Received: 27 January 2021 | Revised: 10 March 2021 | Accepted: 14 March 2021

DOI: 10.1002/cia2.12170

Journal of Cutaneous Immunology and Allergy

WILEY

CASE STUDY

The role and histopathology of oral drug challenge in the evaluation of fixed drug eruptions

Megan Brinkworth Vissing MD | Arveen Bhasin MD | Jason Sluzevich MD

Mayo Clinic Florida, Jacksonville, FL, USA

Correspondence
Jason Sluzevich, Mayo Clinic Florida, 4500 San Pablo Road South, Jacksonville, FL 32224, USA.
Email: sluzevich.jason@mayo.edu

Abstract

This case series describes the role of oral drug challenge in the diagnosis of fixed drug eruption in the setting of polypharmacy. Practical testing guidelines are provided. The literature describing the histopathology of acute fixed drug reaction is also reviewed and compared with the findings in this series.

KEYWORDS
adverse cutaneous drug reaction, dermatopathology, fixed drug eruption

1 | INTRODUCTION

Fixed drug eruption is characterized by one or more, round, erythematous to violaceous plaques that fade with hyperpigmentation commonly on the face, mucosal sites, and genitals. Lesions develop within days to 2 weeks of first exposure and resolve over 2-3 weeks after removal of offending drug. Fixed drug eruption is relatively common and accounts from 9% to 22% of all drug eruptions.[1] Re-exposure to the offending drug results in recurrence of lesions in the same location, usually within 24 h. Occasionally, new lesions develop and/or a more severe generalized eruption can be seen. Common offending agents are antibiotics including tetracyclines and sulfamethoxazole-trimethoprim (SMX-TMP), barbiturates, salicylates, and phenolphthalein.[2]

The histopathology of established lesions is characterized by vacuolar interface dermatitis with basal cell degeneration, epidermal dyskeratosis, and a superficial perivascular lymphocytic infiltrate with rare eosinophils or neutrophils. Dermal melanophages with very mild to no interface dermatitis are seen with end-stage lesions which clinically appear hyperpigmented. In bullous presentations, there is a subepidermal cleft[1,3] in association with the brisk interface dermatitis.

The acute histopathology, assessed within hours of lesion onset, has notable differences. Voorhees et al. described the acute phase of SMX-TMP-induced fixed drug eruption as having moderate diffuse epidermal spongiosis, papillary dermal edema, and a mixed inflammatory infiltrate of neutrophils, eosinophils, and lymphohistiocytic cells with minimal dermal pigment incontinence. Focally, there were dermal collections of neutrophils suggestive of early abscess formation with leukocytoclasia.[4] Other cases have also described a predominance of neutrophilic inflammation with acute fixed drug eruption being biopsied within 48 h of onset.[5]

2 | CASE REPORT

The diagnosis of fixed diagnosis is usually straightforward, but identification of the drug trigger in some instances may be challenging. We present two cases of fixed drug eruption secondary to SMX-TMP established through oral challenge. Both cases occurred in the setting of polypharmacy with multiple antibiotics that in some cases were taken in a rotational fashion making historical identification of a culprit agent unclear.

A 60-year-old woman presented with a history of three recurrent episodes of dusky violaceous, round, indurated plaques the left forearm, right upper knee, right back, and left posterior knee that faded to hyperpigmented patches over 4 weeks. Given prior exposure to both SMX-TMP and doxycycline two weeks ago, the patient underwent graded oral challenge over a 4-h period with a total dose of 1830-366 mg of SMX-TMP. Eight hours later, she developed an intense burning sensation and recurrent erythema within each lesion, in addition to, development of new lesions (Figure 1A). Biopsy of a newly induced lesion showed moderate vacuolar interface,

epidermal dyskeratosis, focal eosinophilic spongiosis, and papillary dermal eosinophils (Figure 1B).

A 48-year-old woman presented with a history of bronchiectasis and immotile cilia syndrome with MRSA and *Achromobacter* airway colonization requiring rotational antibiotics for the last seven months that included SMX-TMP with recurrent violaceous, circular plaques involving the right ring finger, left hand, left buttock, and right leg. She underwent initial oral challenge with one double-strength (DS) SMX-TMP, 800-160 mg. Within 30 min, she developed recurrent erythematous circular plaques in the exact location of prior eruptions (Figure 2A). Biopsy revealed focal vacuolar interface dermatitis, papillary dermal edema, and numerous superficial perivascular eosinophils with dermal pigment incontinence (Figure 2B).

3 | DISCUSSION

In both cases, biopsies were preformed within 24 h of oral challenge and showed superficial dermal eosinophilic infiltrates and focal vacuolar interface change. This differs from previous reports of the acute histopathology of fixed drug eruption which have emphasized neutrophilic infiltrates which were not identified in this series.[4,5] Eosinophils were present in both new and established lesions after oral challenge with the density higher in established lesions, suggesting the eosinophilic infiltrates may be more prominent in lesional skin after repeated drug exposure. The presence of eosinophils is common in many cutaneous drug eruptions and in combination with interface dermatitis and dyskeratosis is a helpful histopathologic clue in separating early fixed drug eruptions from erythema multiforme. Uniquely, one biopsy showed eosinophilic spongiosis which is most associated with contact dermatitis or underlying immunobullous processes[6] and has not been previously reported as a histopathologic pattern seen with acute fixed drug eruption, which emphasizes the need for careful clinicopathologic correlation.

