CLINICAL VIGNETTE

Sulfonamide-induced DRESS Syndrome

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Case Presentation

A 40-year-old male with Type 2 diabetes and obesity presented to the urologist with urinary frequency and urgency. He was diagnosed with prostatitis and placed on a 4-week course of trimethoprim-sulfamethoxazole and tamsulosin. Three weeks later he presented to urgent care for flu-like symptoms including headache and chills. Influenza PCR was negative. He returned to urgent care the next day, with a pruritic maculopapular chest rash which was thought to be a viral exanthem. The next day the rash progressed to his entire torso, arms, and legs, along with facial swelling. Several days later, he developed fevers and night sweats and was seen by a dermatologist who suspected an allergy to trimethoprim-sulfamethoxazole, which was discontinued. He was given a intramuscular dose of corticosteroids followed by a 14-day prednisone taper. The rash and fever resolved, however he presented a month later with fatigue, anorexia, and unintentional 13-kg weight loss over the previous month.

His vital signs included temperature of 36.8° C, blood pressure 125/85 mmHg, heart rate 108 beats/minute. The physical examination was unremarkable. Laboratory examination was notable for white blood cell count of 13,000 with elevated absolute neutrophil count of 7150/uL (upper limit of normal 500/uL), absolute eosinophil count 620/uL (upper limit of normal 500 uL), AST 51 U/L (normal range 13-47), ALT 301 (normal range 8-64 U/L), ALP 162 U/L (normal range 37-114 U/L). Bilirubin and creatinine were normal. Given the elevation in ALT, additional testing including elevated ferritin of 2225 ng/mL with normal saturation. Acute hepatitis panel, EBV, CMV, celiac serologies, alpha-1 antitrypsin, ceruloplasmin, ANA, IgG, anti-smooth muscle antibody were normal. Abdominal ultrasound showed mild hepatic steatosis. He was referred to hepatology who diagnosed with DRESS syndrome. Two weeks later his liver enzymes normalized without additional intervention.

Discussion

Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (DRESS) or drug-induced hypersensitivity syndrome (DiHS) is a rare, potentially fatal, type IV hypersensitivity reaction that involves an extensive rash, lymphadenopathy, eosinophilia, atypical lymphocytosis, and visceral involvement.[1,2] Medications commonly implicated include antiepileptics, sulfonamides, allopurinol, minocycline, vancomycin, and non-steroidal anti-inflammatory medications.[1,3]

The pathogenesis of DRESS may include a drug-induced T-cell response and reactivation of previously latent viral infections of the herpes virus family, including HHV-6, HHV-7, EBV, and CMV.[4] Additionally, several leukocyte antigen (HLA) haplotypes are associated with an increased risk of DRESS syndrome.[5]

Symptoms occur 2 to 8 weeks after initiating the inciting medication. The rash is the most obvious symptom and is usually pruritic, maculopapular, symmetric, affecting the torso and extremities and often covers 50% of the total body surface area.[1,6] The rash may progress to confluent patches and plaques. Less commonly, vesicles, pustules, bulla, purpura, pustules, exfoliative dermatitis may also be seen. Facial edema is present in 70% of cases.[1,6,7]

Systemic symptoms include fever, fatigue, and lymphadenopathy. Hematologic abnormalities of eosinophilia, leukocytosis, neutrophilia, and monocytosis are often seen. Lymphocytosis or atypical lymphocytosis may also be present.[1,2] Most patients have involvement of one or more organs. Liver injury is the most common, reported in 53-90% of cases.[1,6,7] Liver enzyme elevations are typically transient and mild, and may follow a cholestatic, hepatocellular, or mixed pattern. Up to 50% of cases have liver enzymes more than 10 times the upper limit of normal, however, fulminant liver failure is rare.[8] Acute interstitial nephritis, interstitial pneumonitis, or myocarditis may also occur.[1,2,6,7] The mortality rate is up to 10 percent.[6]

DRESS should be suspected in a patient who has received a new medication in the preceding two to eight weeks who presents with generalized rash, fever, lymphadenopathy, and lab evaluation showing eosinophilia with abnormal organ function testing, most commonly elevation of liver enzymes. The differential diagnosis for patients with fever and rash includes bacterial and viral infections, Stevens-Johnson syndrome/toxic epidermal necrolysis, Sézary syndrome, Kawasaki syndrome; systemic lupus erythematous, and serum sickness. Skin biopsy may be useful although it may be non-specific.

Immediate withdrawal of the offending agent is the mainstay of treatment. In mild cases, with liver enzymes less than 3 times the upper limit of normal without evidence of renal or pulmonary involvement, supportive treatment is adequate. This includes managing the pruritic rash with high-potency topical steroids.[9] Oral glucocorticoids are indicated in severe liver

disease or with renal or pulmonary involvement. Doses start at 0.5 to 1 mg per kg per day of prednisone until clinical improvement is noted, then tapered over 8-12 weeks.[9] Resolution is typically seen weeks to months after stopping the offending medication, however, close follow-up is necessary as relapse can occur.

It is important to have a high index of suspicion for DRESS in patients who received a culprit medication in the preceding two to eight weeks and who presents with an acute generalized rash with fever, lymphadenopathy, laboratory abnormalities such as eosinophilia, and evidence of organ involvement, most commonly elevation in liver enzymes. Early intervention with withdrawal of inciting medication can prevent organ failure and mortality.

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