An Atypical Chronic Ulcer Caused by Acute Myeloid Leukemia

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ABSTRACT

Introduction. Atypical chronic wounds are challenging for clinicians because of their identification, diagnosis, and treatment. These wounds may reflect an underlying systemic or malignant disease; therefore, an accurate diagnosis and initiation of the appropriate treatment are necessary. **Case Report.** A 68-year-old man presented with an atypical chronic ulcer on his left shin of 2 years' duration. The ulcer was associated with acute myeloid leukemia. Initially, the surgeon treated the chronic wound with wide debridement and biopsy for pathohistological investigation. Leukemia cutis with accumulation of blast cells in the area of the ulcer was recognized by histological examination. Further, an absorbent cellulose-based core dressing with activated carbon was used, which appeared to be useful in reducing wound pain, odor, and exudate. **Conclusions.** Leukemia cutis is a specific sign of systemic leukemia and the result of dissemination of leukemic cells to the skin. Treatment should be directed towards eradication of the systemic disease, which also improves local manifestation of the disease.

KEY WORDS

atypical wound, acute myeloid leukemia, leukemia cutis, chronic wound, lower extremity

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Atypical chronic wounds comprise < 5% of all chronic wounds.[1] They may present with features the clinician has not previously encountered, therefore raising a diagnostic dilemma and challenge. A full range of pathogenic categories, including vascular, autoimmune, inflammatory, infectious, neoplastic, genetic, and drug-related processes, can cause an atypical ulcer.[1,2] A systemic disease, such as leukemia, can provoke cutaneous manifestations, which may be specific (eg, leukemia cutis [LC]) or nonspecific (eg, inflammatory, paraneoplastic, or secondary to marrow failure). Leukemia cutis is the infiltration of neoplastic leukocytes or their precursors into the epidermis, dermis, or subcutaneous tissues, resulting in clinically identifiable cutaneous lesions.[3] The case of a 68-year-old man diagnosed with acute myeloid leukemia (AML) with an atypical chronic wound of his lower left shin treated with palliative care of LC after an unsuccessful surgical approach is reported.

Etiology and pathogenesis

Acute myeloid leukemia is a malignant neoplasm affecting the hematological system. After the initial phase in the bone marrow and subsequent appearance of the leukemic cells in the peripheral blood, extramedullary manifestations may occur in various organs, including the skin.[4,5] The diagnosis of these extramedullary presentations is clinically important since it may adversely affect prognosis and require special treatment.[5] Further, LC is a specific sign of systemic leukemia and the result of dissemination of neoplastic leukocytes to the skin. It occurs in 2% to 3% of all patients with AML and less frequently in chronic myeloproliferative diseases.[6] Leukemia cutis must be differentiated from the various nonspecific skin manifestations associated with systemic leukemia in which there is no leukemic infiltration of the skin. Histological findings are often helpful for this matter. Nonleukemic skin lesions are mostly a manifestation of bone marrow failure and include petechial bleeding, purpura, ecchymosis, and cutaneous signs of infection.[7] Nonleukemic skin lesions are more common than LC, as they occur in 40% or more of patients with leukemia.[3]

Although the actual mechanism explaining the pathogenesis of LC is not clear, it has been speculated[8] that the chemokine integrin and other adhesion molecules may play a role in skin-specific homing of T and B leukemic cells. The link between some gene abnormalities, such as numerical abnormalities of chromosome 8, and LC remains unkown.[5]

Signs and symptoms

Leukemia cutis usually appears as papules, plaques, or nodules, while erythematous macules, blisters, and ulcers are rare.[9,10] These lesions may be localized or disseminated and can occur on any site of the skin.[11] The most commonly involved anatomic locations are the lower extremities, followed by the upper extremities, lower back, trunk, and face.[6] Multiple

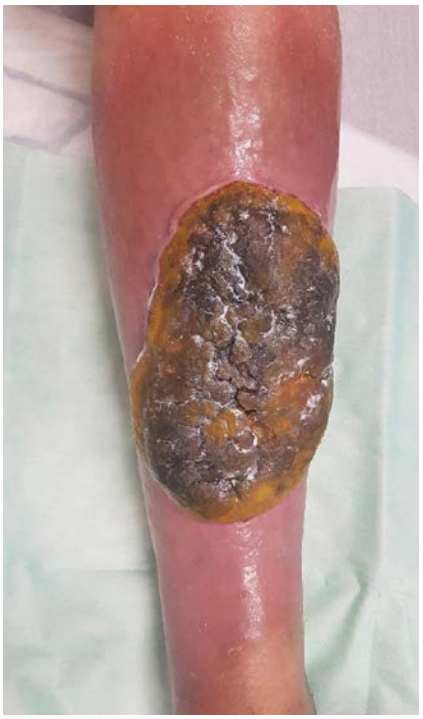

Figure 1. Chronic wound of the lower leg at initial evaluation.

