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Interstitial granulomatous dermatitis and concurrent immunotherapy associated encephalitis with nivolumab and ipilimumab

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Abstract

Immune-related adverse events (irAEs) are common in patients receiving immune checkpoint inhibitors for metastatic melanoma and other advanced malignancies. Cutaneous, gastrointestinal, and endocrine (thyroid) irAEs are most prevalent, whereas neurologic irAEs are rare. We present a 73-year-old man with dementia and metastatic melanoma who developed immunotherapy-associated encephalitis and subsequently, interstitial granulomatous dermatitis with nivolumab/ipilimumab. High-dose corticosteroids successfully treated both conditions, though he never regained his baseline mental status. We review the literature on interstitial granulomatous dermatitis and encephalitis with immunotherapy.

Keywords: granulomatous dermatitis, immunotherapy, interstitial, melanoma

Introduction

Clinical outcomes in advanced melanoma and other tumors have improved significantly since the introduction of immune checkpoint inhibitors (ICIs), such as ipilimumab, which blocks cytotoxic T-lymphocyte antigen-4 (CTLA4) and nivolumab, which blocks programmed cell death-protein one (PD1), [1]. Nevertheless, immune checkpoint inhibitors may result in a broad range of immune-related adverse events (irAEs), with gastrointestinal and skin manifestations being the most common [1]. Neurologic irAEs occur less frequently and include but are not limited to neuropathies, myasthenia gravis, and noninfectious meningitis [2,3]. Herein we present a patient who developed immunotherapy-associated encephalitis after four doses of nivolumab/ipilimumab combination therapy and subsequently developed interstitial granulomatous dermatitis (IGD) nearly 7 months later.

Case Synopsis

A 73-year-old man was diagnosed with a T2aN0 lentigo maligna melanoma of the scalp (Breslow depth 1.4mm, three mitosis/mm^2) and was treated with wide local excision; sentinel lymph node biopsy was negative. The patient had no evidence of disease until four years later when he developed diplopia, dizziness, and gait instability and was found to have metastatic melanoma to the right orbit and clivus. This was treated with external beam radiation to a total of 37Gy in 15 fractions and the patient was started on immunotherapy with nivolumab (3mg/kg) and ipilimumab (1mg/kg) given every three weeks.

After the fourth cycle of combination immunotherapy and over the next 10 months, the patient had several hospital admissions for altered mental status (AMS). The patient had a history of cognitive difficulties consistent with dementia 6 years prior to his cancer diagnosis for which he was not on any medications. Upon his first admission, he presented with weakness, confusion, gait instability and fever, and was found to have a urinary tract infection (UTI). The patient's mental status did not improve after treatment for the UTI. An extensive workup for metabolic and infectious causes of AMS, including cerebrospinal fluid (CSF) studies, electroencephalography, and brain magnetic resonance imaging, were unrevealing. He was discharged, until four days later when he had worsening cognitive decline and difficulty swallowing and was readmitted. He had large volume lumbar punctures this admission with no improvement of gait, and CSF studies were negative for paraneoplastic syndromes. Given his extensive negative workup, a diagnosis of immunotherapy associated encephalitis was made. He was started on methylprednisolone 100mg intravenously (IV) every 12 hours for 10 days with improvement in his mental status but did not return to his baseline; per his family's report, he had persistent agitation and disinhibition. After discharge, intravenous immunoglobulin, (0.5g/kg over four days, for a total of four doses) was initiated to further reverse his encephalitis without further improvement.

