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CASE REPORT

Progressive multifocal leukoencephalopathy following treatment with bendamustine and rituximab

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Abstract A 66-year-old female developed progressive multifocal leukoencephalopathy (PML) 17 months after treatment with bendamustine and rituximab chemoimmunotherapy. During her evaluation for PML, she was found to have a CD4 count of 176 cells/μL (reference range 492–1740). The patient demonstrated spontaneous recovery of symptoms that occurred in parallel with recovery of the CD4 counts. While PML is associated with rituximab therapy, the timing and patients' clinical course are atypical, raising the possibility of a previously unreported association with bendamustine therapy.

Keywords Progressive multifocal leukoencephalopathy · Mantle cell lymphoma · Rituximab · Bendamustine

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Introduction

Mantle cell lymphoma (MCL) comprises six to eight percent of all new cases of non-Hodgkin's lymphoma (NHL) [1]. The natural history of MCL can vary, with some patients following an indolent course, but in most cases the disease behaves aggressively [2]. MCL is generally chemotherapy sensitive, but the induced responses are often short lived [3]. Frontline therapy consists of intensive chemoimmunotherapy [4–6].

Bendamustine, an alkylating agent with a novel mechanism of action [7], was initially developed in the 1960s in Eastern Europe [8]. It had been used for decades in East Germany in the treatment of chronic lymphocytic leukemia (CLL), Hodgkin disease, NHL, multiple myeloma, and lung cancer. Its use as a chemotherapeutic agent for diverse lymphomas has recently increased in the United States and Europe, and in 2008 the US Food and Drug Administration approved its use as a first line agent for CLL and for relapsed indolent B cell NHL [9–11]. Compared to other chemotherapy regimens with comparable efficacy in treating patients with NHL, the toxicity profile of bendamustine appears to be favorable, with the most significant adverse effect being myelosuppression.

Rituximab is an anti-CD20 monoclonal antibody that targets human B cells. When studied in phase III trials for NHL and CLL, rituximab combined with chemotherapy was more effective at inducing tumor remission and

prolonging survival than chemotherapy alone both as first- and second-line treatment [12–14]. However, the widespread success of rituximab has been tempered by the increased risk of developing serious infections in patients treated with this drug [15]. The use of rituximab in the treatment of lymphoma has been linked to reactivation of hepatitis B [16], *Pneumocystis jirovecii* pneumonia [17], and progressive multifocal leukoencephalopathy (PML) [18].

We report a case of a woman who developed PML more than 1 year after receiving bendamustine and rituximab as a third line treatment for MCL, having already received rituximab as part of her front-line regimen. To our knowledge, this is the first reported case of PML in a patient treated with bendamustine.

Case report

A 66-year-old Caucasian female was diagnosed in March 2005 with stage IVa MCL, without central nervous system involvement and was treated with an investigational chemotherapy protocol, R-MACLO-IVAM-T (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosfamide, etoposide, and cytarabine, with thalidomide maintenance) [6], achieving a complete response (CR). However, in September 2007 she presented with a nodal relapse and received ibritumomab tiuxetan, which led to a second CR. The patient had a second relapse in December 2008 for which she received 6 cycles of bendamustine (100 mg/m^2 on days 1 and 2) in combination with rituximab (375 mg/m^2 on day 1), given every 28 days. After completing this regimen, she achieved a CR and remained disease-free for 17 months, until she gradually developed left-sided weakness, dysmetria, ataxia, and brief periods of unresponsiveness over a period of several days. She denied fever, weight loss or any other constitutional symptoms. Neurological exam revealed an alert female, oriented to person, place, and time with fluent and appropriate speech. The patient had a grossly detectable visual field defect in her left hemi-field and had slight facial asymmetry. There was 3 out of 5 power in the left arm and hand. Deep tendon reflexes were hyperreflexic bilaterally, more pronounced on the left side. Gait testing revealed ataxia with imbalance toward the left, and she exhibited left-sided pronation drift. There was no lymphadenopathy and no additional positive findings on the general physical exam. Routine complete blood counts and serum chemistries were unremarkable. The serum lactate dehydrogenase level was within normal limits.

