Clinical Characterization of Leukemia Cutis Presentation

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PRACTICE **POINTS**

- Complete and comprehensive skin examination is important in leukemia patients, as leukemia cutis (LC) lesions can present in all body sites including ocular and oral mucosa as well as the groin.
- Given the wide variability in appearance, symptoms, distribution, and stage of leukemia at presentation, dermatologists and oncologists need to keep LC in the differential diagnosis for any new skin lesion and to have a low threshold for performing skin biopsy.
- Performing thorough skin examination on leukemia patients throughout the course of their disease may help identify LC early so that treatment can be implemented in a timely fashion at initial diagnosis, first sign of relapse, or change in disease state.

Leukemia cutis (LC) is a rare condition that results from infiltration of neoplastic cells into the skin in patients with leukemia, mainly described in case reports or small case series. This study aimed to characterize the clinical presentation of LC and its association with leukemia evolution and prognosis. A single-institution retrospective review of medical records of patients with LC was performed. Biopsy-proven LC cases diagnosed in patients with leukemia were analyzed for a variety of clinical characteristics and prognosis; 46 patients met inclusion criteria. Leukemia cutis most commonly presented in patients with acute myeloid leukemia (AML), though lesions were seen in several other leukemia types. Most LC lesions were identified at initial presentation of underlying leukemia but also occurred with leukemia relapse and at other stages of treatment. Most patients died within 1 year of LC diagnosis. The clinical presentation of LC is highly variable. Lesions occur in different anatomic regions; can present as papules, nodules, or plaques; and have different associated colors and symptoms. Duration between diagnosis of leukemia and death in patients who develop LC, and between LC diagnosis and death, are highly variable. Early detection of lesions might help provide a diagnosis in patients with leukemia and potentially improve prognosis if doing so results in earlier initiation of chemotherapy.

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Leukemia is a malignant, life-threatening neoplasm affecting the hematopoietic system. Extramedullary manifestations can occur in various organs, including skin.[1] Skin findings in leukemia patients are common and varied, including pallor secondary to anemia, petechiae or ecchymoses due to thrombocytopenia, and skin manifestations of neutropenia and chemotherapy.[2] When patients with leukemia develop skin lesions without leukemic infiltration, the resulting nonspecific cutaneous manifestations are known as leukemids.[3] Specific cutaneous manifestations of leukemia resulting from direct invasion of leukemic cells into the epidermis, dermis, or subcutis are referred to as leukemia cutis (LC).[2,3]

Acute myeloid leukemia (AML) is the most common type of leukemia associated with LC, but LC also is seen in other leukemias with various frequencies.[1] The lesions of LC can present anywhere on skin, though it has been reported that LC has a tendency to occur at sites of prior ongoing inflammation,[2,4] most commonly the extremities, trunk, and face.[2,5,6] LC lesions have a range of morphological findings and most commonly present as nodules, papules, and plaques.[1,7]

Most reports of LC in the literature are case reports or case series with small numbers of subjects.[3,6,8] A study of LC patients (N=75) in Korea by Kang et al[7] has been

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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the only one to analyze clinical characteristics of LC since 2000.

The aim of this study was to further contribute to the knowledge of clinical characteristics of LC. Clinical patterns of 46 patients were analyzed to further characterize the presentation of LC and to compare our results with those in the literature.

Methods

We conducted a single-institution retrospective review of medical records of patients with LC diagnosed in the Department of Dermatology at Wake Forest School of Medicine (Winston-Salem, North Carolina) over a 17-year period (2001-2017). The study protocol was approved by the institutional review board of Wake Forest University School of Medicine (IRB No. 00054474). Patients had a leukemia diagnosis established by bone marrow biopsy. Patients were included in this analysis if they had ongoing active leukemia and a skin biopsy consistent with LC. Patients of all sexes and ages were included in the cohort. Patients were excluded if they presented only with nonspecific cutaneous lesions associated with leukemia (leukemids). After removing duplicate records from a total of 60 patients initially identified, 46 unique patients were included in this study.

Results

Demographics—Fifty-six percent (26/46) of patients were male. The average age at diagnosis of leukemia was 58 years (range, 8.5 months–84 years). Eighty-five percent of patients were white (39/46), 11% were black (5/46), 2% were Hispanic (1/46), and 2% were of unknown ethnicity (1/46).

