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Checkpoint Inhibitor Induced Neurotoxicity in a Case of Metastatic Melanoma

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ABSTRACT

Checkpoint inhibitors (CPIs) are increasingly being used in the treatment of malignant melanoma. While showing promise in metastatic melanoma treatment, CPIs are associated with immune-related adverse events in various organ systems. Among these events, checkpoint inhibitor induced neurotoxicity stands out as a particularly rare yet diagnostically challenging and potentially life-threatening occurrence. We report a unique case of checkpoint inhibitor induced neurotoxicity in a patient with metastatic melanoma directly after beginning treatment with checkpoint inhibitor encorafenib. The patient presented with an unclear clinical course, with features of Guillain-Barré syndrome, myasthenia gravis, and brainstem encephalitis. We followed a recently established management algorithm for checkpoint inhibitor-induced neurotoxicity with positive outcomes. This case report highlights the importance of recognizing checkpoint inhibitor induced neurotoxicity as a potential adverse effect of CPIs when treating metastatic melanoma.

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INTRODUCTION

Metastatic melanoma, the most lethal among primary cutaneous neoplasms, poses significant challenges due to its depth of involvement and potential dissemination to lymph nodes and distant sites.[1] Staging of melanoma is contingent upon these factors, with stage I and II denoting the absence of lymph node involvement or metastasis but differing in terms of their risk of recurrence. In contrast, Stage III melanoma involves regional lymph node metastases, while Stage IV is characterized by distant metastases, both of which are associated with lower survival rates. According to the SEER database, in 2018, individuals diagnosed with stage IV disease in the United States had a 5-year survival rate of 29.8%.[2] Projections indicate a substantial increase in new cases of melanoma by 2030.[3]

One critical genetic determinant in melanoma pathogenesis is the v-raf murine sarcoma viral oncogene homolog B1 (BRAF), an essential component of the RAS-RAF-MEK-ERK mitogen–activated protein kinase (MAPK) cell signaling pathway. BRAF mutations have been identified in a substantial percentage of cutaneous malignant melanoma cases, making them a focal point for targeted therapy.[4]

BRAF inhibitors have demonstrated overall response rates ranging from 37% to 81%.[5] As a result, the recommended first-line regimen for patients with BRAFV600-variant melanoma includes a combination BRAF and MEK inhibitor therapy with either dabrafenib and trametinib, vemurafenib and cobimetinib, or encorafenib and orbinimetinib.[6] While checkpoint inhibitors have revolutionized management of metastatic melanoma, they come with a unique set of challenges. Checkpoint inhibitor induced neurotoxicity is a known adverse effect of checkpoint inhibitors that can be challenging to diagnose due to the varied presentation which may resemble myositis, polyneuropathy, myasthenia gravis, Miller Fisher syndrome, radiculoneuritis, and encephalitis among others.[7,8,9]

This is a rare description of checkpoint inhibitor induced neurotoxicity in the setting of metastatic melanoma. While no prospective studies have defined the optimal management for specific immune-related adverse events, several international guidelines exist.[10] This case serves as a compelling example of the effective application of one such guideline.

CASE PRESENTATION

A 72-year-old male, Fitzpatrick skin type 3, presented to the hospital with right upper extremity weakness and neck pain after initiation of checkpoint inhibitor therapy.

The patient's medical history includes a history of nodular basal cell carcinoma of the right nasal ala, treated with successful

Mohs surgery and pigmented basal cell carcinoma of the left cheek. In 2018, metastatic melanoma originating from an intradermal nevus was diagnosed with a Breslow thickness of 2.2 mm, negative margins for invasive melanoma and melanoma in situ, Clark IV staging, weakly positive BRAFR expression, and 20% PD-L1 positivity. Treatment included wide local excision with a 2 cm margin, sentinel node biopsy, and a year-long regimen of Nivolumab. In 2021, a recurrence was confirmed in the left inguinal lymph node. Treatment with cobimetinib and vemurafenib was initiated and stopped due to sun-related dermal redness. Subsequent binimetinib and encorafenib therapy was discontinued when the patient developed pancreatitis. A trial of Trametinib and Dabrafenib was halted due to fever and rigor from Dabrafenib. Treatment shifted to encorafenib and Trametinib, but encorafenib was stopped due to a rash. A subsequent Pembrolizumab trial was unsuccessful due to intolerance.

In 2023, an MRI conducted for surveillance purposes revealed the presence of a new osseous metastasis at the T12 vertebral body. The patient was treated with oral encorafenib on July 6, 2023. The following day, the patient presented to the hospital endorsing muscle atrophy, right upper extremity weakness and neck pain. The weakness progressed to involve the bilateral lower extremities within 5 days. Physical exam was notable for atrophy in the shoulder muscles, bilateral upper and lower extremity weakness, and bilateral Babinski. No new additional metastases were found in the MRI of the brain or spine. At this time, differential diagnosis included cervical disease versus neuromuscular junction syndrome secondary to encorafenib. We followed a suggested management algorithm for Grade 2 checkpoint inhibitor-induced neurotoxicity which included investigation with labs, Electromyography/nerve conduction study, and a lumbar puncture.[7] Management recommendations were also incorporated into the treatment plan. On July 10, encorafenib was discontinued. The patient subsequently became lethargic in the setting of severe hyponatremia (Na 119) which was addressed. A lumbar puncture demonstrated a protein of 94 mg/dL, glucose of 67 mmol/L, white blood cell count of 14 and red blood cell count of 47 consistent with a cytoalbumino-dissociation . Empiric treatment with a five-day course of intravenous immunoglobulin (0.4 gm/kg daily) was initiated. On July 12, the physical exam was notable for lethargy, inability to abduct the right eye, and areflexia. On July 13, the patient acutely decompensated with worsening of mental status and Cheyne-Stokes respirations, inability to follow commands, and withdrawing minimally in the upper extremities putting him at the verge of intubation. Treatment with high dose steroids (Solumedrol 1 gram IV daily for five days) was initiated. On July 14, the patient demonstrated remarkable improvement. He was alert and oriented to person, place, and time, followed commands, and moved all four extremities spontaneously and on command. On July 15, the patient continued to improve and was able to lift and maintain all four extremities antigravity. The patient made a full recovery within a week.

DISCUSSION

We describe a unique case of checkpoint inhibitor induced neurotoxicity in the setting of metastatic melanoma. Early recognition of checkpoint inhibitor induced neurotoxicity, while difficult due to variable presentations, is essential. This case demonstrates the life-threatening sequelae that may occur despite termination of offending checkpoint inhibitors. Increased awareness of checkpoint inhibitor induced neurotoxicity among dermatologists is essential for early recognition and appropriate management.

While the exact mechanisms underlying checkpoint inhibitor induced neurotoxicity are not fully understood, immune dysregulation and inflammation likely play a role in the development of neurotoxicity. By design, checkpoint inhibitors disrupt the balance between immune activation and regulation, which may lead to an immune response against normal tissues, including the nervous system.[11]

Further research is needed to better understand the mechanisms and optimal management strategies for checkpoint inhibitor induced neurotoxicity. Discontinuing the implicated checkpoint inhibitor and initiating a therapeutic regimen involving a combination of intravenous immunoglobulin and high-dose steroids led to favorable outcomes in this particular case.

CONCLUSION

This case underscores the importance of monitoring and managing immune-related adverse events in patients receiving immune checkpoint inhibitor therapy. While no prospective studies have defined the optimal management for specific immune-related adverse events, guidelines, particularly those supported by case reports like this one, should be considered. Management requires early recognition and should be tailored to presenting symptoms.

DISCLOSURES

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