

Strategies for Successful Treatment of Active Tuberculosis in the Setting of DRESS on RIPE

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We describe 2 young, female patients who developed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome while on treatment for pulmonary tuberculosis (TB). Active TB was treated successfully with second-line TB medications, including moxifloxacin, ethambutol, linezolid, and amikacin for 18 months.

Keywords. DRESS; RIPE; tuberculosis.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also referred to as drug-induced hypersensitivity syndrome, is a distinct, potentially life-threatening adverse reaction. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, and multi-organ manifestations including hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities [1]. DRESS may be caused by numerous medications, most commonly anticonvulsant drugs, beta lactam antibiotics, nonsteroidal anti-inflammatory drugs [2], and sulfonamides [1]. Medications used to treat tuberculosis (TB) are implicated in DRESS [3]. When DRESS develops during a standard TB treatment regimen of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE), management is challenging. TB medications may be repeatedly stopped and started or held for long durations while trying to determine which medication is responsible. Patients with severe elevation of liver function tests (LFTs) and rash may have significant interruptions before restarting treatment. This risks disease progression,

treatment failure, or acquired drug resistance. Limited data exist regarding DRESS management in the setting of TB. The Texas Center for Infectious Disease (TCID) is a hospital for the treatment of complicated TB patients in San Antonio, Texas. We report 2 cases referred to TCID for treatment of pulmonary TB in the setting of DRESS.

CASE 1

A 21-year-old Hispanic female diagnosed with cavitary pulmonary TB started RIPE therapy. She improved clinically, but sputum culture and smear remained positive for 6 and 8 weeks, respectively. Isoniazid was discontinued once low-level isoniazid resistance was reported and treatment augmented with amikacin twice weekly and levofloxacin. Approximately 12 weeks into therapy, the patient developed headache, nausea, subjective fevers, chills, and malaise; laboratory studies demonstrated new-onset thrombocytopenia. An acute care provider unaware of her TB treatment diagnosed a urinary tract infection and prescribed ciprofloxacin in addition to levofloxacin. Rash with fever occurred 1 week later. She was hospitalized, ciprofloxacin discontinued, and trimethoprim/sulfamethoxazole started. Maculopapular rash became diffuse, and facial edema developed. One provider described extensive oral ulcerations, but another the same day reported no oral lesions. Laboratory abnormalities included thrombocytopenia, aspartate aminotransferase 5715 IU/L, and alanine aminotransferase 3142 IU/L. Vancomycin, doxycycline, piperacillin/tazobactam, and methylprednisolone were initiated, and all TB medications were discontinued. Her rash and laboratory abnormalities improved, and the patient was discharged after 2 weeks without a definitive diagnosis. Two weeks after discharge, the patient was rechallenged with rifampin. She developed abdominal pain, nausea, fever, diffuse rash, peripheral eosinophilia (15%), and elevated LFTs and jaundice (total bilirubin of 10.9 mg/dL). The patient was diagnosed with possible DRESS due to rifampin. Rifampin was discontinued, and she was referred to TCID. After resolution of her rash, systemic symptoms, and laboratory abnormalities, she was sequentially challenged with standard doses of moxifloxacin, ethambutol, linezolid, and amikacin at 2–3-day intervals. She tolerated this regimen well and completed 18 months.

CASE 2

A 31-year-old Hispanic female was diagnosed with pan-susceptible, cavitary pulmonary TB in Mexico. Her initial TB regimen included rifampin, isoniazid, pyrazinamide, and levofloxacin. About 3.5 weeks after initiation of these medications, she developed a diffuse erythematous, desquamating rash, with fever

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and headaches. No mucosal involvement was reported. About 3–4 days later, she developed anorexia, fatigue, nausea, vomiting, weight loss, abdominal distension, jaundice, and dark urine. Laboratory studies confirmed acute liver failure. All 4 TB medications were discontinued. Due to worsening clinical status, she was transferred several days later to the United States. Allergy consultation confirmed the diagnosis of DRESS. Her LFTs and absolute eosinophil count peaked about 10 days after discontinuation of TB medications with aspartate aminotransferase 2672 IU/L, alanine aminotransferase 1418 IU/L, total bilirubin 16.1 mg/dL, and absolute eosinophil count 4758/ μ L. LFTs dramatically improved over the subsequent few weeks with observation and supportive therapy. She was referred to TCID for TB management. After resolution of her symptoms and laboratory abnormalities, the patient was sequentially challenged with standard doses of ethambutol, linezolid, moxifloxacin, and amikacin at 2–3-day intervals. She tolerated this regimen well, and an 18-month duration was planned.

DISCUSSION

These 2 cases highlight many of the challenges presented with the management of DRESS syndrome in patients on treatment for pulmonary TB. These young women had no known underlying liver disease or other past medical history. Pulmonary TB was confirmed by sputum culture positive for *Mycobacterium tuberculosis*. Patient 1 had low-level isoniazid-resistant TB, while patient 2 had susceptible TB. Both patients were on rifampin as part of previously noted TB regimens when DRESS developed. Rifampin is the most common TB medication associated with DRESS, but isoniazid, ethambutol, pyrazinamide, fluoroquinolones, PAS [4], and streptomycin [5] have also been implicated. Other nontuberculous medications associated with DRESS include aromatic anticonvulsants, especially carbamazepine, phenytoin, and phenobarbital, sulfonamides such as sulfasalazine and dapsone, and allopurinol. Case 1 was treated for a short period of time with trimethoprim/sulfamethoxazole, which may have exacerbated her symptoms. DRESS is a type IV

delayed hypersensitivity reaction. Its etiology has been linked to reactivation of Epstein-Barr virus human herpesvirus-6 and human herpesvirus-7 [6]. DRESS has a later onset than other drug reactions; the onset of symptoms typically occurs 2 to 8 weeks after drug administration but, as noted in Case 1, can occur even later.

