Title
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Leukemia cutis as the presenting symptom of acute myeloid leukemia: report of three cases

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Abstract

Leukemia cutis (LC), a rare cutaneous manifestation of leukemia, can precede, follow, occur concurrently with, or present in the absence of (aleukemic) systemic leukemia. Leukemia cutis is especially rare as the presenting symptom of leukemia and is associated with a poor prognosis. Although more commonly seen in acute leukemias of myeloid and monocytic lineage, lymphocytic/lymphoblastic leukemias can also involve the skin. Three cases of LC presented with diverse skin lesions ranging from an erythematous rash to violaceous macules and papules to subcutaneous nodules. One case clinically mimicked fixed drug eruption. All the patients had acute myeloid leukemia (AML). Lesions showed two overarching histologic patterns: atypical perivascular infiltrate or nodular dermal histiocytoid infiltrate. Our cases expressed myeloperoxidase (MPO), a helpful marker to distinguish myeloid from non-myeloid cells, and CD68, a monocytic marker frequently expressed in cutaneous AML. CD14, a marker of monocyte maturity, was negative. In the absence of systemic leukemia, common diagnostic tools for hematologic malignancies such as bone marrow biopsy and flow cytometry are non-contributory, making morphologic and immunohistochemical analysis of the skin lesions key to diagnosis.

Keywords: leukemia cutis, acute myelogenous leukemia, fixed drug eruption

Introduction

Leukemia cutis (LC) is a rare cutaneous manifestation of leukemia that can present variably associated with systemic symptoms. When cutaneous expression of the disease is the presenting symptom, it is frequently misdiagnosed [1]. A delay in diagnosis could also delay treatment. Thus, a skin biopsy creates an opportunity for early identification and a combination of morphologic, immunohisto-chemical, and molecular genetic methods can be used to diagnose LC.

Chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) are the most frequent subtypes that involve the skin [2]. Leukemia cutis is more common in acute than chronic leukemia but can occur in both; it often signifies a poor prognosis in AML. The prevalence of LC in patients with acute myeloid leukemia (AML) ranges from 10 to 15%, though in certain subtypes of AML, specifically acute myelomonocytic (AMMoL) and monocytic (AMoL) leukemia, up to 50% of patients can have skin involvement [3]. In contrast, LC presenting as the heralding symptom of AML has a lower incidence, ranging between 2.0 and 3.7% [4]. Furthermore, AML patients with LC are more likely to have numerical abnormalities of chromosome 8 and shorter remission duration [5].

Since LC encompasses all leukemias, it can have a varied clinical appearance including nodules, macules, papules, plaques, blisters, and ulcers [2]. Likewise, histologic appearance will vary related to the leukemia subtype. Herein, we present 3 cases of LC in patients with previously undiagnosed AML.

Case Synopsis:

Case 1

A 42-year-old man presented with recurrent fevers, fatigue, and subcutaneous nodules on the neck, trunk, groin, and all extremities (**Figure 1**). The first nodule appeared on his left arm one year prior to presentation. On histology, the lesions showed a dermal nodule composed of histiocytoid cells with prominent nucleoli (**Figure 2**). Immunohisto-chemical stains were positive for CD68 and myeloperoxidase (MPO) and negative for CD14. A follow up bone marrow biopsy showed acute myeloid leukemia with myelomonocytic differentiation. Final diagnosis: AML.

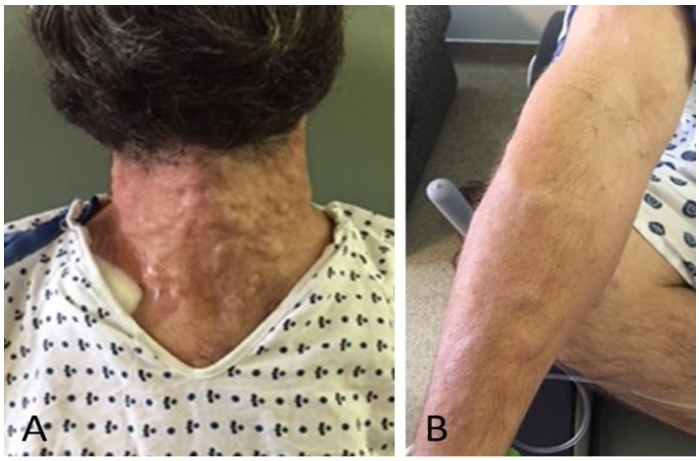

Figure 1. ***(A)*** *Neck nodules.* ***(B)*** *Right forearm nodules.*

Case 2

A 45-year-old woman with a past medical history of hypertension and hyperlipidemia was admitted for a new onset rash, acute kidney injury, and anemia one week after starting sulfamethoxazole/trimethoprim. The rash started five days after initiating antibiotic treatment, appearing as an itchy red rash on her right arm that spread to involve her chest, left arm, abdomen, and back, mimicking a fixed drug eruption.

