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##### \*CORRESPONDENCE

Soichiro Kado,  
✉ m07027sk@jichi.ac.jp

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# Remarkable effect of nivolumab on late liver metastasis recurrence in advanced malignant melanoma

Shoka Fukuizumi<sup>1</sup>, Soichiro Kado<sup>1\*</sup>, Takayo Ando<sup>1</sup>, Atsuko Sato<sup>1</sup>, Koji Kamiya<sup>1</sup>, Takeo Maekawa<sup>2</sup>, Mamitaro Ohtsuki<sup>1</sup> and Mayumi Komine<sup>1</sup>

<sup>1</sup>Department of Dermatology, Jichi Medical University, Tochigi, Japan, <sup>2</sup>Department of Dermatology, Saitama Medical Center, Jichi Medical University, Saitama, Japan

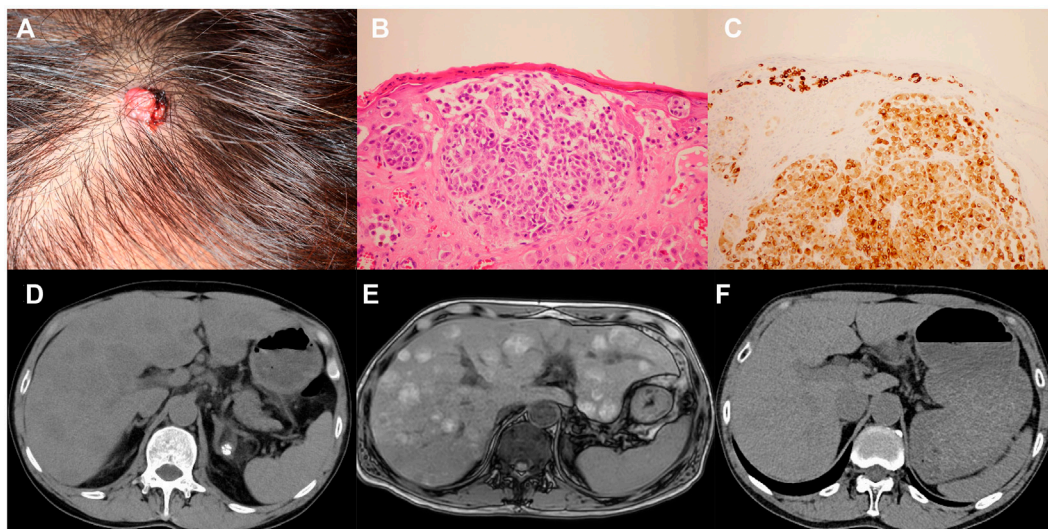
##### KEYWORDS

immune checkpoint inhibitors, late recurrence, liver metastasis, melanoma, nivolumab

A 58-year-old man presented with fever and anorexia. Eleven years earlier, he had undergone wide excision of a primary malignant melanoma on the left parietal scalp (Figures 1A–C) with cervical lymph node dissection (T3bN2aM0; stage IIIB and stage IIIC according to the AJCC 7th and 8th editions, respectively). He had received adjuvant intralesional interferon- $\beta$  therapy for 3 years and was subsequently monitored with computed tomography (CT) scans, showing no distant metastasis 5 months before presentation.

On admission, he exhibited fever (38.3 °C), leukocytosis (16,200/ $\mu$ L), elevated lactate dehydrogenase (701 IU/L), and an elevated C-reactive protein (CRP) level of 27.07 mg/dL. CT revealed multiple hepatic lesions that were absent 5 months earlier (Figure 1D). Metastatic liver tumors and infection were suspected, leading to hospitalization for antibiotic treatment. However, blood cultures obtained before treatment initiation were negative, and antibiotic therapy failed to improve either the fever or the CRP elevation. His condition rapidly deteriorated, with persistent fever, worsening ascites, and performance status decline from 0 to 3. Planned liver biopsy and endoscopic procedures were canceled due to his declining condition. Ascitic cytology showed no malignancy. Despite the lack of histological confirmation, magnetic resonance imaging (MRI) showed T1 hyperintense liver lesions (Figure 1E), and 5-S-cysteinyl-dopa was elevated (124 nmol/L), indicating metastatic melanoma. Nivolumab treatment was initiated, resulting in rapid improvement. The fever resolved within days and CRP promptly decreased (<5 mg/dL by day 10), indicating a tumor-related inflammatory response, rather than infection. After treatment initiation, BRAF testing revealed a V600E mutation, but nivolumab was continued given the clear clinical response. Three months post-treatment, the hepatic lesions became indistinct (Figure 1F), and the patient's performance status returned to 0. He has shown sustained response to nivolumab for over 2 years, monitored with non-contrast CT due to mild chronic kidney disease.

