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A Rare Case Presentation of Vitiligo Associated With Atezolizumab

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Abstract

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used in the treatment of solid and hematologic malignancies. Immune checkpoint inhibitors target the T-cell deactivation system via the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor, programmed cell death protein 1 (PD-1) receptor, and programmed cell death ligand 1 (PD-L1). As a result, the activated T-cell enhances the host tumor response. However, even with their essential clinical benefits, ICIs are associated with a broad spectrum of adverse effects that can be generalized or tissue-specific inflammatory responses known as immune-related adverse events (irAEs). The most common dermatologic toxicity manifests mainly as maculopapular rash and pruritus. Understanding the complexity of immune-mediated response and the importance of clinical histopathologic correlation in recognizing irAEs allows for appropriate intervention and patient care due. We present the case of a 71-year-old African American male diagnosed with a large-cell poorly differentiated neuroendocrine tumor in the gastroesophageal junction of the stomach with mediastinal lymphadenopathy. He was treated with carboplatin, etoposide, and atezolizumab for 4 cycles. However, he developed vitiligo while on maintenance atezolizumab, which is rarely seen with atezolizumab use. Despite the improving clinical outcomes in oncology with ICIs, their adverse effects should not be ignored. When promptly recognized and treated, patients on ICI monotherapy may not need treatment interruption or discontinuation.

Keywords

vitiligo, atezolizumab, immune check point inhibitors

Case Report

A 71-year-old African American male with a past medical history of rheumatoid arthritis, atrial fibrillation, dementia, and benign prostate hyperplasia presented to our facility with shortness of breath. He was admitted for acute hypoxic respiratory failure secondary to COVID-19 viral pneumonia. During his hospitalization, laboratories were significant for microcytic anemia. Given his age, this was further investigated upon discharge with an esophagogastroduodenoscopy (EGD) and colonoscopy. Esophagogastroduodenoscopy showed a 3-cm ulcerated nonobstructive mass at the gastroesophageal junction, which was biopsied. The pathology report showed a poorly differentiated malignant neoplasm characterized by the compact growth of small tubules with a focal glandular appearance. The neoplastic cells had abundant eosinophilic cytoplasm with large, atypical nuclei. Immunohistochemistry showed the cell was positive for CK7, chromogranin, synaptophysin, and CD56 and negative for CK20. The Ki-67 index was >80%. Additional stains showed the tumor was positive for INSM1 and CDX2 and negative for MUC5AC, MUC6, and mucicarmine. The colonoscopy showed a polyp in the cecal region, which pathology revealed to be an adenomatous polyp. Positron emission tomography/computed tomography (PET/CT) scan showed lymphadenopathy within the mediastinum compatible with malignant cause. He received 4 cycles of carboplatin, etoposide, and atezolizumab. While there was treatment response as demonstrated by a repeat EGD that showed no residual tumor. However, during routine follow-up at the cancer center, physical examination was remarkable for hypopigmented macules and patches on his face and genital region, respectively (Images 1 and 2), while on maintenance atezolizumab. This was approximately 11 months following the initiation of atezolizumab.

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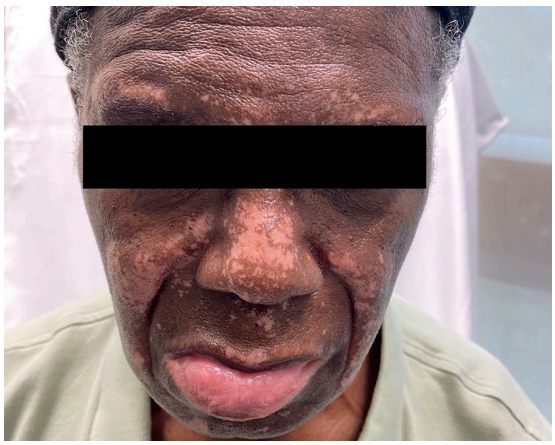

Image 1. Vitiligo associated with atezolizumab use.