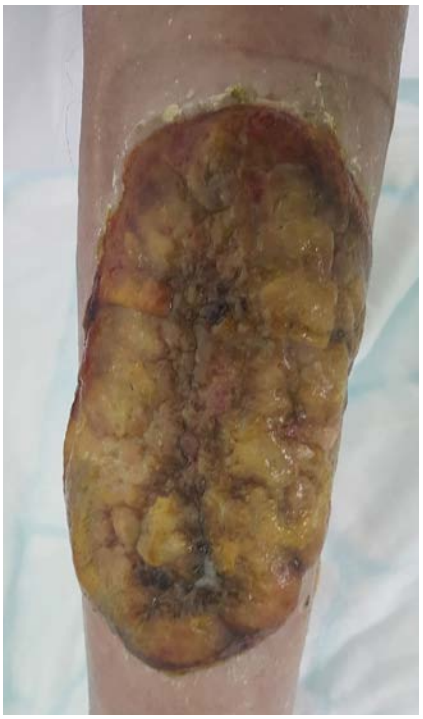

Figure 2. Chronic wound of the lower leg after surgical debridement.

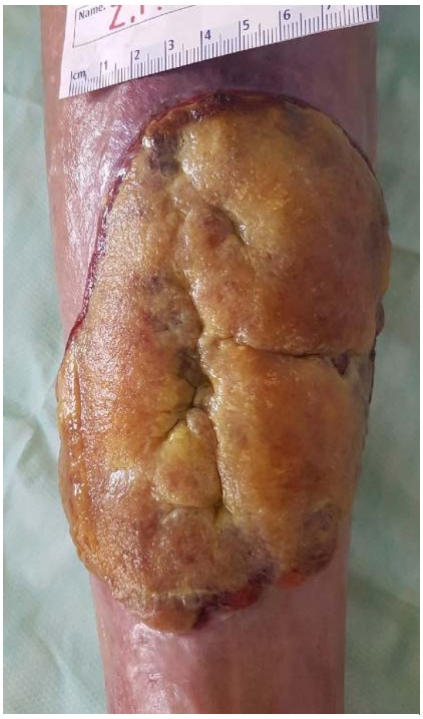

Figure 3. Chronic wound after dressing changes with an absorbent cellulose-based core dressing with activated carbon.

hyperpigmented-infiltrated nodules and plaques on the left shin were found on examination of the patient presented herein. Leukemic infiltration tends to occur at sites of previous or concomitant inflammation, as it has been found localizing to sites of herpetic lesions, trauma, intravenous catheters, and recent surgeries.[6,8] Skin manifestations of LC are most often asymptomatic, though in some types of leukemia, significant pruritus may be present.[12]

Diagnostics

Typically, the diagnosis of leukemia includes a complete blood count, peripheral blood smear, and a bone marrow specimen (an aspirate or core biopsy).[13] The diagnosis of LC is based on the morphologic pattern of skin infiltration, cytological features, and most importantly, the immunophenotype of the tumor cells. Skin biopsies show a characteristic pattern of dermal infiltration by blasts (perivascular, periadnexal, interstitial, or nodular involvement with sparing of the upper papillary dermis). Correlation with clinical data and bone marrow and peripheral blood findings is often helpful to confirm the diagnosis.[3]

Leukemia cutis commonly occurs in the setting of a previously diagnosed systemic leukemia or lymphoproliferative disorder/myelodysplastic syndrome, as is the case in the present patient. In rare cases, LC may be the first manifestation of a systemic disease.[3,12] Thus, a skin biopsy may be helpful in diagnosing leukemia and may facilitate the work-up.[14,15]

