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CORRESPONDENCE

Recurrent advanced rectal malignant melanoma that discontinued anti-PD-1 antibody after complete response and was refractory to rechallenge

Mucosal melanoma (MCM) is a clinically rare melanoma subtype, accounting for less than 1% of all subtypes in the United States.[1] In contrast, MCM is the second most common clinical subtype, accounting for 22.6% of melanoma subtypes, in Asia.[2] Rectal melanoma (RM), accounting for 19% of all MCMs, is the second most common subtype after melanoma of the vulva.[1] The efficacy of anti-PD-1 antibodies for MCM is lower than that for cutaneous melanoma. The complete response (CR) and partial response rates to anti-PD-1 antibodies in unresectable melanoma of the gastrointestinal tract are only 7% and 19%, respectively.[3] We herein report the first case of RM with a rechallenge of anti-PD-1 antibody that was discontinued after CR.

A 70-year-old woman with a 4-year history of anti-centromere antibody positive systemic sclerosis treated with beraprost sodium, developed fecal occult blood. She was diagnosed with RM and underwent a laparoscopic abdominoperineal resection (Figure 1A). Pathological findings showed atypical melanocytic cells had proliferated and infiltrated into the submucosal layer (Figure 1B). One

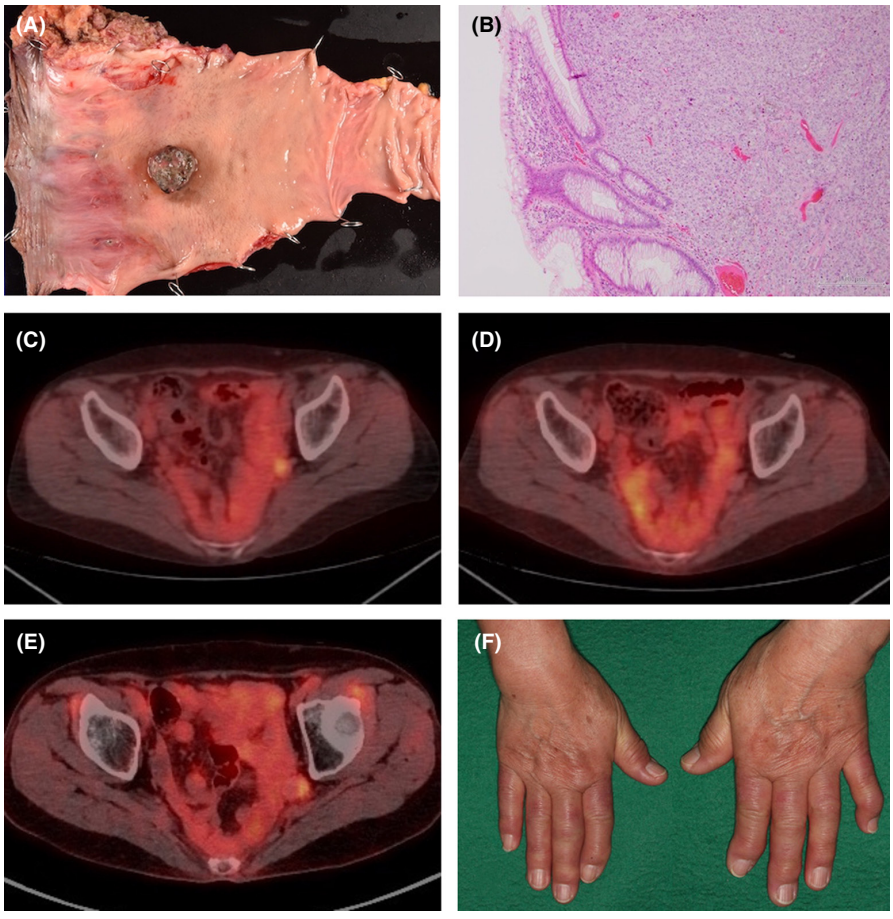

FIGURE 1 (A) Surgical specimen of abdominoperineal resection. 20×20 mm sized tumor on the rectum. (B) Atypical melanocytic cells infiltrated into the submucosal layer. Tumor thickness was 11.0 mm, Stage IIC (according to the 8th American Joint Committee on Cancer for cutaneous melanoma). (C) Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) shows FDG accumulation in pelvic lymph nodes 1 year after the surgery. (D) One year after starting nivolumab, FDG-PET/CT shows a metabolic complete response. (E) Twenty-one months after discontinuation of nivolumab, FDG-PET/CT shows FDG accumulation in pelvic lymph nodes. (F) Clinical features of chilblains-like erythema on the fingers

year after surgery, pelvic lymph node metastasis was detected (Figure 1C). BRAF mutation was not detected. Nivolumab (3 mg/kg every 2 weeks) was started. One year later, she achieved metabolic CR (Figure 1D). Although no immune-related adverse events (irAEs) occurred, nivolumab was discontinued at her insistence. At a follow-up 21 months after the discontinuation of nivolumab, a pelvic lymph node metastasis recurrence (Figure 1E) and a lung metastasis were discovered. Nivolumab rechallenge was initiated (480 mg every 4 weeks). The next day, chilblains-like erythema was observed on her fingers (Figure 1F). Additionally, 1 month later, refractory deep vein thrombosis of the lower extremities and pulmonary thromboembolism developed. We examined the cause of the thrombosis but could not identify it. No autoantibodies other than anti-centromere antibody were detected. Despite postponing the administration of nivolumab, vitiligo rapidly spread over the whole body. Although she was treated with nivolumab only once more, multiple metastases progressed. She requested palliative care treatments and died 9 months after rechallenge.