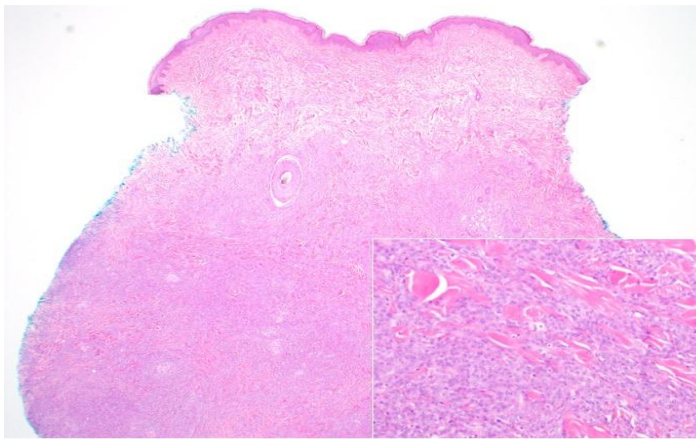

Figure 2. *Incisional biopsy of dermal nodule composed of histiocytoid cells with prominent nucleoli; 2x and 20x magnification, H & E stain.*

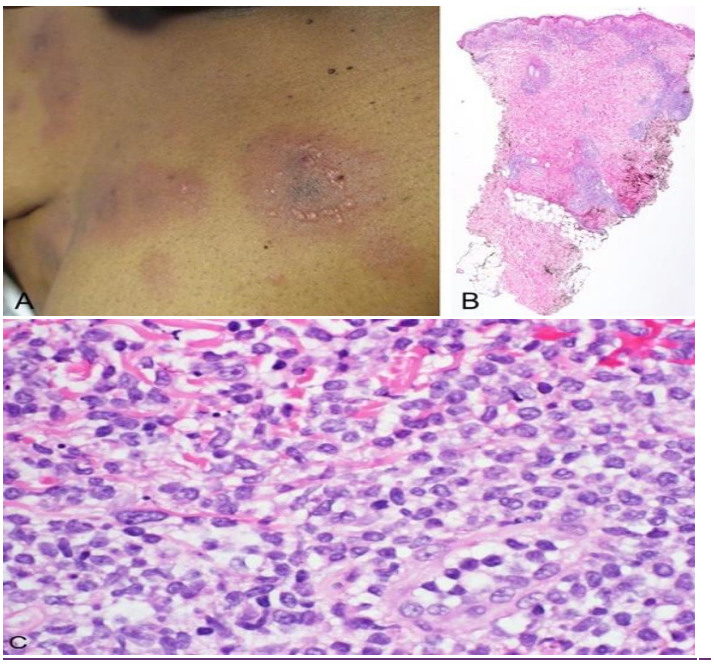

Figure 3. ***(A)*** *Chest nodules.* ***(B)*** *H & E stain, low (2×) and* ***(C)*** *high (40×) power magnification: punch biopsy of dusky plaque showing dense superficial and deep perivascular leukemic infiltrate. The blasts of leukemia cutis often closely resemble histiocytes, which can make the diagnosis challenging.*

The dusky plaques were non-painful and some demonstrated vesicles (**Figure 3A**). Biopsy showed a dense superficial and deep perivascular infiltrate composed of large atypical cells (**Figure 3B, C**). These cells stained positive for CD68, CD4, and MPO, but were negative for CD14 (**Figure 4**).