There is no definitive standard for the diagnosis of DRESS, but diagnostic criteria have recently been established from the European Registry of Severe Cutaneous Adverse Reaction and the Japanese Research Committee on Severe Cutaneous Adverse Reaction scoring systems [1]. According to a scoring system from the British Association of Dermatologists for classifying DRESS (Table 1), both patients had definite DRESS, with scores >6. The 2 patients had similar clinical presentations with fever, rash, peripheral eosinophilia, and markedly elevated LFTs, which prompted consideration of liver transplantation in both patients. Skin biopsies were not performed for either case but can be a useful tool in diagnosis and help to differentiate DRESS from other cutaneous drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. The clinical diagnosis of DRESS syndrome was also based on the relationship between TB treatment and subsequent appearance of the clinical syndrome, absence of other causative medications, and resolution of symptoms with discontinuation of TB medications. Additionally, the recurrence of DRESS signs and symptoms when rifampin was re-administered confirmed the diagnosis in the first patient. DRESS should be included in the differential diagnosis of patients who develop rash, fever, and systemic symptoms while taking TB medications. DRESS was initially not suspected, resulting in a significant delay in the diagnosis.

DRESS can last for a longer duration than other drug reactions. Most patients recover completely after drug withdrawal and appropriate therapy. However, DRESS may result in life-threatening complications, most commonly fulminant hepatitis with hepatic necrosis, with a mortality rate of 10%. Systemic corticosteroids or other immunosuppressive drugs are

Table 1. Scoring System for Classifying Drug Reactions With Eosinophilia and Systemic Symptoms (DRESS)

| Item | | | Present | Absent |
|---|---------------------------|----------------------------|---------|--------|
| Fever $\geq 38.5^{\circ}\text{C}$ (101.3°F) | | | 0 | -1 |
| Enlarged lymph nodes (>1 cm, at least 2 sites) | | | 1 | 0 |
| Eosinophilia: | ≥ 700 or $\geq 10\%$ | ≥ 1500 or $\geq 20\%$ | 1 | 2 |
| Atypical lymphocytes | | | 1 | 0 |
| Rash $\geq 50\%$ of body surface area | | | 1 | 0 |
| Rash suggestive (≥ 2 of facial edema, purpura, infiltration, desquamation) | | | 1 | 0 |
| Skin biopsy suggesting alternative diagnosis | | | -1 | 0 |
| Organ involvement (liver, lungs, heart, kidneys) | 1 | 2 or more | 1 | 2 |
| Disease duration >15 d | | | 0 | -2 |
| Investigation for alternative cause (blood cultures, ANA, serology for hepatitis viruses, mycoplasma, chlamydia) ≥ 3 done and negative | | | 1 | 0 |

Total score <2: DRESS excluded; 2–3: possible DRESS; 4–5: probable DRESS; ≥ 6 : definite DRESS. Adapted from: Kardaun SH, Sidoroff A, Valeyrie-Allanore L, 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; 156:609.

recommended for all cases of DRESS but need to be used with caution in patients with TB due to the risk of overwhelming infection, especially when adequate TB medications have been discontinued. Prednisone 1 mg/kg/d or equivalent is given until clinical improvement, and normalization of laboratory parameters are obtained and then tapered over the ensuing 3–6 months to avoid relapse. Topical corticosteroids may be applied to skin lesions for symptomatic relief [7]. Even in the absence of immunosuppressive drugs, there is risk of TB disease progression when TB medications are held while awaiting the resolution of DRESS.

Autoimmune diseases have been reported in patients months or years after the resolution of the drug reaction. In a retrospective study of 43 patients with DRESS followed for at least 1 year, 4 (10%) patients developed autoimmune diseases, including Grave's disease, diabetic mellitus type 1, and autoimmune hemolytic anemia. Patients may develop chronic kidney disease and require lifelong hemodialysis [8]. Due to the high likelihood of recurrence, medication desensitization is contraindicated after the development of DRESS syndrome [9]. Patients may also have an increased risk of DRESS to other unrelated drugs [10]. When TB therapy is reintroduced, the regimen must be adequate to lead to a cure, prevent drug resistance, and avoid further damage to compromised organ systems.

Hospitalization at a specialized center may greatly facilitate care. A single team of physicians made clinical decisions, and patients were aware of the treatment plan. The diagnosis of DRESS precluded desensitization with firstline TB medications, and neither patient could tolerate hepatotoxic TB medications, including isoniazid, rifampin, and pyrazinamide. They were sequentially challenged with second-line TB medications, including moxifloxacin, ethambutol, linezolid, and amikacin at TCID while being closely monitored. Their treatment regimen was longer due to inability to use the most effective medications, and it also had the potential for more toxicity. During their inpatient admission, both improved clinically, bacteriologically,

and radiographically and were subsequently discharged to outpatient TB treatment.

CONCLUSION

Active TB can be treated successfully despite DRESS using an alternative regimen. Avoidance of the medications causing DRESS is essential. Careful daily evaluation by a single clinical team is recommended to monitor for fever, rash, eosinophilia, or elevated LFTs that may be consistent with reoccurrence of DRESS. Patients unable to tolerate isoniazid and rifampin require treatment with second-line medications for 18 months as if they had multidrug-resistant TB.

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