Multiple Drug Hypersensitivity Syndrome to Antituberculosis Drugs: A Case Report

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a T cell–mediated, delayed-type hypersensitivity reaction and, consequently, a severe cutaneous adverse reaction (SCAR). It is characterized by the combination of skin rash, fever, eosinophilia and other blood abnormalities, lymphadenopathy, and multiorgan involvement [1,2]. DRESS is unique in that it has a long latency period (2-8 weeks) between drug exposure and symptoms, as well as a long disease course with frequent flare-ups despite discontinuation of the suspected culprit drug. DRESS is rare, and its incidence and prevalence are unknown. It has been associated with a mortality rate of 5%-10% [1], although some studies have reported lower rates [2,3].

Multiple-drug hypersensitivity syndrome (MDHS) is characterized by sensitization to ≥2 chemically unrelated drugs [4]. DRESS is the SCAR most frequently associated with MDHS, which can complicate up to 18% of cases of DRESS [5]. MDHS can be distinguished from DRESS flare-ups by the presence of sensitization to multiple drugs proven by skin or in vitro tests [4].

We report the case of a 37-year-old woman who was admitted to the pulmonology department with high fever and pulmonary infiltrates and left pleural effusion, which were described in the CT scan as "loculated empyema with gas inside, suggesting dense exudate". Her previous history included tuberculosis at 12 years of age, which was uneventfully treated with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE). Five months earlier, she had also been

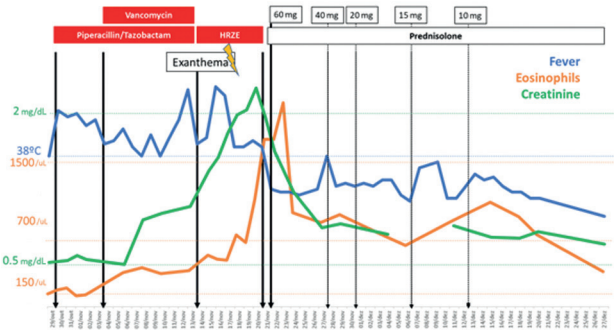

Figure. Clinical parameters and drugs administered over time during DRESS syndrome. Blue line, fever; orange line, eosinophils; green line, creatinine (normal range, 0.5-1.1mg/dL). HRZE indicates isoniazid, rifampicin, pyrazinamide, ethambutol; DRESS, drug reaction with eosinophilia and systemic symptoms.

diagnosed with severe depression, for which she was taking olanzapine, sertraline, and diazepam. Complicated community-acquired pneumonia was assumed, and piperacillin/tazobactam was started, together with vancomycin a few days later (Figure). The patient underwent pleural drainage, which was hampered by loculation. Pleural fluid analysis showed polymorphonuclear leukocytes (59.1%), low glucose (<10 mg/dL), elevated lactate dehydrogenase (1553 U/L), and adenosine deaminase (104 U/L). All fluid samples, including sputum, bronchial aspirate, bronchoalveolar lavage, and gastric aspirate were negative for acid-fast bacilli and *Mycobacterium tuberculosis*. As the patient's clinical condition continued to worsen, antibiotics were stopped, and HRZE was started for suspected tuberculosis. Seven days later, allergists and dermatologists were called to assess a suspected SCAR.

The patient presented with a maculopapular rash and facial edema that started on the first day of HRZE, eosinophilia (1750/µL [baseline, 150/µL]), and acute kidney injury (creatinine >2 mg/mL). Fever >38ºC was present since admission, although this worsened after an initial improvement (Figure). Skin biopsy was compatible with a hypersensitivity reaction. No viral reactivations were observed (cytomegalovirus, parvovirus B19, Epstein-Barr virus, herpes simplex virus types 1, 2, 6, and 7). The patient was diagnosed with DRESS syndrome (RegiSCAR criteria, 6) [3,6]. HRZE was stopped, and prednisolone 1 mg/kg (60 mg) was started [7], with marked clinical and analytical improvement of the signs and symptoms of DRESS syndrome, thus allowing slow tapering of corticosteroids over 8 weeks [7]. However, pleural fluid cultures eventually became positive for M tuberculosis, thus confirming the diagnosis of tuberculosis.