Patch testing has been historically recommended for trigger elucidation in fixed drug eruption, but there is extensive variability in methods, dosing, and interpretation.[7] Patch testing can be done utilizing pharmacy compounding, commercially available topical preparations, or dilution of commercially available drug by the physician which results in variable concentrations that may be much lower or higher than the recommended 10% active ingredient concentration.[1,8] However, patch testing can be logistically cumbersome and has limited sensitivity with only a 40% positive reaction rate.[7]

In contrast in our experience, oral drug challenge is underutilized in the evaluation of fixed drug eruptions. Challenges to adaptation include a lack of published protocols and uncertainty in the severity and management of cutaneous reactions with oral challenge. The protocols described here have been safely utilized in our interdisciplinary practice with rapid results, high sensitivity, and excellent patient tolerability.

Both graded and single-dose oral challenges were performed under continuous provider supervision. In general, patients with less than three presenting cutaneous lesions may begin with the standard average daily dose. If no reaction is seen after 24 h, then twice the daily average dose is administered. If no reaction is seen with twice the average daily dose, then the drug can be eliminated as etiologic. In cases with more than three presenting lesions or if there is a prior history of mucositis, it is recommended to begin with 10% of double the average daily oral dose. This is increased by 10% every thirty minutes until a reaction is seen or until the cumulative drug dose reaches twice the average daily dose. If no reaction is identified after 8 h, a repeat read is performed 24 h later.

While a graded oral challenge may result in a cumulative drug dose that exceeds the single average daily dose, there is an advantage of increased sensitivity as a dose equivalent to a single SMX-TMP tablet was insufficient to trigger a reaction in one patient; additionally, there may be comparative safety advantages as the cumulative dose triggering the positive reaction is often far below twice the average daily dose potentially used in nongraded challenges. New cutaneous lesions were only seen with the graded oral challenge likely reflecting a higher cumulative drug exposure. The use of high potency topical corticosteroids to flared or new lesions resulted in rapid clearing. Neither challenge was associated with bullous lesions or mucositis but we recommend the adjuvant use of oral prednisone in this circumstance.

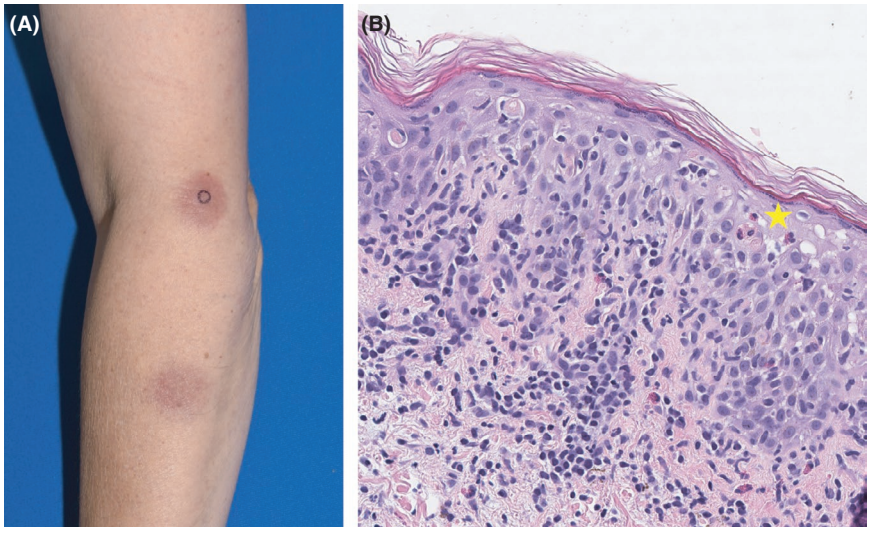

FIGURE 1 (A) Indurated dusky erythematous plaques in areas of prior involvement eight hours developing 8 h after oral challenge. (B) Histopathology (H&E, 120×) shows well-developed interface dermatitis with epidermal dyskeratosis and superficial perivascular lymphocytic inflammation with eosinophils. Focal eosinophilic spongiosis (see star) is also present [Color figure can be viewed at wileyonlinelibrary.com]

