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MORNING REPORT

PHENYTOIN-INDUCED DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME

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The comments in italics are those of the discussant, Michele Fang, MD. Dr. Fang (Michele.Fang@uphs.upenn.edu) is an associate editor of the SGIM *Forum* and an associate professor at the University of Pennsylvania, Perelman School of Medicine.

A 52-year-old African-American male with past medical history of ESRD on dialysis, diabetes, coronary artery disease, stroke, alcohol use, and recently diagnosed seizures presented with fever and a pruritic rash over his body and face for a week. The rash was a diffuse morbilliform rash over his trunk, arms, and face. The rash was not pruritic. He had fevers, but denied cough, dysuria, or diarrhea. He denied headache or mental status changes. Patient was started on phenytoin five weeks prior for new-onset generalized tonic-clonic seizure.

The differential diagnosis for febrile patients with a rash is extensive. Diseases that present with fever and rash are usually classified according to the morphology of the primary lesion. Rashes can be categorized as maculopapular (centrally and peripherally distributed), petechial, diffusely erythematous with desquamation, vesiculobullous, pustular, and nodular. Potential causes include viruses, bacteria, spirochetes, rickettsiae, medications, and rheumatologic diseases. A thorough history and a careful physical examination are essential to making a correct diagnosis. Although laboratory studies can be useful in confirming the diagnosis, test results often are not available immediately. Because the severity of these illnesses can vary from minor (roseola) to life-threatening (meningococcemia), physicians must make prompt management decisions regarding empiric therapy. Hospitalization, isolation, and antimicrobial therapy often must be considered when a patient presents with fever and a rash. Maculopapular eruptions are most frequently seen in viral illnesses and immune-mediated syndromes. Viral etiologies of rashes include rubeola, rubella, erythema infectiosum, and roseola. Drug reactions can present as any dermatologic morphology and show no predilection for age, gender or race. Exanthematous eruptions most commonly occur in association with the administration of penicillins or cephalosporins. The rash usually appears within the first week after the offending drug is started and typically resolves within days after the drug is discontinued. Drug-related reactions can be difficult to distinguish from viral exanthems, but they may be more intensely erythematous and pruritic.

On initial presentation to the ED, patient was febrile (Tmax-103.1) and tachycardic. The patient had diffuse morbilliform rash over the trunk, arms, and face. His cardiac exam showed no murmurs but tachycardia; his lungs were clear. The patient's abdomen was non-tender but did show hepatomegaly and positive fluid wave. The patient's dialysis access was clean, dry, and intact without erythema or drainage. Laboratory results were significant for elevated AST 190 (baseline 20), elevated ALT 193 (baseline 20), elevated Alkaline phosphatase 870 (baseline 536), total bilirubin of 1.1 with 0.7 direct, albumin of 3.3, and INR 1.4. His BUN and Cr were 33 and 4.30, respectively; his last dialysis was one day prior to presentation. Complete blood count was consistent with anemia of chronic disease (unchanged from recent labs), white count of 6.1 and differential was significant for eosinophils of 16%.

The clinical presentation is concerning for sepsis syndrome given fever and tachycardia and the patient's dialysis status. The patient's laboratory values also reflect increase in transaminases and biliary sepsis needs to be evaluated. However, the eosinophilia, rash, and initiation of a new drug, especially phenytoin is also concerning for DRESS.

Ultrasound of the liver was performed which revealed hepatomegaly and ascites as well a thickened gallbladder wall with sludge. In the ED, patient was fluid resuscitated

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and started on empiric antibiotics for concern of sepsis Initial UA and CXR were not suggestive of infection and, blood cultures were negative. A diagnostic paracentesis was performed at bedside. Fluid studies revealed a serum ascites albumin gap of 1.2, suggestive that this patient's ascites was potentially related to chronic portal HTN but no leukocytosis and negative gram stain.

Given the classic rash and eosinophilia with recent initiation of phenytoin, it became clear that the patient did not have sepsis, but had DRESS syndrome.

Patient was started on prednisone 80mg and topical steroid cream. Broad spectrum antibiotics were discontinued as infection was ruled out. His Dilantin was stopped and he was started on oxcarbazepine for seizure. The next day, the patient became afebrile and had significant improvement in rash along with improvement in liver function test. The patient's rash continued to improve clinically over the first few days of hospitalization.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity reaction to certain drugs characterized by fever, morbilliform rash, eosinophilia, and systemic involvement (hepatitis, nephritis). DRESS is potentially life threatening and therefore early recognition and intervention is critical. DRESS refers to an uncommon, potentially life-threatening hypersensitivity response to certain medications. Antiepileptics in particular are classically associated with DRESS, along with allopurinol, sulfa drugs, and various antibiotics. As the name suggests, manifestations of DRESS may include high eosinophil counts (greater than 700 eosinophils/microliter) and damage to many different organ systems. The liver is the internal organ most commonly targeted, with a severe hepatitis being one of the main causes of death; however, DRESS can present with involvement of almost any organ, and symptoms may arise from visceral processes including interstitial nephritis, pericarditis, pancreatitis, and encephalitis. Morbilliform rash is a key external indication of DRESS, and if it is observed in a febrile patient within two to six weeks (longer than the typical time course of a Stevens-Johnson/toxic epidermal necrolysis reaction) of starting a typical inciting medication, DRESS should be given strong consideration in a differential diagnosis. Facial swelling and painful lymphadenopathy are other clinical indicators of a potentially severe drug reaction. If a patient is believed to be experiencing DRESS, labs that should be obtained include a CBC (with a particular interest in the eosinophil count) along with creatinine, BUN, and liver enzymes to investigate possible visceral involvement. The most important initial step is to immediately discontinue recently started drugs that are thought to be the likely culprit of the reaction. The labs previously mentioned should continue to be monitored. Fortunately, the vast majority of patients fully recover after stopping the medication responsible for their reaction. It is imperative that physicians quickly recognize the signs of DRESS in patients recently started on new medications given the possibly fatal consequences of failing to do so.

Management includes oral steroid, topical steroid ointment, antihistamine and supportive care with iv hydration and antipyretics.

Learning point:

DRESS syndrome is a severe hypersensitivity reaction that has been implicated with numerous drugs. Early diagnosis and prompt treatment with corticosteroids is imperative.

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