Correlation Between Toripalimab Immune Therapy and Vitiligo: A Case Report of Complete Response and Adverse Reactions in Advanced Stage Melanoma of Unknown Primary

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ABSTRACT

Melanoma of unknown primary (MUP) is a rare subtype of melanoma, accounting for approximately 3% of cases and characterised by metastasis in the absence of a detectable primary lesion. This report describes the case of a stage IV MUP patient with a BRAF V600E mutation who developed vitiligo, an immune-related adverse event, following treatment with toripalimab, an immune checkpoint inhibitor (ICI). Despite experiencing vitiligo—a common skin toxicity associated with ICI therapy—the patient achieved complete remission. This case highlights the potential for ICIs to induce unexpected skin reactions and underscores the importance of monitoring and managing such events in MUP patients undergoing treatment with toripalimab.

Key Words: *Melanoma of unknown primary, Immunotherapy, Toripalimab, Vitiligo, BRAF V600E*.

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INTRODUCTION

Melanoma of unknown primary (MUP) is a rare subtype of melanoma, accounting for 3% of cases. It is characterised by metastatic melanoma in lymph nodes, skin, subcutaneous tissue, or internal organs without an identifiable primary site.[1] MUP primarily affects middle-aged men. Although its pathophysiology remains unclear, theories suggest either regression of the primary lesion after metastasis or origination from ectopic melanocytes.[2] Since 2006 and 2011, diagnostic advancements such as PET/CT scanning and treatments including immune and targeted therapies have significantly improved outcomes for patients with advanced melanomas.[1] A major breakthrough in cancer treatment has been the introduction of immune checkpoint inhibitors (ICIs), including toripalimab, which has demonstrated efficacy in treating melanomas.[3] Despite adverse effects such as skin toxicity, a noteworthy case involving a stage IV MUP patient reported a positive response to single-agent immunotherapy, accompanied by persistent vitiligo-like skin changes following the cessation of treatment and is presented here.

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CASE REPORT

A 72-year-old male patient with an ECOG score of two presented to a local hospital with back pain. An MRI suggested a metastatic tumour, leading to further referral. Physical examination revealed enlarged lymph nodes (1×1 cm) in the left axilla, and a needle biopsy confirmed malignant melanoma with extensive necrosis (Figure 1A). BRAF gene testing identified a BRAF V600E mutation (Figure 1B). PET/CT scans showed multiple lymph nodes with increased FDG metabolism in the anterior mediastinum, bilateral axillae, abdomen, retroperitoneum, and right groin, indicating possible metastasis. Nodular soft tissue shadows with increased FDG metabolism were noted in the lower right abdominal wall, suggesting a potential primary lesion. Additionally, multiple bone destructions with increased FDG metabolism were observed in the left 8th rib arch, thoracic vertebrae, appendages, and left iliac bone, indicating bone metastasis (Figure 1C). All blood tests, including lactate dehydrogenase (LDH) and liver and kidney functions, were normal. The patient was diagnosed with stage IV MUP origin, characterised by subcutaneous, lymph node, and bone metastases.

Due to financial constraints, the patient declined a combination therapy of BRAF inhibitors and ICIs. Instead, single-agent immunotherapy with toripalimab was initiated. After three cycles, the patient reported reduced back pain and a decrease in lymph node size, and his ECOG score improved from 2 to 1. A CT scan showed partial remission (PR). The patient continued to receive toripalimab for three months, experiencing vitiligo-like

pigmentation loss without other immune-related adverse events (irAEs) (Figure 2). A PET-CT during the second efficacy evaluation revealed enlarged lymph nodes in the left axilla with increased FDG metabolism, indicating metastasis, along with posterior protrusion of the L4 vertebra, a T10 compression fracture, and patchy shadows in the thoracic vertebrae and left iliac bone, all without significant FDG metabolism increase, indicating post-treatment changes (Figure 3A). Toripalimab treatment was continued till 24 month when a PET-CT showed unchanged enlarged lymph nodes and no significant FDG metabolism increase (Figure 3B). The treatment resulted in a complete response (CR), and the patient received toripalimab for a total of two years. The patient is on regular follow-up, with ongoing depigmentation (Figure 4), and the latest evaluation in January 2024 confirmed sustained CR.