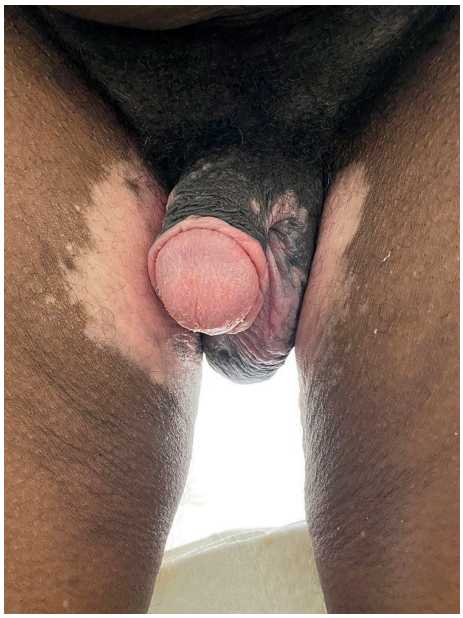

Image 2. Vitiligo associated with atezolizumab use.

Discussion

Immune checkpoint inhibitors are monoclonal antibodies that have now become part of the standard of care for treating various solid and hematologic malignancies.1 Programmed cell death protein 1 and CTLA-4 are important in regulating cellular immune responses, and the effect of ICI is to upregulate the tumor's host T-cell immune response.2 Even with their important clinical benefits, they are associated with a broad spectrum of adverse effects that can be generalized or tissue-specific, inflammatory responses known as irAEs.1,3 The immune response associated with irAEs may originate from the skin, liver, gastrointestinal tract, and endocrine system. Inflammatory skin reactions include maculopapular, lichenoid, eczematous eruptions, immunobullous diseases, vitiligo, and alopecia areata. In addition, rare, life-threatening dermatologic manifestations of drug reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], drug reaction with eosinophilia and systemic symptoms (DRESS) may also occur.1,3

Dermatologic toxicities are prevalent among all ICI therapies, more frequent with the combination therapy of anti-CTLA-4 and anti-PD-1 than with monotherapy with either class of agents.4,5 They are often manifested earlier in the course of treatment with PD-1 and PD-L1 inhibitors; they may appear almost 9 weeks after starting treatment, even though some symptoms may appear months after starting treatment.4 Severe dermatologic irAEs occur in approximately 2% of patients treated with anti-PD-1 monotherapy.1 Patients with pre-existing inflammatory dermatologic diseases, for example, atopic dermatitis, psoriasis, lichen planus, or vitiligo, are likely to experience flare-ups with ICIs. They are generally not severe and easily manageable. However, life-threatening cutaneous skin reactions such as TEN and SJS can also occur.6,7

The most common dermatologic manifestations of irAEs are maculopapular rash and pruritus. Other cutaneous reactions such as vitiligo have also been reported.6,7 Vitiligo is an autoimmune disorder which leads to the loss of functional melanocytes in the epidermis resulting in depigmented macules or patches on the skin which can be diagnosed with a Wood's lamp.1 The underlying mechanism of action has been described as the expression of CXCR3 on CD8+ T-cells and elevated levels of interferon and tumor necrosis factor.1,7 Melanocytes are targeted by these immune effector cells, causing ICI-induced vitiligo.1,7 The clinical phenotype of vitiligo associated with ICI therapy is distinctive, characterized by multiple flecked macules that evolve to large patches on sun-exposed areas such as the face.6,7 There can also be preceding erythema, but this is not often reported.6,7 Patients typically do not have a personal or family history of vitiligo or other autoimmune diseases.6

Immune checkpoint inhibitor-induced vitiligo has been reported mainly in patients with melanoma when compared to other types of cancer. Furthermore, it has been reported to be a positive predictive factor associated with improved treatment response.1,8 The most common ICI-induced vitiligo has been reported with ipilimumab use.8 It has also been reported with nivolumab, pembrolizumab, and rarely with atezolizumab use.7,8

It is rare for dermatologic toxicities to lead to significant morbidity and mortality. However, depending on its severity, the effects of irAEs not only impact the patient quality of life but can also affect the patient's ability to remain on cancer therapy. Identifying cutaneous adverse events and managing them early could prevent the progression of ICI-induced vitiligo and reduce treatment disruption. It is important to recognize and treat irAEs promptly, and in most cases, temporary immunosuppression with tumor necrosis factor-alpha antagonists, steroids, mycophenolate mofetil, or other immunosuppressive agents can be effective.7-9

Declaration of Conflicting Interests

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Ethical Approval

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