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CORRESPONDENCE

Maculopapular erythema caused by previously used chemotherapy drugs after nivolumab treatment for malignant mesothelioma

Dear editor,

Currently, an increasing number of cutaneous adverse reactions resulting from the use of programmed cell death protein 1 (PD-1) inhibitors have been described.[1] Here, we present a case in which drug eruption had not appeared before nivolumab therapy, but was induced by the same chemo drug after nivolumab therapy.

A 56-year-old woman with malignant mesothelioma, diagnosed 3 years ago, underwent thoracolysis of the left lung after three courses of chemotherapy with cis-diamminedichloroplatinum and with pemetrexed sodium hydrate (PEM). After three courses of chemotherapy with carboplatin, PEM, and bevacizumab after the operation, she achieved a nonprogressive disease (non-PD) state for 1 year. However, nivolumab was selected for the second-line treatment owing to the appearance of a recurrent lesion in her left lung apex. The cancer lesion did not expand for 2 years after nivolumab administration. One month after the last nivolumab treatment, PEM monochemotherapy was readministered for the expanded lesion, and a few days later, a generalized rash appeared. Erythema and papules with pruritus were observed in the trunk (Figure 1A,B). Histopathological examination revealed thickening of the epidermis, spongiosis, and a large number of eosinophils and lymphocytes in the upper dermis (Figure 1C,D). Immunostaining of CD4 and CD8 revealed that the number of positive cells was nearly identical for CD4 and CD8 (Figure 1E,F). Blood tests revealed a decrease in the number of white blood cells (1600/μl; lymphocytes, 650/μl). Drug-induced lymphocyte stimulation tests (DLSTs) indicated positive results against PEM (481%; reference index in the Japanese population, <180%). The rash improved within 1 week without any treatment.

Programmed cell death protein 1 inhibitors such as nivolumab are available for almost every cancer type.[1] Depending on cancer type, previously used chemotherapy, which had obtained certain effect, would be selected as the next-line treatment after anti-PD-1 therapy. In cases of progressive malignant mesothelioma during PD-1 therapy, it is recommended to consider monochemotherapy with PEM if the first-line treatment had achieved non-PD by combination regimen with PEM.[2] In the dermatological field, in B-RAF–positive metastatic melanomas, B-RAF/MEK inhibitors could be used prior to anti-PD-1, followed by B-RAF inhibitors after anti-PD-1 administration. Recently, it has been reported that B-RAF inhibitor treatment after anti-PD-1 can result in drug eruption.[3] Additionally, Shinkawa *et al.*[4] reported similar cases with the drug eruptions were observed as a result of administration of antibiotics following anti-PD-1 therapy. The characteristics of these drug eruptions are an increase in CD8-positive cells in histopathology, and Watanabe *et al.*[5] reported that CD8-positive cell activation is associated with a high probability of positive DLST results with these cases. Similar to PEM, antitumor agents such as cytotoxic agents and antimetabolites negatively affect cell proliferation and differentiation. Therefore, DLST tends to be negative. However, strongly positive DLST results against PEM were obtained from blood sample in our case despite the low lymphocyte count.

Unfortunately, evidence that anti-PD-1 therapy could affect the induction of drug eruption is lacking; however, there has been an

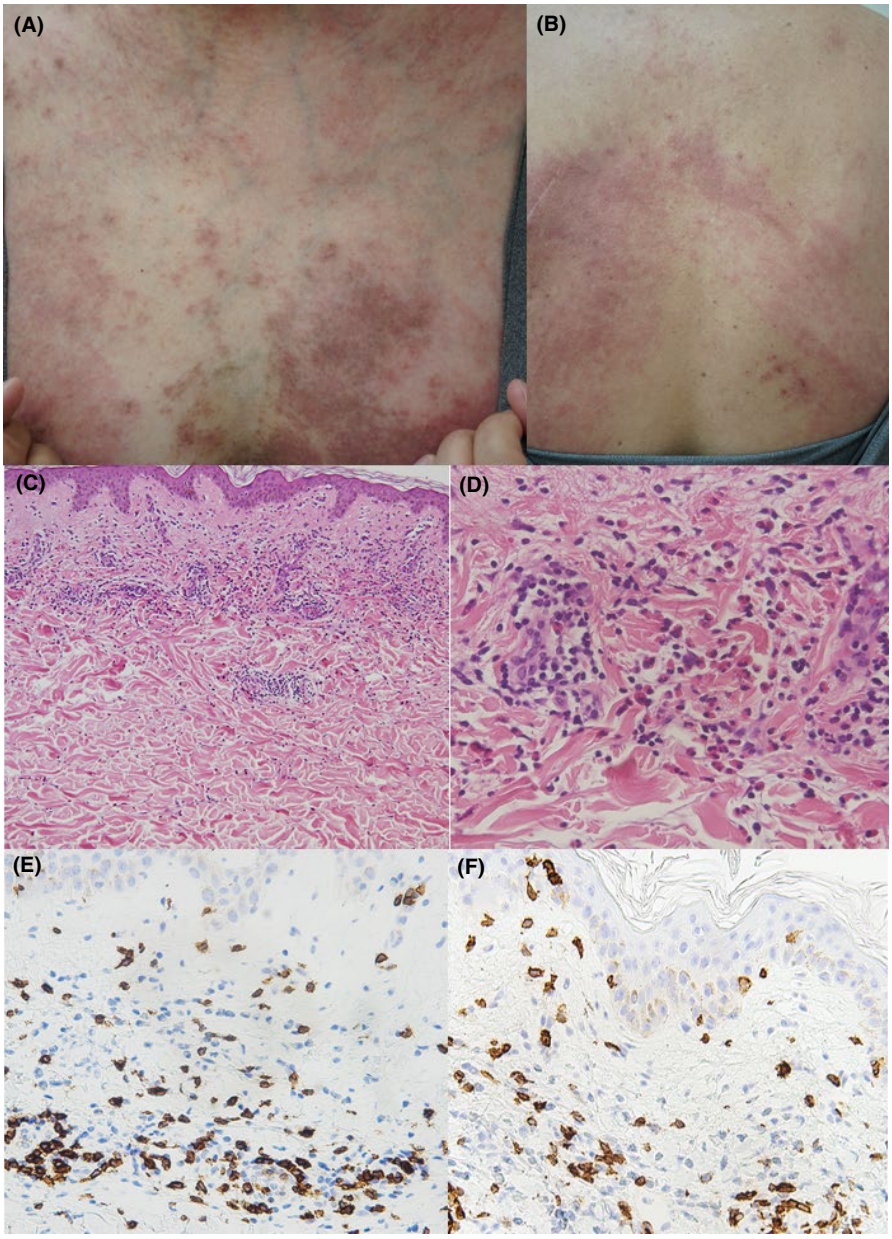

FIGURE 1 Erythema and papules with pruritus were observed in the trunk (A, B). Histopathological examination revealed thickening of the epidermis, spongiosis, and a large number of eosinophils and lymphocytes in the upper dermis. H&E staining; magnification, ×100 (C) and ×400 (D). Immunostaining of CD8 (E) and CD4 (F). CD8-positive cells, which are the almost same numbers as CD4-positive cells, were observed in the dermis. Magnification, ×400

increase in similar reports,[4] it is a topic case that should be noted in the near future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: N/A.

Informed Consent: The written informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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