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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.

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

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.

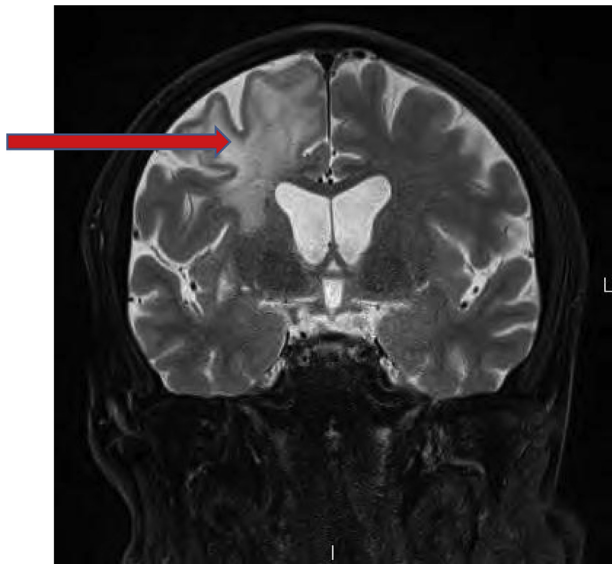

Fig. 1 – Sagittal section of MRI of the brain (T2 weighted) demonstrates hyperintense signal in the right frontotemporal white matter.

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.

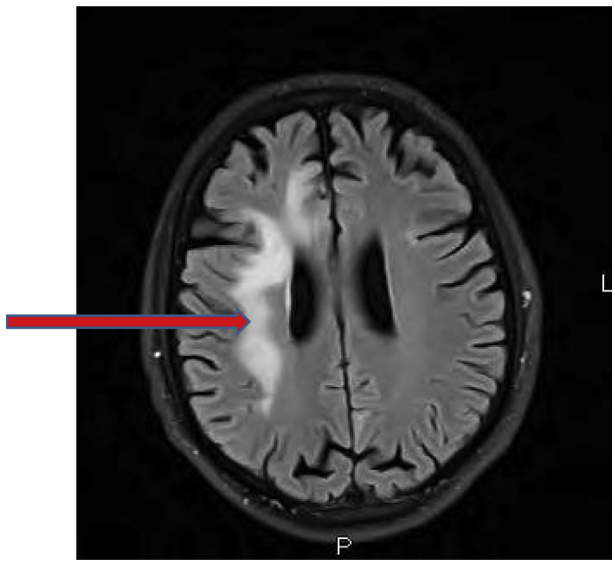

Fig. 2 – Transverse section of MRI of the brain (T2 weighted with gadolinium) demonstrates hyperintense signal in the right frontotemporal white matter.

The patient proceeded to treatment with 6 cycles of plasma exchange followed by intravenous immunoglobulin for 5 days with some improvement. Interval imaging suggests that the lesions are stable in size. Clinically, there was improvement in speech and memory which has been stable in follow-up at 1 year.

Discussion

A literature review was undertaken accessing PubMed and MEDLINE journals from 2009 to 2015 (Supplementary Table 1). Papers were included if patients were in receipt of rituximab therapy before PML diagnosis or symptoms had a confirmed diagnosis of PML based on histologic examination or MRI and CSF polymerase chain reaction positive JCV and no evidence of HIV infection.

A total of 68 cases were included for the review with a median age at diagnosis of 64 years. Underlying diagnoses included B-cell lymphoproliferative disorders (58 patients), systemic lupus erythematosus (2 patients), rheumatoid arteritis (5 patients), chronic lymphocytic leukemia (1 patient), autoimmune pancytopenia (1 patient), and idiopathic thrombocytopenic purpura (1 patient). In 62% (52/68) of cases, the diagnosis was confirmed by MRI and JCV detection in the CSF. Median time from last rituximab dose to PML diagnosis was 1.5 months.

The pathophysiology of rituximab-associated PML while poorly understood relates to underlying viral reactivation after rituximab and B-cell depletion. Pre-B cells can be infected with latent JCV. Immune dysregulation causes the virus to be released into circulation to repopulate B-cells after differentiation [4].

Clinical signs and symptoms are varied. The most common symptoms in PML related to rituximab use are confusion, hemiparesis, incoordination, speech disturbance, and visual problems [2]. There is no distinct treatment for this condition. The monoclonal antibody agents can remain in the body for many months after treatment has stopped; therefore, plasma exchange is used to remove remaining drug from the system. Mirtazapine has been used due to its serotonin receptor blockade properties with variable results. Mefloquine has been found to have anti-JCV activity; however, its efficacy has yet to be determined [6].

