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Bullous leukemia cutis: a rare clinical subtype

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Abstract
Leukemia cutis represents infiltration of the skin by malignant leukocytes and typically presents as firm, red-brown papules and nodules. The bullous clinical subtype is considered a rare entity and can be a diagnostic challenge. This case describes a patient with bullous leukemia cutis mimicking vesiculobullous skin disease.

Introduction
Leukemia cutis (LC) represents infiltration of the skin by malignant leukocytes and it is usually associated with a poor prognosis [1]. Depending on the type of leukemia, cutaneous involvement varies widely and is estimated between 3% to 30% [2]. Leukemia cutis typically presents as firm, red-brown papules and nodules with a predilection for the head, neck, and trunk. The bullous clinical subtype is considered a rare entity and can be a diagnostic challenge [1]. Herein, we describe a patient with bullous LC mimicking vesiculobullous skin disease.

Case Synopsis
A 62-year-old man with a history of acute myelogenous leukemia (AML) presented to the emergency room with a progressive asymptomatic eruption on the face, neck, and extremities including red-brown papules and nodules with tense clear and hemorrhagic bullae. Bullae affected areas of the skin with nodules as well as normal skin (Figures 1-3). The patient reported he was otherwise well. Intravenous acyclovir and airborne precautions were initiated for a presumed diagnosis of disseminated zoster. Acyclovir therapy had no beneficial effect and he continued to develop new lesions subsequently. Blood cultures, multiple viral PCR swabs, and bacterial swabs were negative. When assessed by the dermatology team the patients hemoglobin was 80g/L (normal range 130-180g/L), white blood count 15.7×10⁹/L (normal range 4-11×10⁹/L), and platelets

Figure 1. Red-brown papulonodules and tense clear and hemorrhagic bullae overlying normal skin as well as existing nodules on the head and neck.
8×10⁹/L (normal range 150-400×10⁹/L) with no neutropenia or eosinophilia.

The patient’s medical history was significant for refractory AML (80% blasts, normal karyotype, NPM1 negative with low FLT3) that had not achieved remission despite induction chemotherapy and reinduction chemotherapy five months prior. He continued to receive supportive care and hydroxyurea for count control.

At the time of this presentation there were no other sites of extramedullary disease. There were no new medications introduced. There was no personal or family history of autoimmune vesiculobullous diseases. Our differential diagnosis included autoimmune vesiculobullous diseases, paraneoplastic pemphigus, bullous Sweet syndrome, erythema multiforme, bullous drug eruption, and infectious etiologies.

A pink, well-defined papulonodule with an overlying tense vesicle on the upper right arm was selected for Figure 2: Red-brown papulonodules and hemorrhagic vesicles and bullae on the patient’s forehead and eyelids.

Figure 3: A solitary, non-inflammatory, tense bulla on the patient’s arm.

Figure 4. H&E sections of the skin lesion show a subepidermal bullae with background dense superficial and deep perivascular and interstitial infiltrate of atypical mononuclear tumor cells. There is background spongiosis, brisk dermal edema and extravasated red blood cells. There are patchy foci of fragmented nuclei throughout. There is no vasculitis.

Figure 5. On higher power, tumor cells have enlarged nuclei, moderate amounts of eosinophilic cytoplasm, fine dispersed chromatin and variably prominent nucleoli, H&E. Immunohistochemically, tumor cells are positive for CD43 (inset top right) and CD33 (inset bottom right); magnifications same as H&E. Tumor cells were negative for CD34, CD117 (not shown).
biopsy. Two skin biopsies were completed from this site: a lesional biopsy for routine hematoxylin and eosin and a perilesional normal-appearing site for direct immunofluorescence. A skin biopsy for culture was not performed. The direct immunofluorescence was negative for IgM, IgG, IgA, and C3. Histopathology showed a brisk atypical mononuclear interstitial and perivascular infiltrate (superficial and deep) with subepidermal bulla formation (Figures 4, 5). There was no evidence of viral cytopathic effect and no organisms were seen. Immunohistochemically, atypical mononuclear cells were positive for CD43 and CD33 and negative for CD34, MPO, and CD117, consistent with a cutaneous leukemic deposit (Figures 4, 5). No additional histological or immunohistological stains were performed. Taken together, the dermatologic and pathologic findings were consistent with a diagnosis of bullous LC with hemorrhage. Airborne precautions were discontinued after a two-week time period post-initiation. One month later at follow up, the patient's lesions persisted. He was offered cytarabine by the oncology team for treatment but declined any further chemotherapy at this time.

