

Severe recurrence of drug rash with eosinophilia and systemic symptoms syndrome secondary to rifampicin patch testing in a human immunodeficiency virus-infected man

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Human immunodeficiency virus (HIV)-infected persons are more susceptible to tuberculosis and cutaneous adverse drug reactions (CADRs) to antituberculosis drugs. The eruptions range from mild to life-threatening, and may be associated with interruption of therapy. The limited number of effective first-line antituberculosis drugs complicates the management of HIV-infected persons who develop tuberculosis-associated CADRs. Second-line drugs have additional toxicities and are less effective. Thus, it is sometimes necessary to rechallenge first-line drugs to establish causality and eliminate the offending drug(s) from the treatment regimen. This can be done either *in vitro* or *in vivo*. The *in vitro* methods are not readily available, and are still considered to be experimental (1).

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Case Report

A 34-year-old HIV-infected man presented to us with exfoliative dermatitis, generalized lymphadenopathy, fever, facial oedema, eosinophilia, and hepatitis, with normal renal function and a normal cardiovascular system. He was diagnosed with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. He had been started on isoniazid, rifampicin, pyrazinamide and ethambutol for tuberculosis, and co-trimoxazole for *Pneumocystis jiroveci* prophylaxis, 4 weeks earlier. He had a CD4 count of 329 cells/mm³ and was not on antiretroviral therapy. Antituberculosis drugs and co-trimoxazole were stopped, and he was started on topical clobetasol (Dovate™) daily. Over the next 7 days, the rash and laboratory parameters settled.

Moxifloxacin, streptomycin and ethambutol were then initiated as cover drugs while we awaited rechallenge with first-line antituberculosis drugs. Rechallenge was initiated 17 days after the onset of symptoms of DRESS. The suspected antituberculosis drugs were rechallenged sequentially and additively, in the order isoniazid, rifampicin, pyrazinamide, and ethambutol. A patch test was performed first, and if the result was negative,



Fig. 1. (a) Monomorphic folliculocentric papules on a background of erythema extending beyond the area of the patch test, which was performed on the back. (b) Palmar erythema with areas of focal necrosis.

it was followed by a prick test 96 hr later. If both the patch and prick tests gave negative results, then an oral rechallenge was performed. Patch tests were prepared with ground commercial tablets (and capsules if applicable) in two vehicles (water and olive oil) to achieve a 30% concentration of each active drug. Tests were applied on the upper back in Finn Chambers[®] on Scanpor[®] tape in duplicate. A set of patch tests were removed at 24 and 48 hr, and the readings were performed at 24, 48 and 72 hr, according to the guidelines of the International Contact Dermatitis Research Group. Prick tests were performed as previously recommended by the same group (2). Oral rechallenge was initiated with one-fifth of the initial dose, and this was increased to a full therapeutic dose over a period of 4 days.

Isoniazid was uneventfully rechallenged; however, 48 hr after the rifampicin patch test was performed, the patient complained of generalized pruritus. On examination, he had prominent perifollicular monomorphic papules on a background of erythema extending to most of the body. He also had eosinophilia, hepatitis, facial oedema, conjunctivitis, haemorrhagic cheilitis, erythematous tender palms, and soles with blistering. A skin biopsy taken at this time showed focal basal cell hydropic degeneration and keratinocyte necrosis centred on hair follicles. He continued to progress over the following 4 days, and developed epidermal necrosis on the body,

palms, and soles (Fig. 1). Over the following 28 days, the skin desquamated, and the laboratory parameters normalized. The patient was then successfully rechallenged with pyrazinamide and ethambutol with the same protocol. He was discharged on isoniazid, pyrazinamide, ethambutol, and moxifloxacin.

Discussion

It is well established that treatment interruption during the intensive phase of tuberculosis therapy is associated with up to 3.15 hazard ratios of mortality. The high mortality associated with tuberculosis HIV co-infection and delay in therapy as compared with the risk of a severe rechallenge reaction informed our decision to rechallenge earlier than recommended for DRESS syndrome (1, 3–5). The sensitivity of patch testing in DRESS depends on the offending drug, and the reactions are usually mild and localized to the patch test (6). In our case, the patch test with rifampicin induced a more severe generalized systemic reaction. In conclusion, clinicians should be aware of the possibility of life-threatening drug reactions associated with patch testing in DRESS. Rechallenge should only be performed when the risks associated with suboptimal therapy outweigh those of a rechallenge reaction, and ideally with written informed consent from the patient.

References

- 1 Lehloeny R J, Dheda K. Cutaneous adverse drug reactions to anti-tuberculosis drugs: state of the art and into the future. *Expert Rev Anti Infect Ther* 2012; **10**: 475–486.
- 2 Barbaud A, Goncalo M, Bruynzeel D et al. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001; **45**: 321–328.
- 3 Lehloeny R J, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis* 2011; **15**: 1649–1657.
- 4 Corbett E L, Watt C J, Walker N et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009–1021.
- 5 Santiago F, Goncalo M, Vieira R et al. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Dermatitis* 2010; **62**: 47–53.
- 6 Barbaud A. Drug patch tests in the investigation of cutaneous adverse drug reactions. *Ann Dermatol Venereol* 2009; **136**: 635–644.