Management

Leukemia cutis represents a local manifestation of underlying systemic disease and should be treated as such. Current treatment involves chemotherapy and/or hematopoietic cell transplantation.[8,9] If complete remission of AML is achieved after intensive initial therapy, appropriate post-remission therapy is essential. Continuous infusion cytarabine with an anthracycline remains the mainstay of induction therapy. Standard post-remission strategies include conventional chemotherapy with intermediate dose cytarabine as hematopoietic cell transplantation.[16]

Control of cutaneous involvement is essential for long-term disease control since blasts from the wound may reseed the marrow, resulting in relapse. Skin-directed therapy, such as radiotherapy, can play an important role in the treatment, especially in patients with widespread skin involvement. Moreover, it can provide symptom-relief of lesion-associated pain and pruritus.[6,17]

CASE REPORT

A 68-year-old man presented to the outpatient service of the Department of Surgical Infections at the University Medical Centre Ljubljana (Ljubljana, Slovenia), with an atypical chronic ulcer on his left shin of 2 years' duration. The patient was suffering from chemotherapy-resistant AML following myelodysplastic syndrome. At the time of presentation, his AML was treated only symptomatically with blood transfusions. The patient also developed chronic renal failure and had regular check-up exams at the authors' medical center. Due to a wound infection, he was examined by an infectious disease

specialist in which the patient was pallor, normal vital signs (blood pressure: 135/68 mm Hg, heart rate: 89 beats per minute), and subfebrile (axillary body temperature: 37.1°C). The physical examination was otherwise unremarkable, except for the large ulcer on his left shin measuring 17 cm x 12 cm x 0.5 cm (**Figure 1**). The chronic ulcer did not heal, despite the use of various modern wound dressings. Initially, polyurethane foam with a silicone contact layer (Mepilex; Mölnlycke Health Care, Gothenburg, Sweden) was applied. Because of the large amount of exudate, with risk of maceration and unpleasant odor, the type of wound dressing was changed to an absorbent cellulose-based core dressing with activated carbon (curea P1 DUO active; Curea Medical GmbH, Heilbad Heiligenstadt, Germany).

The wound was tainted with a solid adherent fibrin coating, which could not be removed by wound cleansing and rinsing with local antiseptic hypochlorite solution (Veriforte; P.G.F. Industry Solutions, Elixhausen, Austria). A previous wide surgical debridement failed to cleanse the wound.

He received intravenous antibiotic therapy (imipenem/cilastatin 1000 mg/6 hours for 14 days and ciprofloxacin 400 mg/12 hours). Following the brief antibiotic course, the patient had a check-up exam at the surgery clinic. No significant improvement in ulcer size or appearance was noted. The systemic parameters of inflammation remained high, which was expected due to the underlying disease (**Table**).

Microbiological swabs from the wound tissue showed *Proteus mirabilis*, *Escherichia coli*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Skeletal scintigraphy excluded osteitis in the left shin.

A surgeon was consulted for treatment with wide debridement and biopsy for pathohistological investigation due to its unusual appearance. An accumulation of blast cells in the area of the ulcer was recognized by histological examination. Five days following surgical debridement, accumulations of blast cells covered with a fibrin layer in the wound bed reappeared (**Figure 2**). Considering the patient's age and stage of his disease, the surgeon, infectious disease specialist, and hematologist decided to utilize a palliative approach for wound treatment. This consisted of the absorbent cellulose-based core dressing with activated carbon, which was changed every 2 days for 12 weeks (**Figure 3**). After 3 follow-up appointments, in 4 weeks the patient appeared to be pain-free and wound odor was reduced. In this case, a more aggressive surgical management could have led to extensive hemorrhage and increase the mortality rate.

Table. Laboratory results

TEST		RESULT	REFERENCE RANGE
Hematolotic	Hb, blood	77g/L	130–170g/L
	RBC	$2.58x10^{12}$/L	$4.5–5.5x10^{12}$/L
	WBC	$2.9x10^{9}$/L	$4–10x10^{12}$/L
	Platelet count	$48x10^{9}$/L	$150–410x10^{12}$/L
Systemic parameters of inflammation	CRP	197g/L	<5g/L
	Procalcitonin	1.21mcg/L	<0.24mcg/L
Differential WBC	Monocytes	35%	<10%
	Lymphocytes	56%	20%–50%
	Segmented neutrophils	9%	40%–75%