**Case Discussion**

In the setting of AML, LC is uncommon and may be a presenting sign of the malignancy, either preceding, following, or concurrently with the diagnosis of AML [1]. Leukemia cutis carries a high mortality rate, upwards of 80% at one year post-diagnosis [2]. Although the clinical presentation is most frequently red-brown papulonodules, as seen in our patient, intralesional hemorrhage can often be seen secondary to thrombocytopenia [1]. Treating the underlying leukemia will resolve the cutaneous manifestations [1].

A combination of clinical morphology, clinical history, and skin biopsy are needed to recognize and diagnose LC. Clinically, our aforementioned differential diagnosis included autoimmune vesiculobullous diseases, paraneoplastic pemphigus, bullous Sweet syndrome, erythema multiforme, bullous drug eruption, and infectious etiologies. Bullous pemphigoid, linear IgA bullous dermatosis, and dermatitis herpetiformis were the autoimmune vesiculobullous entities under consideration in this case. In hindsight, bullous pyoderma gangrenosum, bullous arthropod bite reaction, and bullous leukocytoclastic vasculitis could have also been included in our differential diagnosis.

Although more commonly seen in patients with chronic lymphocytic leukemia, a rare entity to keep in mind in patients with AML is eosinophilic dermatosis of hematologic malignancy [3]. Eosinophilic dermatosis of hematologic malignancy can appear polymorphic, including a papulovesicular presentation. Similarly, this entity has also been reported to have been initially misdiagnosed as varicella zoster virus [3].

The term scabies serrupticius was introduced by Cohen in 2017 to encompass all the atypical presentations of scabies mite infestation [4]. One of the many subtypes, bullous scabies, can mimic autoimmune blistering diseases such as bullous pemphigoid [4], making scabies an important polymorphous entity to keep in mind in those presenting with vesiculobullous lesions.

Histologically, LC displays atypical leukemic cells in the dermis and subcutis in a perivascular, periadnexal, and interstitial distribution [2, 5, 12]. A Grenz zone (sparring of the upper papillary dermis), brisk mitoses, and stromal fibrosis can be also be seen [2, 5, 12]. Bullous LC can show subepidermal bulla formation, which clinically form tense bulla, as seen in our patient (Figures 1-3). In myeloid leukemias such as AML, the immunophenotypic profile can be positive for CD43, CD33, CD34, and CD117 [2, 5, 12].

Bullous LC is an unusual variant of LC and therefore difficult to diagnose [6-10]. For example, a reported patient with CLL had her bullous LC misdiagnosed as facial cellulitis [7]. Review of the available retrospective studies of patients with LC reflect the rarity of the bullous clinical subtype. In two retrospective studies totaling 117 patients with LC, only three patients were found to have bullous lesions [8, 10]. Fifty-three patients with LC from three separate retrospective studies were reviewed and none presented with the bullous LC variant [2, 11, 12].
Conclusion
Our case is unique in that it highlights how clinically similar the bullous subtype of LC can appear to other vesiculobullous diseases. Furthermore, we highlight how these similarities can lead to misdiagnosis and negative patient sequela, such as being left on isolation precautions for prolonged periods of time. Thus, it is important for clinicians to be aware of this unique clinical subtype.

Potential conflicts of interest
The authors declare no conflicts of interests.

References