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Immune-Related Adverse Events

irAEs

Severe Epididymo-Orchitis and Encephalitis Complicating Anti-PD-1 Therapy

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Abstract

Background. Immune checkpoint inhibitors such as pembrolizumab and nivolumab have emerged as active treatment options for patients with many cancers, including metastatic melanoma, but can also cause symptomatic or life-threatening immune-related adverse events, including encephalitis. Epididymitis and orchitis are rare complications of these therapies.

Case Presentation. We describe herein a patient with metastatic melanoma who developed epididymo-orchitis followed by encephalitis while receiving pembrolizumab. The patient developed testicular pain and fever after his third dose of pembrolizumab; ultrasound evaluation demonstrated bilateral epididymo-orchitis. He then developed headaches, fever, and altered mental status over the next week and was admitted to the hospital. Lumbar puncture revealed inflammatory changes consistent with meningoencephalitis; he did not improve with broad-spectrum antibiotics, and an extensive workup for infectious etiologies, including cerebrospinal fluid testing using a clinical metagenomic next-generation sequencing assay, was negative. He received high-dose steroids for suspected autoimmune encephalitis, and both his orchitis and meningoencephalitis improved rapidly after one dose. He fully recovered after a 5-week taper of oral steroids.

Discussion. Here, we report a case of epididymo-orchitis complicating immune checkpoint inhibitor therapy. This patient subsequently developed severe encephalitis but rapidly improved with steroids. Clinicians should be aware of rare complications of these agents. ***The Oncologist*** 2019;24:872–876

Key Points

- Epididymo-orchitis is a rare and potentially life-threatening complication of anti-programmed death protein 1 (anti-PD-1) therapy.
- For patients on anti-PD-1 therapy who develop either epididymo-orchitis or epididymitis without clear infectious cause, immune-related adverse events should be considered in the differential diagnosis.
- If severe, epididymo-orchitis related to anti-PD-1 therapy may be treated with high-dose corticosteroids.

Background

Treatment for metastatic melanoma now often includes immune checkpoint inhibitors (ICIs) such as anti-programmed death protein 1 (anti-PD-1) antibodies. However, this immune checkpoint blockade can produce immune-related adverse events (irAEs) affecting any organ, including thyroiditis, pneumonitis, colitis, hepatitis, endocrinopathies, and rashes [1–3]. These irAEs are often treated with systemic immunosuppression such as glucocorticoids. Neurologic toxicities are less common (<5%) and can range from sensory neuropathies to aseptic meningitis, myasthenia gravis, and Guillain-Barré syndrome. Encephalitis is an uncommon toxicity described in several case reports and case series [4–6]. Neurologic toxicity can be treated with high-dose corticosteroids, intravenous immunoglobulin, and/or plasmapheresis but may be fatal in severe cases [1, 6, 7].

Epididymo-orchitis is an inflammatory disease of the epididymis and testis. Epididymitis most often results from infection from bacteria such as from *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Escherichia coli* but can also result from viral or fungal infections [8]. Orchitis, though less

