Acute Generalized Exanthematous Pustulosis Induced by the Second-Generation Antipsychotic Cariprazine

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PRACTICE **POINTS**

- The second-generation antipsychotic cariprazine has been shown to be a potential causative agent in acute generalized exanthematous pustulosis (AGEP).
- Treatment of AGEP is mainly supportive and consists of discontinuation of the causative agent as well as symptom control using cold compresses and topical corticosteroids.

To the Editor:

A 57-year-old woman presented to an outpatient clinic with severe pruritus and burning of the skin as well as subjective fevers and chills. She had been discharged from a psychiatric hospital for attempted suicide 1 day prior. There were no recent changes in the medication regimen, which consisted of linaclotide, fluoxetine, lorazepam, and gabapentin. While admitted, the patient was started on the atypical antipsychotic cariprazine. Within 24 hours of the first dose, she developed severe facial erythema that progressed to diffuse erythema over more than 60% of the body surface area. The attending psychiatrist promptly discontinued cariprazine. During the next 24 hours, there were no reports of fever, leukocytosis, or signs of systemic organ involvement. Given the patient's mental and medical stability, she was discharged with instructions to follow up with the outpatient dermatology clinic.

At the current presentation, physical examination revealed innumerable 1- to 4-mm pustules coalescing to lakes of pus on an erythematous base over more than 60% of the body surface area (Figure 1). The mucous membranes were clear of lesions, the Nikolsky sign was negative, and the patient's temperature was 99.6 °F in the office. Complete blood cell count and complete metabolic panel results were within reference range.

A 4-mm abdominal punch biopsy showed subcorneal neutrophilic pustules, papillary dermal edema, and superficial dermal lymphohistiocytic inflammation with numerous neutrophils, eosinophils, and extravasated red blood cells, consistent with acute generalized exanthematous pustulosis (AGEP) (Figure 2). The patient was started on wet wraps with triamcinolone cream 0.1%.

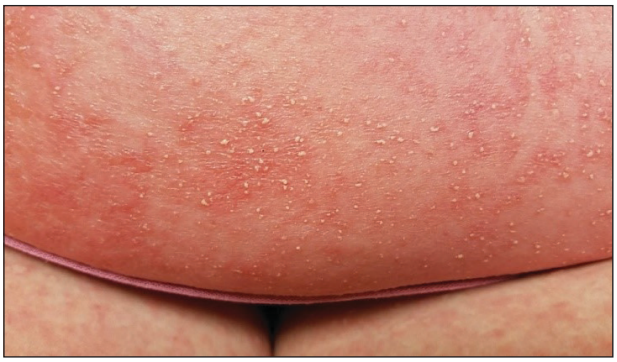

FIGURE 1. Acute generalized exanthematous pustulosis of the abdomen with multiple nonfollicular 1- to 4-mm pustules coalescing into lakes of pus.

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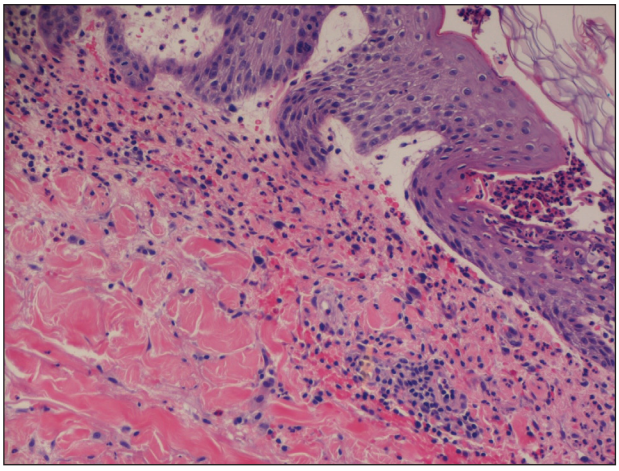

FIGURE 2. An abdominal punch biopsy demonstrated subcorneal, pustular, acute, spongiotic dermatitis with marked intraepithelial spongiosis and papillary edema as well as exocytosis of eosinophils, characteristic of acute generalized exanthematous pustulosis (H&E, original magnification ×100).

Two days later, physical examination revealed the erythema noted on initial examination had notably decreased, and the patient no longer reported burning or pruritus. One week after initial presentation to the clinic, the patient's rash had resolved, and only a few small areas of desquamation remained.

Acute generalized exanthematous pustulosis is a severe cutaneous adverse reaction characterized by the development of numerous nonfollicular sterile pustules on an edematous and erythematous base. In almost 90% of reported cases, the cause is related to use of antibiotics, antifungals, antimalarials, or diltiazem (a calcium channel blocker). This rare cutaneous reaction occurs in 1 to 5 patients per million per year[1]; it carries a 1% to 2% mortality rate with proper supportive treatment.

The clinical symptoms of AGEP typically present 24 to 48 hours after drug initiation with the rapid development of dozens to thousands of 1- to 4-mm pustules, typically localized to the flexor surfaces and face. In the setting of AGEP, acute onset of fever and leukocytosis typically occur at the time of the cutaneous eruption. These features were absent in this patient. The eruption usually starts on the face and then migrates to the trunk and extremities, sparing the palms and soles. Systemic involvement most commonly presents as hepatic, renal, or pulmonary insufficiency, which has been seen in 20% of cases.[2]

The immunologic response associated with the reaction has been studied in vitro. Drug-specific CD8 T cells use perforin/granzyme B and Fas ligand mechanisms to induce apoptosis of the keratinocytes within the epidermis, leading to vesicle formation.[3] During the very first stages of formation, vesicles mainly comprise CD8 T cells and keratinocytes. These cells then begin producing CXC-18, a potent neutrophil chemokine, leading to extensive chemotaxis of neutrophils into vesicles, which then rapidly transform to pustules.[3] This rapid transformation leads to the lakes of pustules, a description often associated with AGEP.

Treatment of AGEP is mainly supportive and consists of discontinuing use of the causative agent. Topical corticosteroids can be used during the pustular phase for symptom management. There is no evidence that systemic steroids reduce the duration of the disease.[2] Other supportive measures such as application of wet wraps can be used to provide comfort.

Cutaneous adverse drug reactions commonly are associated with psychiatric pharmacotherapy, but first- and second-generation antipsychotics rarely are associated with these types of reactions. In this patient, the causative agent of the AGEP was cariprazine, an atypical antipsychotic that had no reported association with AGEP or cutaneous adverse drug reactions prior to this presentation.

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