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Reactivation of drug reaction with eosinophilia and systemic symptoms with ranitidine patch testing

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction (SCAR), with a mortality of 2% to 6%.[1] Ascertaining the causative drug can be challenging and reported sensitivity of various in vivo and ex vivo tests is variable. Skin testing is most widely performed,[2] with patch testing (PT) considered to be low risk.[3] Guidance on performing drug PT has been published.[2,4] However, the safety of re-exposure to the culprit drug in patients with SCAR remains uncertain.

CASE REPORT

We report a case of an immunocompetent 20-year-old male who developed DRESS reactivation following PT to ranitidine 30% pet. He first developed erythema multiforme-like DRESS (RegiSCAR score 6) in July 2016. Initial skin testing (9 months later) demonstrated positive PT and intradermatl test (IDT) results for ranitidine (PT ranitidine 30% pet., undiluted ranitidine solution, IDT ranitidine 1:100).[5] Skin test results to rifampicin and vancomycin were negative (IDT to vancomycin 1:100, rifampicin 1:10 000). However, in vitro T-cell assays (lymphocyte proliferation and enzyme-linked immunospot assays) showed positive responses to all three (ranitidine, vancomycin, and rifampicin). The unexpected in vitro multiple positive responses in the context of negative skin tests to vancomycin and rifampicin raised the possibility of false-positive in vitro test results, and subsequent challenge with oral rifampicin 300 mg resulted in elicitation of DRESS. Therefore, the primary culprit was concluded to be rifampicin.

However, this finding raised the possibility that the ranitidine skin/in vitro testing results may be false positive and prompted further investigation (33 months later). PT (with and without adhesive tape stripping × 10) was performed to ranitidine 30% pet. and rifampicin 10% pet. (both from crushed tablets) and vancomycin 0.05% aq. Pruritus at the site of the ranitidine PT was reported within 24 hours, with a ++ reaction (intense erythema, infiltrated, visible vesicles) on review (Figure 1A), more pronounced on the side with tape stripping. Additionally, distant to the patch test, an urticated exanthem developed on the upper back (Figure 1B). The patient remained afebrile but within 24 hours developed lymphadenopathy and facial swelling with mild lymphopenia (1.0×10^9/L). There was no eosinophilia or organ involvement. He was admitted to hospital and treatment with methylprednisolone commenced (three 500-mg doses) followed by a tapering dose of prednisolone over 18 days. Symptoms resolved and he was discharged after 48 hours. Human herpes virus-6 was not detected on polymerase chain reaction and repeat routine blood tests after a month were normal. HLA-A*32:01 (associated with vancomycin-DRESS) was confirmed on human leukocyte antigen (HLA) typing. Hypersensitivity to ranitidine, in addition to that previously demonstrated for rifampicin, was confirmed. Challenge to vancomycin was not undertaken and therefore, in light of the in vitro assays, hypersensitivity was assumed.

DISCUSSION

Elicitation of systemic symptoms by the PT in cases of DRESS is infrequent, and predominantly reported in patients with human immunodeficiency virus.[6] Despite a localized reaction only on previous ranitidine skin testing, nearly 3 years later, repeat PT induced a DRESS reactivation. It is possible that the tape-stripped PT on the second occasion resulted in increased drug exposure, but it is notable that the previous IDT with ranitidine did not result in DRESS recurrence and would deliver greater drug exposure. In conclusion, a PT is easy to perform and can be a useful tool in the

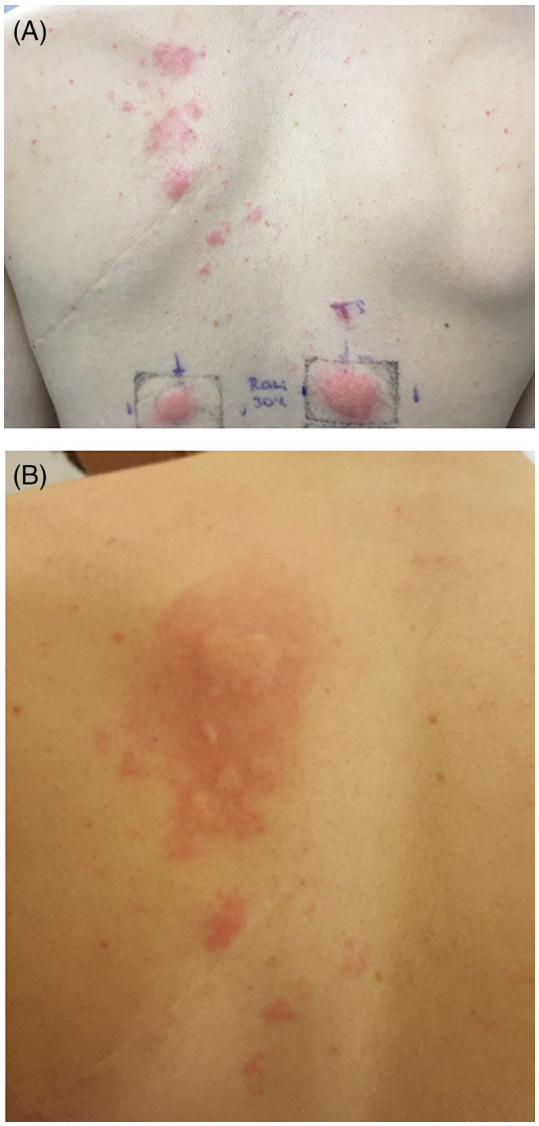

FIGURE 1 Drug patch testing;(**A**) ++ reaction to ranitidine 30% pet. patch testing in duplicate without tape stripping (left) and with tape stripping (right), with separate lesions developing on the left upper back. (**B**) Rash at the nontested site (left upper back) within 24 hours of application of patch testing

evaluation of the culprit drug in delayed drug hypersensitivity. However, this case demonstrates that although investigators may aim to perform a challenge test to confirm negative results in drug allergy, DRESS-specific caution must be employed over the possibility of multiple drug hypersensitivity. In addition, careful counselling of patients in drug PT and follow-up are necessary as there is a risk of triggering a systemic hypersensitivity reactivation, even several years after the index reaction.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Michael Ardern-Jones: Writing-review and editing. **Ying Teo:** Conceptualization; investigation; writing-original draft.

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