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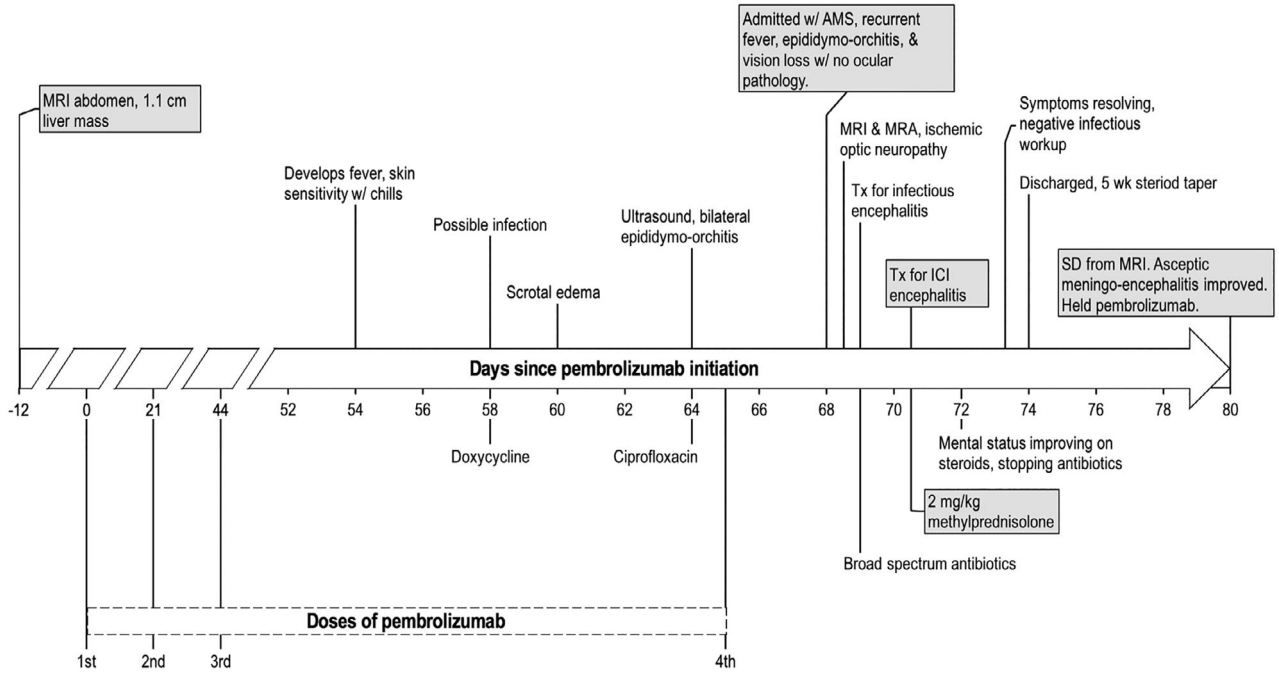

Figure 1. Time course of events surrounding anti-programmed death protein 1-induced epididymo-orchitis and encephalitis. Abbreviations: AMS, altered mental state; ICI, immune checkpoint inhibitor; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; SD, stable disease; Tx, treatment.

common, often occurs in patients with concurrent epididymitis [9]. Other noninfectious causes of epididymitis include vasculitis and autoimmune diseases such as systemic lupus erythematosus or Bechet's disease [10, 11]. To our knowledge, despite the association of epididymitis with autoimmune diseases, only one case of orchitis related to ICIs has been reported, which resolved spontaneously without treatment [12]. Here, we present a case of epididymo-orchitis associated with anti-PD-1 therapy, progressing to fulminant encephalitis with rapid clinical improvement following corticosteroid administration.

Patient Story

A 69-year old man was evaluated in the emergency department for confusion and fever. He was initially diagnosed with uveal melanoma in the right eye in 1997 and treated with laser therapy. He developed a liver recurrence in 2006 and underwent several rounds of radiofrequency ablation and right partial hepatectomy for isolated liver recurrences over the next 11 years. His most recent recurrence was in April 2017 with a new 1.1-cm liver mass. In May 2017 he was started on pembrolizumab (Fig. 1).

Ten days after the third dose of pembrolizumab, he developed fever and chills with mild headache and skin sensitivity. He visited urgent care and was empirically prescribed doxycycline for possible tickborne illness but then developed bilateral testicular tenderness with scrotal edema; urine cultures were negative. Ultrasound with Doppler showed bilateral epididymo-orchitis, and, given that an infectious etiology was suspected, his antibiotics were switched to ciprofloxacin. He reported slight subjective improvement and was afebrile at his clinic visit and received his fourth dose of pembrolizumab.

