Acute generalized exanthematous pustulosis simulating Stevens-Johnson syndrome/toxic epidermal necrolysis associated with the use of vismodegib

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INTRODUCTION

Basal cell carcinoma (BCC) is a common skin neoplasm that usually has a nonaggressive behavior typically managed with local treatment (eg, surgery, photodynamic treatment, topical agents, or radiation). In some cases, BCC has a much more invasive behavior (locally advanced or metastatic BCC), which may require systemic treatment.[1] An abnormal activation of the hedgehog pathway signaling has been linked to the pathogenesis of BCC. Vismodegib is the first-in-class inhibitor of this pathway.[1,2] Patients with inoperable or unresectable disease are candidates for this treatment. Primary concerns while treating with vismodegib are its multiple adverse effects[3,4]: muscle spasms, diffuse alopecia, dysgeusia, weight loss, asthenia, and anorexia. Most patients suffer at least 1 adverse effect. Most adverse effects appear early in the course of treatment, are mild or moderate (grade 1-2), and are thought to be related to the inhibition of hedgehog signal transduction. The most common serious adverse effects reported are pneumonia, worsening of general physical health, squamous cell carcinoma, and dehydration. In the largest clinical trial,[4] vismodegib-induced cutaneous adverse effects were described as alopecia, folliculitis, maculopapular rash, or dermatitis. In this study, 2 patients (0.4%) presented a grade 3 maculopapular rash; nevertheless, no further information about these cases is provided by the investigators. Moreover, there are no reports of severe mucocutaneous reactions to vismodegib in the literature.

Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
BCC:	basal cell carcinoma
SJS/TEN:	Stevens-Johnson syndrome/toxic epidermal necrolysis

CLINICAL CASE

A woman in her 90s was admitted to the emergency department presenting fever (38.4°C), rash, and malaise of 1 days' duration. Eight days before the onset of the symptoms, oral vismodegib, 150 mg/d, was initiated for orbit bone-infiltrating BCC. The patient had a history of high blood pressure, IgG monoclonal gammopathy of undetermined significance, chronic kidney disease, and osteoarthritis. She was receiving chronic treatment with indapamide and oxycodone hydrochloride for more than 10 years. Physical examination found confluent, erythematous, edematous plaques with purpuric centers affecting predominantly her head, folds, and trunk. Nikolsky sign was not present. Oral, conjunctival, and genital mucosae were spared. A clinical diagnosis of exanthematous drug eruption was suspected, and vismodegib was suspended. Routine laboratory tests showed an elevated C-reactive protein, moderate lymphopenia, and marked neutrophilia (12800 cells/μL). After 24 hours, 15% of the patient's body surface area presented skin detachment in absence of mucosal involvement.

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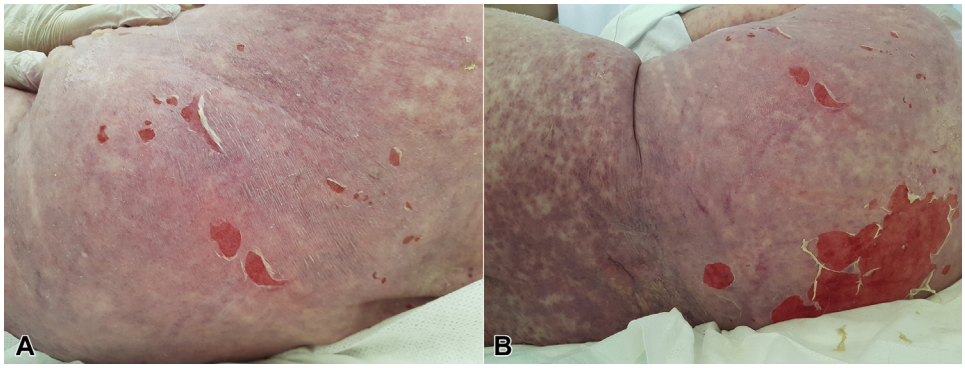

Fig 1. Clinical photograph. **A** and **B**, Confluent erythematous and edematous plaques with purpuric center affecting predominantly the trunk with a positive Nikolsky sign. Subtle pustules can be seen (**A**).

