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CORRESPONDENCE

Autoimmune hemolytic anemia during long-term administration of nivolumab for metastatic melanoma

A 79-year-old Japanese male had received the programmed cell death (PD)-1 inhibitor nivolumab (2 mg/kg every 3 weeks) for 50 cycles (34 months) to treat hepatic metastasis of malignant melanoma (MM; pT4aN0 M0, stage IIIB; Figure 1A,B). The hepatic metastasis remained stable during treatment, and no remarkable adverse events occurred.

However, the patient emergently presented to our hospital due to the sudden onset of general fatigue and edema after the 50th cycle of nivolumab. He exhibited generalized jaundice and conjunctival pallor. We consulted a hematologist. Laboratory investigations showed a low hemoglobin level (Hb) (5.8 g/dL), haptoglobin level (<1 mg/dL), and red blood cell count (1.28×10^6/μL), as well as a high white blood cell count (12.66×10^3/μL) and reticulocyte percentage (13.5%) and elevated levels of total bilirubin (3.7 mg/dL), direct bilirubin (1.2 mg/dL), lactate dehydrogenase (LDH; 585 U/L), and urinary urobilinogen (4.0 mg/dL). Direct and indirect antiglobulin tests were both positive. At baseline, his platelet count, prothrombin time, activated partial thromboplastin time, and levels of Hb, fibrinogen, ferritin, and LDH were within the normal range. CT revealed no new metastatic lesions or enlargement of the existing hepatic metastasis. The patient was diagnosed with autoimmune hemolytic anemia secondary to nivolumab (nivolumab-AIHA).

We discontinued nivolumab and administered oral prednisolone therapy (1 mg/kg/d) and red cell transfusion. The patient's anemia improved after he began the prednisolone treatment. We gradually tapered the prednisolone dose at a rate of 5 mg every 2 weeks, with an eventual maintenance dose of 10 mg/day. However, the patient hoped palliative treatment and died due to rupture of the hepatic metastasis 5 months after stopping nivolumab.

Inhibitors of PD-1 or PD death ligand 1 (PD-L1) are common immune checkpoint inhibitors (ICIs). Our case report is the first in Japan in which nivolumab-AIHA occurred in a patient with MM.

Programmed cell-1/PD-L1-AIHA is a rare immune-related adverse event. Tanios *et al.*[1] reported that the incidence of PD-1/PD-L1-AIHA in patients receiving ICIs was 0.15%–0.25%.

Leaf *et al.* defined the criteria of ICI-AIHA as follows: (a) an abrupt decrease in Hb of ≥2 g/dL; (b) at least two laboratory findings characteristic of hemolysis; (c) AIHA occurring after initiation of an ICI; (d) exclusion of other causes of anemia; and (e) ICI therapy considered as the most likely cause of AIHA by the treating physician.[2] All of these criteria were met in our case.

The differential diagnosis included drug-induced AIHA, disseminated intravascular coagulation (DIC), and hemophagocytic syndrome (HPS). Our patient did not receive any additional drugs, and DIC and HPS were ruled out based on laboratory findings.

Interestingly, our patient developed AIHA long after starting nivolumab (34 months). In past reports, nivolumab-AIHA occurred within 2–80 weeks of starting nivolumab, and the median time to ICI-AIHA was reported to be 50 days.[1–4] There are no reports of AIHA occurring after long-term administration of nivolumab, as in

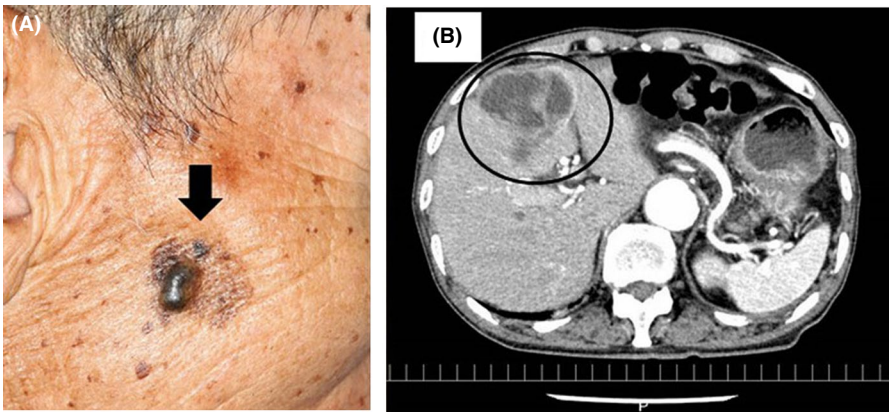

FIGURE 1 (A) Physical examination revealed an irregularly shaped, 25 mm ×25 mm area of pigmentation associated with an oval black nodule on the right cheek (arrow). (B) CT scan showing the hepatic metastasis (circle)

our case. As ICI-AIHA is usually serious, clinicians should be aware of the risk of ICI-AIHA even in patients who have been treated with ICIs for a long period of time.

KEYWORDS

anemia, jaundice, melanoma, metastasis, nivolumab

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DECLARATION SECTION

Approval of the research protocol: N/A.

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