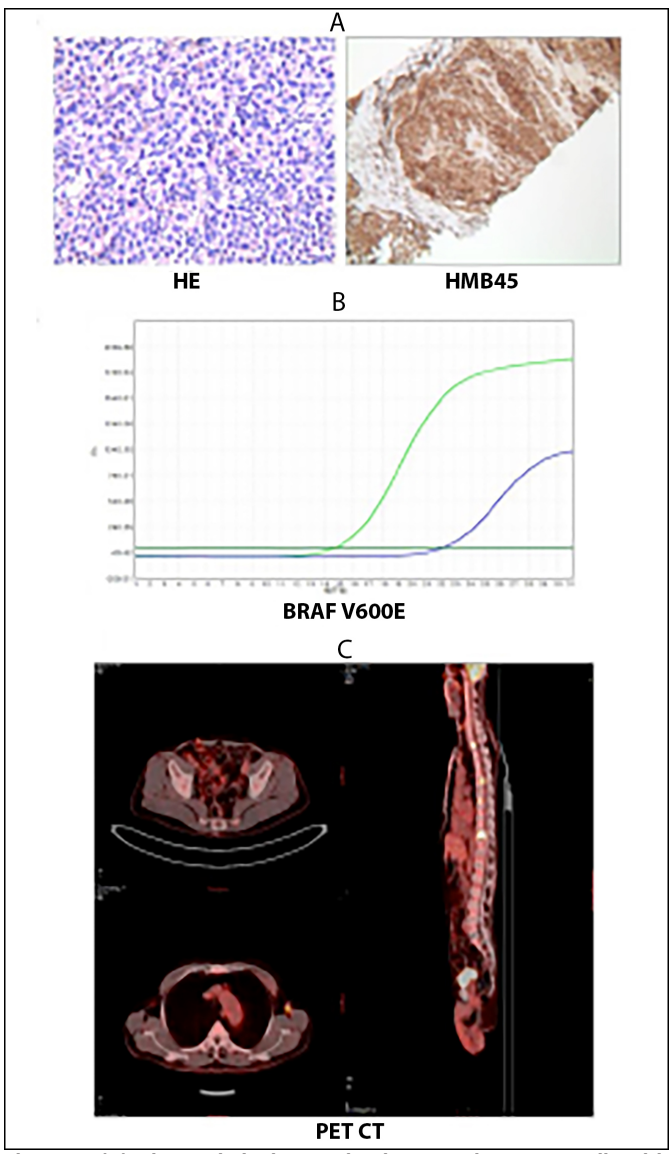

Figure 1: (A) Histopathologic examination reveals tumour cells with extensive necrosis and HMB45-positive staining. (B) BRAF gene mutation test shows a positive result for the BRAF-V600E mutation. (C) PET-CT scan displays increased fluorodeoxyglucose (FDG) uptake in multiple lymph nodes and bones, including the right abdominal wall primary lesion, left axilla, and vertebral bodies.

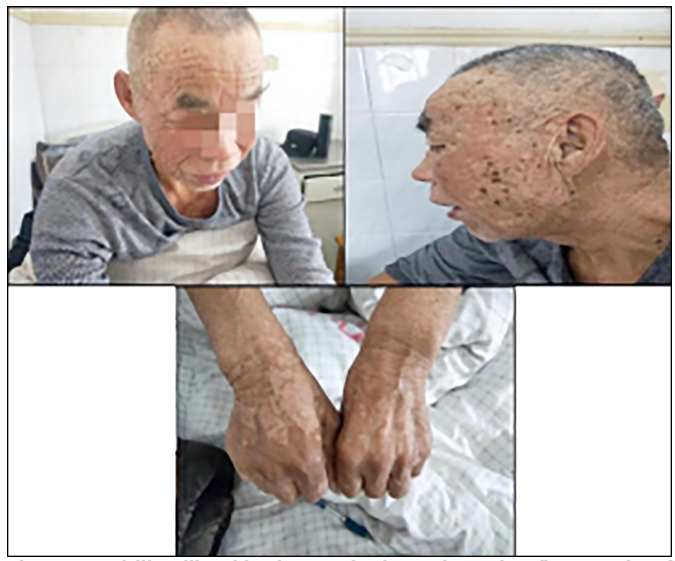

Figure 2: Vitiligo-like skin changes in the patient after five months of treatment with toripalimab.

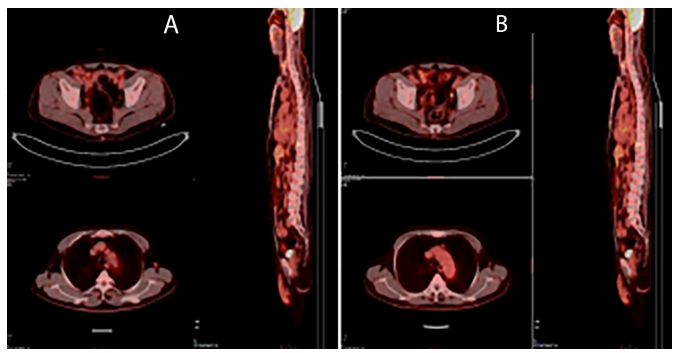

Figure 3: (A) Following six months of toripalimab monotherapy, PET-CT showed increased fluorodeoxyglucose (FDG) uptake only in the left axillary lymph node, indicating a partial response (PR). (B) After 24 months of therapy, no increased FDG uptake was detected anywhere, demonstrating a complete response (CR).