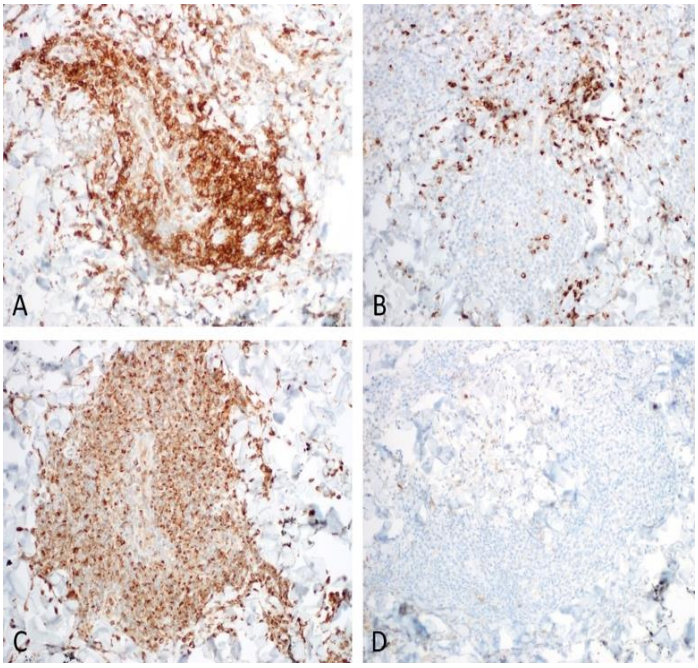

Figure 4. *Perivascular leukemic infiltrate, 20×. **(A)** CD4 positive, **(B)** Myeloperoxidase (MPO) positive, **(C)** CD68 positive, **(D)** CD14 negative.*

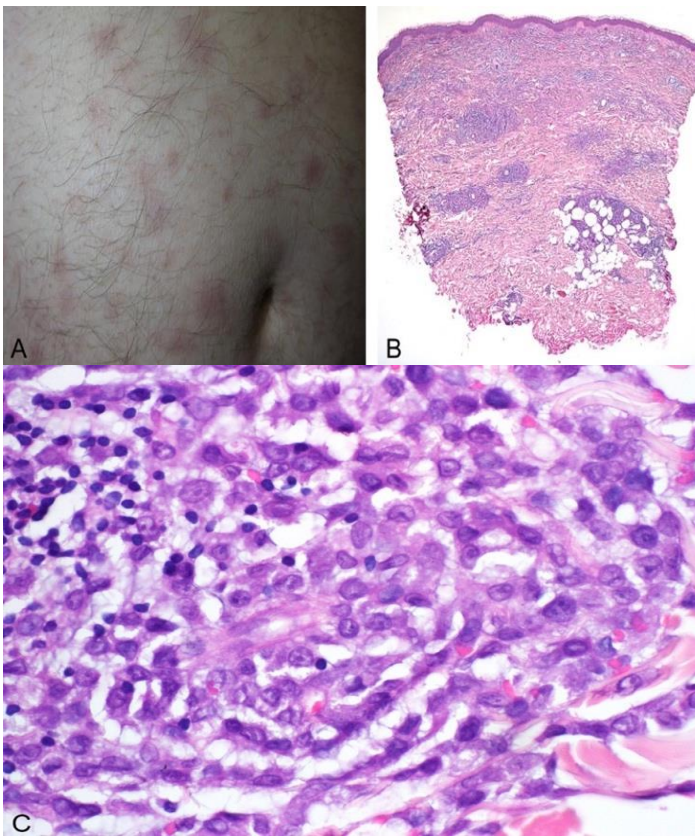

Figure 5. ***(A)** Plum colored macules and papules on trunk. **(B)** H & E stain, low (2×) and **(C)** high (40×) power magnification: punch biopsy showing dense superficial and deep perivascular as well as interstitial leukemic infiltrate.*

A concurrent bone marrow biopsy showed AML with 23% blasts by flow cytometry. One week after starting chemotherapy, the patient died after a myocardial infarction. Cause of death was acute coronary syndrome. Final diagnosis: AML.

Case 3

A 79-year-old Caucasian man with a past medical history of polycythemia vera presented with an eruption on the trunk. The rash, composed of plum-colored macules and papules, began one week after completing a course of azithromycin for an upper respiratory tract infection and continued to spread over two months to involve the back, chest, abdomen, and extremities (**Figure 5A**). The rash did not resolve despite a steroid injection and 5-day prednisone taper. A punch biopsy of one plum-colored papule showed a dense superficial and deep perivascular as well as interstitial dermal infiltrate (**Figure 5B, C**). These cells stained positive for CD68 and lysozyme. The patient is alive 18 months after diagnosis of leukemia cutis. Treatment was initiated at an outside institution; details of treatment are not known. Final diagnosis: AML

Case Discussion

Leukemia cutis is a rare presenting symptom of AML [6], occurring in only 2.0 – 3.7% of AML [3]. It is even less commonly reported in CLL [2]. Identification of LC can be important for early diagnosis of systemic disease and prognostic assessment. Prognosis is worse when LC is present compared to acute systemic leukemia presenting without LC [3]. This may be related to chromosomal abnormalities, which are more commonly found in LC [5].