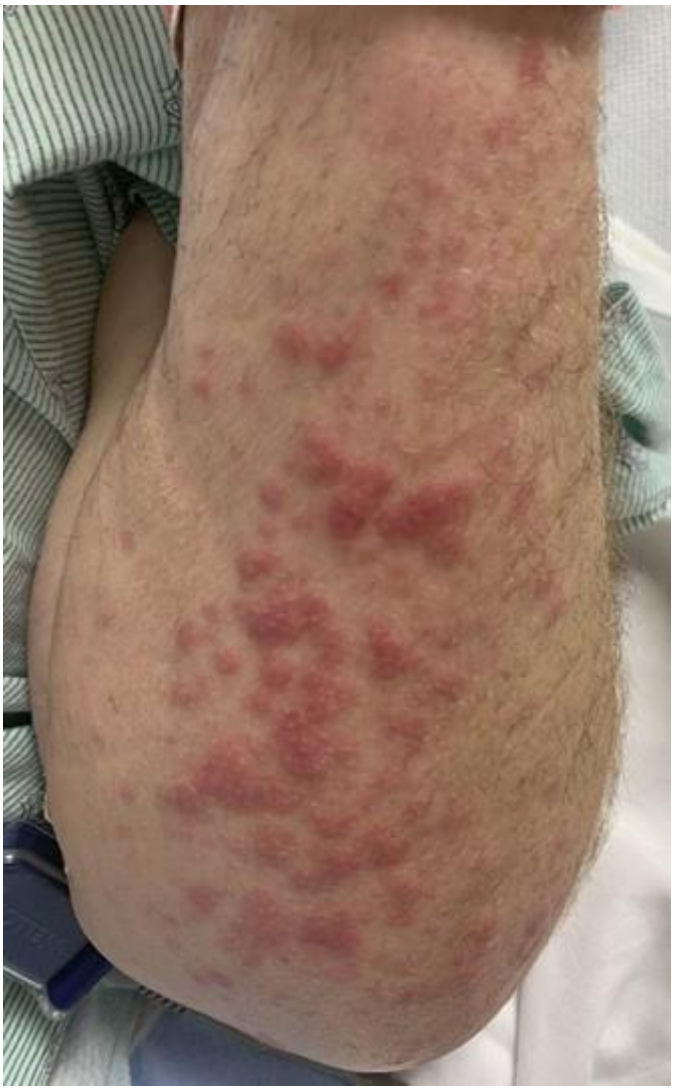

Figure 1. *Pink papules coalescing into plaques on the left forearm on day 11 of admission.*

Seven months after this initial admission for immunotherapy associated encephalitis, the patient developed worsening AMS. On admission new, raised erythematous papules and plaques were noted on the left hand. Complete blood count, including differential, liver function, basic metabolic panel, and COVID-19 PCR were normal. Blood and urine cultures were negative, though he was treated empirically with vancomycin and cefepime for 9 days. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were not checked. His mental status continued to worsen over the next three days as he was unable to follow commands and was arousable to only strong physical stimuli. In addition, his rash progressed with 20-30 scattered pink papules and plaques on the bilateral dorsal hands, forearms, and arms, some of which were edematous (**Figure 1**). In the following three days, new eyelid erythema and blanching, pink, thin dermal papules on the bilateral palms developed. The patient had no history of a similar rash prior to admission. A skin punch biopsy of the infiltrative plaque on the left forearm was performed and showed an interstitial granulomatous process involving the dermis (**Figure 2**). Fite, Gram, and Grocott methenamine-silver stains were negative for fungi and bacteria, including acid-fast bacteria. Spirochete and varicella-zoster immunohisto-chemical stains were negative as well. After multidisciplinary evaluation, the diagnosis was favored to be recurrence of his immunotherapy

