# Acute Generalized Exanthematous Pustulosis Secondary to Application of Tapinarof Cream 1%

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## PRACTICE **POINTS**

- Tapinarof cream 1% can be absorbed systemically and cause acute generalized exanthematous pustulosis (AGEP).
- Clinical configuration and histology can be useful to distinguish AGEP from mimickers.
- Topical application of drugs in general, particularly over large body surface areas, may lead to systemic drug eruptions.

To the Editor:

For many years, topical treatment of plaque psoriasis was limited to steroids, calcineurin inhibitors, vitamin D analogs, retinoids, coal tar products, and anthralin. In recent years, 2 new nonsteroidal treatment options with alternative mechanisms of action, roflumilast 0.3% and tapinarof 1%, have been approved by the US Food and Drug Administration.[1] Roflumilast 0.3%, a topical phosphodiesterase 4 inhibitor, was shown in phase 3 clinical trials to reach an Investigator Global Assessment response of 37.5% to 42.2% in 8 weeks using once-daily application with minimal cutaneous adverse effects.[1] Furthermore, it has demonstrated efficacy in treating psoriasis in intertriginous areas in subset analyses.[1] Tapinarof is an aryl hydrocarbon receptor agonist that suppresses Th17 cell differentiation by downregulating IL-17, IL-22, and IL-23.[1] In phase 3 clinical trials, 35% to 40% of patients who used tapinarof cream 1% once daily demonstrated improvement in psoriasis compared with 6% who used the vehicle alone.[2] In these studies, 18% to 24% of patients who used tapinarof cream 1% experienced folliculitis.[2]

Acute generalized exanthematous pustulosis (AGEP) is a nonfollicular pustular drug reaction with systemic symptoms that typically occurs within 2 weeks of exposure to an inciting medication. Systemic antibiotics are the most commonly reported cause of AGEP.[3] There are few reports in the literature of AGEP induced by topical agents.[4,5] We report a case of AGEP in a young man following the use of tapinarof cream 1%.

A 23-year-old man with a history of psoriasis presented to the emergency department with fever and a pustular rash. One week prior to presentation, he developed a pustular eruption around plaques of psoriasis on the arms and legs. The patient had been prescribed tapinarof cream 1% by an outside dermatologist and was applying the medication to the affected areas once daily for 1 month prior to onset of symptoms. He discontinued tapinarof a few days prior to the eruption starting, but the rash progressed centrifugally and was associated with fevers and fatigue despite treatment with a brief course of empiric cephalexin prescribed by his primary care provider.

At presentation to our institution, the patient had widespread erythematous patches studded with pustules located on the arms, legs, and flexural areas as well as plaques of psoriasis involving approximately 20% of the body surface area (Figure 1). Furthermore, the patient was noted to have large noninflammatory bullae along the legs. The new eruption occurred on areas that were both treated and spared from the tapinarof cream 1%.

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Laboratory evaluation showed neutrophil-predominant leukocytosis (white blood cell count, $15.9\times10^3/\mu L$ [reference range, $4.0\text{-}11.0\times10^3/\mu L$]; absolute neutrophil count, $10.3\times10^3/\mu L$ [reference range, $1.5\text{-}8.0\times10^3/\mu L$]), absolute eosinophilia ($1930/\mu L$ [reference range, $0\text{-}0.5\times10^3/\mu L$]), hypocalcemia (8.4 mg/dL [reference range, 8.5-10.5 mg/dL]), and a mild transaminitis (aspartate aminotransferase, 37 IU/L [reference range, 10-40 IU/L]; alanine aminotransferase, 53 IU/L [reference range, 7-56 U/L]). Histopathology demonstrated spongiosis with subcorneal and intraepidermal pustules and mixed dermal inflammation containing eosinophils (Figure 2). Direct immunofluorescence revealed mild granular staining of C3 at the basement membrane zone.

The patient was started on 1 mg/kg/d of prednisone tapered over 20 days, and he rapidly improved. Alanine aminotransferase levels peaked at 120 IU/L 2 weeks later. At that time, he had complete resolution of the original eruption and was transitioned to topical steroids for continued management of the psoriasis (Figure 3).

The differential diagnosis for our patient included AGEP, generalized pustular psoriasis (GPP), miliaria pustulosa, generalized cutaneous candidiasis, exuberant allergic contact dermatitis (ACD), and linear IgA bullous dermatosis (LABD). Based on the clinical manifestations, laboratory results, and histopathologic evaluation, we made the diagnosis of AGEP secondary to tapinarof with systemic absorption. Acute generalized exanthematous pustulosis has been reported with topical use of morphine and diphenhydramine, among other agents.[4,5] To our knowledge, AGEP due to tapinarof cream 1% has not been reported. In the original clinical trials of tapinarof, folliculitis was contained to sites of application.[2] Our patient developed pustules at sites distant to areas of application, as well as systemic symptoms and laboratory abnormalities, indicating a systemic reaction. It can be difficult to distinguish AGEP clinically and histologically from GPP. Both conditions can manifest with fever, hypocalcemia, and sterile pustules on a background of erythema that favors intertriginous areas.[6] Infection, rapid

