



Letters

A case of DRESS syndrome induced by the antituberculosis drugs, prothionamide, and para-aminosalicylic acid

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug-induced reaction characterized by skin eruptions, fever, hematologic abnormalities, and internal organ involvement.¹ Here, we describe a case of DRESS syndrome caused by the second-line antituberculosis (anti-TB) drugs prothionamide (PTH) and para-aminosalicylic acid (PAS) in a patient with multi-drug resistant TB.

A 33-year-old man presented with a persistent spiking fever and skin rash that appeared 3 weeks after he had taken anti-TB drugs. The patient had been diagnosed with pulmonary multi-drug resistant TB and treated with second-line anti-TB drugs, including kanamycin (KM), moxifloxacin (MFX), cycloserine (CS), PTH, and PAS. The patient had no drug allergy history or previous adverse reaction to first-line chemotherapy (isoniazid, rifampin, ethambutol, and pyrazinamide). A physical examination revealed the presence of a high fever (39°C), tachycardia, generalized maculopapular exanthema, facial edema with desquamation, and cervical lymphadenopathy. A complete blood cell count revealed the following laboratory values: white blood cell count, 13,202/mm³ (15% eosinophils, 52% neutrophils, 17% lymphocytes, and 8% monocytes); platelet count, 122,000/mm³; and C-reactive protein, 22.37 mg/L. Liver function test results were abnormal: direct bilirubin, 0.7 mg/dL; indirect bilirubin, 0.4 mg/dL; aspartate aminotransferase (AST), 1,091 U/L; alkaline aminotransferase (ALT), 1,483 U/L; alkaline phosphatase, 220 U/L; γ -glutamyltransferase, 132 U/L; and serum albumin, 3.2 g/dL. Serologic tests for viral infections, including hepatitis A through C, Epstein-Barr virus, human immunodeficiency virus, cytomegalovirus, and herpes simplex virus, were negative. Auto-antibody screening was negative for antinuclear and anti-smooth muscle antibodies. A skin biopsy of the erythematous rash on his anterior chest wall showed superficial dermal edema and perivascular lymphocytic infiltration. Based on the patient's clinical, laboratory, and pathologic findings, he was diagnosed with DRESS syndrome, and all medications were immediately discontinued. After the administration of systemic corticosteroids, the patient's clinical symptoms and laboratory abnormalities gradually resolved over 4 weeks. To identify the DRESS-causative drug(s), we rechallenged the patient with anti-TB drugs. He had no adverse reaction to an injection of KM; however, after receiving 250 mg PTH, the patient presented with a fever and generalized maculopapular rash reaction within 24 hours. Laboratory testing showed similar findings, with eosinophilia (753/ μ L) and liver function test abnormalities (AST, 119 IU/L, and ALT, 252 IU/L). To reduce his symptoms, the patient was given 20 mg oral prednisolone for 7 days. Other second-line anti-TB

drugs, including MFX and CS, were readministered one by one, but no adverse reactions were found. When we added 3.3 g PAS, the patient presented with the same systemic reactions within several hours after taking the drug (Fig 1). His adverse drug reactions subsided after receiving systemic corticosteroids. Thereafter, he was treated with MFX, CS, and KM by injection without DRESS recurrence, and a resectional surgery was planned.

DRESS is a severe cutaneous adverse drug reaction that typically develops 2 to 8 weeks after initiation of the drug responsible for the reaction. It is commonly caused by aromatic anticonvulsants such as phenobarbital, carbamazepine, phenytoin, lamotrigine, and sulfonamides.² Anti-TB drugs are associated with diverse cutaneous adverse drug reactions. Pruritus, skin eruptions, maculopapular exanthema, urticaria, and erythema nodosum are relatively common and can be controlled with oral antihistamines.³ However, few case reports exist of severe adverse reactions to anti-TB drugs, including ethambutol- or streptomycin-induced DRESS syndrome⁴ and rifampin- or pyrazinamide-induced vasculitis.⁵ The pathogenesis of DRESS is not fully understood and may be multifactorial, involving immunological mechanisms and drug detoxification pathways.⁶ Although patch tests are useful *in vivo* methods for detecting non-immediate drug reactions, the sensitivities vary depending on the vehicle used and the drugs tested. In particular, the clinical usefulness of a lymphocyte transformation test was reported to be minimal in patients with anti-TB drug-induced immune adverse reactions.⁷ The drug provocation test is generally accepted as the gold standard for confirming the culprit drug.⁸ In our patient, we performed a drug provocation test to find the causative drug as well as to minimize treatment interruptions; the test confirmed PTH and PAS as the causative drugs. To our knowledge, this is the first case of PTH- and PAS-induced DRESS syndrome. Considering the potential gravity of the syndrome and the increasing use of anti-TB drugs, all clinicians who treat tuberculosis must be aware of this severe hypersensitivity reaction to anti-TB drugs.

