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Resolution of direct antiglobulin test-negative autoimmune hemolytic anemia without corticosteroid therapy after discontinuation of nivolumab plus ipilimumab therapy for subungual melanoma

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autoimmune hemolytic anemia, direct antiglobulin test, immune checkpoint inhibitor, immune-related adverse events, malignant melanoma

Dear Editors,

Immune checkpoint inhibitors (ICIs) are widely used for the treatment of unresectable or advanced malignant melanoma and have markedly improved patient outcomes. However, ICIs can cause immune-related adverse events (irAEs) affecting various organs. Hematologic irAEs are uncommon, and autoimmune hemolytic anemia (AIHA) is particularly rare [1, 2]; among AEs reported with anti-PD-1/PD-L1 and anti-CTLA4 agents, the reported frequency has been estimated at 0.15%–0.25% and 0.06%, respectively [3]. We report a case of AIHA associated with nivolumab plus ipilimumab therapy in a patient with subungual malignant melanoma.

A 52-year-old Japanese man with a history of alcohol-related liver dysfunction presented with an ulcerated nodular tumor involving the nail unit of the right thumb. The tumor measured 27 × 20 × 19 mm, was broad-based and elevated, and showed a dark-red to violaceous surface. A 17 × 6-mm black macule was also observed on the fingertip (Figures 1A,B). He subsequently underwent right thumb amputation and right axillary sentinel lymph node biopsy. Histopathological examination of the amputated specimen revealed proliferation of atypical epithelioid to spindle-shaped tumor cells on hematoxylin and eosin staining (Figure 1C). The tumor cells were positive for Melan-A (Figure 1D), HMB-45 (Figure 1E), and S-100. Based on these findings, the final diagnosis was malignant melanoma. The tumor was staged as pT4bN0M0 (Stage IIC) according to the 8th edition of the American Joint Committee on Cancer staging system. BRAF V600 mutation testing revealed wild-type.

Ten months after surgery, contrast-enhanced computed tomography (CT) showed multiple bilateral pulmonary metastases (Figure 1F). Subsequently, nivolumab plus ipilimumab therapy was initiated. After two cycles, the patient presented with a three-day history of fatigue and headache. Physical examination revealed mild conjunctival pallor. Laboratory investigations revealed severe anemia (hemoglobin, 7.6 g/dL; baseline, 13.0 g/dL), elevated lactate dehydrogenase (LDH, 1283 U/L), reticulocytosis (203,000/μL), and a low haptoglobin level (1.5 mg/dL). Both the direct antiglobulin test (DAT) and indirect

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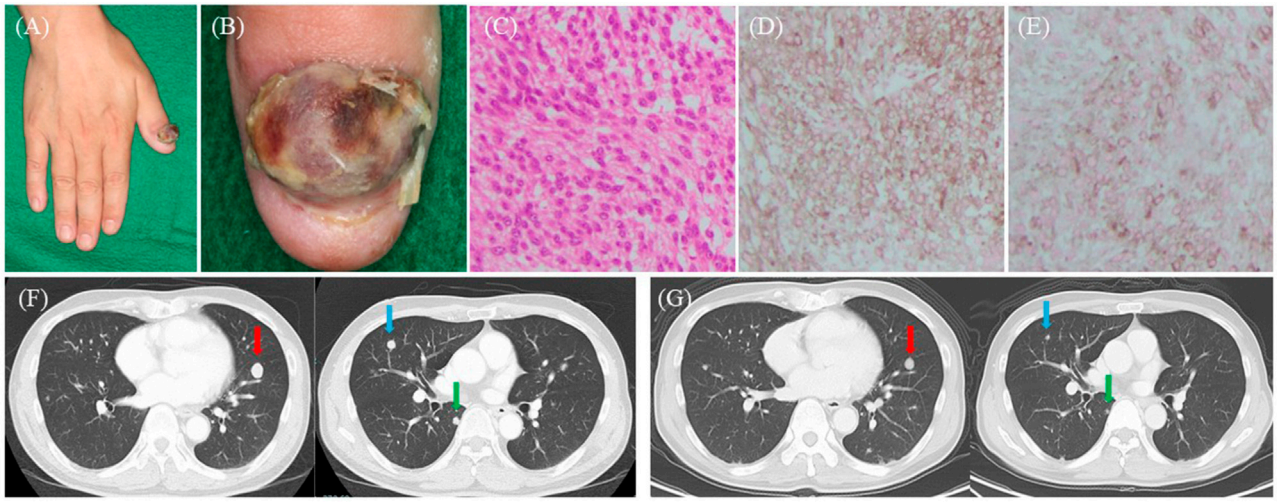

