Palm Pustules Induced by Pemetrexed

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A 69-year-old man with recurrent postoperative lung adenocarcinoma (negative for EGFR mutation and ALK rearrangement) was administered a combination therapy of pembrolizumab, carboplatin, and pemetrexed every 3 weeks. He received four cycles of induction treatment and one cycle of maintenance treatment with pembrolizumab and pemetrexed. Dexamethasone (9.9 mg for induction treatment and 6.6 mg for maintenance treatment) was used only on day 1 of each cycle because he had poorly controlled diabetes mellitus. Although the tumor burden was reduced, he developed lip erosion (Fig. 1A) and crusted eruptions on his shoulder, back, and arms (Fig. 1B). Drug-induced erythema multiforme or Stevens-Johnson syndrome was clinically suspected. Therefore, the treatment was discontinued. Skin biopsy result of the crusted eruptions revealed capillary dilatation and lymphocytic infiltration in the superficial dermis (Fig. 2). These symptoms resolved after treatment with oral prednisolone and topical steroid ointment. Concurrent with the symptomatic improvement, palm pustules appeared on both hands (Fig. 3). Skin biopsy result of a palm pustule on his left fourth finger also revealed capillary dilatation and lymphocytic infiltration in the superficial dermis, although the finding of pathologic inflammation was more notable (Fig. 4). The series of skin symptoms were initially diagnosed as immune-related adverse events owing to pembrolizumab use. Nevertheless, the lymphocyte transformation test for pembrolizumab (2.5 mg/mL) using drug leftover after dispensing was negative (stimulation index [SI] = 96%; cutoff = 180%), whereas that for pemetrexed (25 mg/mL) was positive (SI = 628%). Consequently, pemetrexed-induced dermatitis was diagnosed. Pharmacologic stress testing was omitted because of the risk and the limited drug availability. The patient’s symptoms gradually improved over 2 months by initiating oral prednisolone (starting with 10 mg/day and gradually decreased) and topical steroid ointment. At the latest follow-up, 12 months after discontinuing anticancer treatment, the tumor had remained in shrinkage.

Pemetrexed is one of the key drugs for nonsquamous NSCLC.1,2 Immune checkpoint inhibitors (ICIs) are widely used for the treatment of advanced NSCLC.3 Recently, the combination of cytotoxic chemotherapy and an ICI has become standard therapy for advanced NSCLC.4 Nevertheless, identifying which drug causes adverse events is often difficult in multidrug treatment. Particularly, ICIs can cause diverse symptoms of immune-related adverse events. Although ICI combination therapy makes diagnosis more difficult, accurate diagnosis of adverse events is needed to avoid losing multiple key drugs. The incidence of skin problems by

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pemetrexed is moderately frequent. There has been a previous report of generalized exanthematous pustulosis induced by pemetrexed. To the best of our knowledge, localized palm pustules induced by pemetrexed have not been reported previously. In this case, the shortened period of dexamethasone administration may have contributed to the skin symptoms. We initially diagnosed the symptoms as immune-related adverse events because signature skin findings occurred and lymphocytic infiltration was observed on pathology. Nevertheless, the final diagnosis was pemetrexed-induced dermatitis on the basis of the results of the lymphocyte transformation test. Nyfeler and Pichler reported that the lymphocyte transformation test for drug allergy had a sensitivity of 75% and a specificity of 85% (cutoff of SI = 200%). In our case, the SI of pembrolizumab was low (96%), although that of pemetrexed was very high (628%). The minimum required amount of pembrolizumab for the lymphocyte transformation test is unclear. The test result for pembrolizumab may have been negative because the sample dose was low (2.5 mg/mL). Although the lymphocyte transformation test can yield a false-positive or false-negative result, the results in this case indicated a strong allergic reaction to pemetrexed. Therefore, pemetrexed-induced dermatitis was finally diagnosed. In conclusion, we report the first case of palm pustules induced by pemetrexed. Remarkable dermatitis after ICI administration is not always an immune-related adverse event.

Figure 1. (A) Lip erosion and (B) crusted eruptions on the patient’s back.

Figure 2. Histologic image of skin biopsy from crusted eruptions stained with hematoxylin and eosin. Hyperkeratosis and crust are present in the epidermis. Capillary dilatation, lymphocytic infiltration, and melanin incontinence are observed in the superficial dermis. Edema is also observed in the dermis.

Figure 3. Palm pustules on both hands. Skin biopsy was performed on the palm pustule on the patient’s left fourth finger (purple circle in the figure).
CRedit Authorship Contribution

Kazuhisa Nakashima: Attending doctor, Writing—original draft preparation.

Yukari Tsubata: Reviewing and editing.

Hiroyuki Niihara: Attending doctor.

Asuka Araki: Pathologic diagnosis.

Takeshi Isobe: Supervision.

References


Figure 4. Histologic image of skin biopsy from palm pustules stained with hematoxylin and eosin. Hyperkeratosis and thickness are present in the epidermis. Lymphocytic infiltration and edema are present in the dermis. The histologic finding is similar to that of the crusted eruptions (Fig. 2), but more remarkable.