Eighty percent (37/46) of patients with LC had AML; 3 of these patients had a prior diagnosis of chronic myeloid leukemia (CML) and 2 had myelodysplastic syndrome (MDS) that did not develop LC until after they had transitioned to AML. Other subtypes of leukemia in this patient population included acute lymphoblastic leukemia (ALL)(n=2), plasma cell leukemia (PCL)(n=2), undifferentiated leukemia (n=2), chronic lymphocytic leukemia (CLL)(n=1), myelodysplastic syndrome (n=1), and Burkitt-type leukemia (n=1).

Distribution and Morphology of LC Lesions—The clinical appearance of LC was widely variable in morphology and anatomic location (Table 1 and Figure). Eighty-four percent of LC occurrences involved more than one lesion (n=32); 14% were a solitary lesion (n=6). For the 2 patients who had 2 separate episodes of LC, the initial presentation of LC was multiple lesions; recurrent LC at relapse presented as a solitary lesion in both cases. Most LC lesions (77% [67/87]) occurred on the trunk or extremities; 23% (20/87) of LC lesions occurred on less common sites, such as the groin, face, hands, feet, and mucosa. Papules (38% [22/58]) and nodules (31% [18/58]) were the most common morphology; macules, plaques, and ulcers were observed less frequently. Clinical descriptions of LC lesions varied widely, with the most common descriptive characteristics being erythematous (57% [20/35]), violaceous (31% [11/35]), and asymptomatic (84% [32/38]). Rare descriptors included flesh colored, hyperpigmented, tender, pruritic, edema, crusting, and confluent erythematous.

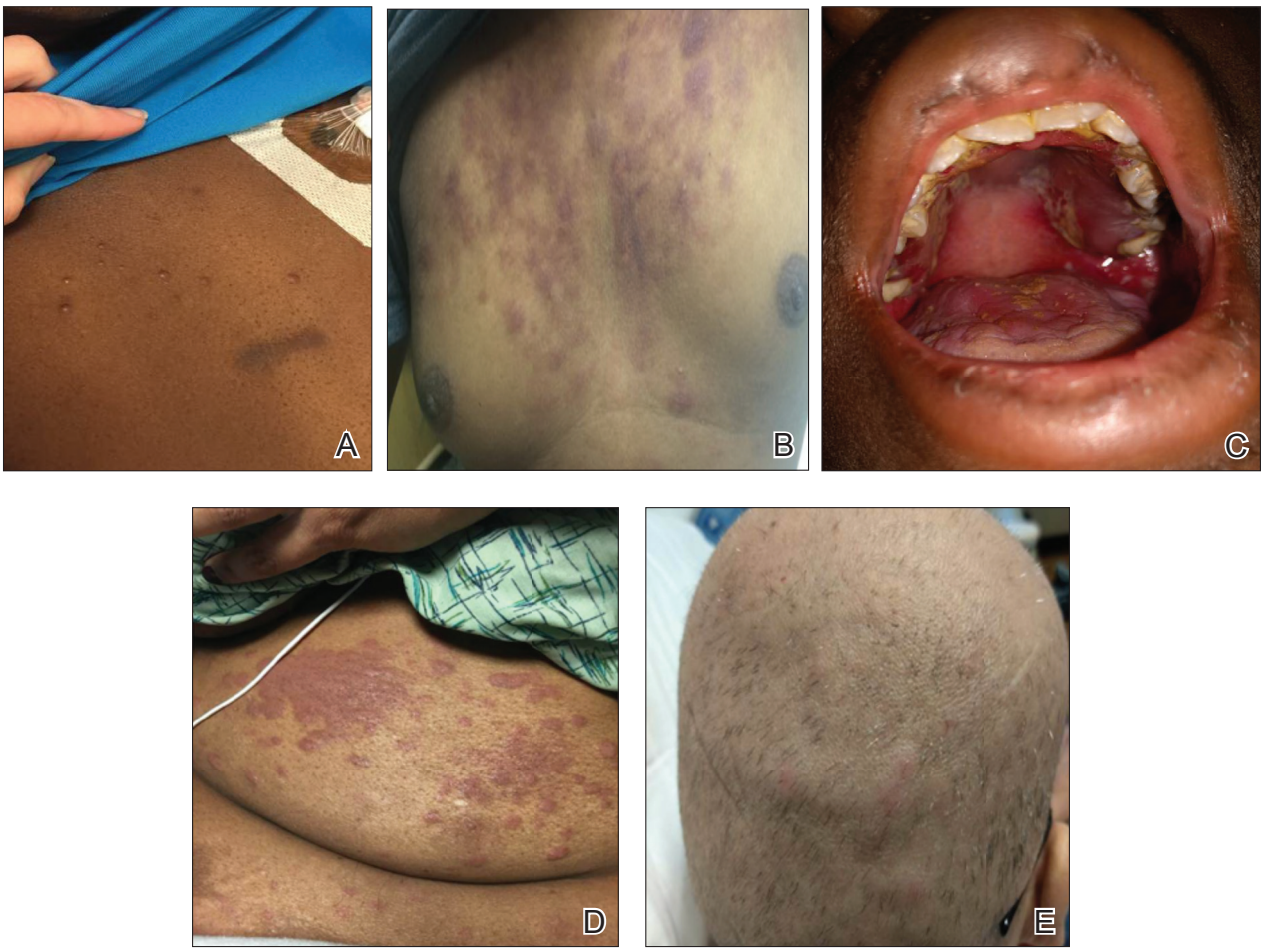
Interval Between Leukemia Diagnosis and LC Diagnosis—Approximately 59% (n=27) of patients had LC as a presenting finding of their leukemia (Table 2). Twenty-two percent (n=10) developed LC at the time of leukemia relapse; 20% (n=9) developed LC during consolidation or salvage chemotherapy. Two AML patients had recurrent episodes of LC both at initial presentation of leukemia and when AML relapsed. Two other AML patients received a diagnosis of LC at the same time as a negative concurrent bone marrow biopsy (ie, aleukemic LC). Mean duration between diagnosis of leukemia and diagnosis of LC was 0.4 months (CLL), 1.0 month (ALL), 4.7 months (AML), and 7.15 months (PCL). In cases of MDS and CML transformation to AML, the interval was 6.5 and 4.9 months, respectively.

