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CORRESPONDENCE

Nail toxicity with nail bed ulceration associated with pembrolizumab

Pembrolizumab is an immune checkpoint inhibitor (ICI) that exerts its anti-tumor effect by inhibiting the binding of PD-1 on T cells to PD-L1 on tumor cells. While its efficacy has been extensively evaluated, immune-related adverse events (irAEs) have become problematic.

A 70-year-old Japanese man was diagnosed with bladder cancer at his previous urologist's department 2 years prior to his first visit. He had undergone resection, but the disease recurred 1 year later. Despite treatment with gemcitabine and cisplatin, he experienced progressive disease, and started pembrolizumab 9 months before the first visit to our department. After six courses of pembrolizumab, subungual hemorrhage appeared in his fingers and toes, and the nails subsequently detached and fell off. The nail lesions were thought to be caused by pembrolizumab, so the drug was discontinued, and he was scheduled for additional surgery. No irAEs other than nail symptoms were observed. He was referred to the Department of Urology at our hospital for surgery and to our department for management of nail symptoms. At the time of the first visit, all the nails on his fingers and toes had fallen off, and the nail beds were ulcerated (Figure 1A, B).

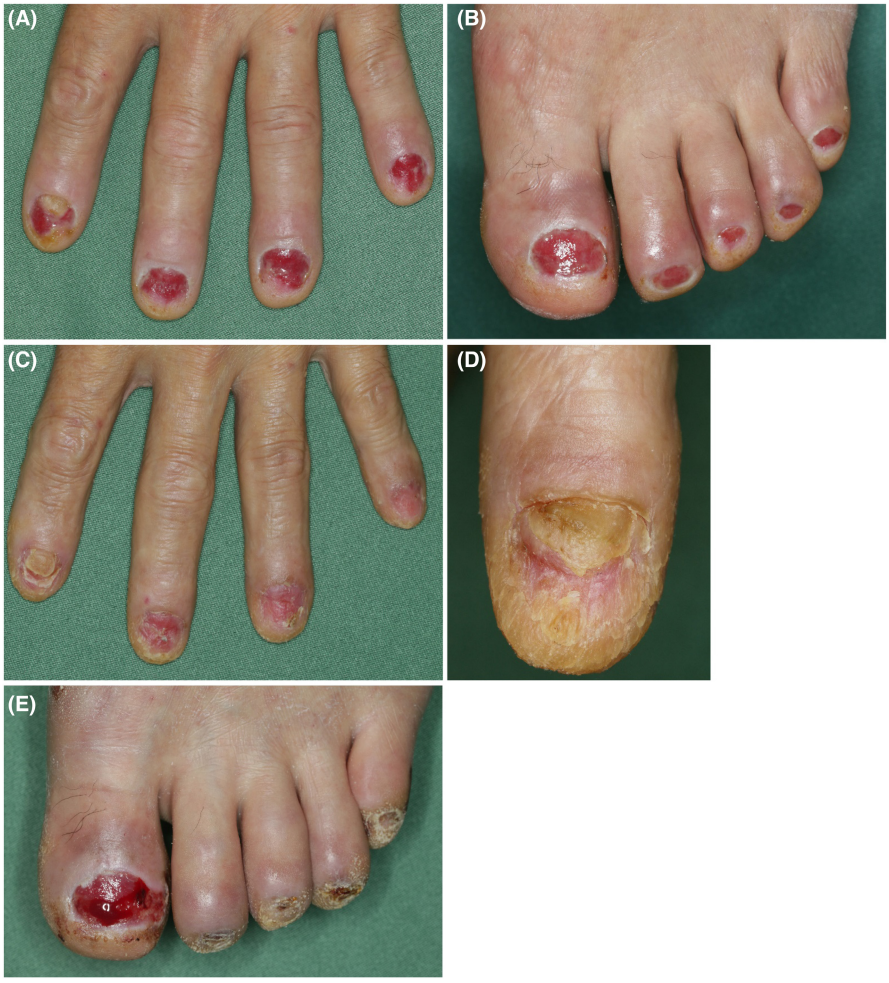

FIGURE 1 Clinical findings of left hand and left foot at first visit (A, B), and after topical steroid and prostaglandin E1 therapy (C–E). (A) The patient's fingernails detached from the nail matrix, and the nail beds were ulcerated. (B) All the toenails had fallen off, and the nail beds were ulcerated. (C, D) Clinical findings of left fingers (C) and left thumb (D). The nail beds of all fingers were epithelialized, and nail regrowth was observed in the thumbs and index fingers. (E) The toenails were epithelialized, except for those of the first toes. No toenails regrew.

The nails of the thumbs and index fingers of both hands had partially regrown. Since the patient was scheduled for surgery, he was not treated with oral prednisolone but rather with topical steroids. Epithelialization of the nail beds did not progress; therefore, the patient was switched to topical prostaglandin E1 ointment. Two months after the first visit, the nail beds were almost epithelialized, but the nails did not regrow, except for those of the both thumbs and index fingers (Figure 1C-E).

Four reports of cases of nail toxicity caused by pembrolizumab have been published,[1–3] all of which occurred in patients older than 70 years; the number of cycles administered until nail toxicity were observed ranged from 7 to 29. Although their symptoms were confined to the toes, two of these cases had ulcerated nail beds and most of the nails did not regrow,[1] similar to the present patient. It is important to note that in these four previous cases, prior gemcitabine and platinum treatment might have affected nail symptoms; furthermore, nail symptoms were only treated with topical steroids. No other cases of ulceration of all the nail beds of the fingers and toes as in the present case have been reported; therefore, the present case appears to reflect the most severe case of nail side effects caused by pembrolizumab reported thus far. Histological findings were not available because the patients did not consent to skin biopsy. The histological findings of cases 1 and 2 showed a lichenoid reaction,[1] the similar mechanism is thought to be present in this case. However, the mechanism underlying severe inflammation confined to the nail matrix and nail bed in patients treated with ICIs remains unclear. Although this is a rare side effect, the number of reports of similar irAEs is expected to increase as the indications of ICIs expand.

KEYWORDS

immune checkpoint inhibitor, irAE, nail bed ulceration, nail toxicity, pembrolizumab

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol: Not applicable.
Informed consent: Informed consent was obtained from the patient.
Registry and the registration no.: N/A.
Animal studies: N/A.

Shintaro Maeda MD, PhD[1]
Yasuhito Hamaguchi MD, PhD[1]
Kaori Sawada MD, PhD[1]
Kyoko Shimizu MD[1]
Kyosuke Oishi MD, PhD[1]
Katsushige Taniuchi MD, PhD[2]
Takashi Matsushita MD, PhD[1]

[1]*Department of Molecular Pathology of Skin, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan*
[2]*Division of Dermatology, Noto General Hospital, Nanao, Japan*

Correspondence
Shintaro Maeda, Department of Molecular Pathology of Skin, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan.
Email: maeda@med.kanazawa-u.ac.jp

ORCID

Shintaro Maeda https://orcid.org/0000-0001-7824-7060
Yasuhito Hamaguchi https://orcid.org/0000-0001-5305-7770

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