Previous studies have discussed the relationships between the discontinuation of anti-PD-1 antibodies after CR and the maintenance of a good response.[4] According to the KEYNOTE-001 study, approximately 90% of patients who discontinued anti-PD-1 antibody after CR survived, with a CR maintained for a median of 22 months. It has been reported that the risk of recurrence is lower if the duration of treatment with anti-PD-1 antibody is more than 6 months.[5] However, these studies did not include enough cases of MCM.

In our patient, the nivolumab rechallenge was ineffective, and the patient developed vitiligo. Generally, patients who have discontinued anti-PD-1 antibody after CR respond well to rechallenge. Furthermore, there are no reports on the frequency of irAEs associated with dosage changes of anti-PD-1 antibodies. Results of clinical trials are pending with regard to safe discontinuation after CR.[6] We are presently unable to discuss the ideal duration and dose of anti-PD-1 antibody in MCM. Further studies are needed on the withdrawal and rechallenge of immune checkpoint inhibitors in MCM.

DECLARATION SECTION

Approval of the research protocol: N/A.
Informed Consent: The patient provided written informed consent.
Registry and the Registration No.: N/A.
Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Bishop KD, Olszewski AJ. Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer. 2014;134:2961–71.
2. Chi Z, Li S, Sheng X, Si L, Cui C, Han M, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases. BMC Cancer. 2011;11:85.
3. Nakamura Y, Namikawa K, Yoshikawa S, Kiniwa Y, Maekawa T, Yamasaki O, et al. Anti-PD-1 antibody monotherapy versus anti-PD-1 plus anti-CTLA-4 combination therapy as first-line immunotherapy in unresectable or metastatic mucosal melanoma: a retrospective, multicenter study of 329 Japanese cases (JMAC study). ESMO Open. 2021;6:100325.
4. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol. 2018;36:1668–74.
5. Jansen YJL, Rozeman EA, Mason R, Goldinger SM, Geukes Foppen MH, Hoejberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. Ann Oncol. 2019;30:1154–61.
6. Mulder E, de Joode K, Litiere S, Ten Tije AJ, KPM S, Boers-Sonderen MJ, et al. Early discontinuation of PD-1 blockade upon achieving a complete or partial response in patients with advanced melanoma: the multicentre prospective safe stop trial. BMC Cancer. 2021;21:323.