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LETTER TO THE EDITOR

Type 1 diabetes mellitus in a melanoma patient treated with adjuvant nivolumab therapy

To the Editor,

Immune checkpoint inhibitors (ICIs) are well known to cause inflammatory side effects that are known as immune-related adverse events (irAEs).[1] Although irAEs can occur in any organ, they are relatively rare in type 1 diabetes mellitus (T1DM), occurring in less than 1% of the patients treated with ICIs.[2] There have been also known that a few cases may develop T1DM during adjuvant use of programmed death-1 inhibitors,[3,4] but its clinical course has not ever been described in detail. We herein report the clinical course of a patient who suffered from T1DM during adjuvant nivolumab therapy.

A 44-year-old Japanese man presented with a reddish nodule, measuring 30 × 20 mm, on the right plantar arch. He had no history of diabetes mellitus. Physical examination revealed right inguinal lymphadenopathy. As computed tomography revealed no evidence of distant metastases, we performed wide local excision and inguinal lymph node dissection. A histopathological finding was malignant melanoma (Stage IIIC, pT4b pN1b M0, tumor thickness: 8.0 mm, AJCC 8th edition). *BRAF* mutation was not identified. Adjuvant nivolumab therapy (nivolumab at 240 mg/day) every 2 weeks) was started. He had not experienced any irAEs until 8 courses of adjuvant nivolumab therapy; however, he complained of fatigue and thirst at the 9th administration of nivolumab. Laboratory examination showed plasma glucose and glycated hemoglobin A1c (HbA1c) elevated to 298 mg/dL and 6.9%, respectively (Figure 1). Additional blood tests revealed elevation of total ketone bodies (689 μmol/L) and low C-peptide level (0.62 ng/mL) at the onset of T1DM. In addition, anti-glutamic acid decarboxylase and anti-tyrosine phosphatase IA-2 were negative. Based on the clinical findings, he was diagnosed as having T1DM due to adjuvant nivolumab therapy. Forty-nine days after the initiation of insulin replacement therapy, the adjuvant nivolumab therapy was resumed.

T1DM has been reported to occur in 0.2% of advanced melanoma patients who receive ICI therapy, with approximately half of these patients graded 3 or higher.[2] Of note, the insulin deficiency is usually irreversible and requires permanent insulin replacement therapy. In addition, the onset ranges from a few weeks to one year after the initiation of ICI therapy. As for the clinical characteristics, symptoms of T1DM related to ICI therapy consist of polyurea, polydipsia, fatigue, weight loss, and dehydration. In laboratory findings, the C-peptide level is low while the HbA1c level is usually not very high.[5] These clinical features are also consistent with the present case. The incidence of T1DM during adjuvant settings has been reported in 5 pembrolizumab cases and 2 nivolumab cases. Of 8 cases including the present case, 7 were grade 3 or higher.[3,4] These facts suggest that T1DM related to adjuvant use of ICIs is also likely to severe.

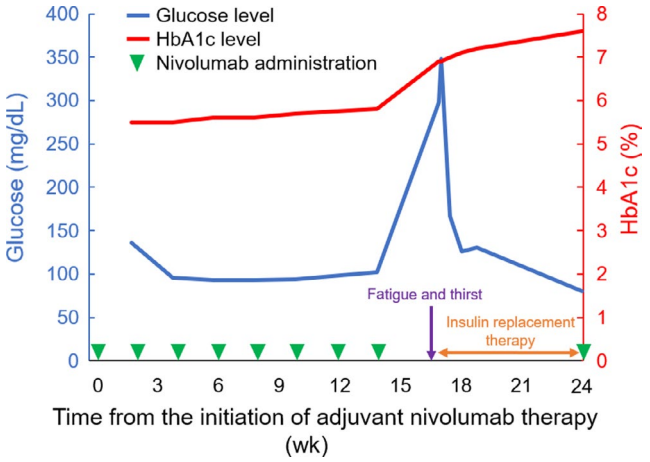

FIGURE 1 The clinical course of the present case. The x-axis indicates weeks elapsed after the initiation of adjuvant nivolumab therapy. The y-axis indicates serum glucose (left-hand y-axis: mg/dL, blue) and HbA1c level (right-hand y-axis: %, red)

In conclusion, we described the clinical course of T1DM related to adjuvant nivolumab therapy. Because T1DM due to ICIs usually requires permanent insulin replacement and is likely to be severe as it was in the present case, we should consider more carefully about the appropriate use of ICIs in adjuvant settings.

CONFLICTS OF INTEREST

None to declare.

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