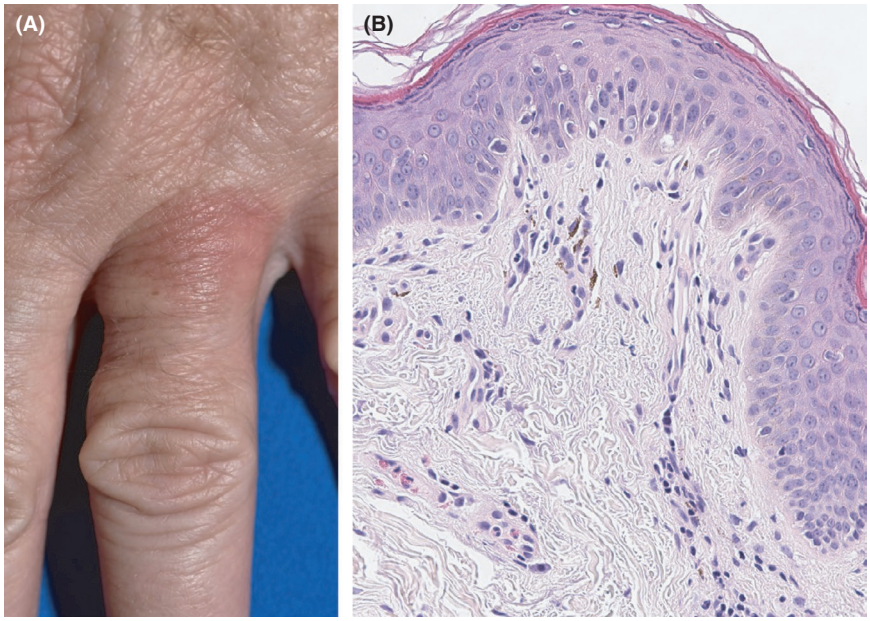

FIGURE 2 (A) Ovoid erythematous smooth patch on left 4th digit developing within 30 min of oral challenge. (B) Histopathology (H&E, 200×) shows papillary dermal edema, numerous superficial perivascular eosinophils, and mild focal vacuolar interface dermatitis. The dermal pigment incontinence is prominent and is characteristic of prior interface dermatitis [Color figure can be viewed at wileyonlinelibrary.com]

There are no evidence-based guidelines with respect to oral challenge in the workup of patients with fixed drug eruption. The use of patch testing as an initial modality[7,9] likely reflects the theoretical concern for emergent generalized or bullous fixed drug eruptions with oral challenge. Our experience suggests, however, that this risk is manageable as one case presented at baseline with generalized fixed drug lesions and did not experience widespread flaring or exacerbation with a controlled graded oral challenge.

In summary, we found the histopathologic findings in acute fixed drug eruption have less developed vacuolar interface, significant numbers of eosinophils, and isolated eosinophilic spongiosis compared with histopathology obtained days to weeks after development. We suggest consideration of oral challenge over patch testing in cases where drug trigger is unclear and elucidation is necessary. In our experience, this is a safe, reliable, and more efficient manner for diagnosis. In general, a graded oral drug challenge offers the potential of higher sensitivity but may result in new skin lesions. High potency topical corticosteroid for the treatment for testing induced lesions is recommended.

DECLARATION SECTION

Approval of the research protocol: In accordance with the Institutional Review Board policies.
Informed Consent: Written consent for all clinical photography.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Jason Sluzevich https://orcid.org/0000-0001-7604-7073

REFERENCES

1. Lee AY. Fixed drug eruptions. Incidence, recognition, and avoidance. Am J Clin Dermatol. 2000;1(5):277–85.
2. Flowers H, Brodell R, Brents M, Wyatt JP. Fixed drug eruptions: presentation, diagnosis, and management. South Med J. 2014;107(11):724–7.
3. Calonje JE, Brenn T, Lazar AJ, McKee PH. Pathology of the skin. 4th ed. New York, NY: Mosby Ltd; 2011.
4. Van Voorhees A, Stenn KS. Histological phases of Bactrim-induced fixed drug eruption. The report of one case. Am J Dermatopathol. 1987;9(6):528–32.
5. Suzuki S, Ho J, Rosenbaum M, Bhawan J. Neutrophilic fixed drug eruption: a mimic of neutrophilic dermatoses. Clin Exp Dermatol. 2019;44(2):236–8.
6. Ruiz E, Deng JS, Abell EA. Eosinophilic spongiosis: a clinical, histologic, and immunopathologic study. J Am Acad Dermatol. 1994;30(6):973–6.
7. Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang Y-S, Chung W-H, et al. Controversies in drug allergy: testing for delayed reactions. J Allergy Clin Immunol. 2019;143(1):66–73.
8. Brajon D, Menetre S, Waton J, Poreaux C, Barbaud A. Non-irritant concentrations and amounts of active ingredient in drug patch tests. Contact Dermatitis. 2014;71(3):170–5.
9. Lammintausta K, Kortekangas-Savolainen O. Oral challenge in patients with suspected cutaneous adverse drug reactions: findings in 784 patients during a 25-year-period. Acta Derm Venereol. 2005;85(6):491–6.

How to cite this article: Vissing MB, Bhasin A, Sluzevich J. The role and histopathology of oral drug challenge in the evaluation of fixed drug eruptions. *J Cutan Immunol Allergy*. 2021;4:120–122. https://doi.org/10.1002/cia2.12170