A magnetic resonance imaging (MRI) scan of the brain revealed multiple, predominantly peripheral, enhancing lesions suspicious for relapsed lymphoma versus PML (Fig. 1a, b). A combined whole-body positron emission tomography/computed tomography (PET/CT) scan showed no areas of hypermetabolic activity to suggest relapsed lymphoma. Pre-operative MR spectroscopy of one of the largest enhancing lesions showed an elevated choline:creatine ratio and decreased *N*-acetylaspartate (NAA). A stereotactic brain biopsy of this lesion revealed enlarged oligodendrocytes with intranuclear hazy inclusions, suggesting a viral infection (Fig. 2a, b). The enlarged oligodendrocytes were surrounded by reactive astrocytes and a reactive perivascular lymphocytic infiltrate composed of T cells. There was no morphologic or immunophenotypic evidence of lymphoma. An immunohistochemical stain of the biopsy material was positive for the *John Cunningham virus* (JCV) and negative for herpes simplex virus type 1, consistent with the diagnosis of PML. Examination of T cell subsets revealed a CD4 count of 176 cells/μL (reference range 492–1740), an absolute CD3 count of 522 cells/μL (reference range 840–3060), and an absolute CD8 count of 368 cells/μL (reference range 180–1170).

At follow-up 2 weeks after her initial evaluation, strength in her left arm and hand improved to 4 out of 5. However, she remained with facial asymmetry, bilateral hyperreflexia, ataxia, and imbalance toward the left. When seen 3 weeks later, she still had 4 out of 5 strength in the left upper extremity, but her ataxia had improved, as noted by improvement in her tandem gait. A follow-up MRI 3 months after her initial scan showed initial progression as evidenced by interval increase in size of areas with high FLAIR signal accompanied by decreased T1 signal (not shown), suggesting progressive regional white matter destruction (Fig. 1c, d). Physical exam at that time was unchanged. However, evaluation following another 3 months revealed complete resolution of her weakness and a stable gait, with slight ataxia. Detailed motor exam showed mild discoordination in movement between right and left hand on performance of adiadochokinesis test. Serial examinations since this point have demonstrated residual symmetric hyperreflexia, mild ataxia, and mild dysdiadokokinesis. The patient received no further treatment for her MCL and her T cell counts have slowly increased. Evaluation of her T cell subsets 20 months after her initial presentation showed a CD4 count of 417 cells/μL, an absolute CD3 count of 1180 cells/μL, and an absolute CD8 count of 838 cells/μL. MRI showed interval decrease in size of areas with FLAIR signal abnormalities with further decrease in T1 signal (not shown) and progressive atrophy of the involved parenchyma accompanied by ex vacuo ventricular dilatation (Fig. 1e ,f). After over a year and a half of follow-up, the patient remains without evidence of relapsed MCL and her neurologic symptoms have stabilized without therapy.