Over the next three days he developed daily fevers and progressive confusion and weakness. On presentation to the emergency room, he was hypotensive and had recurrent fevers to 101 F, with leukocytosis (12.1×10^3 cells per μL) and acute renal failure (creatinine of 3.96 mg/dL). Blood cultures were drawn, and he was started on empiric vancomycin and cefepime for possible meningitis. Scrotal ultrasound showed persistent although improving epididymo-orchitis. Urine culture remained negative. Lumbar puncture with cerebrospinal fluid (CSF) analysis showed 81 nucleated cells per μL (34% neutrophils, 30% lymphocytes, 36% monocytes), zero red blood cells per μL, glucose of 42 mg/dL (normal range, 45–75), and protein of 267 mg/dL (normal range, 15–40), prompting concern for bacterial meningitis. He continued to have altered mental status and recurrent fevers, so ampicillin and doxycycline were added. Cefepime was later changed to ceftriaxone, and acyclovir was added until viral studies for herpes simplex virus and varicella zoster virus returned negative. Other negative viral tests included HIV, Epstein-Barr virus (EBV), cytomegalovirus, enterovirus, and John Cunningham virus. Fungal studies also returned negative *(Cryptococcus*, *Histoplasma*, *Aspergillus*, 1,3-beta-D-glucan). Blood and CSF bacterial cultures, as well as *Rickettsia* serology, returned negative. Metagenomic next-generation sequencing testing of CSF (performed subsequently as a research test) using a clinically validated assay did not detect any viruses (RNA and DNA), bacteria, fungi, or parasites above preestablished reporting thresholds [13–15]. His acute kidney injury improved rapidly with fluid administration.

His negative infectious workup (Table 1) and progressive clinical worsening prompted concern for an inflammatory, pembrolizumab-related etiology. Thus, antimicrobials were discontinued and replaced with high-dose intravenous steroids

Table 1. Patient laboratory testing and imaging

Study	Results
CSF	
Nucleated cells	81 per μL
Neutrophils	34%
Lymphocytes	30%
Monocytes	36%
Red blood cells	0 per μL
Glucose	42 mg/dL
Protein	267 mg/dL
Cytology	Negative for malignancy
Microbiology	
Blood	
Bacterial culture	Negative
HIV antibody	Negative
EBV PCR	Negative
CMV PCR	Negative
Aspergillus antigen	Negative
1,3-beta-D-glucan	Negative
RMSF serology	Negative
Ehrlichia PCR	Negative
Urine	
Bacterial culture	Negative
Histoplasma antigen	Negative
CSF	
Bacterial culture	Negative
HSV 1/2 PCR	Negative
HSV IgM/IgG	Negative
VZV PCR	Negative
Enterovirus PCR	Negative
JC virus PCR	Negative
Cryptococcus antigen	Negative
VDRL	Negative
Imaging	
MRI/MRA brain and orbit	Suspected left vertebral artery occlusion, known cavernous venous malformation, chronic right optic nerve atrophy
Scrotal ultrasound	Bilaterally enlarged epididymides with associated mild increased vascularity of the testicles and epididymis, both decreased from previous exam
Metagenomic next-generation sequencing	
Viruses	None detected
Bacteria	None detected
Fungi	None detected
Parasites	None detected

Abbreviations: CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; JC, John Cunningham; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus.

(methylprednisolone 2 mg/kg daily) approximately 24 hours after admission. His mental status rapidly improved after a single dose of methylprednisolone, and his fevers and testicular pain resolved. He was transitioned to oral prednisone for the remainder of his admission. Following discharge, he received a steroid taper over 5 weeks. His pembrolizumab was discontinued, and he did not develop additional fevers, confusion, or testicular pain. His initial surveillance liver magnetic resonance imaging (MRI) revealed stable disease, which was maintained for approximately 6 months.

Discussion

ICIs are known to cause irAEs that can affect essentially any organ by blocking regulators of self-tolerance. Indeed, PD-1 and its ligand play critical roles in mitigating autoimmune insults to inflamed tissue. Common irAEs include rash and/or pruritis, diarrhea and/or colitis, hepatitis, endocrinopathy, and pneumonitis. Less common toxicities include pancreatitis, hematologic and cardiac events, and neurologic toxicities [16–18].