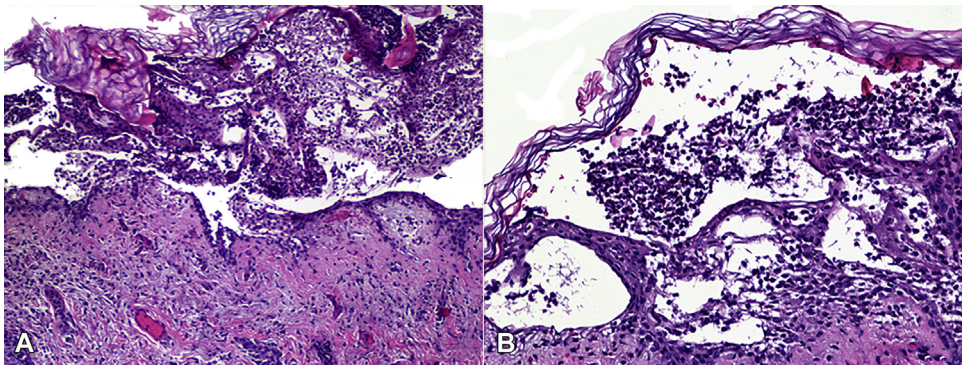

Fig 2. Histologic picture. **A**, Low power view of a very large, confluent, subcorneal pustule. Collections of neutrophils are present in the dermis. **B**, Under a large pustule with blisterlike features and massive spongiosis, the dermis shows sparse mixed infiltrate without eosinophils.

Nikolsky sign was positive (Fig 1). A clinical diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap associated with vismodegib was established. The patient was admitted to the burn unit for supportive therapy, and cyclosporine was initiated. Histopathologic examination of skin biopsy found neutrophilic spongiotic pustules without epidermal necrosis (Fig 2). Direct immunofluorescence results were negative. Final diagnosis of acute generalized exanthematous pustulosis (AGEP) clinically presenting with SJS/TEN overlaplike features was stablished. After 2 weeks, the patient was completely healed. No recurrences were observed. The patient declined patch testing of vismodegib.

DISCUSSION

Both AGEP and SJS/TEN are considered severe mucocutaneous reactions. Although their pathogenesis is not completely understood, they are thought to be immune-mediated conditions, generally triggered by medications.[5] SJS/TEN are regarded as a continuum of diseases whose characteristic sign is keratinocyte necrosis, secondary detachment of the epidermis, and mucous membrane involvement. SJS usually affects mucous membranes, but skin detachment is less than 10% of total body surface. TEN involves detachment of more than 30% of body surface area and mucous membrane involvement is the rule. SJS/TEN overlap is defined by skin detachment of 10% to 30% of body surface area. In contrast, AGEP is considered a less severe condition, with less mucosal involvement and with a shorter latency and faster resolution after the withdrawal of the culprit drug. This disease is characterized by generalized pinhead pustules and spongiform subcorneal or intraepidermal pustules.[6] It can present with a positive pseudo-Nikolsky sign because of the skin detachment consequence of the coalescence of pustules, as in our patient. Although treatment of AGEP and SJS/TEN remains a controvert topic, prompt drug withdrawal and supportive care are the cornerstones of therapy.[5,6] In some patients, clinical distinction can be challenging. In acute stages, AGEP can present with atypical targetlike

lesions and blisters mimicking SJS/TEN.[5-7] Nevertheless, clinical course and histopathologic findings are the key to a correct diagnosis. Patch tests of the suspected drug are more often positive in AGEP patients than in those with SJS/TEN.

Our clinical case merits further discussion because of its atypical presentation. First, clinical onset was 8 days after drug initiation. Interestingly, 2 different patterns of presentation have been described for AGEP[7]: (1) a median of 1 day of exposure to antibiotics before onset of the rash and (2) a median of 11 days of exposure to a nonantibiotic drug before AGEP onset. Therefore, it is reasonable to assume that AGEP induced by vismodegib has a delayed onset. Second, pustules were not easily identified when skin detachment occurred but were observed in the following days. Third, no more pustules appeared 5 days after drug withdrawal. However, the patient required 2 weeks for complete skin healing because of comorbidity and age. Finally, a clinical diagnosis of SJS/TEN overlap by vismodegib was established at first because of the time elapsed between drug introduction and cutaneous eruption and the presence of Nikolsky sign. Nevertheless, the absence of mucosal involvement and keratinocyte necrosis in the pathology examination, late-onset of pustules, and rapid improvement of the patient were against a diagnosis of SJS/TEN. We established a definite diagnosis of AGEP based on the Sidoroff modified criteria[6,7] (9 points) and histopathologic findings. Although there are case reports[8,9] of AGEP and SJS/TEN overlap, it remains unclear if these patients truly have coexisting clinical and histopathologic features or have been misclassified.[6]

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