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CASE REPORT

Progressive multifocal leukoencephalopathy during ixazomib-based chemotherapy

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system that most often affects immunocompromised individuals. It is caused by the reactivation of the John Cunningham virus (JCV), which is found in latent form in the majority of adults. We describe a 59-year-old man with multiple myeloma who developed severe neurological deficits during treatment with ixazomib-based chemotherapy. A diagnosis of PML was established with gadolinium-enhanced magnetic resonance imaging (MRI) and by detection of JCV in the cerebrospinal fluid. Despite cessation of chemotherapy and treatment with mirtazapine, he had an inexorable neurological decline and died two months after presenting to hospital. Multiple myeloma and its treatments can predispose patients to opportunistic infections including PML. Although there have been case reports of PML in patients with multiple myeloma treated with bortezomib (a different proteosome inhibitor), this is, to our knowledge, the first documented case of PML in a patient treated with a regimen that includes ixazomib.

Key Words Progressive multifocal leukoencephalopathy, ixazomib, multiple myeloma

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INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare and serious demyelinating disease of the central nervous system, occurring most often in immunocompromised patients. Historically, PML occurred predominantly in patients with human immunodeficiency virus (HIV)[1]. More recently, the growing development and use of biologic immunosuppressant medications has led to the emergence of PML in new populations, including natalizumab-associated PML in patients with multiple sclerosis (MS)[2]. Patients with cancer- and drug-related immunosuppression have also been found to be susceptible. Progressive multifocal leukoencephalopathy is caused by the reactivation of a latent polyoma virus, John Cunningham virus (JCV)[3], in the brain. Signs and symptoms may include motor weakness, visual field defects, gait abnormalities, and language problems[4], but the specific neurological deficits depend on which brain regions are affected. Cases of PML have been documented in patients with hematological malignancies, including multiple myeloma and acute myelogenous leukemia, treated with chemotherapeutic agents[5–9]. Here we describe a case of PML in a patient with multiple myeloma treated with ixazomib, a novel proteosome inhibitor[10].

CASE DESCRIPTION

A 59-year-old man with a history of multiple myeloma presented to the emergency department with severe neurological deficits. At the age of 50 he had presented to his family doctor with anemia and was soon diagnosed with multiple myeloma complicated by systemic light chain amyloidosis involving the heart and kidneys. His medical history included atrial fibrillation and obstructive sleep apnea. He was initially treated with bortezomib and dexamethasone as pre-transplant treatment, then with autologous stem cell transplant to good effect. This was followed by thalidomide maintenance therapy for two years. After four years of full remission, he developed light chain deposition disease and was started on lenalidomide and dexamethasone.

After several years of remission, he again showed signs of accelerating multiple myeloma progression and was started on low-dose cyclophosphamide. After one month of this treatment, the patient's wife noted he seemed to be intermittently forgetful and confused. The decision was made to stop the cyclophosphamide and undertake a trial of ixazomib, as he had had success with a proteosome inhibitor in the past. He was prescribed weekly oral ixazomib 2.3 mg and dexamethasone 20 mg.

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After receiving three rounds of ixazomib and dexamethasone therapy, he presented to hospital with new weakness, confusion, and trouble walking. His other medications at the time were daily oral acyclovir 400 mg, allopurinol 200 mg, bisoprolol 5 mg, furosemide 40 mg, and warfarin 3 mg.

On examination, he was found to be disoriented, and had anterograde amnesia, a left homonymous hemianopsia, severe left-sided neglect, and subtle left-sided ataxia. Ixazomib and dexamethasone were stopped for work-up of these neurological symptoms.

Initial investigations revealed hemoglobin 84 g/L (normal 135 to 170 g/L), white blood cells 6.5 × 10^9 cells/L (normal 4 to 10 × 10^9 cells/L), and platelets 26 × 10^9 cells/L (normal 150 to 400 × 10^9 cells/L). Free Ig kappa chains were 249.7 mg/L (normal 3.3 to 19.4 mg/L) and free Ig lambda chains were 14.9 mg/L (normal 5.7 to 26.3 mg/L), with a ratio of 16.76 (normal 0.26 to 1.65). Testing for HIV was negative. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain revealed a T1-hypointense, T2-hyperintense, non-enhancing, diffusion-restricting lesion of the right parietal white matter, with extension into the right occipital lobe and some extension across the corpus callosum into the left hemisphere (Figures 1 and 2). Lumbar puncture was performed, and routine analysis of the cerebrospinal fluid, including cytology, was unremarkable. Specialized analysis of the cerebrospinal fluid for presence of JCV DNA by polymerase chain reaction (PCR) was positive with 9.45 × 10^5 copies/mL. This result, in combination with the neurological symptoms and imaging findings, confirmed the diagnosis of PML.

