Bullous drug eruption with leukemic cell infiltrate in the setting of new-onset acute myeloid leukemia

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INTRODUCTION

Bullous drug eruptions are cutaneous dermal hypersensitivity reactions to systemically administered medications. Classically, these eruptions appear 5 to 14 days after the initiation of the offending agent.[1] On histopathologic examination, dermal hypersensitivity reactions are characterized by a superficial perivascular lymphocytic infiltrate, often with admixed eosinophils.[2] We report an unusual case of a bullous drug reaction, histologically characterized by leukemic cells in a patient with new-onset acute myeloid leukemia (AML).

Abbreviation used:

AML: acute myeloid leukemia

CASE REPORT

A 26-year-old man with no previous medical history presented with a 1-day history of a diffuse eruption consisting of erythematous papules and thin plaques as well as periaxillary bullae and vesicles. Two weeks prior, the patient experienced odynophagia and fevers, and group A Streptococcal pharyngitis was diagnosed, which was treated with a 10-day course of penicillin. After a course of antibiotics, the patient's pharyngitis did not resolve, and a repeat throat culture found persistent group A Streptococcal infection. He was treated with azithromycin, which he took for 4 days and self-discontinued on the fourth day when a cutaneous eruption developed. The patient noted a small, raised erythematous papule on his chest. The next morning, the eruption had evolved to innumerable scattered erythematous papules and thin plaques on his face, trunk, and extremities, including his palms and soles (Fig 1). The lesions were confluent in many areas, with small 3- to 5-mm vesicles and larger bullae in a periaxillary distribution. Asboe-Hansen and Nikolsky signs were absent. The patient denied skin pain or pruritus.

The patient presented to our institution, and laboratory evaluation found a leukocytosis with a white blood cell count of $29.6 \times 10^3/\mu L$, anemia with a hemoglobin of 10.8 g/dL, and thrombocytopenia with platelets $126 \times 10^3/\mu L$. Peripheral blood had 55% myeloblasts with the following phenotype: $CD34^+$, $CD117^+$, $CD33^+$, $CD13^{+/-}$, $HLA\text{-}DR^+$, $CD38^+$, $CD43^+$, $CD64^{+/-}$, $CD11c^{+/-}$, and largely negative MPO. The presence of at least 20% blasts in the peripheral blood and sufficient myeloid markers led to a new diagnosis of AML.[3]

Based on the patient's cutaneous eruption and newly diagnosed AML, the differential diagnosis included leukemia cutis, Sweet syndrome, erythema multiforme, a viral exanthema, and a bullous drug eruption. Two skin biopsies were performed, one from an intact vesicle on the left periaxillary skin and the second from an erythematous plaque of the chest. Histologic examination of the specimen from the chest found marked papillary dermal edema with a perivascular mononuclear cell infiltrate (Fig 2). The biopsy from the left periaxillary lesion found an intraepidermal vesicle and prominent papillary dermal edema with a perivascular mononuclear cell infiltrate. Immunostains showed that the infiltrate was $CD3^-$ and strongly positive for CD43 and