Malignant melanoma is a skin cancer with a high risk of recurrence and metastasis [1, 2]. The interval between initial treatment and subsequent recurrence or metastasis typically shortens with disease progression. In a large Duke University cohort (7,104 patients), only 168 patients (2.4%) developed their first recurrence after a 10-year disease-free interval; the majority of these patients had early-stage disease (92.9% stage I and 6.5% stage II), whereas only one patient (0.6%) initially presented with stage III disease [1]. These findings indicate that late first relapse more than 10 years after initial treatment is uncommon, and that such relapse is particularly rare in patients who initially present with stage III melanoma. Nevertheless, our patient developed hepatic



**FIGURE 1**

(A) Clinical appearance of the primary lesion 11 years before presentation: a 4 × 4-mm nodule on the left parietal scalp. (B) Hematoxylin and eosin staining (original magnification ×200) showing proliferation of atypical melanocytes forming nests within the epidermis, with extension into the dermis. (C) Melan-A immunohistochemistry (×100) highlighting atypical melanocytes in both the epidermis and dermis. (D) Non-contrast CT obtained before nivolumab initiation demonstrating multiple low-density lesions in the liver. (E) T1-weighted MRI showing corresponding hyperintense hepatic lesions, consistent with melanoma metastases. (F) Follow-up non-contrast CT 3 months after nivolumab initiation showing that the hepatic lesions had become indistinct, with no identifiable metastatic foci. CT, computed tomography; MRI, magnetic resonance imaging.

metastases 11 years after surgery despite initially having stage III disease, highlighting that metastatic melanoma should remain in the differential diagnosis when evaluating new hepatic lesions even after a prolonged disease-free interval, including in patients with initially advanced-stage disease.

The mechanisms underlying late recurrence of melanoma remain incompletely understood, but long-term tumor dormancy followed by disruption of immune control or tumor immune escape has been proposed. Reschke et al. suggested that melanoma cells may detach from the primary tumor and disseminate via lymphatic or hematogenous routes several decades before distant metastases become clinically apparent [2]. They discussed tumor dormancy as a multifactorial process involving immune-mediated growth control, cell-cycle arrest with reduced metabolic activity, and angiogenic regulation. They also proposed that individual immune surveillance may control residual melanoma cells for more than a decade, whereas advanced age and increasing comorbidities may disturb the immunological balance and contribute to overt recurrence [2]. Tissue-resident memory T cells (TRM) may be one component of this immune-mediated dormancy. Plunkett et al. reviewed evidence that TRM can maintain melanoma in a state of immune-mediated equilibrium, preventing progression to macroscopic disease [3]. In preclinical models, TRM surveilled skin regions containing melanoma cells and mediated protection in a TNF- $\alpha$ -dependent manner. However, the mechanisms by which occult melanoma subsequently becomes clinically overt remain unclear. Plunkett et al. described a possible immune-escape mechanism involving CD8-positive T cells and the PD-1/PD-L1 axis. In this model, engagement of PD-1 on CD8-positive T cells by tumor-expressed PD-L1 attenuates T-cell receptor

signaling, proliferation, and cytotoxicity, thereby suppressing anti-tumor immune responses. This PD-1/PD-L1-mediated impairment of CD8-positive T-cell activity may represent one mechanism by which dormant melanoma cells escape long-term immune surveillance and eventually progress to clinically apparent recurrence [3]. In the present case, the 3-year course of adjuvant intralesional interferon- $\beta$  therapy may have been one of several factors contributing to prolonged immune-mediated tumor control, although its role cannot be determined. Conversely, age-related alterations in immune surveillance may have disrupted this equilibrium and contributed to the abrupt clinical manifestation of recurrence.

In this case, MRI played a pivotal role in diagnosing liver metastasis. Malignant melanoma often exhibits hyperintense signals in T<sub>1</sub>-weighted MRI images [4], a critical characteristic finding under challenging histological confirmation. MRI can be especially useful in such cases, where biopsy or other tissue-based diagnostic methods are not feasible.

Despite liver metastases—a factor associated with diminished clinical benefit from immune checkpoint blockade [5]—our patient showed a rapid and sustained response to nivolumab. If late relapse in this case reflected immune escape through mechanisms such as those discussed by Plunkett et al. [3], restoring antitumor immunity via PD-1 blockade could be biologically plausible and may have contributed to the marked response observed. However, whether late first relapse is associated with enhanced sensitivity to immune checkpoint inhibitors remains uncertain. The efficacy of immune checkpoint inhibitors for late recurrence in ICI-naïve patients has not been well characterized; in this regard, further case accumulation is required to better define benefit predictors.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required because this manuscript describes a single case report and does not constitute a research study. Written informed consent for publication was obtained from the patient. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

SF and SK drafted the manuscript. All authors contributed to the article and approved the submitted version.

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