

Letter

FIXED DRUG ERUPTION CAUSED BY MESNA

Mesna administration usually accompanies the use of cyclophosphamide to prevent hemorrhagic cystitis. Case reports have described adverse reactions to mesna, including maculopapular rash, urticaria, and fixed drug eruption (FDE).^{1,2} Among the reported cases, the appearance of FDE lesions occurred soon after the administration of mesna and before cyclophosphamide administration.¹ We report a case of FDE where the diagnosis was obscured because the lesions appeared after the completion of cyclophosphamide infusion.

A 41-year-old, African American woman, employed as a police officer at the World Trade Center site after its destruction in 2001, was diagnosed as having scleroderma and interstitial lung disease in 2004. She had an inadequate response to mycophenolate mofetil treatment in mid-2005, which was discontinued in 2007, and in 2008 she was prescribed oral cyclophosphamide followed by the intravenous preparation. She received monthly cyclophosphamide infusions for a total of 6 doses. Mesna was administered 15 minutes before each cyclophosphamide infusion, just after the infusion, and with 2 additional doses 4 and 8 hours later. Several hours after the fourth cyclophosphamide infusion, the patient experienced itching and burning. After the fifth cyclophosphamide infusion, she developed sharply demarcated pruritic erythematous plaques on her face and upper body. The lesions were first reddish, within 1 to 3 hours changed to a dark-brown color, and faded away after 7 days. Hyperpigmented spots remained on the skin for the next few years. The patient was advised to discontinue cyclophosphamide therapy in 2008 for fear of FDE to cyclophosphamide. No biopsy was performed.

Because our patient clinically required a reintroduction of cyclophosphamide, she was referred for drug allergy evaluation. It was unclear whether she reacted to cyclophosphamide or mesna. Therefore, the patient underwent percutaneous, intradermal, and patch skin testing with mesna at the previously affected skin areas and a control site. Skin test results were negative on reading at 20 minutes and strongly positive on delayed readings (Table 1). A skin test with cyclophosphamide was not performed.

The patient then underwent a provocation test with cyclophosphamide, with aggressive hydration preceding each cyclophosphamide administration. A total of 500 mg of cyclophosphamide was

administered as a graded challenge: 1/100, 1/10, and the rest of the dose administered 1 hour apart. The patient tolerated the provocation test with no adverse events.

Previously reported allergic reactions to mesna have included fever, hemodynamic instability, macular rash, pruritus, and FDE.^{1,3} Mesna-induced FDEs have been reported at previous sites of systemic lupus erythematosus-induced skin lesions and in dermatomyositis patients.^{1,3} Several adult patients with rheumatoid arthritis, Wegener granulomatosis, and polyarteritis nodosa have developed a macular eruption a few hours after administration of mesna.⁴

The timing of reactions to mesna is variable, ranging from several hours to a few days or weeks after administration. Delayed reactions representing FDEs may appear several weeks after initial mesna exposure.^{1,4} Our patient developed FDEs several weeks into the therapy and after mesna and cyclophosphamide administrations, thereby making the identification of the culprit drug challenging.

The differential diagnosis of the FDEs in our patient included reaction to mesna and reaction to cyclophosphamide. Previously reported reactions to cyclophosphamide have included erythema multiforme, dermatitis, and urticaria.² There have been reports of delayed reactions to cyclophosphamide, confirmed by positive skin test results to cyclophosphamide metabolites.⁵ To our knowledge, there have been no reports on cyclophosphamide-induced FDEs.²

Skin testing to mesna helped to diagnose FDEs in our patient. Although our patient was initially thought to have had a reaction to cyclophosphamide due to the confusing time course of her symptoms, it is important to suspect an allergy to mesna. Confirmation of mesna-induced FDEs allows the patient to resume treatment for interstitial lung disease with cyclophosphamide.

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Table 1. Skin Testing Results: Prick, Patch, and Intradermal (ID, 0.02 mL) Testing

Compound and test placement	Prick testing, 10% at 20 min	ID testing, 0.1% and 1% at 20 min	ID testing, 0.1% at 48 and 96 h	ID testing, 1% at 48 and 96 h	Patch testing, 0.1% at 48 and 96 h	Patch testing, 50% at 48 and 96 h
Mesna (hyperpigmented lesions)	Negative	Negative	2+	4+	Negative	Positive
Mesna (control skin site)	Negative	Negative	Negative	Negative	Negative	Negative
Saline	1+	Negative	Negative	Negative		
Histamine	2+	Not done	Not done	Not done		

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