He was started on oral daily mirtazapine 15 mg; however, his neurological condition continued to decline. He developed progressive dysphagia and impaired level of consciousness and died of respiratory failure two months after his neurologic presentation.

DISCUSSION

Progressive multifocal leukoencephalopathy is a rare and devastating infection of the central nervous system. It is caused by reactivation of JCV, which is present in latent form in most adults[3]. In one study of over 7,000 patients with MS, the incidence of anti-JCV antibodies was 57.1%[11]. The virus enters the body via the upper respiratory tract and infects cells in the tonsils. This is followed by persistent infection of CD34+ progenitor cells in the bone marrow and other hematopoietic niches[12]. In the majority of immunocompetent individuals, JCV does not invade the brain or cause any neurologic or systemic disease[13]. It is yet unclear how

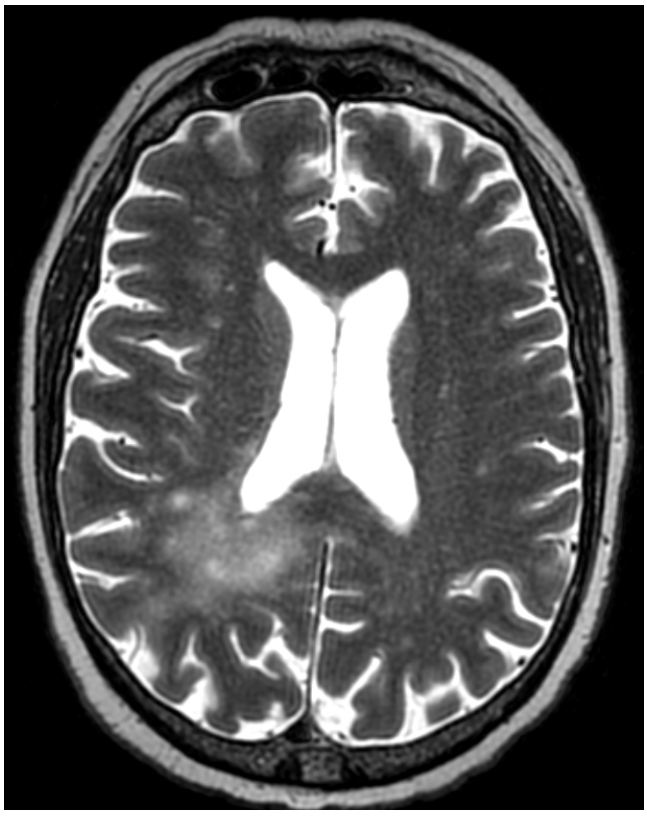

FIGURE 1 T2-weighted magnetic resonance image of the brain shows an ill-marginated focus of right parietal white matter hyperintensity with some occipital extension. There was no gadolinium enhancement of this lesion (not shown).

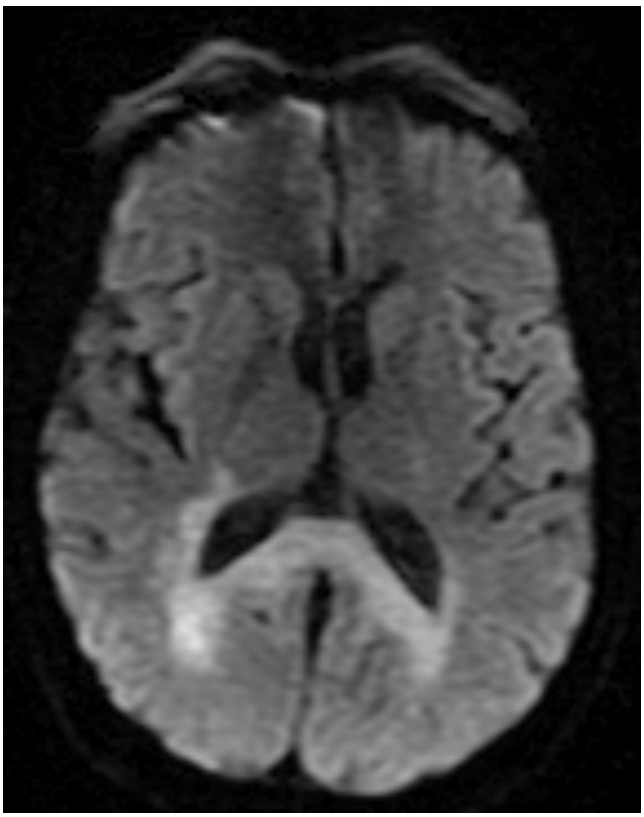

FIGURE 2 Diffusion-weighted magnetic resonance image of the brain shows diffusion restriction within the abnormal area seen on the T2-weighted image, which was confirmed with an apparent diffusion coefficient map (not shown). The signal abnormality crosses the posterior corpus callosum into the left hemisphere, though the primary focus is in the right hemisphere.