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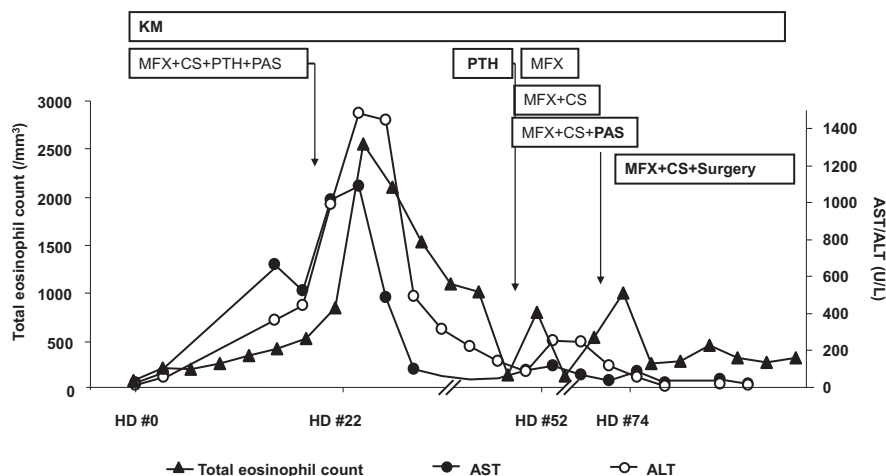


Figure 1. Clinical course, laboratory data, and re-challenge with second-line anti-tuberculosis drugs. AST, aspartate aminotransferase; ALT, alkaline aminotransferase; CS, cycloserine; HD, hospital day; KM, kanamycin; MFX, moxifloxacin; PAS, para-aminosalicylic acid; PTH, prothionamide; TEC, total eosinophil count.

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Persistent papilloma and polyoma virus infection in common variable immunodeficiency with progressive multifocal leukoencephalopathy

Common variable immunodeficiency (CVID) is a heterogeneous syndrome in which the main characteristic is hypogammaglobulinemia and impaired specific antibody responses with both B- and T-lymphocyte involvement.¹ Progressive multifocal leukoencephalopathy (PML) is an opportunistic demyelinating disease of the central nervous system caused by John Cunningham (JC) virus, a member of polyoma group DNA virus.² Any level of the central neuraxis may be affected, but the cerebral hemispheric white matter is the most common site, followed by cerebellar and bulbar localization.³ A study based on national inpatient diagnosis codes analyzed 9,675 PML cases from 1998 to 2005, including 82% with HIV, 8.4% with hematologic cancers, 2.83% with solid organ cancers, and 0.44% with hematologic diseases.⁴ JC virus receptor is present in several organs, including kidney, epithelial cells, B lymphocytes, platelets and in the central nervous system on glial cells and neurons. Although PML usually affects individuals with profound cellular immunosuppression, it has also been diagnosed in patients with no initial clinically apparent immunosuppression.⁵ PML is uncommon in CVID patients.⁶ Narula⁷ reported a 40-year-old man with CVID and PML and abnormal CD8 +T-cell subset,⁷ and Snyder⁸ reported a 21-year-old man with CVID and PML.

We describe a 29-year-old woman with CVID who underwent splenectomy because of thrombocytopenia and who was affected by JC virus–associated PML, and, despite progressive disease, CD4 and CD8 numbers remained normal, before and after PML.

Case Report

We describe a 29-year-old woman with a history of recurrent sinopulmonary infections since 3 y/o age. She developed splenomegaly and thrombocytopenia at 7 y of age. Bone marrow examination showed no significant abnormality. Splenectomy was performed at 9 years of age because of refractory thrombocytopenia. Immunologic studies showed only undetectable serum immunoglobulin A (IgA); hence, selective IgA deficiency was considered.

She developed 2 episodes of meningitis at 15 and 18 years of age, and, according to further work ups, CVID diagnosed. Immunologic findings are shown in Table 1. IVIG (Intratec, Manufactured from Iranian plasma farma GmbH, Germany, ordered by I.B.R.F) 400 mg/Kg was infused monthly since 18 y-o age which resulted in decreased frequency of sinopulmonary infections. She was referred to our allergy and immunology ward at 22 y of age because of multiple large palmar and plantar planar warts. Immunologic assays, including screening tests for humoral and cellular immunity, revealed normal results of the lymphocyte transformation test with phytohemagglutinin and candida and also normal values of delayed type hypersensitivity with candida and purified protein derivative but antibody response before and after vaccination failed to perform. Rheumatologic assays were within normal limits.

Results of imaging studies, including abdominal sonography and High Resolution Computed Tomography of the chest, were normal. Pulmonary function test revealed reversible obstructive airway disease. She experienced 1 episode of left knee septic arthritis. The patient remained well until 14 months ago, when she developed