Interval Between LC Diagnosis and Death—As a whole, 17% (n=8) of patients were living at the time this article was written (eTable). Of patients who are still living, 10.9% (n=5) have AML. Looking at the cohort of patients with AML and LC, average age at AML diagnosis was 59.8 years. Average time from diagnosis of leukemia to death was 17.3 months (range, 0.6–49.6 months) for AML; 17.0 months (range, 10.0–24.0 months) for CML transformation to AML; 15.0 months (range, 12.0–18.0 months) for PCL; 14.75 months (range, 11.0–18.5 months) for undifferentiated leukemia; and 8.95 months (range, 4.2–13.7 months) for MDS transformation to AML. The interval between leukemia diagnosis and death was notably shorter for the CLL patient (4.0 months) and the deceased ALL patient (2.4 months). Mean duration between LC diagnosis and death was 11.7 months (AML), 11.2 months (undifferentiated leukemia), 9.9 months (CML transformation to AML), 2.75 months (PCL), and 2.4 months (MDS transformation to AML). The shortest intervals between LC diagnosis and death were seen in CLL (0.5 months) and ALL (0.4 months).

Discussion

Cutaneous manifestations are not uncommon in leukemia patients and can have a number of causes, including paraneoplastic cutaneous manifestations, such as pyoderma gangrenosum and Sweet syndrome; infection; cutaneous toxicities from antineoplastic agents; and LC.[2] Leukemia cutis can be confused with other skin lesions in leukemia patients; diagnosis requires biopsy.[2,9]

We analyzed clinical characteristics and prognosis of 46 patients with LC over a 17-year period. To the best of our knowledge, this is the largest study of LC patients published in the United States. A similar study by Kang et al[7] analyzed 75 patients in Korea; however, the incidence of LC among different types of leukemia



Clinical presentation of leukemia cutis. A, Erythematous papules on the trunk. B, Violaceous infiltrative plaques on the chest. C, Violaceous firm nodule on the oral mucosa. D, Violaceous infiltrative plaques on the breast. E, Erythematous firm nodules on the occipital scalp.

in the Korean population cannot be applied to Western countries. We did compare the clinical characteristics of our cohort of patients to those reported by Kang et al[7] and other studies including a smaller number of patients.