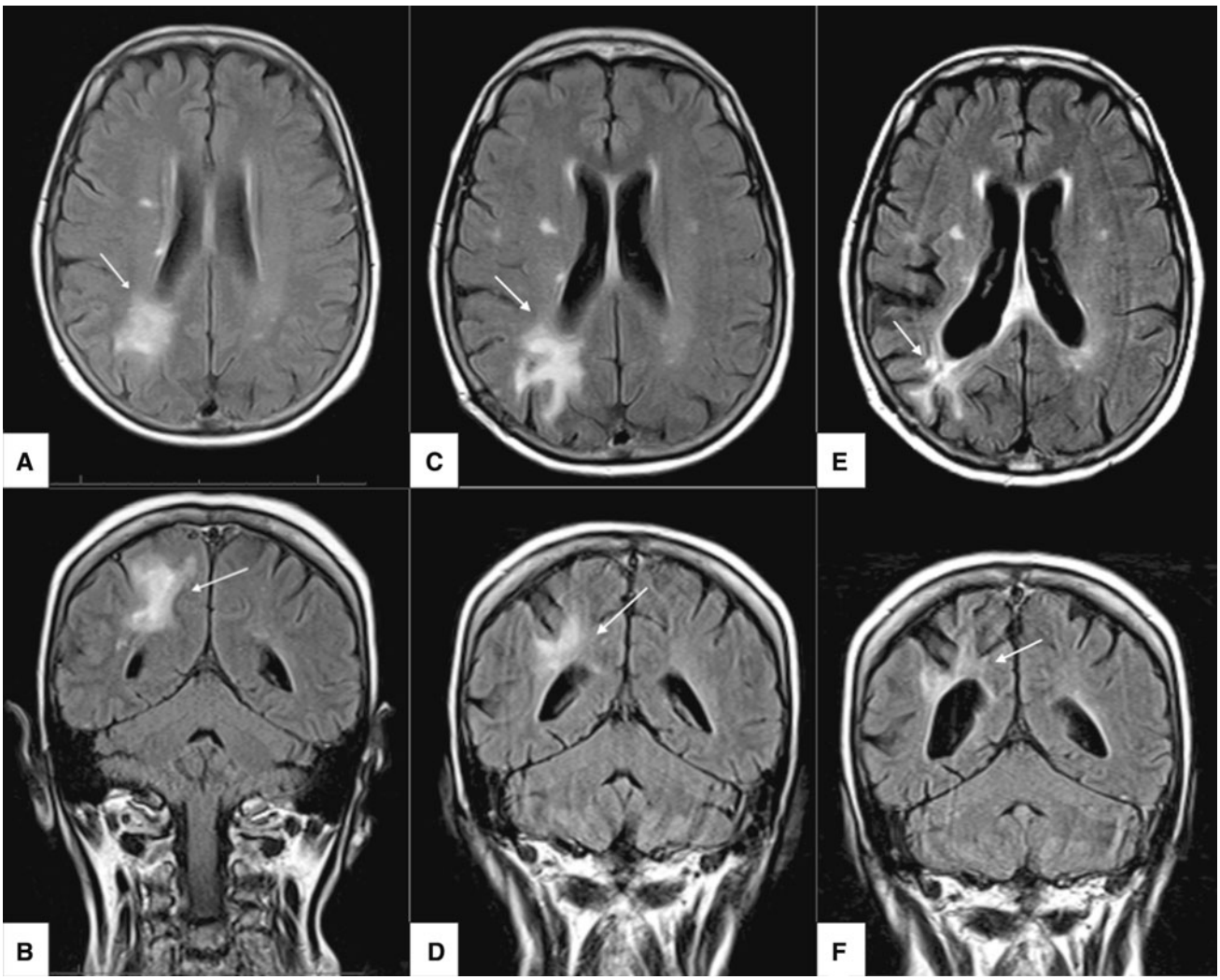

Fig. 1 **a**, **b** Magnetic resonance imaging scan of the brain at the time of presentation with progressive multifocal leukoencephalopathy. The axial (panel **a**) and coronal FLAIR images (panel **b**) demonstrated multiple hyperintense lesions with the largest one visualized in the right posterior parietal lobe (*arrow*). The lesions did not demonstrate restriction on diffusion weighted imaging and were hypointense on T1 weighted images (not shown). A small amount of peripheral enhancement was demonstrated after administration of gadolinium. **c**, **d** Follow-up MRI 3 months later shows initial progression as evidenced by interval increase in size of areas with high FLAIR signal (*arrow*) accompanied by decreased T1 signal (not shown), suggesting progressive regional white matter destruction. **e**, **f** MRI at 20 months after initial presentation shows interval decrease in size of areas with FLAIR signal abnormalities (*arrow*) with further decrease in T1 signal (not shown) and progressive atrophy of the involved parenchyma accompanied by ex vacuo ventricular dilatation

Discussion

The polyomaviruses that infect humans include JCV, SV40 and BK virus [19]. PML and renal disease, associated with JCV and BK virus respectively, can occur in immunocompromised patients. Although most commonly associated with HIV/AIDS, cases of PML have also been associated with various drugs, including monoclonal antibodies, antiretrovirals, and immunosuppressive agents [20]. A recent study reviewed two international spontaneous adverse drug reaction report databases, as well as MEDLINE to locate all reported cases of drug-induced PML [20]. Overall, 472 cases of drug-induced PML were identified, 82 of which involved rituximab.

