

Isolated testicular vasculitis due to immune checkpoint inhibitor

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Abstract

Immune checkpoint inhibitors are increasingly being used to treat various malignancies; consequently, more rheumatological side effects, ranging from arthritis to vasculitis, are being reported. Here we present, for the first time, a case of vasculitis involving the testicle in the setting of an immune checkpoint inhibitor. As reported in previous cases, recurrence of a malignancy, as opposed to vasculitis, was initially suspected, thus creating a diagnostic dilemma. These rheumatological side effects have garnered attention as they potentially provide a window into the pathogenesis of rheumatological diseases.

Keywords: Vasculitis, immune checkpoint inhibitors, malignancy

Introduction

To combat malignancy, immune checkpoint inhibitors are used to augment antitumor activity by enhancing unopposed T-cell activity (1). However, exploiting this aspect of the immune system has led to a variety of inflammatory side effects deemed immune-related adverse events (IRAEs) (2). Rheumatologists should be aware of these complications, as there are increasing reports of rheumatological sequelae such as arthritis, myositis, and sicca syndrome (3). Vasculitis is a less commonly reported rheumatologic IRAE, and we present, to our knowledge, the first case report of isolated testicular vasculitis induced by the checkpoint inhibitor ipilimumab, an antagonist of cytotoxic T lymphocyte-associated protein 4 (CTLA-4).

Case Presentation

A 61-year-old man with no history of any autoimmune disease was diagnosed with stage IIIB malignant melanoma. He was treated with wide excision of the cancer followed by adjuvant ipilimumab (10 mg/kg) therapy. One week after the second ipilimumab dose, he developed a rash consistent with a cutaneous IRAE, which was treated with a short course of methylprednisolone. Then, 1 week later, he developed acute abdominal discomfort with fever (body temperature, 39.4°C) and leukocytosis (leukocyte count, 16,200/ μ L), prompting an initial concern for checkpoint inhibitor-mediated colitis. Imaging studies were consistent with diverticulitis, and antibiotics were initiated. Two days after developing abdominal pain, he developed bilateral testicular pain. Bilateral epididymal and testicular tenderness, induration, and enlargement (left greater than right) was noted; pelvic magnetic resonance imaging revealed solid bilateral testicular masses. Concern for malignant metastasis to the testes prompted a left groin exploration and orchiectomy. Intraoperatively, the testicle was grossly necrotic in appearance, concerning for bilateral necrotizing orchitis. Pathological examination revealed medium-vessel vasculitis of the left testicle and no malignancy (Figure 1).

The antinuclear antibody, antineutrophil cytoplasmic antibody, and hepatitis B and C serology results were negative, and urinalysis findings were normal. C-reactive protein (CRP) levels were elevated (149 mg/L; normal range, <4.9 mg/L). Given the lack of evidence for systemic vasculitis, the patient was diagnosed with isolated testicular vasculitis. Ipilimumab was discontinued, and 100 mg (1 mg/kg) of prednisone was initiated and tapered over 6 weeks. There was no recurrence of testicular vasculitis or development of a systemic vasculitis. CRP levels normalized, and no additional immunosuppression was needed.

Literature Review

Vasculitis is one of the less commonly reported rheumatologic IRAEs (4). Interestingly, while systemic vasculitis diseases, such as giant cell arteritis, have been reported, there have been reports of single-organ vasculitis (5). For example, in addition to our report of the isolated testicular vasculitis, vasculitis involving the retina (6), uterus (7), and brain (8) has been reported. Treatment for most cases included checkpoint

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Cite this article as: Weiner R, Hanson B, Rehman J, Sun B. Isolated testicular vasculitis due to immune checkpoint inhibitor. *Eur J Rheumatol* 2020; 7(1): 35-6.