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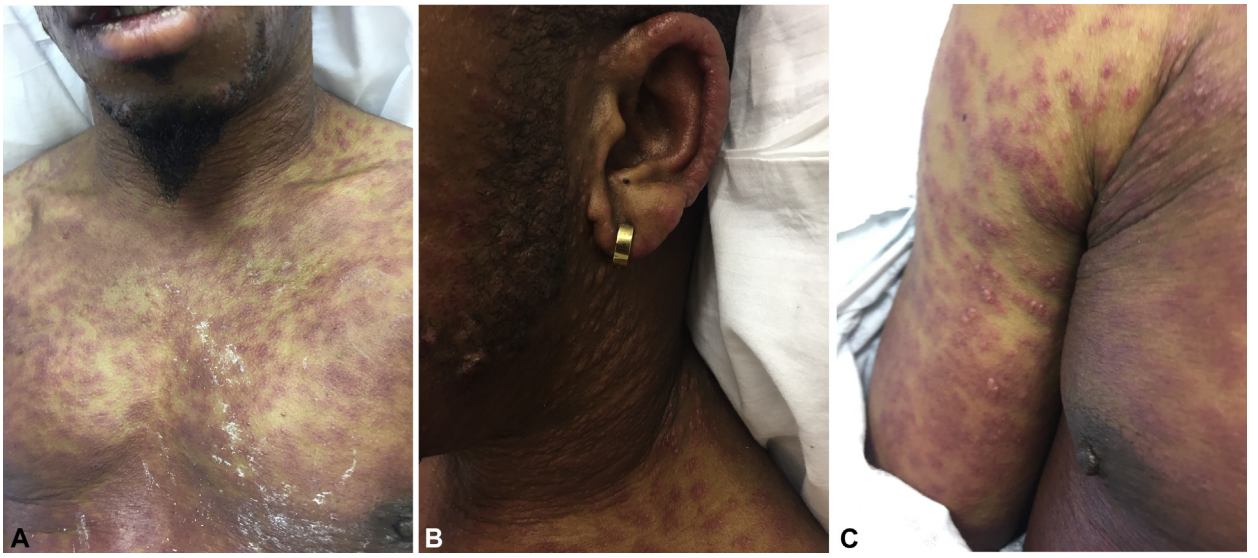

Fig 1. A, Erythematous papules and plaques on the neck, chest, and abdomen. **B**, Erythematous papules and plaque on the neck, erythematous papules and vesicles on the pinna. **C**, Erythematous papules and plaques on the chest and arm as well as vesicles in the periaxillary area.

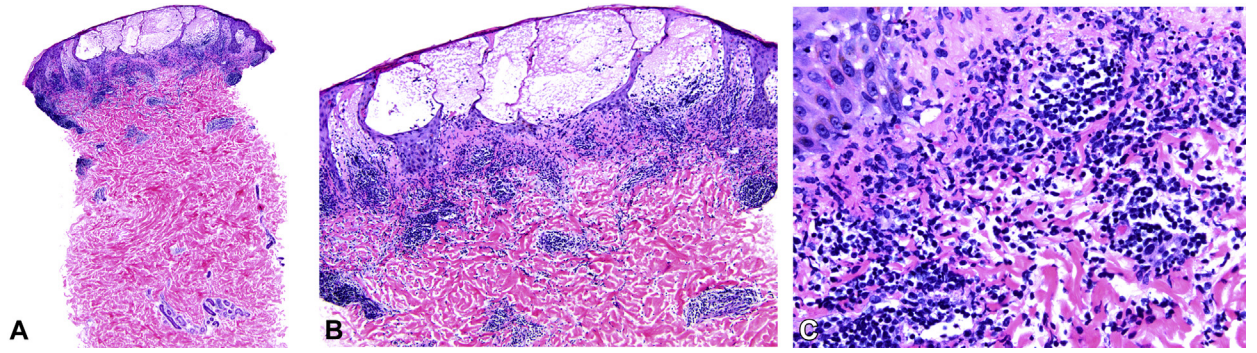

Fig 2. Hematoxylin-eosin stain of a skin biopsy from a left periaxillary vesicle. **A** and **B**, An intrapidermal veisicle and prominent papillary dermal edema with a perivascular mononuclear cell infiltrate. **C**, A mononuclear cell infiltrate. (Original magnification: **A**, ×4; **B**, ×10; **C**, ×40.)

CD33. Immunostains for CD117, CD20, CD34 and myeloperoxidase were negative. These findings support a leukemic cell infiltrate at the site of this eruption. These results were consistent with those of a bullous dermal hypersensitivity reaction pattern with a leukemic cell infiltrate.

