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Case Report

Progressive multifocal leukoencephalopathy secondary to rituximab-induced immunosuppression and the presence of John Cunningham virus: a case report and literature review

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ARTICLE INFO

Article history:
Received 11 May 2016
Received in revised form
7 June 2016
Accepted 15 June 2016
Available online 18 July 2016

Keywords:
Rituximab
Non-Hodgkin's lymphoma
Progressive multifocal leukoencephalopathy

ABSTRACT

We present the case of a 60-year-old man who developed subacute neurologic changes, in the setting of stage III non-Hodgkin's follicular lymphoma, and was treated with induction chemotherapy, followed by a year of maintenance rituximab. Magnetic resonance imaging of the brain with gadolinium was pathognomonic for progressive multifocal leukoencephalopathy (PML). He was treated with sequential plasmapheresis and intravenous immunoglobulin with clinical improvement. A literature review of the diagnostic workup of rituximab-induced PML was undertaken. This case and the literature review demonstrate the important role of magnetic resonance imaging of the brain in diagnosis and follow-up of rituximab-induced PML. Specific radiologic features in combination with cerebrospinal fluid can be diagnostic and avoid the morbidity and mortality of a diagnostic brain biopsy. Plasmapheresis and intravenous immunoglobulin have a therapeutic role and demonstrate symptom improvement and disease control. Follow-up imaging in combination with clinical response is important in demonstrating a treatment response.

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No funding was obtained for this research.
Consent was obtained from the patient for review and publication of his case and radiologic images.
All research was carried out in accordance with local and international ethical policies.
Competing Interests: The authors have declared that no competing interests exist.

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http://dx.doi.org/10.1016/j.radcr.2016.06.003

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Introduction

First described in 1958 by Astrom et al. [1], progressive multifocal leukoencephalopathy (PML) is a rare infectious disease of the central nervous system caused by the John Cunningham virus (JCV). Approximately 50% of the adult population are asymptomatic carriers of the JCV [2]. However, immunocompromised persons can develop disseminated cerebral infection. The virus targets oligodendrocytes and astrocytes causing cell lysis [3], ultimately resulting in demyelination. The first cases of PML were described in patients with hematologic malignancies, autoimmune conditions, and immunocompromised states. Throughout the 80s, PML was considered an AIDS-defining illness. With the advent of immunomodulatory therapy in the last 2 decades, the incidence of PML is rising.

Rituximab is an anti-CD20 monoclonal antibody therapy [3] licensed for use in follicular lymphoma, diffuse large B-cell Non Hodgkins lymphoma, and chronic lymphocytic leukemia. It is also used in autoimmune conditions such as severe rheumatoid arthritis, Wegener granulomatosis, and microscopic polyangiitis. Rituximab was first licensed in the US Food and Drug Administration in 1997, followed by European Union equivalents 1 year later [4]. The incidence of rituximab-associated PML has been quoted at 1 of 30,000 cases in 1 review [3]. It is likely that the risk of developing PML also depends on the patient's underlying diagnosis and may be higher on those with lymphoproliferative disorders.

Case report

We report the case of a 60-year-old man presenting with subacute personality change, speech and attention deficits in the setting of stage III non-Hodgkin's follicular lymphoma treated with 6 cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy followed by a year of maintenance rituximab. He presented in October 2013 with enlarging right inguinal lymph nodes. Computed tomography of thorax, abdomen, and pelvis revealed bilateral inguinal adenopathy. Biopsy of inguinal lymph node demonstrated follicular lymphoma. He received 6 months of RCHOP chemotherapy and continued on maintenance rituximab for another 6 months.

Four months after completion of his rituximab, he presented with fatigue, personality change, and short-term memory impairment on a background of a high-functioning baseline. This was associated with apraxia of the upper limbs, ataxia, and right upper limb tremor. On admission to the hospital, he was noted to have aprosody, perseveration of speech and left cortical inattention. On objective cognitive testing in the form of an Montreal Cognitive Assessment, he scored 25 of 30 with deficits reflecting temporofrontal dysfunction. At this point, he had been symptomatic for approximately 6 months. Screening for tuberculosis, *Chlamydia pneumoniae*, cryptococcal antigen, syphilis, *Coxiella burnetii*, hepatitis, HIV, and Creutzfeldt–Jakob disease was negative.

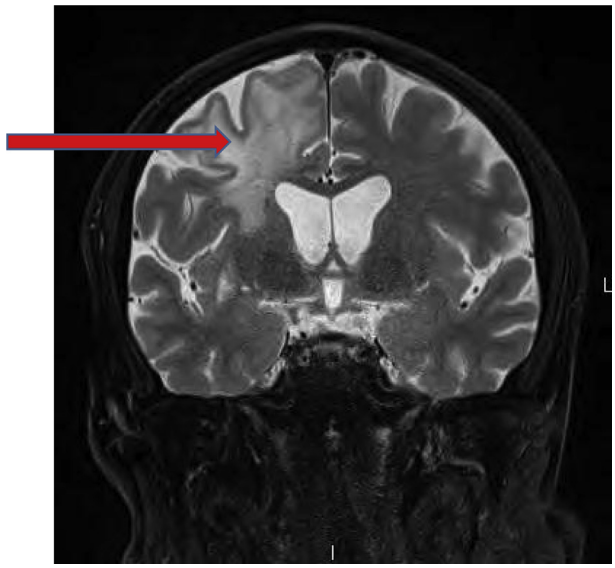

Fig. 1 – Sagittal section of MRI of the brain (T2 weighted) demonstrates hyperintense signal in the right frontotemporal white matter.

Magnetic resonance imaging (MRI) brain with gadolinium showed T2 hyperintense signal in the frontotemporal white matter on the right which decussated across the brainstem to involve the contralateral medulla (Figs. 1 and 2). There was no enhancement, and there was a lack of mass effect. The patient's cerebrospinal fluid (CSF) returned as polymerase chain reaction positive for JCV. The gold standard for diagnosis is a brain biopsy; however, there is an associated 8.4% risk of morbidity and a 2.9% risk of death [5]. As such, the combination of JCV in the CSF and the characteristic imaging confirmed the diagnosis of PML.

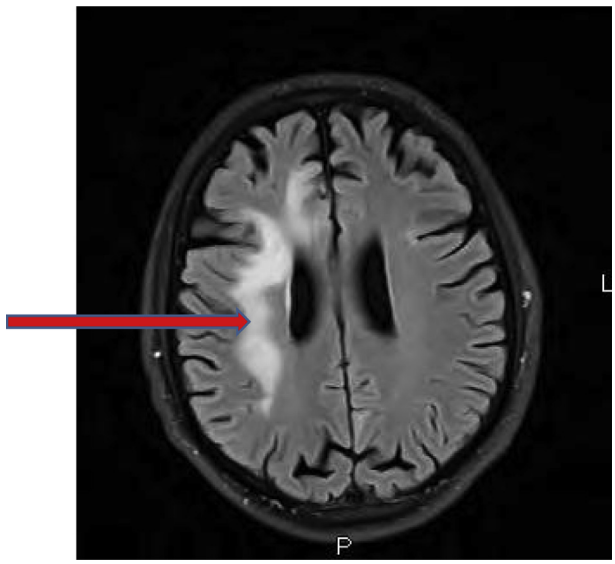

Fig. 2 – Transverse section of MRI of the brain (T2 weighted with gadolinium) demonstrates hyperintense signal in the right frontotemporal white matter.

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