Clinical Image

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Acute generalized exanthematous pustulosis with systemic involvement

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A 79-year-old man with a history of hypertension, chronic kidney disease stage IV, hyperlipidemia, heart failure, type II diabetes, chronic obstructive pulmonary disease (COPD), and atrial fibrillation presented to the emergency room (ER) in September 2021 with a body rash associated with pruritus, which he had for several days. The rash initially started on his trunk and spread to his extremities over a few days. Diltiazem was initiated for arrhythmia 1 week before the onset of the rash. The patient denied recent use of antibiotics or antifungal medications. He has been taking losartan 100 mg daily and amlodipine 10 mg daily for hypertension. He is also taking furosemide 20 mg twice daily. Physical examination identified diffuse pustules on the erythematous base located on the trunk, back, and bilateral proximal extremities, largely sparing the face, as seen in Figure 1. No oral lesions or lymphadenopathies were identified. Diltiazem was discontinued, and he was discharged with follow-up to the dermatology clinic the next day. At the dermatology clinic, he was found to be short of breath and hypotensive, with a blood pressure of 86/57 on two measurements, and he was referred back to the ER.

In the ER, repeat blood pressure was 95/54, and his blood pressure improved after he received 500 cc of intravenous fluid bolus. The patient reported decreased oral intake because he was feeling unwell over the previous 2 days. He denied fever, worsening cough, dizziness, and syncope. Labs showed leukocytosis of 19 (range, 4–11), neutrophilia of 16.6 (range, 1.5–8), and a normal eosinophil count. He also had elevated liver enzymes with alanine transaminase (ALT) of 73 (range, 17–65) and aspartate aminotransferase (AST) of 86 (range, 12–39). His alkaline phosphatase (ALP) was 191 (range, 40–129). His total bilirubin, albumin, and calcium were all within normal limits (WNL). Creatinine was 3.4 compared to his baseline of 2.7 (range, 0.75–1.20). Two blood cultures were negative. His urinalysis was WNL, and he had negative troponin. There were no ischemic changes on his electrocardiogram (EKG), and his transthoracic EKG showed stable heart function and structure. An extensive workup was performed for elevated liver enzymes and renal injury, but no specific etiology was found. No acute abnormality was found on chest X-ray. A punch skin biopsy revealed a subcorneal pustule containing neutrophils and a superficial perivascular and interstitial neutrophilic infiltrate. Focal areas of spongiosis were seen in the epidermis. Both periodic acid–Schiff (PAS) and Grocott–Gomori methenamine silver (GMS) stains were negative. History and histology findings were consistent with diltiazem-induced acute generalized exanthematous pustulosis (AGEP), possibly affecting multiple systems. He was admitted to the hospital and managed with triamcinolone and Vanicream. The patient later developed desquamation, which follows the normal course for AGEP. He remained afebrile throughout his hospitalization course, while his elevated liver enzymes continued to improve. Additionally, his renal injury resolved. The rash completely resolved at his 6-week follow-up.

AGEP is usually drug-induced and manifests as nonfollicular, sterile, and numerous small pustules on an erythematous base associated with pruritis [1]. The mucous membrane may also be involved in 20–25 % of cases [2]. Common drugs with an adverse reaction resulting in AGEP include hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, and fluconazole [1]. For antibiotic drug exposure, the reaction usually starts within 24–48 h, whereas diltiazem has course of eruption of 4–12 days [3]. Leukocytosis with neutrophilia and fever are common in AGEP [1]. Eosinophilia can be seen in 30 % of patients with AGEP [2]. Systemic involvement of the hepatic, renal, and pulmonary systems is usually seen in 17 % of cases [4]. The etiology for renal injury of the patient was difficult to establish in the setting of acute AGEP and comorbidities along with medication interactions. Pre-existing renal disease and hypovolemia due to an inflammatory state may account for prerenal injury. The patient presented with only slight elevations of AST, ALT, and ALP.

According Hotz et al. [4], liver involvement can manifest with hepatocellular injury or cholestatic features or both in

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Figure 1: Diffuse pustules on the erythematous base located on the trunk, back, and bilateral proximal extremities.

AGEP patients. In one retrospective case series study, O'Brian et al. [5] reported that among 88 patients hospitalized with AGEP, 19 patients (22 %) had hemodynamic instability likely attributed to AGEP while excluding infectious or cardiogenic etiologies. Of the 19 patients with likely AGEP-related hemodynamic instability, 10 patients had hypotension with organ dysfunction, 3 patients had hypotension, and 6 patients had shock [5]. The study also noted that comorbid conditions such as hypertension and obesity likely increased the risk of AGEP-induced hemodynamic instability [5]. In this patient, hypotension resulting from cardiogenic or infectious causes was ruled out. The hypotension was likely caused by a combination of factors including increased blood flow to the skin and an inflammatory response due to AGEP. Additionally, reduced oral intake and potential exacerbation from his home antihypertensive medications may have contributed to his low blood pressure.

The differential diagnosis of the skin manifestations in this patient should include drug rash with eosinophilia and system symptoms (DRESS) syndrome (pustular subtype), Stevens–Johnsons syndrome (SJS), and acute generalized pustular psoriasis (GPP). The DRESS syndrome pustular subtype was considered on the differential diagnosis, and it typically appears 2–8 weeks after initiating culprit drugs such as allopurinol, carbmazepine, and phenytoin [6]. It usually presents with small pustules on the face, trunk, and extremities and can present with systemic symptoms similar to AGEP, including fever, organ injury of lungs, kidneys, and liver [6]. Although eosinophilia is common in DRESS syndrome, it is not always present [7]. However, the DRESS pustular type is less likely given that the patient was afebrile, the pustular eruptions spared the face, and the timeline of rash eruption was 1 week after starting diltiazem, all of which favor AGEP. Another differential includes SJS, which usually occurs 4 days to 4 weeks after initiating the culprit drug [8]. However, the characteristics of the patient's rash make SJS less likely, given the absence of blistering and mucous membrane involvement. Additionally, there was no epidermal detachment or histological full-thickness epidermal necrosis on histopathology [9]. GPP is less likely due to the absence of papillomatosis and acanthosis on histopathology and the patient's lack of previous psoriasis or arthritis [9]. COVID-19 infection was considered but unlikely given the patient's negative polymerase chain reaction (PCR) test. Mononucleosis is also a possible differential diagnosis but less likely due to the patient's age and lack of symptoms such as fever, lymphadenopathy, and sore throat. The patient's clinical course, pustular rash with a specific distribution pattern and onset of eruption 1 week after starting diltiazem, histopathologic findings of a subcorneal pustule surrounded by spongiosis, as well as laboratory results, were all consistent with a diagnosis of AGEP.

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