



Subacute cutaneous lupus erythematosus with melanocyte elimination induced by pembrolizumab

Journal:	<i>The Journal of Dermatology</i>
Manuscript ID	JDE-2019-1283.R1
Wiley - Manuscript type:	Letter to the Editor
Date Submitted by the Author:	n/a
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Keywords:	SCLE, anti-SSA, pembrolizumab, vitiligo, immune-related adverse events
Abstract:	

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Letter to the Editor

Subacute cutaneous lupus erythematosus with melanocyte elimination induced by
pembrolizumab

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Funding sources: None

Conflict of interests: None

Word count: **500/500** words

Dear Editor,

Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 (PD-1) have been efficacious treatments in oncology. However, the administration of ICI induces a large spectrum of autoimmune side effects, known as immune-related adverse events (irAEs). Cutaneous toxicity is thought to be among the most prevalent irAEs.¹

A man in his 80's presented multiple metastatic melanomas on the face, which were judged as unresectable, and treatment with pembrolizumab was started. After the fifth pembrolizumab administration, a grade 2 skin rash (multiple annular erythema) appeared, mainly on the trunk. The primary melanoma and its multiple metastases regressed significantly without any new lesions forming. Since the skin symptoms progressed to grade 3 (Fig. 1a), pembrolizumab was stopped after the ninth administration, and the administration of oral prednisolone (PSL) at 1 mg/kg/day with topical steroid was started. Sicca, fever, fatigue, mucosal involvement, and liver dysfunction were not observed. A biopsy specimen from annular erythema on the back showed strong liquefaction degeneration, and superficial dermal edema (Fig. 1d). Direct immunofluorescence tests for the deposition of immunoglobulins and complements and

serum anti-ssDNA were negative. Anti-Ro52/TRIM21 and SS-A/Ro60 were detected by immunoblot and were confirmed by mass spectrometric analyses and ELISA. Anti-Ro52 and anti-Ro60 antibodies had remained for three months after the PSL treatment (Supplementary File: Table 1). Unfortunately, this patient was unable to resume ICI treatment because of progressive dementia, although he was a good responder. He stopped coming to our hospital three months after the PSL treatment started. Some of the erythema regressed, leaving incomplete depigmentation of the skin at his last visit (Fig. 1b). MART-1 and c-Kit immunostaining showed no positively stained melanocytes in the basement membrane zone of a skin sample from the fresh annular erythematous lesions on his back (Fig. 1d).

Patients with drug-induced cutaneous lupus erythematosus (DI-CLE) tend to be anti-SS-A-positive (74%), and anti-SS-A-positive DI-CLE patients mainly show SCLE.² We diagnosed the present case as DI-SCLE showing persistent, characteristic annular erythema with the production of anti-SS-A/Ro antibodies along with a rash, but without any systemic symptoms or mucosal involvement.

SCLE/CLE erythema is known to cause depigmentation. A previous paper reported the elimination of melanocytes from depigmentation after CLE/SCLE erythema.³ Our report is the first to show melanocytes in SCLE skin lesions to be depleted from fresh

erythematous lesions. In our case, melanocytes were absent even in the part of the basal cell layer with fewer inflammatory cell infiltrates, and this elimination seems to be caused not by chronic inflammatory damage, but by melanocyte-specific cellular immunity.

Vitiligo frequently occurs in melanoma patients treated with anti-PD-1 agents, and such vitiligo is thought to be due to a T cell cross-reaction against melanoma cells and melanocytes, and is associated with a favorable response to ICI in melanoma patients.¹ To our knowledge, five SCLE cases induced by anti-PD-1 treatment without vitiligo have been reported (Supplementary File, References). Clarifying whether this early melanocyte depletion is a common disease course of SCLE or whether it is anti-PD-1 specific requires further investigation.

References

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Figure legends

Fig 1. Skin manifestations and histopathology of the present patient

(a) The patient shows a cutaneous adverse event (Grade 3) from anti-PD-1 administration. (b) Three months after the prednisolone treatment, the annular erythema has regressed, but depigmentation is seen on his back. (c) A skin biopsy sample from annular erythema on the back reveals dense infiltration of lymphocytes in the basement membrane zone, the superficial dermis, and perivascular regions (hematoxylin-eosin stain, original magnification x200) (d) MART-1-positive melanocytes are not seen in the basement membrane zone of a skin sample from the annular erythema with depigmentation in the back (MART-1 stain, original magnification x200).

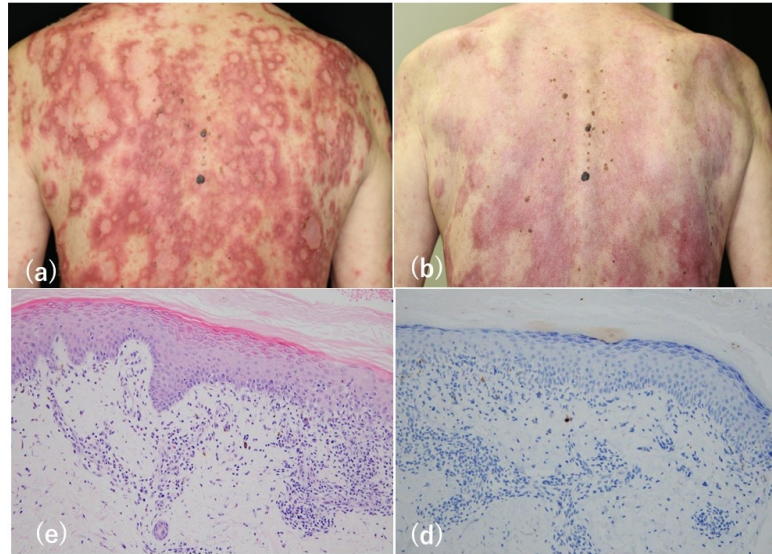


Figure1

338x190mm (96 x 96 DPI)