An MRI of the brain with gadolinium in combination with CSF can be diagnostic and avoid the morbidity and mortality of a diagnostic brain biopsy. Typical radiologic features of PML include multiple areas of white matter demyelination do not conform to cerebrovascular territories, bilateral changes, lack of mass effect or contrast enhancement, decreased signal on T1-weighted images, and increased signal on T2-weighted and fluid sequences [3,7]. Common territories involved include the corpus callosum, brainstem, pyramidal tracts, cerebellum, and periventricular and subcortical areas [3,7]. Differentials for these findings include HIV encephalopathy, primary CNS lymphoma, stroke, brain tumor, CNS vasculitis, reversible posterior leukoencephalopathy, varicella-zoster virus encephalopathy, and multiple sclerosis (MS).

The primary goal of management revolves around restoring the host adaptive immune response, discontinuing and starting plasma exchange PML and glucocorticoids [8].

Intravenous immunoglobulin (IVIG) and plasmapheresis have been previously used in patients with MS treated with natalizumab who developed PML. Dahlhaus et al. [9] reviewed 15 patients with MS who developed PML on natalizumab. Five patients were treated with plasmapheresis, 1 had IVIG 5 times, and 9 patients had combination IVIG + plasmapheresis. At a median follow-up of 21.5 months, none of the 15 patients died. Twenty percent had mild disability, 60% had moderate disability, and 20% had severe disability. The consensus currently is that plasmapheresis with or without IVIG has the potential to provide a therapeutic benefit in drug-induced PML.

There are risk management guidelines for natalizumab with regard to testing for JCV, assessing risk, informed decision-making, and restricting prescription [2]. However, given the significant clinical benefit versus the rarity of rituximab-induced PML, there is at present no international consensus on risk management of rituximab-induced PML. Good practice should include education for physicians and patients and reporting of all cases. An abstract presented at American Society of Clinical Oncology of 26,597 non–HIV-infected veterans with chronic lymphocytic leukemia who developed PML demonstrated the rituximab increased the risk of recurrence 19.9 ($P < .05$) [10]. The study authors proposed serial measurement of JCV titers during long-term rituximab therapy non–HIV-infected patients. Features associated with survival include good performance status before diagnosis, younger age, localized brain lesions on MRI, and a shorter time from symptom onset to PML diagnosis [2].

In conclusion, rituximab-induced PML in the setting of a previous Non Hodgkins lymphoma is extremely rare. Physicians should have a high index of suspicion in patients presenting with even minor neurologic symptoms as early diagnosis and management can impact outcomes. MRI of the brain with gadolinium is useful in diagnosing PML associated with rare cases of immune dysregulation. Specific radiologic features in combination with CSF can be diagnostic and avoid the morbidity and mortality of a diagnostic brain biopsy. Plasmapheresis and IVIG have a therapeutic role. The clinical benefit of rituximab currently outweighs the risk of developing PML; however, it should be discussed as part of a collaborative decision-making process with patients. Currently, there is no evidence for screening of JCV in this cohort.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.radcr.2016.06.003.

REFERENCES

[1] Aström KE, Mancall EL, Richardson Jr EP. Progressive multifocal leukoencephalopathy: a hitherto unrecognized

complication of chronic lymphatic leukemia and Hodgkin's disease. Brain 1958;81:93–111.
[2] Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113(20):4834–40.
[3] Whiteman ML, Post MJ, Berger JR, Tate LG, Bell MD, Limonte LP. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. Radiology 1993;187(1):233.
[4] Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010;9(4):425–37.
[5] Skolasky RL, Dal Pan GJ, Olivi A, Lenz FA, Abrams RA, McArthur JC. HIV-associated primary CNS lymorbidity and utility of brain biopsy. AUJ Neurol Sci 1999;163(1):32.
[6] Zaheer F, Berger JR. Treatment-related progressive multifocal leukoencephalopathy:current understanding and future steps. Therepeutic advances in Drug Safety 2012;3(5):227–39.
[7] Skiest DJ. Focal neurological disease in patients with acquired immunodeficiency syndrome. Clin Infect Dis 2002;34(1):103.
[8] Sano Y, Nakano Y, Omoto M, Takao M, Ikeda E, Oga A, et al. Rituximab-associated progressive multifocal leukoencephalopathy derived from non-Hodgkin lymphoma: neuropathological findings and results of mefloquine treatment. Intern Med 2015;54(8):965–70.
[9] Dahlhaus S, Hoepner R, Chan A, Kleiter I, Adams O, Lukas C, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. J Neurol Neurosurg Psychiatr 2013;84(10):1068–74.
[10] Norris LB, Georgantopoulos P, Rao GA, Oliver Sartor A, Bennett CL. Rituximab is associated with increased risk of Progressive Multifocal Leukoencephalopathy developing among non-HIV-infected Veterans with Chronic Lymphocytic Leukemia. J Clin Oncol 2015;33 (suppl; abstr e18033).