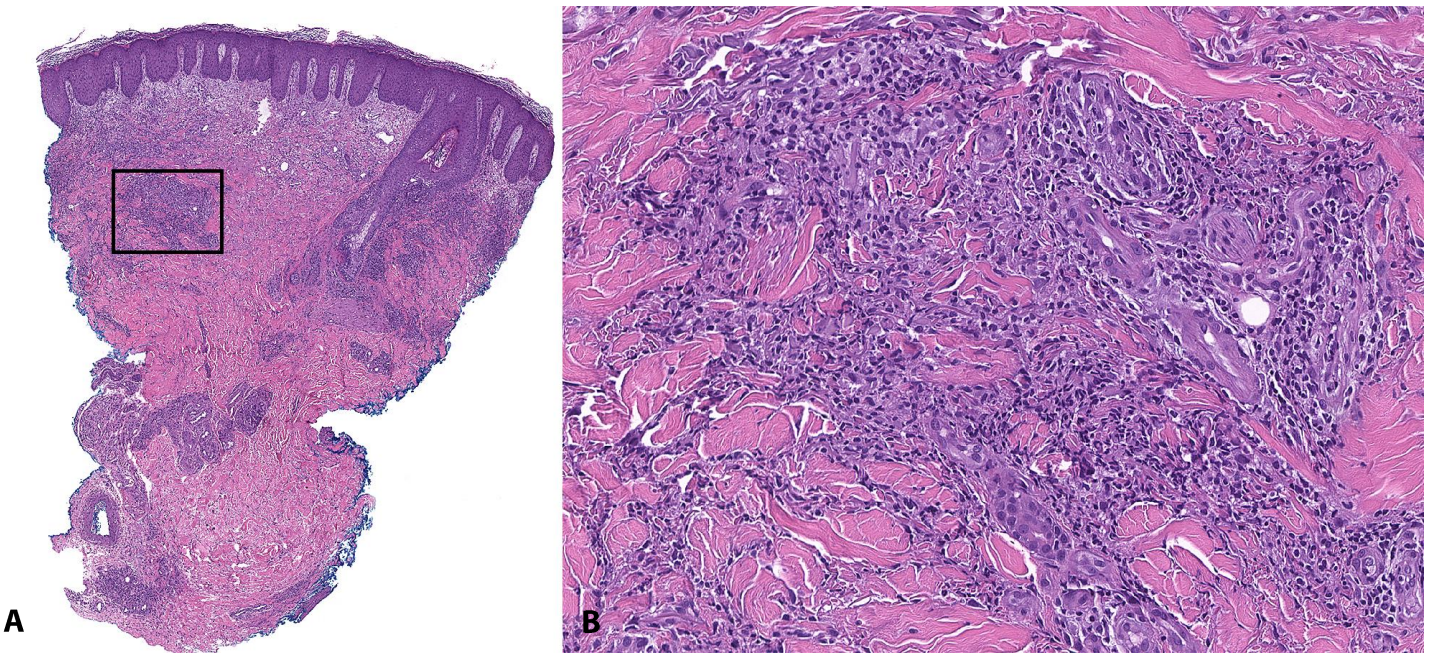

Figure 2. *H&E histopathology of left forearm skin punch biopsy.* ***A)*** *Low power magnification of skin punch biopsy of left forearm shows a dermal interstitial infiltrate also involving periadnexal areas. The overlying epidermis shows acanthosis, 40×.* ***B)*** *The dermal infiltrate is composed of histiocytes and scattered lymphocytes and eosinophils that arrange around skin adnexae and between collagen bundles. No well-formed granulomas are seen. The histopathological findings are those of an interstitial granulomatous dermatitis, 200×.*

associated encephalitis and interstitial granulomatous dermatitis. The patient was started on methylprednisolone 100mg IV twice daily for 9 days, while also receiving 5 days of plasmapheresis treatment. Triamcinolone was applied to the skin lesions 2-3 times daily as well. The patient's skin and mental status improved, as he became more alert, appropriately answered questions, and had more social awareness. He completed an additional four days of methylprednisolone 90mg IV twice daily and was discharged with a prolonged corticosteroid taper, starting with prednisone 125mg every morning and 100mg every evening, decreasing by 20mg every five days. Trimethoprim-sulfamethoxazole was started for pneumocystis pneumonia prophylaxis. His rash remained in remission after the corticosteroid taper and ultimately his encephalitis was managed with neuropsychology follow up, memantine, and citalopram pharmacotherapy.