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Submitted: April 25, 2019

Accepted: May 27, 2019

Available Online Date: November 25, 2019

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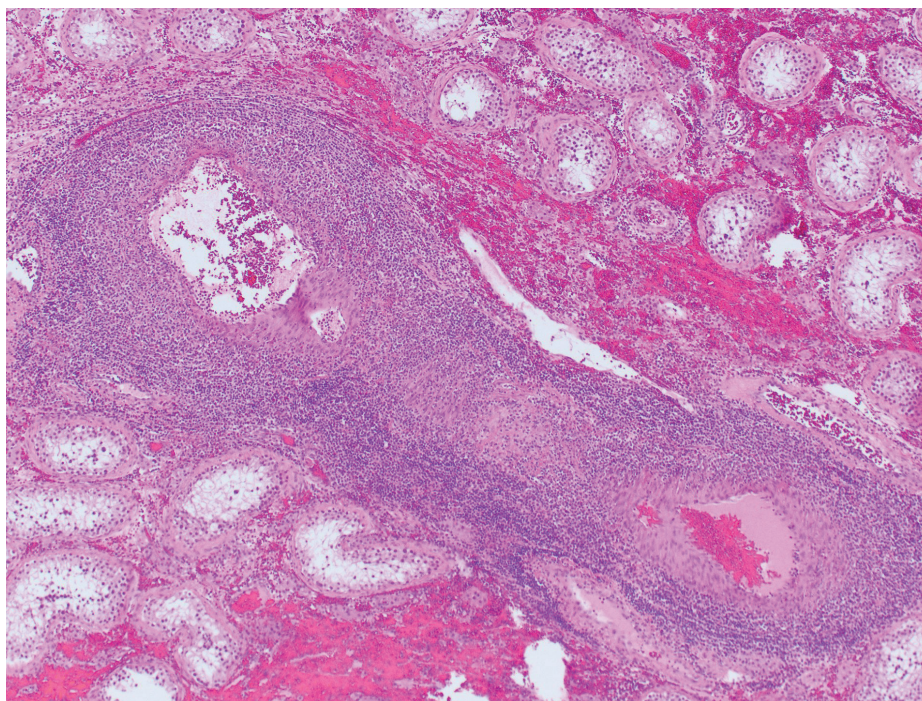


Figure 1. A muscular artery is involved by an inflammatory process that spans the full thickness of the vessel wall. Endothelial damage is evidenced by extravasated red blood cells and sloughing of the endothelial lining. Involved cell types include eosinophils, lymphocytes, plasma cells, and neutrophils. The seminiferous tubules of the testicular parenchyma in the background remain uninvolved by the inflammatory infiltrate.

inhibitor cessation and high-dose corticosteroids, which resulted in a rapid clinical improvement. No recurrences were noted in any cases, and additional immunosuppression was not required. It is imperative to distinguish an IRAE from a malignant metastasis in patients receiving immune checkpoint inhibitors. In the present case, as well as the other three isolated organ vasculitis cases, the initial concern was metastatic spread, rather than the actual diagnosis: autoimmune vasculitis induced by an immune checkpoint inhibitor.

As the use of immune checkpoint inhibitors continues to grow, we suspect that more cases of vasculitis induced by these medications will be reported, which will help further

elucidate the trends. By understanding the mechanism of rheumatologic IRAEs induced by checkpoint inhibitors, hopefully more insight can be gained into the pathogenesis of rheumatological diseases. Ongoing research seeks to determine whether there are predispositions to vasculitis based on depleted levels of costimulatory molecules (9). These studies demonstrate low levels of programmed death-ligand 1 (PD-L1) in temporal artery biopsies of patients with giant cell arteritis (10). This finding, which mimics the fundamental principle of a checkpoint inhibitor, may shed light on the mechanism of vasculitis induced by checkpoint inhibitors (11). PD-L1 and CTLA-4 levels have been shown to be integral in the development of inflammatory conditions. Further research may help determine whether it is possible to manipulate the levels of these immune checkpoint inhibitors to prevent autoimmune potentiation.

Conclusion

The relationship between immune checkpoint inhibitors and rheumatological conditions continues to evolve. When using immune checkpoint inhibitors, one must be aware that there is a possibility of occurrence of vasculitis, as opposed to recurrence of a malignancy. The increasing reports of vasculitis occurring in the setting of immune checkpoint inhibitors will lead to a better understanding of the pathogenesis of vasculitis.

Informed Consent: Verbal informed consent was obtained from the patient whose case has been presented in this case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.S., R.W.; Literature Search - B.S., R.W., B.H., J.R.; Writing Manuscript - B.S., R.W., B.H., J.R.; Critical Review - B.S., R.W., B.H., J.R.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Main Points

- Vasculitis can be a complication of immune checkpoint inhibitors.
- It is important to distinguish an immune-related adverse events from a malignant metastasis in patients receiving immune checkpoint inhibitors.
- The mechanism of rheumatologic immune-related adverse events induced by checkpoint inhibitors may provide a greater understanding of the pathogenesis of rheumatological diseases.