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CASE REPORT

Listen to the Patient: A Case Report and Literature Review of DRESS

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement.[1-3] DRESS initially was observed in patients treated with anticonvulsants in the early 1930s, when phenytoin first became available.[4] Many clinical terms have been used to describe DRESS, including hypersensitivity syndrome and mononucleosis-like syndrome.[2] In 1996, Bocquet et al.[1] proposed the term DRESS "to decrease the ambiguity of the denomination of hypersensitivity syndrome" and to give a more accurate description of this clinical syndrome. The incidence of DRESS ranges from 1 in 1000 to 1 in 10,000 drug exposures.[5]Aromatic anticonvulsants (especially phenytoin, carbamazepine, and phenobarbital) and sulfonamides (such as dapsone and sulfasalazine) are the most common causes of DRESS.[1,6]

This case report and review revisits the association between sulfasalazine and DRESS and reminds clinicians to consider this entity as part of a broad differential diagnosis when evaluating patients who experience unusual clinical manifestations after starting this culprit medication.

CASE REPORT

A 46-year-old African American female with Crohn's disease, complicated by enterocutaneous fistulas and status-post small bowel resection, acid reflux, and chronic migraines presented in early 2016 for new onset rash involving her face, arms, abdomen, and upper thighs. She had seen her rheumatologist 1.5 weeks prior to admission, at which time she was started on sulfasalazine. Her primary care physician around the same time had started her on ranitidine for acid reflux. Both agents were stopped prior to admission, but the rash persisted. She [illegible] benzaprine, diclofenac gel, diphenhydramine, ergocalciferol, fluticasone, lidocaine patch, morphine SR, ondansetron, and oxycodone as needed. She was not on steroids prior to arrival.

On admission, she was febrile, tachycardic, tachypneic, and appeared ill. She had an erythematous, pruritic, maculopapular rash involving her face, arms, abdomen, and upper thighs without drainage. No abscesses were noted. Her labs revealed a sodium level of 125 mmol/L (low), a total bilirubin of 2.5 mg/dL (high), an alkaline phosphatase of 136 U/L (high), a lactate of 2.7 mmol/L (high), white blood cell count of 5,800/mcL, platelet count of 123,000/mcL, hemoglobin of 11.8 gm/dL (low), and 18% "other cells". Peripheral smear revealed reactive and atypical lymphocytes with mild monocytosis. LDH was elevated at 500 U/L, haptoglobin was low at < 30 mg/dL, and reticulocyte count was elevated; all consistent with acute hemolysis. The acute hepatitis panel was negative.

She initially was started on broad-spectrum antibiotics for suspected severe sepsis of undetermined etiology in the setting of chronic immunosuppression from Crohn's disease. The other differentials on admission were drug reaction versus DRESS. Dermatology initially was unconvinced about the diagnosis of DRESS since the patient's rash did not fit the typical chronological pattern consistent with DRESS. It had been only 1.5 weeks since she had begun the suspected medications.

Hematology was consulted due to the patient's hemolytic anemia. A Coomb's test, plasma free hemoglobin, and G6PD test were within normal limits. Flow cytometry revealed reactive T cell lymphocytosis. The patient had an abdominal ultrasound which showed a peripheral splenic infarct. Infectious disease tested for an Epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus 6, parvovirus B19, and adenovirus PCRs, HIV antigen/antibody, and syphilis and Cryptococcus antigens. Only the EBV panel was positive. Other pertinent negative tests included ceruloplasmin, anti-neutrophil cytoplasmic antibodies, anti-Saccharomyces cerevisiae antibodies, antimitochondrial antibody, antinuclear antibody, and alkaline phosphatase.

The patient developed severe facial edema within a few days of admission. Otolaryngology performed a flex exam revealing no oropharyngeal or supraglottic swelling and a patent airway. Biopsy performed by dermatology was most consistent with DRESS and showed no evidence of Stevens Johnson syndrome or toxic epidermal necrolysis. Dermatology suspected the culprit drug was sulfasalazine over ranitidine. Antibiotics were discontinued at that time and high-dose systemic corticosteroid therapy was initiated (prednisone 80 mg daily). She also was started on a proton pump inhibitor, calcium, vitamin D supplementation, and dapsone for prophylaxis for Pneumocystis jiroveci pneumonia (PJP) while on a prolonged systemic corticosteroid course.

Aerosolized pentamidine and atovaquone were discussed with the patient but dapsone was considered best option due to cost. Dapsone can cause DRESS, but the patient was initiated on high-dose systemic corticosteroid therapy and the risk for PJP was deemed very high.

There was a risk-benefit discussion with the patient and she elected to take dapsone therapy. The patient's symptoms markedly improved and she had appropriate follow-up. The patient did well on dapsone therapy and did not develop any complications.

DISCUSSION

This patient's symptoms and clinical findings were difficult to interpret on admission. First, the onset of symptoms with DRESS typically occurs two to six weeks after drug administration. Our patient's symptoms started only 1.5 weeks after starting sulfasalazine. Second, there was no evidence of peripheral eosinophilia or facial edema on admission (although she experienced facial edema later in her course). Last, there was no evidence of an elevated serum alanine aminotransferase (ALT) level. Despite the atypical time course, our patient's rash started 1.5 weeks after a culprit drug (sulfasalazine) was initiated. Statistically speaking, sulfasalazine (and less likely ranitidine) was considered to be the cause of DRESS in this patient since sulfasalazine has been implicated in 10 cases according to the RegiSCAR's Score and ranitidine was not included.[7] Ranitidine is even labeled as a "miscellaneous cause" by Criado et al.[8]

In approximately 30% of cases, there is eosinophilia in DRESS syndrome but it can be delayed for one to two weeks.[1,9] Liver abnormalities with elevated serum ALT are found in approximately 70% of patients with DRESS syndrome, although one series of 27 patients found it in more than 95% of them.[10,11] The most common skin biopsy findings are a dense, perivascular lymphocytic infiltrate in the papillary dermis, with the presence of extravasated erythrocytes, eosinophils, and dermal edema.[2] Our patient's skin biopsy revealed a perivascular lymphoid infiltrate with rare neutrophils and extravasated erythrocytes.

According to RegiSCAR diagnostic criteria,[12] our patient met criteria for DRESS. The patient must: 1) have an acute rash, 2) have drug-related symptoms, 3) require hospitalization, and three of the following four signs: fever > 38C, enlarged lymph nodes involving > 2 sites, involvement of > 1 internal organ, and blood count abnormalities. Final scores: < 2: excluded; 2 – 3: possible; 4 – 5: probable; > 5: definite.[13] The diagnosis of DRESS should be suspected with the presence of skin rash, liver involvement, hyper-eosinophilia, and lymphadenopathy in the setting of fevers. The standard of care is to stop the suspected causative agent and initiate systemic corticosteroids. Systemic corticosteroids are the current mainstay of treatment. A recommended starting dose is 1.0 – 1.5 mg/kg/day of prednisone or an equivalent drug and this dosage should be slowly tapered over 6 - 8 weeks to avoid a flare-up of symptoms.[14] Further studies are needed to recommend specific treatment guidelines.

CONCLUSION

Often in medicine, physicians are confronted with diagnostic dilemmas. Our case highlighted the importance of the history and physical examination in maintaining a broad differential and making an accurate diagnosis. Internists must be aware of DRESS and its common culprit medications, as it is a potentially fatal diagnosis if left untreated. Prompt diagnosis is important to treat the underlying disease process.

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