In this study, the male to female ratio was 1.3 to 1 compared to the 2:1 ratio reported by Kang et al.[7] The mean age of leukemia diagnosis among our patients was 58 years, which is notably older than the mean age previously reported.[7] In this cohort, 4 patients (8.7%) were 34 years or younger, including 1 infant aged 8.5 months; 24 (52.2%) were aged 35 to 64 years; and 18 (39.1%) were 65 years and older.

Consistent with other studies,[2,5,7] the most common type of leukemia in patients who developed LC was AML (80%). Among AML patients, the mean age at AML diagnosis (59.8 years) was notably younger than the reported US average age of patients who had a diagnosis of AML (68 years).[10] Gender breakdown was slightly different than US statistics: 63% of AML patients in our group were male, whereas AML is only slightly more common among men in the United States.[10]

Clinically, skin lesions observed most commonly were (in decreasing order) papules, nodules, macules, plaques, and ulcers. Papules (38%) were the most common lesion overall in our study, which differed from the Kang et al[7] report in which nodules were the most common. Nodules (31%) were the second most common LC morphology among our patients. Among AML patients, papules were seen in 56% of patients (18/32); nodules were seen in 44% (14/32). The extremities (when combined together) were the most common location of LC lesions (46% [arms, 24%; legs, 22%]); the trunk was the second most common body region (31%). Our study did not find a difference among most common LC anatomic sites compared to other studies.[5,7] Less common sites in our cohort included the head, scalp/ears, neck, hands, mucosa, and feet. All body sites were represented, including ocular and oral mucosa and groin, a finding that underscores the importance of complete and comprehensive skin examinations in this patient population. The terms *erythematous* and *violaceous* were used to describe the color of most lesions (88%), which

TABLE 1. Characteristics of Leukemia Cutis Skin Lesions

Characteristics	No. of Patients (%)[a]
Clinical Appearance	
Papules	22 (38)
Nodules	18 (31)
Macules	8 (14)
Plaques	7 (12)
Ulcers	3 (5)
Anatomic Location	
Trunk	27 (31)
Arms	21 (24)
Legs	19 (22)
Face	6 (7)
Scalp/ears	6 (7)
Groin	3 (4)
Neck	2 (2)
Hands	1 (1)
Feet	1 (1)
Mucosa	1 (1)
Color	
Erythematous	20 (57)
Violaceous	11 (31)
Flesh colored	3 (9)
Hyperpigmented	1 (3)
Solitary or Multiple	
Multiple lesions	32 (84)
Solitary lesion	6 (16)
Symptoms	
Asymptomatic	32 (84)
Tender	4 (11)
Pruritic	2 (5)

[a]Total number of patients represents the sum of each subcategory.

commonly presented as multiple lesions (84%) and often were asymptomatic (84%).

It has been reported that, first, in most cases of LC, the condition develops in patients who have already been given a diagnosis of leukemia and, second, simultaneous manifestation of systemic leukemia and LC is less common.[11,12] Leukemia cutis also can precede peripheral or bone marrow leukemia (known as aleukemic LC).[1,13] Two AML patients (4.3% [2/46]) in this study met criteria for aleukemic LC because they had LC at the same time as negative bone marrow biopsy, which is consistent with a prior report that aleukemic LC can affect as many as 7% of patients.[1] Our results differed slightly from prior studies in that most of our patients had LC as one of the presenting manifestations of their leukemia.[3,7]

Regardless of leukemia type, patients were likely to die within 1 year of LC diagnosis, on average, which is consistent with prior reports.[7,11,12] However, the time between diagnosis of LC and death varied greatly among our patients (range, 12 days to 4.1 years). From 2007 to 2013, the 5-year relative survival rate overall for leukemia patients in the US population (by type) was 86.2% (CLL), 71.0% (ALL), 68.0% (CML), and 27.4% (AML).[14] Compared to these national statistics, the relative survival rate in LC is poor, with patients who have AML surviving, on average, less than 8 months from time of leukemia diagnosis, whereas ALL and CLL patients survive less than 6 months.