The median time from the last dose of rituximab to diagnosis of PML is reported to be 5.5 months [18]. PML in this setting is associated with a fatal outcome in 90 % of cases, with a median time from PML diagnosis to death being 2 months. However, there was difference in mortality depending on the timing of PML diagnosis relative to the last dose of rituximab. While all the patients diagnosed with PML within 3 months of receiving their last dose of rituximab died, 16 % of those diagnosed more than 3 months after receiving their last dose of rituximab

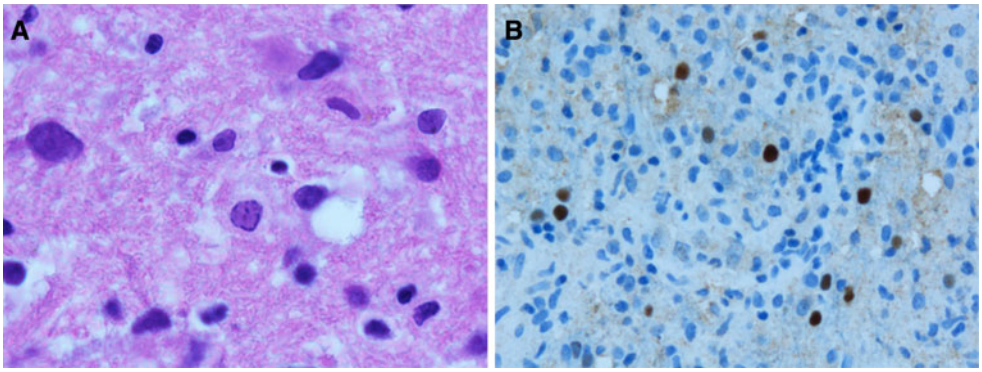

Fig. 2 **a** Brain biopsy, hematoxylin and eosin stain, ×100 magnification; centrally located is an oligodendrocyte with an ill-defined hazy intranuclear inclusion suggestive of viral infection. Surrounding cells consist predominantly of reactive astrocytes. **b** Brain biopsy, stained for *John Cunningham virus* (JCV), ×20 magnification; positive nuclear staining in scattered oligodendrocytes

remained alive. The CD4 count at the time of diagnosis with PML was also associated with survival, with 100 % mortality among patients with CD4 counts less than 200 cells/μL versus 62.5 % mortality in those with CD4 counts greater than 200 cells/μL.

Much has been reported on the incidence of serious infections associated with rituximab, but data on bendamustine are scarce. To date, there have been two cases reported of *Pneumocystis jirovecii* pneumonia [21, 22] and one report each of severe cytomegalovirus reactivation [23] and hepatitis B reactivation [24] associated with bendamustine, but no reports of PML. While it is possible to attribute our case of PML to rituximab exposure, several factors do not fit with the typical presentation of rituximab-associated PML. Our patient developed PML well after completing rituximab (17 months compared to the reported median of 5.5 months) and survived, despite presenting with a low CD4 count. She had been exposed to rituximab 4 years prior to her diagnosis of PML and had no neurologic sequelae at that time.

While several studies have observed grade III/IV leukopenia in patients who received bendamustine, the leukocyte nadir typically occurs 3 weeks after treatment, usually with spontaneous recovery [25]. However, fludarabine, a purine analog with a mechanism of action similar to that of bendamustine, has been observed to profoundly suppress leukocytes, specifically T cells, for up to 3 years [26]. As a result of these prolonged immunosuppressive effects, PML has been reported in several patients who received fludarabine as part of the treatment for leukemia or lymphoma. Apart from the present case demonstrating CD4-positive T cell depletion with bendamustine, there is at least one other report of CD4 cell depletion with bendamustine, associated with the development of *Pneumocystis jirovecii* pneumonia [22]. We hypothesize that this CD4 depletion may be responsible for the association with PML and *Pneumocystis jirovecii* pneumonia.

In summary, herein we present a case of documented PML following treatment with bendamustine and rituximab. While bendamustine therapy is usually associated with relatively minor side effects, physicians should be aware of a possible association with PML. As the usage of bendamustine in combination with rituximab increases, further reports will clarify the extent of this potential serious side effect.

Conflict of interest The authors declare that they have no conflicts of interest.

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