Hb: hemoglobin; RBC: red blood cell count; WBC: white blood cell count; CRP: C-reactive protein

DISCUSSION

Although LC is relatively rare, it is clinically significant and poses therapeutic dilemmas, as was the case in the presented patient. Leukemia cutis often requires collaboration among a multidisciplinary group of clinicians. The treatment of LC should be directed towards eradication of the systemic disease. Long-term prognosis and durable cutaneous remission are dependent on systemic disease control.[6] In general, its occurrence is a poor prognostic indicator and strongly correlates with additional sites of extramedullary involvement.[9,15,18] In patients with AML without skin lesions, the reported survival rate is 30% at 2 years compared with 6% in patients with skin lesions.[8]

CONCLUSIONS

As a specific sign of systemic leukemia, LC is often diagnostically and therapeutically challenging for the treating physician. Regarding treatment options, it is important to consider the prognosis of the underlying disease, treatment cost, additional risks, and likelihood of healing as well as the patient's opinion and desire. Aggressive surgical treatment is often unsuccessful and might be a risk factor for complications, such as bleeding and surgery-associated pain. A palliative approach using modern wound dressings may be helpful for pain relief and reduction of wound odor. As long-term prognosis of LC is dependent on systemic disease control, chemotherapy and/or hematopoietic cell transplantation are considered to be the best treatment options known for AML.[17]

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REFERENCES

1. Situm M, Kolic M. Atypical wounds: definition and classification [Article in Croatian]. *Acta Med Croatica*. 2012;66(Suppl 1):5–11.
2. Hoffman MD. Atypical ulcers. *Dermatol Ther*. 2013;26(3):222–235.
3. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. *Am J Clin Pathol*. 2008;129(1):130–142.
4. Wagner G, Fenchel K, Back W, Schulz A, Sachse MM. Leukemia cutis - epidemiology, clinical presentation, and differential diagnoses [published online November 17, 2011]. *J Dtsch Dermatol Ges*. 2012;10(1):27–36.
5. Agis H, Weltermann A, Fonatsch C, et al. A comparative study on demographic, hematological and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis [published online January 23, 2002]. *Ann Hematol*. 2002;81(2):90–95.
6. Bakst RL, Tallman MS, Douer D, Yahalom J. How do I treat extramedullary acute myeloid leukemia [published online July 27, 2011]. *Blood*. 2011;118(14):3785–3793.
7. Watson KM, Mufti G, Salisbury JR, du Vivier AW, Creamer D. Spectrum of clinical presentation, treatment and prognosis in a series of eight patients with leukaemia cutis. *Clin Exp Dermatol*. 2006;31(2):218–221.
8. Rao AG, Danturty I. Leukemia cutis. *Indian J Dermatol*. 2002;57(6):504.
9. Gawai SR, Binesh VG, Betsy A, Jisha KT. An unusual initial manifestation of acute myeloid leukemia [published online September 27, 2016]. *Int J STD AIDS*. 2017;28(4):418–420.
10. Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2007;48(5):855–865.
11. Kang YS, Kim HS, Park HJ, et al. Clinical characteristics of 75 patients with leukemia cutis [published online March 27, 2013]. *J Korean Med Sci*. 2013;28(4):614–619.
12. Ramnarayanan J, Singhal S. Leukemia cutis. *E Med Dermatol*. https://emedicine.medscape.com/article/1097702-overview.
13. Davis AS, Viera AJ, Mead MD. Leukemia: an overview for primary care. *Am Fam Physician*. 2018;89(9):731–738.
14. Jin X, Li F, Li X, et al. Cutaneous presentation preceding acute monocytic leukemia: a CARE-compliant article. *Medicine* (Baltimore). 2017;96(10):e6269.
15. Su WP, Buechner SA, Li CY. Clinicopathologic correlations in leukemia cutis. *J Am Acad Dermatol*. 1984;11:121–128.
16. Döehner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136–1152.
17. Backst R, Yahalom J. Radiation therapy for leukemia cutis [published online April 29, 2011]. *Pract Radiat Oncol*. 2011;1(3):182–187.
18. Jiang X, Wang W, Zhang M. Leukemia cutis: an unusual presentation of acute lymphoblastic leukemia in a child. *Indian J Dermatol*. 2015;60(6):636.