Case Report: DRESS Syndrome

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A 63 year-old Chinese woman presents to the emergency department (ED) complaining of a rash that started two days earlier, as well as fever and decreased appetite. She has a history of mixed connective tissue disorder, hypertension, diabetes, and psoriatic arthritis. She completed a course of azithromycin about one week ago for an upper respiratory infection. Due to the persistence of symptoms her doctor prescribed clotrimazole lozenges and trimethoprim-sulfamethoxazole two days prior to arrival. In addition to these medications above, she takes numerous medications daily for her chronic conditions, which her husband states he will bring to the hospital later.

Upon initial physical examination, she was awake, alert and oriented. Vital signs were: blood pressure, 119/55 mmHg; heart rate 92 beats/minute; respiratory rate 18 breaths/minute; and temperature 99.8˚ F. A diffuse blanchable maculopapular rash was noted on upper and lower extremities, chest, and abdomen. No rash was present on her palms or soles and there was no mucosal involvement. Scleral icterus and mild abdominal tenderness were the only other significant exam findings.

Initial pertinent laboratory results were as follows: Complete blood count: white blood cell count, 12,300 cells/mm^3; and an absolute eosinophil count of 861 cells/mm^3. Chemistry: sodium 124 mEq/L, potassium 5.2 mEq/L, chloride 106 mEq/L, bicarbonate 10 mEq/L, blood urea nitrogen 38 mg/dL, creatinine 1.6 mg/dL, glucose 277 mg/dL. Hepatic studies: AST 1,063 IU/L; ALT 604 IU/L; alkaline phosphatase 1425 IU/L, total bilirubin 7.3 mg/dL; direct bilirubin 5.3 mg/dL; albumin 3.4 gm/dL.

What clinical syndrome should be considered in this case?

This patient appears to be having a severe adverse cutaneous drug reaction that included abnormalities of bone marrow, liver and renal function. Together these form the basis for the DRESS syndrome, an acronym for “drug rash with eosinophilia and systemic symptoms.” DRESS syndrome is commonly accepted to include previously described drug hypersensitivity syndromes such as for anticonvulsant or sulfonamides syndrome.

How does one make the diagnosis of DRESS syndrome?

The triad of rash, fever and internal organ involvement are the key features in making this diagnosis. It is usually seen 2-8 weeks after the initiation of a new drug or within a day of re-exposure. The rash, which can vary in appearance and severity, is most commonly morbilliform (measles-like). The eruption of the rash often precedes or coincides with the development of a fever and non-specific findings including malaise, pharyngitis, facial edema, and lymphadenopathy.

DRESS may be clinically indistinguishable from other cutaneous syndromes such as Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Kawasaki disease, Still’s disease, and bacterial infections. SJS/TEN, a life threatening cutaneous drug rash,

differs from DRESS in that SJS/TEN features prominent mucosal involvement, target lesions, and epidermal necrosis leading to skin sloughing.

The diagnosis of DRESS requires the presence of eosinophilic infiltration of the internal organs. This most commonly manifests as acute hepatitis, and can progress to fulminant hepatic failure. Interstitial nephritis, encephalitis, pneumonitis, and thyroiditis are also relatively common. Internal organ involvement is determined initially through laboratory analysis, which should include renal, hepatic, and thyroid studies. The initial studies of bone marrow activity (e.g. CBC with differential) demonstrate atypical lymphocytes and eosinophilia.

Which medications have been observed to cause DRESS syndrome?
Anticonvulsants and sulfonamides have been the most common drugs reported to cause DRESS syndrome, with an incidence ranging from 1 in 1,000 to 1 in 10,000 exposures. Some of the other drugs implicated in this syndrome include: phenytoin, carbamazepine, phenobarbital, lamotrigine, minocycline, dapsone, allopurinol, nevirapine, and abacavir.

Case Continuation:
The patient's husband brought to the hospital a large bag of medications including the following: acetylsalicylic acid, allopurinol, folic acid, gemfibrozil, glipizide, lansoprazole, leflunomide, metformin, simvastatin, and valsartan. The prescriptions came from several different pharmacies and physicians. The patient had only taken two or three doses of trimethoprim-sulfamethoxazole before her symptoms began, and further investigation by calling several of her primary care physicians and pharmacies revealed that she had never previously used this drug, making this an unlikely etiologic factor. Allopurinol was initiated six weeks prior to presentation, making it the most likely cause of DRESS syndrome in this patient.

What is the mechanism of DRESS syndrome?
The exact cause of DRESS is unclear and for each drug a different mechanism may exist. Most proposed mechanisms infer an unwarranted immunological response to the drug itself or its metabolites. For example, various endogenous enzymes create active metabolites from aromatic anticonvulsants that are thought to be detoxified by epoxide hydroxylase. If this process is faulty these metabolites may induce an auto immune response by creating neoantigens to which the immune system responds. Evidence also suggests that active human herpes virus 6 infection may also play a role by interfering with the removal of toxic drug metabolites.

How is DRESS syndrome treated?
Nothing is more important to reducing morbidity and mortality than rapid recognition of DRESS syndrome and immediate cessation of all potential offending agents.

Corticosteroid treatment to suppress the inflammatory eosinophilic involvement of the skin and internal organs remains controversial for several reasons. Viral activation may play a role in the cause of DRESS syndrome and there are concerns that systemic corticosteroids may enhance this process. Corticosteroids do not seem to have an

outcome benefit in similar diseases such as in SJS/TEN, likely due to the increased septic complications associated with the presence of mucocutaneous lesions. But complications of DRESS syndrome are more commonly due to internal organ derangement rather than cutaneous effects. Despite the lack of randomized control trials and the potential harm, systemic corticosteroids are typically recommended and many patients seem to respond favorably.

IV N-acetylcysteine is used to treat DRESS syndrome related hepatitis, given its proven nonspecific beneficial role in a variety of other causes of fulminant hepatic failure. But this therapy remains unproved and controversial, with benefit suggested in some case reports and possibly an increased rate of anaphylactoid reactions in others.

Although DRESS is typically due to a specific drug, other drugs in a similar class, such as the aromatic anticonvulsants (i.e, phenobarbital, phenytoin, carbamazepine), may cause a similar reaction in an affected individual. Therefore patients who survive DRESS syndrome need specific education and ongoing medication reconciliation to prevent exposure to other potential offending agents.

Evidence has linked genetic components to several medications that are known to cause DRESS syndrome, therefore counseling family members must be a part of treatment. It has been described that in patients of Chinese descent there is a very strong association with HLA-B*5801 allele and DRESS syndrome caused by allopurinol. This patient is an immigrant from China.

Case Conclusion:
Shortly after presenting to the ED, the patient became obtunded and an ABG showed: pH,7.1; pCO2, 30 mmHg; pO2, 62 mmHg; bicarbonate, 9 mEq/L. Her initial clinical course was complicated by respiratory failure requiring intubation, fulminant hepatic failure, refractory hypotension requiring vasopressors, and renal failure requiring hemodialysis. She was given a course of IV N-acetylcysteine, and IV corticosteroids. After two weeks her liver and renal failure improved dramatically, but she suffered from several hospital-related septic complications. Her family was educated on the potential for a genetic link.

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