Multiple drug hypersensitivity syndrome to anti-TB drugs – a case report

Carneiro-Leão L[1,2], Gomes I[3], Freitas C[2,3], Costa e Silva M[4], Viseu R[5], Cernadas J[1,6]

[1]Allergy and Clinical Immunology Department - Centro Hospitalar e Universitário de São João, Porto, Portugal

[2]Faculty of Medicine, University of Porto, Porto, Portugal

[3]Pulmonology Department - Centro Hospitalar e Universitário de São João, Porto, Portugal

[4]Immunology and Molecular Biology Lab, Allergy and Clinical Immunology Department - Centro Hospitalar de Setúbal, Setúbal, Portugal

[5]Dermatology Department - Centro Hospitalar e Universitário de São João, Porto, Portugal

[6]Allergy and Clinical Immunology Unit - Hospital dos Lusíadas, Porto, Portugal

Corresponding author

Leonor Carneiro-Leão

Serviço de Imunoalergologia - Centro Hospitalar Universitário São João. Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal.

E-mail: mailto:leonorcarneiroleao@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0446

doi: 10.18176/jiaci.0446

Key words: drug allergy, DRESS, multiple drug hypersensitivity syndrome, anti-tuberculosis drugs

Palabras clave: Alergia a medicamentos, DRESS, Síndrome de hipersensibilidad a múltiples medicamentos, Medicamentos antituberculosis

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a T-cell mediated, delayed type, hypersensitivity severe cutaneous adverse reaction (SCAR), characterized by the combination of skin rash, fever, eosinophilia and other blood abnormalities, lymphadenopathy and multiorganinvolvement [1,2].DRESS has the uniqueness of a long latency period of 2 to 8 weeks between drug exposure and symptoms, as well as a long disease course, with frequent flare-ups, despite drug discontinuation.DRESS is rare, with unknown incidence and prevalence, being associated with a mortality of 5-10% [1], although some studies have shown lower death rates [2,3].

Multiple drug hypersensitivitysyndrome (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 DRESS cases [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 describe the case of a 37-year-old female, admitted to Pulmonology Department for high fever, pulmonary infiltrates and left pleural effusion, described in CT scan as “loculated empyema with gas inside, suggesting dense exudate”.Her previous history included tuberculosis (TB) at 12 years of age, uneventfully treated with isoniazide, rifampicin, pyrazinamide andethambutol (HRZE) and severe depression 5 months earlier, for which she was on olanzapine, sertraline and diazepam. Complicated community acquired pneumoniae was assumedand piperacillin/tazobactamand,a few days later, vancomycin,were started (figure 1), along with pleural drainage, hampered by loculation. Pleural fluid analysis showed

doi: 10.18176/jiaci.0446

polymorphonuclear leukocytes (59.1%), low glucose (<10mg/dl), elevated LDH (1553U/L) and adenosine deaminase (104U/L). All fluid samples, including sputum, bronchial aspirate, bronchoalveolar lavage and gastric aspirate were negative for Acid-fast bacilli (AFB) and *M. tuberculosis* DNA. As clinical condition kept worsening, antibiotics were stoppedand HRZE wasstarted for suspected TB. Seven days later, Allergy and Dermatology specialists were called for a suspected SCAR.

The patient presented a maculopapular rash and facial edema that started on the first day of HRZE, eosinophilia of 1750cells/µL (baseline: 150) and acute kidney injury (creatinine >2mg/ml). Fever over 38ºC was present since admissionbutworsenedafterinitial improvement (figure 1). Skin biopsy was compatible with a hypersensitivity reaction; no viral reactivationswere observed (CMV, Parvovirus B19, EBV, Herpes simplex 1&2, herpes 6&7).A diagnosis of DRESS syndrome was made (RegiSCAR criteria=6)[3,6]. HRZE was stopped and prednisolone 1mg/kg (60mg) was started [7], with marked clinical and analytical improvement of DRESS signs and symptoms, allowing slow tapering of steroids over 8 weeks [7]. However, pleural fluid cultures eventually becamepositive for *M. tuberculosis*, confirmingTB.