This case describes a rare case of anti-PD-1-induced epididymo-orchitis. Although bacterial or viral causes remain in the differential diagnosis, multiple negative cultures (from blood, urine, and CSF), negative CSF testing using a clinical metagenomic sequencing assay, continued worsening despite appropriate antimicrobials, and rapid improvement with steroids after discontinuation of antibiotics argue that this was an inflammatory, pembrolizumab-mediated event. Biologically, a role for anti-PD-1-induced inflammation is plausible, given the key role of PD-1 in maintaining self-tolerance and the prior reports of inflammation in essentially every other organ system. A case of orchitis related to nivolumab and ipilimumab has been reported, which resolved spontaneously without treatment [12]. Notably, although it is not clear whether ICI-induced epididymo-orchitis affects future fertility, other causes of this condition may reduce sperm count and impair fertility. Thus, a fertility evaluation following symptom resolution may be indicated in patients desirous of maintaining fertility [19, 20].

Our patient progressed to a more clinically severe and potentially devastating complication of ICIs: encephalitis. Although neurologic toxicities are not common (<5%), they can range in severity from mild sensory neuropathies to encephalitis, myasthenia gravis, and Guillain-Barré syndrome [6, 21]. Clinical presentations can be challenging to diagnose, particularly when complications that are cancer related (e.g., spinal cord compression, brain metastases) or treatment related (e.g., endocrinopathies causing fatigue and weakness) may be more common considerations. Imaging showing contrast enhancement and/or lumbar puncture showing an inflammatory profile can be helpful in diagnosing neurologic toxicity. High-dose corticosteroids remain the cornerstone of treatment, but other disease-specific therapies may also be indicated (e.g., plasmapheresis for myasthenia gravis or Guillain-Barré syndrome).

Laboratory findings of ICI-induced encephalitis often show leukocytes in the CSF, varying from lymphocytic to neutrophilic pleocytosis, as well as elevated protein and often low to normal glucose (as in our case). Brain MRI findings may

reveal temporal lobe enhancement or other findings but may also be unremarkable, as in our patient. Symptoms may include headaches, confusion, fevers, and focal neurologic deficits (including aphasia and ataxia) [4, 5, 22, 23]. This case was notable in that the neurologic symptoms occurred after an episode of epididymo-orchitis. Interestingly, other cases of anti-PD-1-associated encephalitis have been reported with preceding symptoms suspicious for infection, such as flu-like symptoms or upper respiratory and sinus infection [4, 5]. Our case occurred approximately 10 weeks into therapy, consistent with other reports showing that neurologic toxicities arise at a median of 6–10 weeks into treatment [6, 24].

The pathogenesis and molecular mechanisms of irAEs are not well understood, although they could relate to preexisting autoimmunity or environmental factors [25–27]. Notably, it is unclear why our patient experienced both epididymo-orchitis and encephalitis. One could posit that antigens shared in immune-privileged locations (brain and testicle) could have been recognized and targeted following anti-PD-1 therapy. Notably, relapse of leukemia in the tests and brain are common sites for childhood leukemia, which may be due to drug penetration [28]. However, testicular lymphoma also has a high incidence of relapse in the central nervous system, which could potentially suggest that certain inflammatory or neoplastic cells have tropism for these organs [29]. One study has shown that high-frequency T-cell clones may infiltrate both tumor and inflamed tissue, suggesting shared antigens may be targets of both antitumor and autoimmunity [30]. Notably, in this work, inflammation was also shared between skeletal and cardiac muscle (with no other organ involvement), perhaps analogous to our case with two distinct organs involved. Although the testis is thought to be an immunologically privileged site protected from autoimmunity, adoptive transfer of T lymphocytes was shown to cause autoimmune orchitis in animal models [31]. In this case, given the symptom profile, we also posited that the inhibition of PD-1 could have amplified the inflammatory manifestations of an otherwise minimally symptomatic virus (e.g., mumps, EBV, or Powassan virus) [32] but found no evidence of active viral infection in the CSF, despite testing with a clinical metagenomic sequencing assay that is able to detect a broad range of pathogens. However, viral or other environmental triggers of irAEs should be explored on a larger scale.

This case highlights the importance of monitoring patients on ICIs for toxicities. This patient did not develop any of the more common adverse effects but did have life-threatening consequences from pembrolizumab. It is important to recognize these less common toxicities, as diagnostic uncertainty can significantly delay the cornerstone of treatment for irAEs: corticosteroids. As the use of ICIs become more common for the treatment of many cancers, early awareness and treatment of these toxicities will be essential to optimize long-term outcomes for patients.

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Disclosures

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