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Progressive Multifocal Leukoencephalopathy Treated with Nivolumab

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Abstract

Therapy for progressive multifocal leukoencephalopathy (PML) remains challenging since there are no anti-viral therapies available for JC virus. Immune reconstitution has improved the prognosis in many settings where PML occurs, but it often is not possible in PML patients with hematologic malignancies. We describe the first biopsy proven PML case where the PD-1 inhibitor nivolumab appears to have stimulated immune activation resulting in effective control of PML in a patient with hematologic malignancy. This report supports further investigation of the utility of checkpoint inhibitors for treating PML where other immune reconstitution options are not available.

Keywords

Progressive multifocal leukoencephalopathy; PML; nivolumab; PD-1 inhibitor; JC virus

Introduction

Progressive multifocal leukoencephalopathy (PML) is a JC virus caused demyelinating brain disorder that occurs almost exclusively in chronically immune suppressed patients. Where immune suppression is rapidly reversible, such as with antiretroviral initiation in HIV patients, prognosis for PML has greatly improved.(Melliez et al., 2018),(Clifford, 2014) However, patients with hematologic malignancy and PML continue to have the worst prognosis among PML patients.(Mateen et al., 2011),(Neil & DeAngelis, 2017) In the absence of effective JC virus therapy, alternative immune reconstitution approaches that apply in the setting of malignancy would be particularly valuable. We report a case

suggesting programmed death –1 inhibitor (PD1) inhibitor therapy should be considered in this setting.

Case

A 65-year-old woman with refractory stage IV nodular sclerosing Hodgkin lymphoma (HL) presented with progressive left-sided weakness. She had a distant history of discordant diffuse large B-cell lymphoma and HL. The HL recurred 11 years after initial treatment with R-CHOP, and subsequent therapies included ICE (ifosfamide, carboplatin, etoposide) followed by a BEAM (busulfan, etoposide, cytarabine, melphalan) autologous stem cell transplant, brentuximab vedotin, GVD (gemcitabine, vinorelbine, doxil), everolimus, and protein-bound paclitaxel (Abraxane) on a clinical trial. Three weeks after the last dose of paclitaxel, she began treatment with nivolumab dosed 3 mg/kg every two weeks. At the time of treatment initiation, the patient had an ataxic gait and an ECOG performance status of 2 (ambulatory and capable of all selfcare). Within 24 hours of the first nivolumab dose, the patient was admitted for worsening weakness and incontinence. Magnetic resonance imaging (MRI) of the brain revealed a “mild cortical diffusion reaction and contrast enhancement involving the medial superior bilateral frontal cortex... with additional punctate foci in the anterior right frontal centrum semiovale,” thought to “represent sequela of a subacute infarct.” (Figure 1) There was no evidence of spinal cord compression. Cerebrospinal fluid (CSF) was negative for JC virus and malignant cells. Gram stain, culture, Lyme disease antibody, and Ehrlichia PCR were negative. The symptoms were considered unrelated to therapy, and she received the second dose of nivolumab on schedule 2 weeks following the first dose.

One week later, the patient developed worsening hemiparesis. MRI showed “interval increase in size and number of the bilateral focal and confluent cerebral FLAIR hyperintense lesions and patchy/tiny enhancing lesions,” concerning for CNS involvement by lymphoma. (Figure 1) Blood culture, Histoplasma antigen, and Toxoplasma PCR were negative. A brain biopsy was performed 4 weeks after initiation of nivolumab. Sections showed an inflammatory process centered predominantly in the white matter. The inflammatory infiltrate included numerous foamy macrophages that were most prominent in areas of vacuolation and white matter destruction. The adjacent gray matter showed neuronal hypoeosinophilia indicative of necrosis. A lymphocytic infiltrate of CD3+ T-cells (approximately equal numbers of CD4+ and CD8+ cells) was present in the parenchyma and perivascular space. The pronounced viral cytopathic change in affected cells and a positive immunohistochemical stain for the SV40 antibody were diagnostic of progressive multifocal leukoencephalopathy (PML). In situ hybridization for the JC virus DNA confirmed the diagnosis. The overall picture was that of PML with immune reconstitution inflammatory syndrome (IRIS). (Figure 2)

Because of presence of PML with IRIS, the patient was started on a 5-day course of IV methylprednisolone (5 g total, followed by an oral taper). She had improvement in left arm and left leg muscle strength and tone, and MRI showed interval decrease in the number of foci throughout cerebral hemispheres with persistent scattered foci predominantly involving frontal lobes. She went on to receive four more doses of nivolumab at 2 week intervals with

only partial response of her refractory lymphoma. Additional nivolumab therapy was reinitiated 4 months after the last dose in the first cycle and continued through 13 cycles at 2 week intervals.

Follow-up MRI (Figure 3) and clinical function improved although here severe arthritis was problematic, and she developed parkinsonism that was only partially responsive to dopamine agonist therapy. Treatment for lymphoma with bendamustine led to transient complete remission of the tumor after 13 years of treatment. Two years after diagnosis of PML the lymphoma recurred, but by MRI no activation of PML occurred. (Figure 3) She died from progressive Hodgkin's lymphoma almost three years following initial diagnosis of PML.

