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Potential PD-1 inhibitor immune dysregulation as a risk factor for *Listeria monocytogenes* bacteremia and meningitis

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Abstract: As immune checkpoint inhibitor (ICI) therapy becomes increasingly popular for the treatment of cancer, there is a growing body of literature on opportunistic infections associated with ICI therapy. Pembrolizumab binds specifically to the PD-1 receptor on T cells, preventing PD-1's interaction with PD-L1 and PD-L2. This blockade interrupts the inhibitory signal and restores a T cell's ability to recognize and attack tumor cells. We present a case of invasive *Listeria* infection associated with ICI therapy. The case also suggests treating patients undergoing active ICI therapy as potential immunocompromised hosts due to possible immune dysregulation related to ICI therapy.

Keywords: immunotherapy; immune dysregulation; opportunistic infection; *Listeria monocytogenes*; meningitis

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Introduction

The proportion of patients with cancer eligible for immune checkpoint inhibitor (ICI) treatment grew from 2% to 44% from 2011 to 2018 in the United States [1]. Pembrolizumab binds specifically to the PD-1 receptor on T cells, preventing PD-1's interaction with PD-L1 and PD-L2. This blockade interrupts the PD-1-dependent inhibitory signal and restores a T cell's ability to recognize and attack tumor cells. Based on this mechanism of action, it was originally thought that ICIs alone would not increase risk of opportunistic infections. ICI therapy is widely known to cause autoinflammatory

side effects, which then require treatment with immunosuppressive agents, and many reports have described opportunistic infections in such scenarios [2]. However, as ICI use expands, a growing body of the literature has described opportunistic infections in individuals receiving ICI therapy and in the absence of additional immunosuppression treatment for autoinflammatory side effects.

Opportunistic infections associated with ICI therapy alone include bacterial infections (e.g., *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and atypical mycobacteria), fungal infections (e.g., *Aspergillus* infection), and the reactivation of latent viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV), and hepatitis B [2,3]. We are unaware of any previously reported cases of invasive *Listeria* infection associated with ICI therapy.

Case Presentation

A 69-year-old man on pembrolizumab for the treatment of cholangiocarcinoma and hepatocellular carcinoma presented with altered mental status, headache, and fever lasting 2 days. His other medical history included chronic portal vein thrombosis, type 2 diabetes mellitus, and benign prostatic hyperplasia. On arrival, his vital signs were notable, with a temperature of 38.9 °C. Lab results were notable, revealing a hemoglobin concentration of 5.7 g/dL, a white blood count of 7.1×10^3 cells/uL, sodium 120 mmol/L (from a prior recent baseline of 126 mmol/L), and a hemoglobin A1c value of 5.5%. A chest x-ray demonstrated left basilar opacity; the computed tomography scan of the head and cervical spine were grossly unremarkable. Blood cultures were obtained, and the patient was given one dose of piperacillin–tazobactam for possible pneumonia and admitted for further evaluation. Two sets of blood cultures obtained in the emergency department grew *Listeria monocytogenes*. Given the patient's initial presentation symptom of altered mental status, there was concern that the patient had *Listeria* meningitis. Further questioning did not reveal any risk factors for *Listeria* acquisition, such as consumption of deli meats or unpasteurized cheese. The patient's HIV-1 and HIV-2 antigen/antibody test results were negative, and quantitative immunoglobulins were within normal limits. A course of ampicillin and gentamicin was initiated. Magnetic resonance imaging (MRI) of the brain with contrast was obtained and showed restricted diffusion along the left frontoparietal sulci, the interhemispheric falx, and the bilateral occipital horns, provoking concern regarding debris/pus formation secondary to possible meningitis and ventriculitis without signs of an abscess (Figure 1). Given the MRI findings and the neurotropism of *Listeria*, the overall clinical picture was consistent with *Listeria* meningitis, and lumbar puncture was deferred as it would have been unlikely to dissuade the clinical team from treating the patient for central nervous system listeriosis. The patient's mental status and headache improved with antibiotic treatment.

The patient's hospital course was complicated by vancomycin–resistant *Enterococcus* (VRE) bacteremia secondary to acute cholangitis, so he was switched to linezolid for the treatment of both VRE and *Listeria* [4]. Repeat MRI of the brain prior to discharge demonstrated decreased debris in the subarachnoid spaces and resolution of debris in the lateral ventricles and no new areas of enhancement.

