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Case report/ Kazuistyka

Rituximab-associated progressive multifocal leukoencephalopathy after a single cycle of R-CHOP for T-cell/histiocyte-rich large B-cell lymphoma

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a disease of immunocompromised patients caused by reactivation of the John Cunningham polyomavirus (JCV). A monoclonal anti-CD20 antibody rituximab is widely used as an important part of therapy for B-cell non-Hodgkin lymphomas and various autoimmune diseases. It is not fully explained how rituximab reactivates JCV.

In this report, we present the case of a 61-year-old man with T-cell/histiocyte-rich large B-cell lymphoma who was treated with R-CHOP and intrathecal methotrexate. Two weeks after the first R-CHOP course he developed dysarthria, diplopia, and disturbances in motor coordination. Based on CT/MRI results showing 3 cm × 2 cm large hypodense white matter lesion in left cerebellar hemisphere, and detection of JCV in the cerebrospinal fluid (14 300 viral copies/mL), the patient was diagnosed with PML. Despite treatment attempt with cidofovir and IVIG, the patient's neurological status continued to worsen. He developed progressive motor neuron deficits but retained intact cognitive functions. The patient deceased nearly three months after onset of rituximab treatment.

Rituximab is a milestone in treatment of many hematological and autoimmune diseases. Considering how widespread has the use of rituximab become, the overall risk of developing PML is relatively low. Nevertheless, since the end of 1990s several reports were published on PML development in association with usage of rituximab. The authors would like to emphasize that although the total risk of PML occurrence in patients treated with rituximab is low, it is important that physicians administrating rituximab therapy are aware of this serious complication.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare, albeit often fatal, central nervous system (CNS) demyelinating disorder caused by reactivation of a latent John Cunningham polyomavirus (JCV) [1–3]. The disease was first described in 1950s by a Swedish neuropathologist Karl-Erik Åström as a complication occurring in patients with chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma [1]. Primary JCV infection is usually asymptomatic and occurs in school age. After that, the virus is latent in 70–90% of the adult population [2]. Latent JCV can be found in kidney epithelial cells, CD34+ hematopoietic cells and possibly early B-cell precursors [4]. It was proposed that hematopoietic stem cells, which carry JCV, can act as Trojan horses and thus enable the virus to pass the blood-brain barrier. During the active phase of the PML, JCV particles are replicated in oligodendrocytes. The virus induces then destruction of myelin sheath and cell death [2].

PML is usually associated with a decreased T-cell response, and it was very infrequent disease until the time of HIV-epidemics in the 1980s [5]. The incidence of PML increased 50 times between 1979 and 1994, but then it has decreased gradually due to the introduction of antiviral treatment of HIV infection.

The rate of PML progression may initially be slow, making the disease difficult to diagnose. Patients present gradual worsening of cognitive functions, speech and vision [1, 2]. Symptoms become more prominent with time, and patients develop motor neuron deficits and ataxia. With disease progression, neurologic deficits accelerate with occurrence of dementia, blindness, pareses, followed by coma and decease. PML diagnosis is confirmed by JCV detection by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) [2]. Magnetic resonance imaging (MRI) demonstrates typical pictures of multifocal asymmetrical white matter lesions, located in cerebral hemispheres and less often in cerebellum or brain stem. Diagnosis can also be obtained through biopsy, with histopathological analysis of the tissue and complementary immunohistochemical stains (Table I) [2, 6].

Rituximab is a monoclonal anti-CD20 antibody used for treatment of many types of CD20-positive non-Hodgkin lymphomas (NHLs) including CLL [2]. It is also successfully used in autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Expression of CD20 antigen is observed on both healthy and malignant B-cells, but not on hematopoietic stem cells. Rituximab produces a rapid and almost complete clearance of B-cells from peripheral blood, with the effect persisting up to 12 months after completed therapy [7].

Case presentation

A 61-year-old previously healthy Swedish man with a periodical alcohol abuse, presented with a three-months-long history of diffuse abdominal pain, tiredness and weight loss. Computed tomography (CT) imaging revealed abdominal and thoracic lymphadenopathy at multiple sites as well as prominent splenomegaly. Lymph node biopsy disclosed infiltration of T-cell/histiocyte-rich large B-cell lymphoma. The patient was scheduled for 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) at 14-day intervals and intrathecal methotrexate. He was also found to have undergone hepatitis B, and treatment with lamivudin (Zeffix™) was initiated.

Two weeks after the first R-CHOP-14 course the patient came for a follow-up visit and evaluation before the next treatment course. He presented dysarthria and reported experiencing diplopia, disturbances in motor coordination and loss of large muscle group strength for several days before. Lymphoma therapy was postponed and the patient was admitted to the department of neurology. Brain CT was performed on the same day, and revealed the presence of 3 cm × 2 cm large hypodense white matter lesion in left cerebellar hemisphere as well as numerous nonspecific white matter lesions. These findings were later confirmed by MRI and tentative radiological diagnosis was lymphoma or PML or low grade tumor. Lumbar puncture was performed, with extensive examination for potential infectious agents. The initial assessment suggested CNS involvement by lymphoma since only one major lesion was detected and its location was atypical for PML.

Results of JCV-PCR analysis in the CSF sample were received 3 weeks after initiation of the first R-CHOP-14 course, demonstrating 14 300 viral copies/mL (Fig. 1). Other assays failed to reveal any bacteria, virus or fungal infection. A brain biopsy was discussed with neurosurgeons, but they advised against biopsy as clear signs of PML were already identified.

The patient's clinical status has gradually improved, and 4 weeks after R-CHOP treatment onset he was in neurologically nearly normal condition apart from minor problems with his body balance. At that time, the number of

Table I – Diagnostic signs and symptoms of progressive multifocal leukoencephalopathy

Clinical findings	Rapidly progressing neurological deficits and worsening of motor neuron functions; usually cognitive defect and impaired field of vision
Histopathology of brain tissue (if biopsy performed)	Characteristic histopathological findings [7]: • Demyelinisation • Bizarre astrocytes • Enlarged oligodendroglial cell nuclei • JCV demonstrated by immunohistochemical stain or in electron microscopy
Laboratory findings	Detection of JCV in CSF by means of PCR
Radiological findings	MRI or CT (with contrast) shows multifocal white matter lesions with no or only discrete contrast enhancement