Discussion

Given the generally dismal outlook for PML in the setting of advanced malignancy and transplant cases, the complete control of PML associated with use of the PD-1 inhibitor nivolumab is unexpected and suggests that the immune reconstitution associated with this drug may have controlled this infection. Mateen reported that median survival following symptom onset was 6.4 months in solid organ and 19.5 months in bone marrow recipients, with case fatality rate of 84%. (Mateen et al., 2011) A recent review of PML in the setting of hematologic malignancy reports a median survival from PML diagnosis of 2.0 months (range, 0.4-6.7 months). (Neil & DeAngelis, 2017) The three year survival achieved in this patient is thus exceptional and consistent with the hypothesis that nivolumab may have driven effective immune reconstitution in this case. However, it is critical to recognize the limitations of single case reports in such complex clinical settings. The serendipitous timing of initiating nivolumab shortly after symptoms of her undiagnosed PML appeared, likely resulted in immune reconstitution and initial acceleration of the clinical manifestations of PML associated disability when the IRIS occurred. The brain biopsy demonstration of IRIS, and the prompt clinical improvement occurring with corticosteroid therapy with recovery of the ability to walk in the month following the brain biopsy is consistent with response of IRIS to corticosteroid therapy. Effective immune reconstitution controlled PML throughout the rest of this patient's life even with subsequent chemotherapy required for the lymphoma.

We postulate that nivolumab can actually stimulate potentially life saving immune responses to JC virus. Our patient is the first biopsy proven PML patient demonstrating immune reconstitution and long survival after nivolumab used with PML. Others have reported preliminary exploration of this mechanism consistent with our observations. (Cortese et al., 2016) A case report has recently been published of a patient with Hodgkin's lymphoma treated with nivolumab who subsequently developed PML. (Martinot et al., 2018) Martinot et al postulate that PML may have been an adverse effect of nivolumab, but we suspect this case occurred despite the nivolumab therapy in a high risk patient. Indeed, this case survived at least 5 months, suggesting a PML course better than anticipated for lymphoma associated PML.

Currently no antiviral therapies have demonstrated efficacy for JC virus, but immune reconstitution does improve the course of PML. PD-1 inhibitors are an alternative approach to immune reconstitution. Others have proposed that PD-1 inhibitors may be an adjunctive

therapy for chronic infections including TB, HIV, and hepatitis.(Rao, Valentini, Dodoo, Zumla, & Maeurer, 2017) Nivolumab functions as a checkpoint inhibitor by blocking the inhibition of T cell activation. Activated T cells upregulate the immune checkpoint molecules such as PD-1 and release cytokines which increases PD-L1 expression on tumor cells.(Dyck & Mills, 2017) In PML, PD-1 expression is elevated in total CD4 and CD8 lymphocytes, while JCV-specific CD8+ cytotoxic T-lymphocytes express PD-1 more frequently. (Tan et al., 2012) This finding is consistent with the pathologic evidence of an upregulated CD8 and CD4 immune response in the PML lesions of our patient, and an effective control of PML most likely through the action of the JCV specific CD8 cells.

Although PML is usually fatal in this situation, many patients survive in settings where immune reconstitution is possible. Severe disability from PML can often be avoided with aggressive treatment of the disease by early immune reconstitution. However, randomized clinical trials have not demonstrated a therapy which has improved outcomes. While PD-1 inhibitors have many potential toxic effects, their use in cancer therapy has been transformative, and PML is a sufficiently serious complication that their use can reasonably be entertained if convincing evidence of efficacy is obtained.(Dyck & Mills, 2017; Kim & Evoli, 2017; Postow, Sidlow, & Hellmann, 2018) Future studies should evaluate the efficacy of checkpoint inhibitors such as nivolumab in the treatment of PML where safer means of immune reconstitution is not available.

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At presentation**3 weeks later**

Figure 1. Brain MRI findings prior to biopsy.

Routine brain MRI including pre- and post-contrast T1, T2, FLAIR with fat suppression, and DWI sequences were obtained at presentation and 3 weeks later. At presentation, there were several enhancing lesions associated with FLAIR hyperintensity and diffusion restriction, including along the medial aspect of the right superior frontal gyrus (yellow arrows) and in the right superior frontal white matter (red square). Subsequent brain MRI 3 weeks later showed an expansion of all of the lesions. The FLAIR hyperintensity now showed increased signal centrally, which correspond in some cases to a central clearing of diffusion restriction but ongoing diffusion restriction along the periphery.

Figure 2. Right frontal lobe brain biopsy

Right frontal brain biopsy 4 weeks after nivolumab therapy showing progressive multifocal leukoencephalopathy with inflammatory changes. A Central pallor in region of demyelination with patches of inflammatory cells and reactive astrocytes. (hematoxylin and eosin stain, magnification 200x) B: Myelin stain demonstrating the margin of a demyelinated lesion (arrows) with an adjacent area of relatively preserved blue-stained myelin (LFB-PAS, magnification 200x) C: Numerous lymphocytes invading the biopsy tissue are identified by CD3 immunoreactive staining clustered in patches in the same distribution as demyelinated lesions consistent with immune reconstitution inflammatory reaction (IRIS) in PML lesion (CD3 IHC, magnification 100x) D: In situ hybridization for the JC virus demonstrates a population of large labeled cells consistent with PML (arrow) (Magnification 400X) E: High magnification images demonstrate CD8 cytotoxic inflammatory cells in the demyelinated foci (CD8 IHC). (Magnification, 400X) F: However, the reaction includes also many CD4 helper inflammatory cells in the same tissue fragment (CD4 IHC) (Magnification 200X)

1 year later

Figure 3. Brain MRI findings 1 year after diagnosis.

Routine brain MRI was performed approximately 1 year after initial presentation using a similar imaging protocol. The previously noted lesions had all evolved such that there was no residual enhancement nor diffusion restriction (yellow arrow and red square). In its place were areas of FLAIR hyperintensity and T1 hypointensity, likely reflecting regions of gliosis. Biopsy changes were also noted in the right frontal white matter (red square).