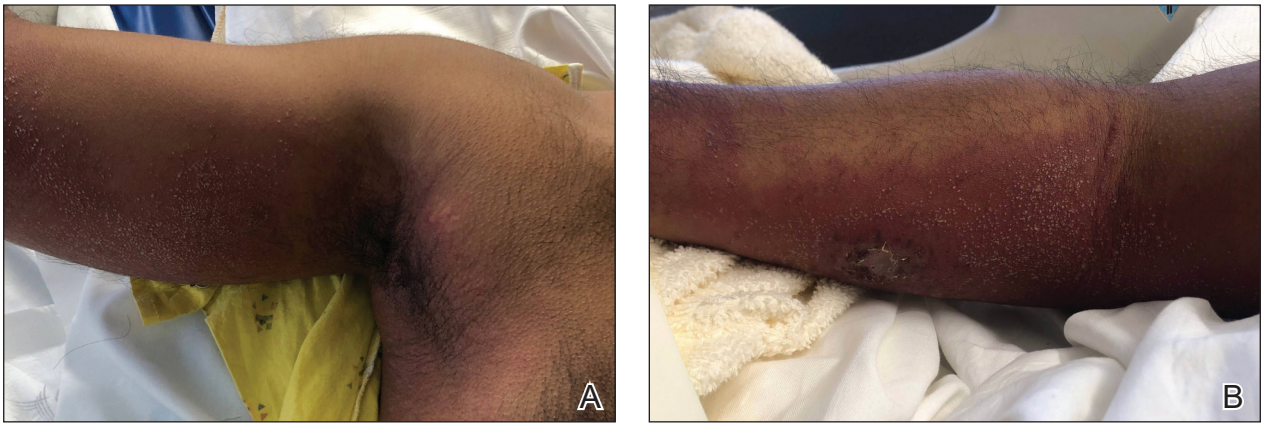


**FIGURE 1.** A, Nonfollicular pustules involving the right axilla. B, Coalescing nonfollicular pustules on an erythematous base surrounding a psoriasiform plaque and extending proximally on the right arm.

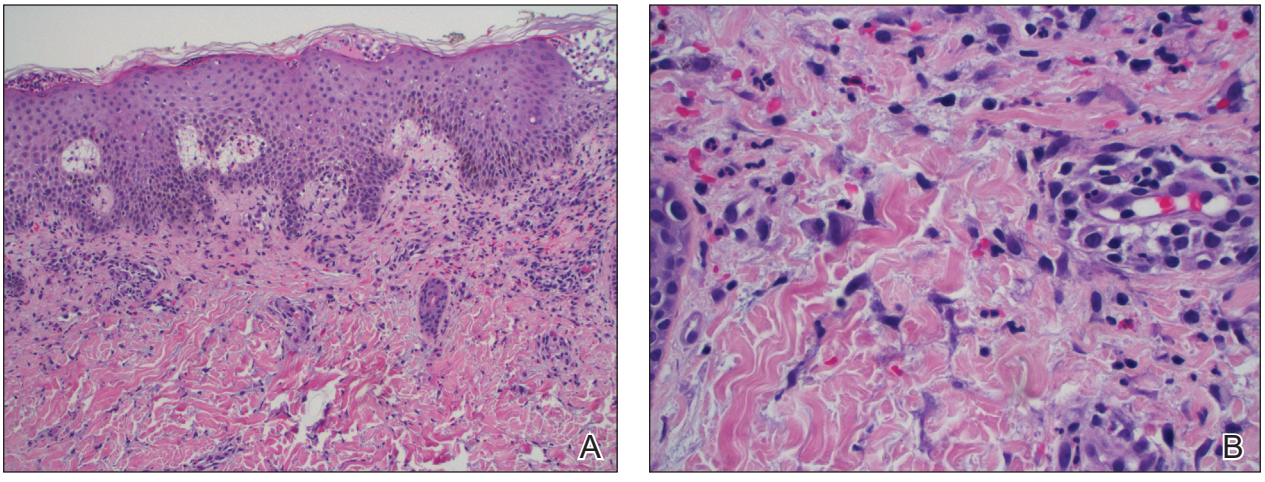


**FIGURE 2.** A and B, On histopathology, a biopsy of the arm showed spongiosis with subcorneal and intraepidermal pustules and dermal inflammation containing eosinophils (H&E, original magnification ×10 and ×40, respectively).