FIGURE 1
Clinical, histopathological, radiological findings. **(A,B)** Clinical findings of the tumor on the right thumb. **(C)** Hematoxylin and eosin staining showing atypical epithelioid to spindle-shaped tumor cells. Tumor cells were positive for Melan-A **(D)**, HMB-45 **(E)**. **(F)** CT before nivolumab plus ipilimumab therapy showing multiple pulmonary metastases. **(G)** CT 2 months after treatment initiation showing reduction in pulmonary metastases.

antiglobulin test were negative. Follow-up contrast-enhanced CT demonstrated a reduction in the size of the pulmonary metastases, consistent with a partial response (Figure 1G). No evidence of bleeding, bone marrow suppression, infection, or exposure to other new medications was identified. Based on laboratory findings of acute hemolysis and exclusion of other causes, he was diagnosed with ICI-associated DAT-negative AIHA.

Nivolumab plus ipilimumab therapy was discontinued immediately. Because the hemoglobin level began to increase during the evaluation period, corticosteroid therapy was not initiated, and the patient was observed with supportive care alone. The hemoglobin level gradually returned to baseline, and LDH level decreased accordingly. The severity of AIHA was classified as grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Because the risk of recurrent hemolysis on rechallenge was considered to be unacceptably high, anti-PD-1 monotherapy was not selected as subsequent treatment. Two months after improvement of AIHA, treatment was switched to dacarbazine, and four cycles were administered. However, follow-up CT revealed progression of pulmonary metastases, with new subcutaneous metastases in the left buttock and pleural metastases, consistent with progressive disease. The patient opted for palliative care and died 12 months after discontinuation of nivolumab plus ipilimumab therapy.

Leaf et al. proposed diagnostic criteria for ICI-associated AIHA (Supplementary Table S1) [4]. Our patient fulfilled these criteria, including an abrupt decrease in hemoglobin level, laboratory evidence of hemolysis, development after ICI initiation, and exclusion of other causes of anemia. This case also suggests that selected patients with ICI-associated AIHA may improve after ICI discontinuation without corticosteroid therapy, although close monitoring is essential because hemolysis can progress rapidly.

A recent review summarized 92 cases of ICI-associated immune hemolytic anemia [5]. In the review, melanoma accounted for 38 of 84 cases with reported tumor types, representing the most frequently reported malignancy. The median time from ICI initiation to onset was 62 days, corresponding to a median of three treatment cycles. Regarding the triggering ICIs, pembrolizumab and nivolumab were the most frequently reported agents, whereas nivolumab plus ipilimumab accounted for 11 of 92 cases [5]. In the present case, AIHA developed after two cycles of nivolumab plus ipilimumab therapy, which was consistent with the typical timing reported in previous cases.

DAT negativity does not rule out ICI-associated AIHA. The same review reported negative DAT results in 16 of 88 patients who underwent direct antiglobulin testing.

Regarding management, most reported cases required active intervention. A recent review of 92 cases showed that ICI therapy was withheld in 87 patients, pharmacological treatments, predominantly high-dose glucocorticoids, were administered in 90 patients, and transfusion support was required in 58 patients. In our patient, corticosteroids and transfusion were withheld because he remained hemodynamically stable and showed an early upward trend in hemoglobin during evaluation. Close inpatient monitoring would have allowed prompt intervention if his condition had worsened. Hemoglobin and LDH levels subsequently improved after discontinuation of nivolumab plus ipilimumab therapy. This favorable course should be regarded as exceptional, and corticosteroid therapy remains the standard therapeutic option for clinically significant or progressive ICI-associated AIHA.

This case highlights the need for vigilance when unexplained anemia develops during ICI therapy. AIHA should be considered when abrupt anemia is accompanied by biochemical evidence of hemolysis, even if the DAT result is negative. Although our patient improved after ICI discontinuation without corticosteroid therapy, ICI-associated AIHA can deteriorate rapidly; therefore, careful

monitoring and appropriate therapeutic intervention according to clinical severity are essential.

Data availability statement

No datasets were generated or analyzed for this case report. The relevant clinical information is included in the article.

Ethics statement

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

MN and SS were involved in patient care and drafted the manuscript. All authors contributed to patient care, interpretation of clinical findings, and manuscript revision. All authors approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. The authors used ChatGPT (OpenAI) for language editing assistance. The authors reviewed and edited all AI-assisted content and take full responsibility for the final content of the manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jcia.2026.17320/full#supplementary-material

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