In all our cases, the patient's cutaneous involvement included the back. In the two cases that did not start on the back, both started on an upper extremity and progressed to involve the trunk. Previous studies have suggested that LC has no preferred sites and the trunk, extremities, and head are equally involved [2].

Table 1. *Case histories; MPO, myeloperoxidase; AML, acute myeloid leukemia.*

Case	Age/Sex	Location	Preceding history	Concurrent or subsequent symptoms	Histologic pattern	IHC	Final Diagnosis
1	42/M	Left arm, then neck, trunk, groin and extremities	None	Fever and fatigue	Dermal nodule	CD68+, MPO+, CD14-	AML
2	45/F	Right arm, then chest, left arm, abdomen and back	Treatment with sulfamethoxazole/ trimethoprim 1 week prior	Acute kidney injury, anemia, pruritic rash	Superficial and Deep Perivascular infiltrate	CD68+, MPO+, CD4+, CD14-	AML
3	79/M	Back, chest and abdomen	Treatment for URI with azithromycin 1 week prior. Hx of polycythemia vera	None	Superficial and Deep Perivascular infiltrate	CD68+ Lysozyme+	AML

In half the cases, the first presentation of LC occurred one week after antibiotic use. It is unclear whether the antibiotics acted as a trigger or are simply a distracting factor from true diagnosis. To the best of our knowledge, there is no literature to support antibiotics acting to incite or exacerbate LC. It is more likely that the timing of the patients' history would make the clinician inclined to suspect a drug reaction rather than malignancy. In such cases, biopsy with histologic and immunohistochemical analysis can help diagnose LC.

Conclusion

Leukemia cutis has been described in several case reports with variable clinical rash presentations and histologic morphologies [3]. We found this to hold true in our cohort of three patients with different descriptions and distributions of the eruptions and rate of progression, as well as histologic patterns ranging from dermal histiocytoid nodules to perivascular infiltrates of atypical hematopoietic cells. Immunohistochemical stains for myeloid and myelomonocytic differentiation including CD68, CD4, and MPO can be helpful in identifying leukemias of myeloid lineage. This supports previously published guidelines for diagnosing LC stating that in cases when LC is the first manifestation of acute leukemia and when flow cytometry of peripheral blood or bone marrow is non-contributory, immunohistochemical analysis of the skin lesions is required [7]. Furthermore, immunohistochemical stains CD34 and CD117, which are markers of blasts in the bone marrow, are rarely expressed in myeloid LC, making them of limited use in the workup of skin biopsies for suspected AML [7]. This discrepancy must be considered when diagnosing myeloid and monocytic LC in the absence of systemic leukemia.

References

1. Barzilai A, Lyakhovitsky A, Goldberg I, Meytes D, Trau H. Aleukemic monocytic leukemia cutis. *Cutis* 2002;69(4):301-4. [PMID: 12080951].
2. Wagner G, Fenchel K, Back W, Schulz A, Sachse MM. Leukemia cutis – epidemiology, clinical presentation, and differential diagnoses. *J Dtsch Dermatol Ges* 2012;10:27-36. [PMID: 22115500].
3. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. *Am J Clin Pathol* 2008;129:130-142. [PMID: 18089498].
4. Rao AG, Danturty I. Leukemia cutis. *Indian J Dermatol* 2012;57(6):504. [PMID: 23248383].
5. Agis H, Weltermann A, Fonatsch C, Haas O, Mitterbauer G, Müllauer L, Schreiber S, Schwarzinger I, Juretzka W, Valent P, Jäger U,

Lechner K, Geissler K. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. *Ann Hematol* 2002 Feb;81(2):90-5. [PMID: 11907789].

6. Hussein MR, Al bshabshe AA, Dalati T. Leukemia cutis: case report and review of literature. *Appl Immunohistochem Mol Morphol* 2010 Mar. 18(2):190-1. [PMID: 19956066].
7. Cronin DMP, George TI, Sundram UN. An Updated Approach to the Diagnosis of Myeloid Leukemia Cutis. *Am J Clin Pathol* 2009; 132:101-110. [PMID: 19864240].