A review of the electronic clinical history showed that the patient was first treated with piperacillin/tazobactam for 14 days plus vancomycin for 10 days; these drugs were then switched to HRZE. Although the rash started on the same day as HRZE, eosinophil counts >700/µL were present before initiation of the antituberculosis drugs. Although vancomycin cannot be excluded as a causative agent, the longer exposure time to piperacillin/tazobactam made it a more likely culprit.

Because the patient received HRZE for 7 days during the most severe phase of DRESS syndrome, the possibility of sensitization to these drugs in the setting of MDHS was considered [4]. The severity of initial respiratory symptoms meant that tuberculosis needed to be addressed quickly, and allergy tests were deemed unfeasible, as the patient was still taking prednisolone [8]. Therefore, we decided to reintroduce HRZE on an inpatient basis, 1 drug at a time, with a 3-day interval between drugs, starting with the most urgently needed drugs. Six days after reintroduction of isoniazid, and 3 days after introduction of ethambutol, the maculopapular rash relapsed, eosinophil counts doubled to 440/μL, and treatment was discontinued.

Patch tests with piperacillin/tazobactam, vancomycin, isoniazid, ethambutol, rifampicin, and pyrazinamide were performed according to previously published guidelines [8,9], as was the lymphocyte transformation test (LTT). Patch test results were positive for isoniazid at 10% and 30% (Figure 2A, Supplementary files), and the results of LTT were positive (stimulation index [SI] >2) to all drugs (Figure 2B, Supplementary files), thus confirming MDHS [4].

At this point, we were faced with a patient diagnosed with tuberculosis and DRESS syndrome thought to have been induced by piperacillin/tazobactam or vancomycin. In addition, the situation was complicated by MDHS to HRZE and the fact that leaving tuberculosis untreated was not an option. Finally, the toxicity associated with an alternative HRZE-free treatment was unacceptable.

Although the LTT result was positive for all antituberculosis drugs tested, reevaluation of its results (Figure 2B, Supplementary files) made it possible to identify a higher SI to isoniazid and rifampicin, as well as a dose-response curve to both drugs, which was not present for ethambutol and pyrazinamide. In view of these results, an alternative schedule was designed; this included ethambutol, pyrazinamide, levofloxacin, and linezolid for 18 months. Ethionamide was considered but avoided based on possible cross-reactivity with isoniazid and a positive LTT result (SI = 11.4 plus presence of a dose-response curve). Drugs were planned to be introduced sequentially according to the ensuing "rules", as follows: (1) start with one drug at a time, (2) start with the drugs posing a higher risk (ethambutol, pyrazinamide), (3) allow a 7-day interval between each new drug to clearly establish tolerance, and (4) start with full doses of each drug to reduce the risk of resistance of tuberculosis to treatment.

Ethambutol was started on day 1, pyrazinamide on day 8, levofloxacin on day 22, and linezolid on day 34, with delays caused by complaints of isolated, episodic skin pruritus. The patient has been successfully treated with these drugs for the last 12 months, with no significant adverse effects.

In summary, we report a case of MDHS confirmed by positive skin and in vitro test results [4] and positive rechallenge with isoniazid in the setting of DRESS syndrome to piperacillin/tazobactam or vancomycin. Many questions remain unanswered with respect to our findings. Did we sensitize the patient to isoniazid during the first reintroduction attempt or was she already sensitized? Which are the best criteria for evaluating LTT results (SI alone vs SI plus dose-response curves)? Despite the challenging combination of severe tuberculosis with DRESS and MDHS induced by the main antituberculosis drugs, the judicious use of a combination of allergy tests and the dedicated involvement of a multidisciplinary team enabled the patient described here to successfully receive the most effective and least toxic treatment possible.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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