Review of electronic records showed that the patientwas first treated with piperacillin/tazobactam for 14 days, plus vancomycin for 10 days, which were then switched to HRZE. Although the rash started on the same day as HRZE, eosinophil counts >700cells/µL were present before anti-TB drugs introduction. Although vancomycincannot be excludedas causative, the longer exposure time to piperacillin/tazobactammade it a more likely culprit.

Because the patient received HRZE for seven daysduring the most severe phase of DRESS syndrome, the possibility of sensitization to these drugs,in the setting ofMDHS,was considered[4]. The severity of initialrespiratory symptoms meant that TB needed to be

doi: 10.18176/jiaci.0446

quickly addressed and allergy tests were deemed unfeasible, as the patient was still onprednisolone [8]. Therefore, HRZE reintroduction was decided to be trialed in an inpatient regime, one drug at a time, with a three days interval, starting with the most needed drugs. Six days after reintroduction of isoniazid (INH), and three days after ethambutol (EB), maculo-papularrash relapsed, eosinophil counts doubled to 440cells/μL and treatment was withheld.

Patch tests to piperacillin/tazobactam, vancomycin, INH, EB, Rifampicin (RFP), Pyrazinamide (PZA)were performed according to previously published guidelines [8,9], as well as lymphocyte transformation tests (LTT).Patch were positive to INH at 10 and 30% (figure 2A, supplementary files) and LTT were positive (stimulation index [SI]>2) to all drugs (figure 2B, supplementary files), confirming MDHS [4].

At this point: 1)we had a patient with a diagnosis of TB and a DRESS, suspected to be induced by piperacillin/tazobactam or vancomycin, complicated by MDHS to HRZE;2) not to treat TB was not an option;3)toxicities associated with an alternative treatmentfree of HRZE were unacceptable.

Although LTT was positive for all anti-TB drugs tested, reevaluation of its results (figure 2B, supplementary files)allowed the identification of higher SI to INH and RFP, as well as a dose-response curve to these two drugs, which was not present for EB and PZA.In view of these results,an alternative schemewas devised, which included EB and PZA, levofloxacin and linezolid for 18 months. Ethionamide was considered but avoided based on possible cross-reactivity with INH and a positive LTT (SI = 11.4plus presence of a dose-response curve). Drugs were planned to be sequentially introduced following the ensuing “rules”: 1) start with one drug at a time, 2) start with the drugs posing higher risk (EB and PZA), 3) allow a seven days interval between each new drug, to clearly establish tolerance, 4) start with full-doses of each drug to reduce the risk of TB resistance to treatment.

doi: 10.18176/jiaci.0446

EB was startedat day 1, PZA at day 8, levofloxacin at day 22 and linezolid at day 34, with delays caused by complaints of isolated, episodic,skin pruritus. The patienthas been successfully treated with these drugs for the last 12months, without significative side effects.

In summary, we report a case of MDHS, confirmed by positive skin and*invitro* tests [4] and positive rechallengeto INH, in the setting ofDRESS syndrome to piperacillin/tazobactam or vancomycin.Some unanswered questions hamper this work: have we sensitized the patient to INH during the first reintroduction attempt or was she already sensitized? Which arethe best criteria to value LTT results (SI alone *vs* SI plus dose response curves)?Despite the challenging combination of severeTB with DRESS and MDHS to the most important anti-TB drugs, the judicious use of a combination of allergy tests and the devoted involvement of a multidisciplinary team allowed this patient to successfully receive the most effective and less toxic treatment possible.

Conflicts of interest: The authors declare no real or perceived conflicts of interest.

Funding sources: none

doi: 10.18176/jiaci.0446

References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250-7.
2. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Allergol Select. 2017;1(1):96-108.
3. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-80.
4. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple Drug Hypersensitivity. Int Arch Allergy Immunol. 2017;172(3):129-38.
5. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013;168(3):555-62.
6. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609-11.
7. Roujeau JC, Haddad C, Paulmann M, Mockenhaupt M. Management of nonimmediate hypersensitivity reactions to drugs. Immunol Allergy Clin North Am. 2014;34(3):473-87, vii.
8. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57(1):45-51.
9. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests withdrugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis. 2001;45(6):321-8.

doi: 10.18176/jiaci.0446

Figure 1. 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: isoniazid, rifampicin, pyrazinamide, ethambutol.