Case Discussion

This case highlights a unique presentation of encephalitis and interstitial granulomatous dermatitis associated with ICI for metastatic melanoma. The differential diagnosis for altered mental status with diffuse associated rash in this case was broad and included neurosarcoidosis, systemic vasculitis, and infectious etiologies. Interstitial granulomatous dermatitis was ultimately determined to be the best diagnosis based on clinical and histopathologic findings.

Generally, IGD presents as linear cord-like plaques or erythematous-to-violaceous patches and plaques on the trunk and proximal extremities, often in a symmetric distribution [4]. The pathogenesis of IGD is poorly understood, though it is considered to be a result of immune complex deposition [4]. Interstitial granulomatous dermatitis may be associated with various autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus. Cornejo et al. (2019) published an extensive review on granulomatous reactions due to ICI, including patients with sarcoidosis-like reactions, granuloma annulare, granulomatous panniculitis, granulomatous dermatitis, and granulomatous foreign body reaction [8]. Four patients with granulomatous dermatitis were described who presented with coalescing papules and plaques

primarily on the torso or extremities, similar to our patient who had torso, extremity, and palmar involvement. The onset of granulomatous dermatitis after starting immunotherapy has ranged from two to 277 weeks and has been reported with both CTLA4 or PD1 inhibitor monotherapy and combination therapies; the patient in our case developed IGD 270 days (38.6 weeks) after starting nivolumab/ipilimumab. There has also been a case of a granulomatous reaction occurring 5 weeks after starting nivolumab in a patient who had trialed ipilimumab 6 months prior [9]. Cases of granulomatous skin disease with ipilimumab when combined with targeted therapies, including BRAF inhibitors, have been reported as well [10]. A range of other irAEs have been reported with immunotherapy-related granulomatous skin disease including uveitis, hepatitis, thyroiditis, pneumonitis, and inflammatory arthritis. However, no reports to our knowledge have included occurrences of both neurologic disease and IGD after immunotherapy, as was observed in our patient.

The cause of this patient's cognitive impairment was multifactorial and related to his immunotherapy, cerebrovascular changes, mood disorder, and cerebral atrophy. In one study including 35 patients with neurologic irAEs on nivolumab with or without ipilimumab, 6 patients developed encephalitis within a median time onset of 55.5 days [2]. This is similar to our patient who developed immunotherapy-associated encephalitis 63 days after beginning nivolumab/ipilimumab. Most patients presented with confusion, weakness, and general altered mental status similar to our patient, whereas some had aphasia and seizure-like episodes. Four of the 6 patients (two of which also had IVIG) improved with high dose IV corticosteroids within three weeks. One patient had no response to IV corticosteroids or IVIG, but had symptom improvement over 6 months after treatment with cyclophosphamide and rituximab. The authors did not state whether any of the patients with encephalitis had skin toxicities with the immunotherapy. Wang et al. (2018) showed that among ICI-related fatalities, neurologic etiologies account for 2% and 3% of patients on monotherapy with anti-CTLA-4 and anti-PD1 drugs, respectively. The percentage is higher (16%) for deaths among patients on anti-PD1/PDL plus CTLA4 combined therapies. Other concomitant irAES have been reported in patients with immunotherapy-associated encephalitis, including liver toxicity and hypophysitis [6]. Neurologic irAEs with immune checkpoint inhibitors are not fully understood and could be caused by shared onco-neural antigens or due to an unmasking of an otherwise suppressed autoimmune disease [7].

Conclusion

With increasing utilization of ICI for advanced malignancies, physicians and healthcare providers must be able to recognize the wide variety of irAEs patients experience. This case highlights how granuloma pathogenesis can be influenced by ICIs and may occur in patients with neurologic irAEs. Future studies are needed to characterize the clinical significance and appropriate management of granulomatous dermatitis and immunotherapy-associated encephalitis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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