RESEARCH LETTER

Consistently Reproducible Fixed Drug-induced Urticaria in a Patient with Metastatic Melanoma Under Immunotherapy

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To the Editor,

Immune checkpoint inhibitor (ICI)-induced cutaneous reactions are frequent and range from mild skin manifestations to very severe cutaneous adverse reactions (1, 2). So far, however, fixed drug-induced eruption (FDE) has been reported only once in this context (3). We report the first case of fixed drug-induced urticaria (FDU) occurring as a small solitary urtica during every nivolumab infusion procedure.

A 51-year-old woman with stage IV melanoma (pT1a,Nc1,M1a(0)) started combined immunotherapy using ipilimumab plus nivolumab after having experienced tumour progression under 13 cycles of pembrolizumab therapy. After the first cycle of ipilimumab plus nivolumab she first noticed an elevated reddish lesion about 1 cm in diameter on her décolleté (**Fig. 1**). The lesion always developed approximatively 30 min after the start of immunotherapy infusions. After about 3 h the lesion spontaneously regressed again. She had no oral or intravenous comedication during her anticancer therapy. The patient had no complaints and interpreted the lesion as a sign of efficacy of her medication. Hence, this minor fixed skin eruption did not come to the awareness of the medical stuff. During a skin cancer screening after her nivolumab medication, however, the solitary urticarial lesion on her décolleté was noticed and discussed with the patient. Over the next 4 cycles of nivolumab, we consistently observed FDU occurring exclusively at the previously described site (Fig. 1). We performed a punch biopsy of the acute lesion revealing on histopathology a superficial perivascular dermatitis with dermal oedema and eosinophils (**Fig. 2**A). Giemsa and CD117 stains revealed discrete immunoreactivity. CD63 staining (Fig. 2B), which is capable of detecting activated mast cells, showed few immunoreactive cells. Prick (0.02 ml), intracutaneous (0.03 ml), and subcutaneous (0.1 ml, 0.5 ml, 1 ml) testing using nivolumab was negative. Blood count and other laboratory parameters were within the normal range, except for 30.1% eosinophilia (1,640/µl [35–440]).

FDE is a recurrent cutaneous reaction in which each re-exposure to the culprit drug triggers a distinct lesion at the same anatomical site(s). Although classical FDE usually presents as well-demarcated, violaceous sometimes bullous or hyperpigmented patches/plaques that may persist for days, there exists a rare variant termed FDU, characterized by transient wheals that spontaneously resolve within hours yet unfailingly reappear at the identical location upon each drug challenge (4–8). FDE

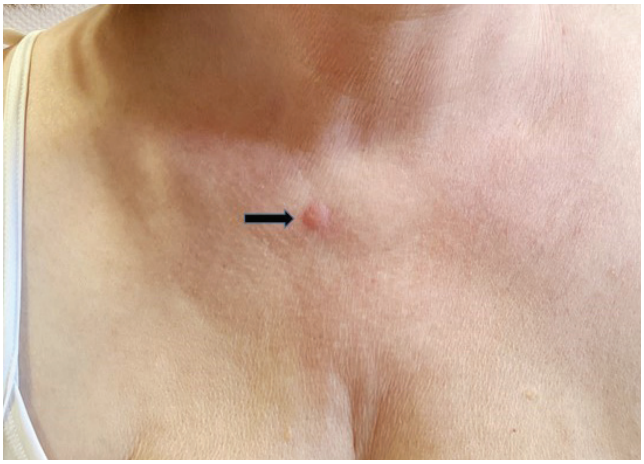

Fig. 1. A melanoma patient who always developed a solitary wheal on her décolleté during immunotherapy with nivolumab.

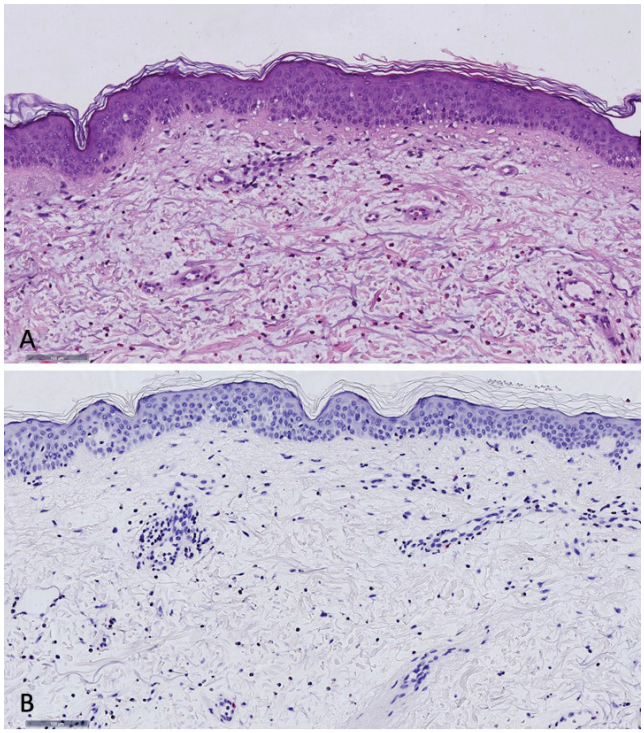

Fig. 2. (A) HE (100 µm) stain showing dermal oedema with superficial perivascular lymphocytic infiltrates and abundance of focally degranulated perivascular and interstitial eosinophils. (B) CD63 staining (100 µm) revealed few immunoreactive cells corresponding to activated mast cells.

usually shows features of interface dermatitis with necrotic keratinocytes on histopathology, whereas histology of FDU is similar to common urticaria as demonstrated in the present case. Immunologically, both forms very likely hinge on localized memory T cell responses. A subset of tissue-resident memory (TRM) T cells, often $CD8^+$ but supported by $CD4^+$ helper subsets, remains embedded in the skin after an initial exposure. These TRM cells can lie dormant for extended periods, retaining a "memory" of the offending agent. When the drug is encountered again, the TRM population is reactivated and rapidly secretes cytokines (such as IFN-γ and TNF-α), recruiting additional inflammatory cells.

Even though classical urticaria is commonly IgE-mediated, the transient wheal in FDU may be driven by T cell-induced mast cell activation via non-IgE pathways. This explains why the lesion remains site-specific yet does not rely on systemic IgE crosslinking. The specialized microenvironment at that single site fosters T cell residency, while repeated drug exposures perpetuate the same cutaneous reaction. Consequently, FDE exemplifies how T cell-driven processes can produce recurrent, site-locked eruptions, whether manifested as persistent plaques or fleeting urticarial wheals, without necessitating classical IgE-based mechanisms. Thus, repeated site-specific reactivation underscores the pivotal roles of local T cell memory and microenvironment in shaping cutaneous drug hypersensitivity (4–10). The patient presented here consistently exhibited FDU during systemic immunotherapy. However, her FDU could not be triggered by skin testing and significant mast cell activation did not play a role in the present patient.

In conclusion, this is the first reported case of FDU occurring during ICI treatment. We hypothesize that ICI may exacerbate or unmask cutaneous drug hypersensitivity by amplifying the specific T cell pathways responsible for the site-specific FDU lesions.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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