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CLINICAL VIGNETTE

Hydroxychloroquine-induced DRESS Syndrome

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Case Report

A 58-year-old Caucasian male with a history of recently diagnosed seropositive nodular rheumatoid arthritis, hypertension, and hyperlipidemia was seen in rheumatology clinic and was noted to have persistent synovitis despite leflunomide 20 mg daily. He was prescribed hydroxychloroquine 200 mg twice a day to take in addition to leflunomide. About ten days later, he developed a diffuse pruritic macular rash throughout his back, abdomen, and extremities, stopped the hydroxychloroquine, and went to the Emergency Department where he was prescribed prednisone 10 mg daily for three days as well as diphenhydramine 25 mg as needed for pruritus. The patient returned to the Emergency Department two days later because he developed weeping pustular lesions. He also reported myalgias, diarrhea, sore throat, and chills but no fever.

The patient's vital signs were remarkable for a heart rate of 107 beats/min and blood pressure 138/70 mmg Hg. On physical examination, he had superficial fine pustules with diffuse erythema over his face, upper chest and back and pruritic erythematous macules and papules over the arms and legs, but no lesions of the palms, soles, or oropharynx. There were areas of eroded pustules. The patient's white blood cell count was 14,600 with 12.2% eosinophils, his creatinine was 1.7 mg/dL (normal range 0.5-1.4), albumin 2.9 g/dL (normal range 3.2-4.8) and the rest of his labs were unremarkable.

The patient was diagnosed with drug-induced rash with eosinophilia and systemic symptoms (DRESS) syndrome and admitted to the hospital. His acute kidney injury resolved with intravenous fluids. A punch skin biopsy of the back was performed and showed superficial perivascular and interstitial dermatitis of mixed cell type with eosinophilic predominance, slightly psoriasiform and spongiotic, with extravasated red blood cells. Prednisone was begun at 60 mg daily and slowly tapered over the next several weeks after discharge.

Discussion

DRESS syndrome was coined in 1996 to describe a rare, but serious hypersensitivity reaction to medications that involved fever, rash, lymphadenopathy, and internal organ involvement along with peripheral eosinophilia[1].It has been more commonly reported with anticonvulsants, sulfasalazine, allopurinol, nonsteroidal anti-inflammatory drugs, and antibiotics such as sulfonamides and minocycline. There is one report in the English literature of DRESS syndrome associated with hydroxychloroquine, an antimalarial medication that inhibits the actions of toll-like receptors involved in B cell activation[2]. DRESS syndrome typically occurs 1-8 weeks after exposure to the offending drug and a chronic papulo-pustular skin eruption is often seen which can progress to exfoliative dermatitis. Hepatitis, interstitial nephritis, myocarditis, pneumonitis, and colitis are some of the systemic manifestations of DRESS syndrome.

Several investigators have proposed that human herpesvirus-6 infection or reactivation may trigger the onset of DRESS syndrome and contribute to internal organ involvement and the relapse of symptoms observed long after discontinuation of the causative drugs[3]. Antiviral T cells are generated that may cross-react with the offending drug, reactivating human leukocyte antigen molecules and play a key role in DRESS syndrome similar to graft-versus-host disease[4]. B cells are also likely involved as transient hypogammaglobulinemia has been observed at the onset of DRESS syndrome and drugs that have been implicated in

this syndrome inhibit differentiation of B cells to immunoglobulin-producing cells *in vitro*[5].

Central to this case is the distinction between DRESS and a typical drug eruption. Drug eruptions or "drug rashes" are by far the most common adverse drug reactions affecting the skin. The drug rash often occurs between 4 and 14 days after beginning a new drug, and can even occur 1 to 2 days after cessation of the drug. The onset can be more abrupt in the setting of a repeat exposure to a previously offending drug. It consists of erythematous macules or papules that are often symmetric, begin on the trunk or upper extremities, and become confluent. Although the eruptions may be polymorphous, they do not typically affect mucous membranes, and do not involve organ dysfunction.

The key issue with DRESS syndrome to note is that the rash does not simply resolve with discontinuation of the drug; systemic corticosteroids (prednisone 0.5 – 1 mg/kg/d) and monitoring of laboratory tests for visceral involvement are indicated. The most common organ to be involved in DRESS syndrome is the liver and mortality for the syndrome is approximately ten percent especially in patients with severe multi-organ involvement[6]. Care must be taken not to mistake DRESS syndrome for infectious diseases such as measles and infectious mononucleosis. The differential should also include drug-induced lupus erythematosus, Kawasaki syndrome, serum sickness-like reaction, hypereosinophilic syndrome, drug-induced pseudolymphoma, and staphylococcal toxic shock syndrome. Significant morbidity with the DRESS syndrome may occur because serious internal organ involvement may go undetected due to its great variability and severity and it may be observed even several months post onset of the rash[5].

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