Although leukemic cells were present, the histologic pattern was not consistent with the dense aggregates of atypical cells that are present in leukemia cutis. Sweet syndrome is associated with myeloid leukemias, but the tissue did not reveal a neutrophilic dermal infiltrate. There were no necrotic keratinocytes or basement membrane degeneration to support erythema multiforme or Stevens-Johnson syndrome. In the setting of both penicillin and azithromycin therapy within the preceding 2 weeks, a diagnosis of bullous drug eruption was made, although it is impossible to determine which of the 2 medications is the culprit. The patient remained off antibiotics and was treated with topical triamcinolone 0.1% ointment and emollients. Over the course of the next 2 weeks, the cutaneous eruption resolved.

DISCUSSION

In addition to leukemia cutis, patients with AML may have other cutaneous eruptions, including drug reactions, infections, vasculitis, and purpura.[4] Leukemic cells have been identified in herpes simplex lesions, psoriasis vulgaris, and in various epidermal neoplasms.[5] However, to our knowledge,

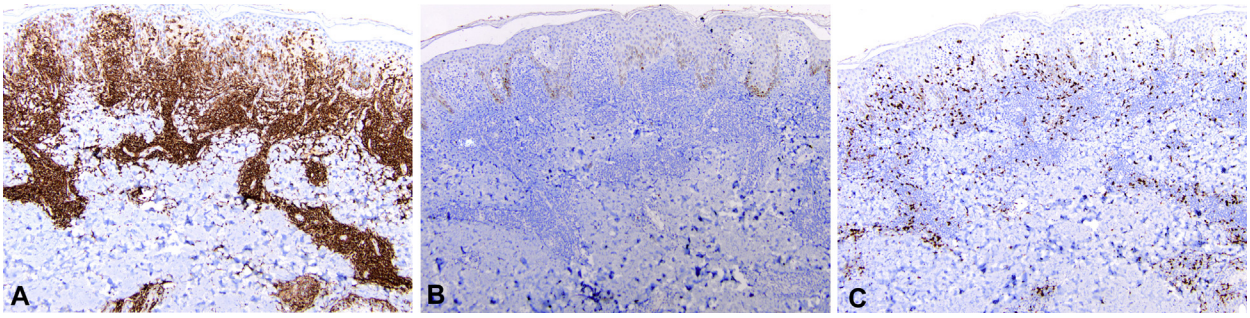

Fig 3. Immunostains performed on chest specimen. **A**, CD43; **B**, CD20; **C**, CD3.

a drug-induced dermal hypersensitivity reaction with a leukemic cell infiltrate is a rare finding.

In our case, the patient's cutaneous eruption was that of a dermal hypersensitivity pattern, with dermal edema and perivascular lymphocytes but also with a leukemic cell infiltrate. On low-power magnification, the cells developing a dermal hypersensitivity reaction pattern did not appear to be leukemic. Because of the patient's newly diagnosed AML, we performed immunostains to evaluate for the presence of leukemic cells. The leukemic infiltrate was confirmed by immunohistochemistry findings with stains positive for CD43 and CD33. CD43 is an effective marker for myeloid tumors, as it stains granulocytes and their precursors.[6] When CD33 is positive along with CD43, the immunostain findings confirm there are leukemic cells in the infiltrate.

Immunophenotypic characteristics of leukemia cutis in AML have been described in the literature. A study of 33 cases of myeloid leukemia cutis found 97% CD43, 42% MPO, 94% CD68, 25% CD163, and 47% CD56. CD34 and C117 were predominantly negative.[7] In all cases, there was discordance between bone marrow and skin flow cytometry. There is often heterogeneity in phenotypes in different locations, including the immaturity markers, CD34 and CD117. Another review reported that immunohistochemical assessment of AML may include $CD56^{+/-}$, $CD68^{-}$, $CD117^{+}$, $CD34^{+}$, and $TdT^{+/-}$.[8]

The authors propose that in patients with AML, it is possible for a bullous drug eruption to be associated with a leukemic cell infiltrate. In patients with AML, the leukemic cells may be recruited to what is otherwise a typical reaction pattern that one would associate with a dermal hypersensitivity reaction to a systemically administered medication.

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