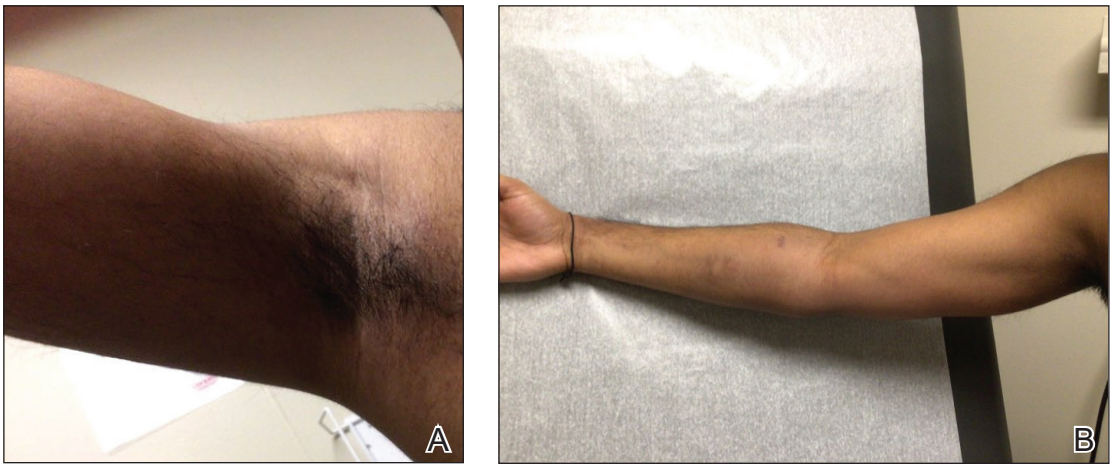


**FIGURE 3.** A and B, Complete resolution of the original eruption was seen following treatment with prednisone.

oral steroid withdrawal, pregnancy, and rarely oral medications have been reported causes of GPP.[6] Our patient did not have any of these exposures. There is overlap in the histology of AGEP and GPP. One retrospective series compared histologic samples to help distinguish these 2 entities. Reliable markers that favored AGEP over GPP included eosinophilic spongiosis, interface dermatitis, and dermal eosinophilia (>2/mm$^2$).[7] In contrast, the presence of CD161 positivity in the dermis with at least 10 cells favored a diagnosis of GPP.[7] In our case, the presence of spongiosis with eosinophils in the dermis favored a diagnosis of AGEP over GPP.

Miliaria pustulosa is a benign condition caused by the occlusion of the epidermal portion of eccrine glands related to either high fever or hot and humid environmental conditions. While it can be present in intertriginous areas like AGEP, miliaria pustulosa can be seen extensively on the back, most commonly in immobile hospitalized patients.[8] Generalized cutaneous candidiasis usually is caused by the yeast *Candida albicans* and can take on multiple morphologies, including folliculitis.[9] The eruption may be disseminated but often is accentuated in intertriginous areas and the anogenital folds. Predisposing factors include immunosuppression, endocrinopathies, recent use of systemic antibiotics or steroids, chemotherapy, and indwelling catheters.[9] Outside of recent antibiotic use, our patient did not have any risk factors for miliaria pustulosa, making this diagnosis unlikely.

Given the presence of overlapping bullae along the lower extremities, an exuberant ACD and LABD were considered. Bullae formation can occur in ACD secondary to robust inflammation and edema leading to acantholysis.[10] While a delayed hypersensitivity reaction to topical tapinarof cream 1% was considered given that the patient used the medication for approximately 1 month prior to the onset of symptoms, it would be unlikely for ACD to present with a concomitant pustular eruption. Linear IgA bullous dermatosis is an autoimmune blistering disease in which antibodies target bullous pemphigoid antigen 2, and there is characteristically linear deposition of IgA at the dermal-epidermal junction that leads to subepidermal blistering.[11] This often manifests clinically as widespread tense vesicles in an annular or string-of-pearls appearance. However, morphologies can vary, and large bullae may be seen. In adults, LABD typically is associated with inflammatory bowel disease, malignancy, or medications, notably vancomycin.[11,12] Our patient did not have any of these predisposing factors, and his biopsy for direct immunofluorescence did not reveal the classic pattern described above.

Interestingly, there have been reports in the literature of bullous AGEP in the setting of oral anti-infectives. One report described a 62-year-old woman who developed widespread nonfollicular pustules with multiple tense serous blisters 24 hours after taking oral terbinafine.[13] Another case described an 80-year-old woman with a similar presentation following a course of ciprofloxacin (although the timeline of medication administration was not described).[14] In this case, patch testing to the culprit medication reproduced the response.[14] In both cases, a biopsy revealed subcorneal and intraepidermal pustules with marked dermal edema.[13,14] As previously described, spongiosis is a common feature of AGEP. We hypothesize that, similar to these reports, our patient had a robust inflammatory response leading to spongiosis, acantholysis, and blister formation secondary to AGEP.

Dermatologists should be aware of this case of AGEP secondary to tapinarof cream 1%, as reports in the literature are rare and it is a reminder that topical medications can cause serious systemic reactions.

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