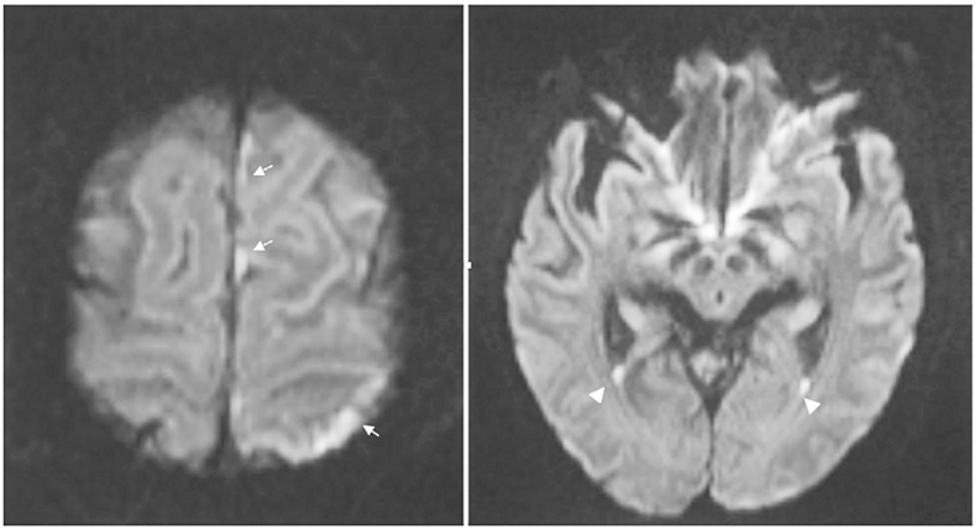

Figure 1: MRI of the brain showing restricted diffusion provoking concern regarding debris/pus formation along the left frontoparietal sulci (arrow), interhemispheric falx (dashed arrows), and bilateral occipital horns of the lateral ventricles (arrow heads).

Discussion

Listeria monocytogenes generally causes a self-limiting gastrointestinal infection in immunocompetent patients, though it can cause invasive disease in older, neonatal, and immunocompromised patients. The incubation period for listeriosis varies according to clinical presentation, but it can take upwards of 6 weeks before the diagnosis is made [5]. In this case concerning a 69-year-old man who was found to have *Listeria* meningitis, it was important to consider that the patient was receiving pembrolizumab, a PD-1 inhibitor. The patient was not on any additional immunosuppressive medications such as corticosteroids, suggesting that PD-L1 inhibition may have been an important risk factor causing invasive listeriosis [6]. PD-L1 is essential in the role of T cell priming and immunity; in vivo models show that PD-L1 blockade prior to primary *Listeria* infection resulted in delayed bacterial clearance and T cell expansion [7,8]. Notably, in mouse models, PD-L1 inhibition showed marked reductions in T cell expansion and proliferation after infection with virulent *Listeria monocytogenes* resulting in delayed bacterial clearance [8]. There are no guidelines for the duration of treatment of invasive listeriosis for patients on ICIs, though given the development of other opportunistic infections associated with ICIs, we felt it was prudent to treat him as an immunocompromised patient, with prolonged ampicillin and then ultimately linezolid for a total of 6 weeks of anti-*Listeria* therapy. Typically, *Listeria* meningitis in an immunocompetent host is treated for 3 weeks.

As the use of ICIs becomes more common in the treatment of various cancers, there is a growing body of literature that suggests a new pattern of infections, which may be associated with immune checkpoint deficiency. These phenomena are described by Morelli et al. as constituting immunotherapy infections due to dysregulated immunity (ITI-DI), in which host immune inhibition by ICIs counterintuitively favors the pathogen [2]. Emerging examples of ITI-DI-associated infections with PD-1/PD-L1 blockade include *Mycobacterium tuberculosis* reactivation, hepatitis B reactivation, human herpesviridae infection (e.g., VZV, EBV, and CMV), pulmonary aspergillosis, and *Clostridium difficile* infection (in the absence of antibiotics or immunosuppressive medication) [2]. The proposed mechanism for these infections is suspected to be hyperinflammatory states and PD-1 blockade negatively affecting host interactions with the offending organism, similar to the proposed mechanism of the patient with *Listeria* meningitis described in this case.

Our patient's older age is a known risk factor for invasive listeriosis; therefore, an important limitation of our study is that we cannot definitively prove that pembrolizumab was an independent risk factor for this patient's infection. Nevertheless, we aim to increase awareness of PD-1/PD-L1 blockade as a possible risk factor for invasive listeriosis and encourage vigilance in reporting additional cases either in the peer-reviewed literature or in post-marketing surveillance programs. As PD-1 inhibitors and other ICIs gain importance in cancer treatment, a robust understanding of infection risk will better enable the communication of benefits and potential harm for patients and create opportunities for interventions to mitigate such risks.

Conclusions

As the use of immunotherapy becomes more prevalent, clinicians must consider patients so treated to have dysregulated T cell immunity and an increased risk of acquiring severe opportunistic infections. Notably, this case report describes severe systemic *Listeria monocytogenes* infection in a patient receiving ICI therapy without additional immunosuppressive medications. This case adds to the list of potential opportunistic infections related to dysregulated immunity caused by immunotherapy. These reports of opportunistic infections highlight the need for careful screening for infection prior to the initiation of immunosuppression for patients receiving ICI therapy and presenting with inflammatory syndromes.

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