When LC is a late presentation of B-cell CLL or when it presents as myeloid leukemia, blastic transformation (Richter syndrome), or T-cell CLL, it is occasionally associated with poor prognosis, though LC does not affect survival.[15-17] In a study of the association of LC with survival in AML, 5-year survival among 62 AML patients with LC was 8.6%, shorter than 28.3% among the 186 matched patients with AML without LC.[18] Similarly, the estimated 5-year survival for all patients with AML, according to Surveillance, Epidemiology, and End Results Program data (2007-2013), was 27.4%.[14] Based on those results, LC might be a good prognostic indicator in patients with AML.

Conclusion

This study characterized the clinical presentation of LC, which is highly variable in appearance, symptoms, distribution, and stage of leukemia at presentation. In our study cohort, LC most commonly presented as asymptomatic erythematous or violaceous papules or nodules in older male AML patients at leukemia diagnosis. Given such wide variability, dermatologists and oncologists need to keep LC in the differential diagnosis for any new skin lesion and to have a low threshold for performing skin biopsy. Complete and thorough skin examinations should be performed on leukemia patients throughout the course of their disease to identify LC early so that treatment can be implemented in a timely fashion at initial diagnosis, first sign of relapse, or change in disease state.

TABLE 2. Interval Between Leukemia Diagnosis and Leukemia Cutis Diagnosis

Leukemia Type	No. of Patients	Duration of Interval (Range), mo	Stage of Therapy, n			
			Initial Presentation	Relapse	Consolidation	Salvage
Acute myeloid leukemia	32	4.7 (0–43.6)	19	7	6	0
Transformation of chronic myeloid leukemia to acute myeloid leukemia	3	4.9 (0–8)	2	1	0	0
Transformation of myelodysplastic syndrome to acute myeloid leukemia	2	6.5 (0–13)	1	1	0	0
Acute lymphoblastic leukemia	2	1.0 (0–2)	1	0	0	1
Burkitt-type leukemia	1	LC was diagnosed 2 d before leukemia was diagnosed	1	0	0	0
Chronic lymphocytic leukemia	1	0.4	0	0	0	1
Myelodysplastic syndrome	1	LC was diagnosed 1 mo before leukemia was diagnosed	1	0	0	0
Plasma cell leukemia	2	7.15 (3.7–10.6)	0	1	0	1
Undifferentiated leukemia	2	In 1 case, LC was diagnosed 4 mo before leukemia was diagnosed; in the other case, LC and leukemia were diagnosed on the same day	2	0	0	0

Abbreviation: LC, leukemia cutis.

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APPENDIX

eTABLE. Interval Between Diagnosis of Leukemia and Death and Between Diagnosis of Leukemia Cutis and Death

Leukemia Type	No. of Patients	Mean Duration Between Leukemia Diagnosis and Death (Range), mo	Mean Duration Between Leukemia Cutis Diagnosis and Death (Range), mo
Acute myeloid leukemia	32[a]	17.3 (0.6–49.6)	11.7 (0.7–49.5)
Transformation of chronic myeloid leukemia to acute myeloid leukemia	3[a]	17.0 (10.0–24.0)	9.9 (3.3–16.5)
Transformation of myelodysplastic syndrome to acute myeloid leukemia	2	8.95 (4.2–13.7)	2.4 (0.6–4.2)
Acute lymphoblastic leukemia	2[a]	2.4	0.4
Burkitt-type leukemia	1	Alive	Alive
Chronic lymphocytic leukemia	1	4.0	0.5
Myelodysplastic syndrome	1	Alive	Alive
Plasma cell leukemia	2	15.0 (12.0–18.0)	2.75 (1.5–4.0)
Undifferentiated leukemia	2	14.75 (11.0–18.5)	11.2 (3.9–18.5)

[a]Four acute myeloid leukemia patients, 1 chronic myeloid leukemia–acute myeloid leukemia transformation patient, and 1 acute lymphoblastic leukemia patient were alive at the time the manuscript of this article was written. One acute myeloid leukemia patient was lost to follow-up.