JCV accesses the central nervous system in immunocompromised individuals[12]. It has been shown, however, that JCV in PML is a different quasispecies from that found in normal exposed people[14].

Ixazomib, a proteosome inhibitor, was approved for the treatment of multiple myeloma in Canada in 2016 and is the first of its kind to be offered in an oral formulation[10,15]. No previous cases of PML in the setting of ixazomib have been reported, but cases of PML have been documented after treatment with a related proteosome inhibitor, bortezomib[8,9]. In 2008, Kesari *et al*. reported on a woman with acute myelogenous leukemia (AML) who presented with dysarthria and left facial weakness two years following a course of treatment with bortezomib, idarubicin, and cytarabine[8]. She was diagnosed with PML and started on mirtazapine. She made a dramatic recovery, remaining stable for another 28 months until she died from progression of the AML. In 2016, Yokokawa *et al*. reported a 62-year-old man with a history of multiple myeloma who presented with gait disturbance and speech difficulty one year after receiving a course of bortezomib and dexamethasone therapy[9]. He was diagnosed with PML and treated with mirtazapine and mefloquine. He remained stable over one year after receiving the diagnosis.

Although there are differences in the underlying immunocompromise in natalizumab-associated PML in MS patients and the oncology patients discussed above, a comparison with the natalizumab literature may be instructive. For example, in MS, prior immunosuppression increases the risk of PML in patients treated with natalizumab[16]. In the cases of cancer-related PML discussed above, the patients had previous exposure to a number of immunosuppressive agents, possibly putting them at higher risk for PML. By contrast, with natalizumab, the risk of developing PML is related to treatment duration[16]; this does not seem to be the case with the oncology cases discussed here.

The prognosis for patients with PML is poor. One study estimated the one-year survival for HIV-negative patients to be 58%[17]. Another study found patients with a hematological malignancy who developed PML had a 12% survival at 10 months[18]. In the MS population, a number of poor prognostic risk factors have been identified[16]. In our patient, these risk factors include older age, high JCV concentration based on *cerebrospinal fluid* p*olymerase chain reaction* (CSF PCR), widespread disease on MRI, and use of immunosuppressive medications. The approach to treatment for PML is immune reconstitution where possible[13]. In medication-related cases, immunosuppressant drugs should be stopped; however, with this comes a risk of immune reconstitution inflammatory syndrome[13]. Low-quality evidence, comprised mainly of case reports and cohort studies, suggests that mirtazapine and mefloquine may positively impact the clinical course in PML not associated with HIV[19,20]; however, a recent systematic review failed to find a benefit of mirtazapine except for natalizumab-associated PML[21]. In this type of PML, prompt plasmapharesis is recommended as it accelerates drug clearance[2,22]. As ixazomib is a highly protein-bound drug, plasmapharesis might also accelerate its clearance and possibly improve outcomes; however, this remains unproven[23,24]. Regardless of treatment approach, a heightened vigilance for—and early detection of—PML is key to achieving better outcomes.

This is, to our knowledge, the first documented case of PML in a patient receiving ixazomib-based chemotherapy. As with most cases of PML that arise with multidrug therapy, it is impossible to know to what degree each drug contributed to his development of PML. Given the time course of events, we speculate the patient had begun to develop early and low-grade PML while on cyclophosphamide, and the addition of ixazomib caused a dramatic acceleration of the disease course.

SUMMARY

This case report illustrates an important intersection between hematology, neurology, and infectious disease. Multiple myeloma and its treatments can lead to opportunistic infections including PML. To our knowledge, this is the first case report of PML in a patient treated with a regimen including ixazomib. Although there are also cases of the occurrence of PML after treatment with bortezomib, a different proteosome inhibitor, currently there is insufficient evidence to support an association between the disease and the entire class of medications. Due to the potential for devastating outcomes, clinicians must maintain a high index of suspicion for PML in patients being treated for multiple myeloma who present with neurological symptoms.

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CONFLICTS OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and declare that we have none.

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