML for lymphoma patients requires further study.

The use of biologic agents in patients with lymphoma is less documented than in rheumatological diseases. A 74-year-old woman with lymphoma treated with R-CHOP developed neurological symptoms after three cycles of chemotherapy [12]. The sixth cycle of CHOP chemotherapy was withheld and three additional cycles of rituximab were given. Subsequently, a brain biopsy showed PML and the patient rapidly deteriorated and died [12]. A second case was a 48-year-old female patient with diffuse large B-cell lymphoma treated with R-CHOP therapy. During the fifth cycle of R-CHOP, she had progressive neurological symptoms. Magnetic resonance imaging showed hyperintensity in the right cerebellar hemisphere on T2-weighted images. In contrast to the first case described above, polymerase chain reaction-based tests of the cerebrospinal fluid was positive for JC virus [13]. Another patient with diffuse large B cell lymphoma was treated with R-CHOP and developed PML [2]. Interestingly, this patient, similar to our patient, had fluorodeoxyglucose-emission tomography (FDG-PET/CT) and showed the total remission of disease [2]. A summary of PML cases in patients treated with R-CHOP is shown in Table 1.

PML developed after six cycles of R-CHOP in the presented case. In HIV-negative patients treated with rituximab who developed PML, the median time from first dose of rituximab to PML diagnosis was 16 months, the median time from last dose to PML diagnosis was 5.5 months, and the median time from PML diagnosis to death was two months [14]. In five patients with lymphoid malignancies, those patients had PML after a median of three Brentuximab vedotin doses and within a median of seven weeks of therapy [15].
Similar to the present case, the neuroimaging of PML typically shows symmetric or asymmetric multifocal demyelination with no mass effect and no contrast enhancement [16]. The presence of contrast enhancing lesions and local mass effect were described in PML in association with HIV after initiation HAART therapy in patients with multiple sclerosis or Crohn’s disease treated with natalizumab and in the case of post-immune reconstitution inflammatory syndrome [16].

The occurrence of neurological symptoms in patients with lymphoma who receive R-CHOP should direct a prompt search for the occurrence of CNS lesions, such as PML. Further studies are needed to quantify the risk and identify the patients for whom rituximab should be avoided.

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**Competing interests**

The authors have no conflicts of interest to disclose.

**Ethical approval**

The study was approved by the IRB.

**References**