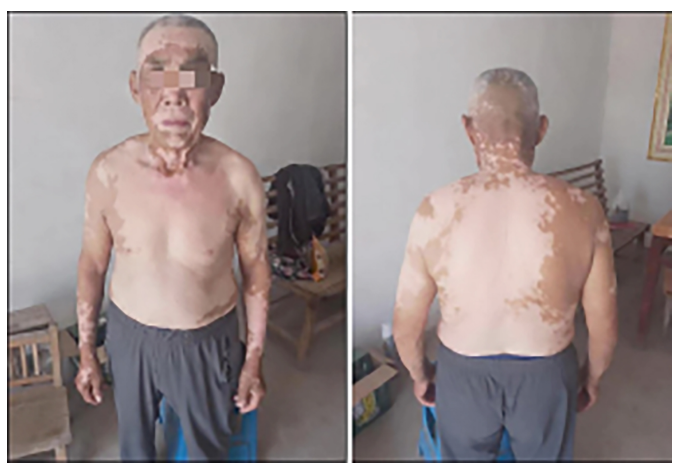

Figure 4: Progression of vitiligo-like skin changes after two years of treatment.

DISCUSSION

The eighth edition of the AJCC melanoma staging manual classifies lymph node metastasis as stage III, while all other metastases are categorised as distant stage IV. Stage IV is further divided into M1a (distant metastasis to skin, subcuta-

neous tissue, muscle, or distant lymph nodes), M1b (lung metastases with or without other site metastases), M1c (metastases to any visceral sites excluding the CNS), and M1d (CNS metastases, including the brain, spinal cord, and leptomeninges). The patient in this case falls under the M1c category due to bone metastasis and normal LDH levels. MUP tumours exhibit high somatic mutation rates, similar to UV-induced melanomas, with comparable prevalence of BRAF and NRAS mutations. Although no specific treatment guidelines exist for MUP, strategies generally align with those for stage-matched melanoma known primary (MKP) patients, based on clinical and molecular similarities, including BRAF/NRAS mutation patterns, between MUP and MKP at corresponding stages.[1]

The treatment of MUP primarily involves surgery, but early non-specific symptoms often lead to late diagnoses. Recent therapies such as immunotherapy and targeted therapy have improved survival rates, with treated stage IV MUP patients having a median overall survival (OS) of 18 months.[1] For BRAF V600E mutation patients, a combination of BRAF and MEK inhibitors is preferred. Verver *et al*.[1] assessed chemotherapy combined with targeted therapy in MUP patients. In stage III MUP, five-year OS was 48.5% without new therapies and 50.2% with them ($p = 0.948$). In stage IV, OS improved from 4 months without new therapies to 11 months with their use ($p < 0.001$). A study of 173 MUP patients found that shorter OS correlated with positive lymph node count ($p = 0.01$), but not with the number removed ($p = 0.79$).[4] Chemotherapy and targeted therapy yielded lower survival rates, while immunotherapy resulted in higher rates. Thus, optimal MUP treatment combines surgery and immunotherapy. Chinese patients with advanced MUP had a 12.5% objective response rate (ORR) with second-line pembrolizumab. Surgical intervention in stage III MUP or metastatic kidney cancer (MKP) may improve survival by reducing tumour burden.[5] A stage IV MUP patient with the BRAF V600E mutation achieved nearly three years of complete remission (CR) with toripalimab, suggesting immunotherapy's potential effectiveness. Thus, it may be a viable option for MUP patients with BRAF V600E mutations, especially those unable or unwilling to pursue targeted therapy.

Skin toxicities, including vitiligo, are frequent irAEs in patients treated with anti-PD-1/PD-L1 therapies, affecting about 30-40% of individuals.[6] These events are believed to be T cell-mediated, potentially due to shared antigens between cancerous and normal skin tissues.[7] Vitiligo, which manifests as depigmentation, has been linked to a positive treatment response and better survival outcomes in melanoma patients undergoing immunotherapy.[8] There are clinical and histological differences between traditional vitiligo and ICI-induced vitiligo-like lesions. Research suggests that ICI-induced vitiligo may arise from cross-reactivity to antigens shared by melanoma cells and normal melanocytes, such as MART-1, GP100, TRP1-2, or tyrosinase.[9] It typically develops a few months after immunotherapy begins, often with symmetrical distribution and progressive spread. This case report describes a stage IV MUP patient who developed vitiligo during toripalimab treatment and achieved CR. It emphasises the importance of early lesion identification in melanoma, managing ICI-related adverse reactions, and toripalimab's potential as an immunotherapy for MUP patients, particularly those with BRAF V600E mutations.

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PATIENT'S CONSENT:
Informed consent was obtained from the patient for the publication of this case report and the use of related data. The patient understood that all identifying information would be anonymised, and the data would be used solely for academic and research purposes.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
TZ: Designed the study, collected and analysed data, and drafted the manuscript.
YC: Conducted literature review and contributed to the manuscript revision.
YL: Analysed imaging data and contributed to the discussion section.
YL: Managed patient follow-up and contributed to the data collection.
RW: Supervised the study, provided expert guidance, and finalised the manuscript.
All authors approved the final version of the manuscript to be published.

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