Vulvar leukemia cutis: A case report and review of the literature

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INTRODUCTION

Leukemia cutis (LC) is the infiltration of the skin by neoplastic leukocytes, and typically presents after the diagnosis of systemic leukemia.[1] Clinical findings include nodular lesions and plaques, with rarer manifestations of erythematous macules, blisters, and ulceration.[2] LC can affect any body part, although genitourinary involvement is rare.[3]

The frequency of LC in chronic lymphocytic leukemia (CLL) is estimated at 4%-27%.[2] Diagnosis is made by matching cutaneous leukemic infiltrates with peripheral blood and/or bone marrow leukemic cells by molecular pathology.[2] It portends a poor prognosis. Treatment of LC consists of treating the underlying leukemia.[2]

In this report, we describe a case of LC presenting as an ulcerative lesion on the vulva years after the initial diagnosis of CLL. Following the case, we review the literature for previous reports of CLL-associated vulvar LC and their response to therapy.

Abbreviations used:

ATM:	ataxia-telangiectasia mutated gene
BIRC3:	baculoviral IAP repeat-containing protein 3
BTK:	Bruton's tyrosine kinas
CT:	computed tomography
cGY:	centigray
CLL:	chronic lymphocytic leukemia
HPV:	human papilloma virus
IL-4, IL-5:	interleukin-4, interleukin-5
LC:	leukemia cutis
PIK3R1:	phosphatidylinositol 3-kinase regulatory subunit 1
PLC:	phospholipase C
PET:	positron emission tomography
WHO:	World Health Organization
ZAP-70:	zeta-chain-associated protein kinase-70

CASE REPORT

A 67-year-old female with a history of B-cell CLL (ATM [ataxia-telangiectasia-mutated] deletion +, trisomy-12 +, Zap-70 -, Rai Stage I) on ibrutinib, and the WHO (World Health Organization) grade I ileal carcinoid tumor status/post resection presented with 2 months of vaginal drainage. On presentation, she had a tender right labial ulcer with malodorous yellow drainage. Tests for *Candida*, *Gardnerella*, and *Trichomonas* were negative, and urinalysis was unremarkable. Additional medical history was notable for human papillomavirus positivity, hypertension, hyperlipidemia, and type II diabetes. Dermatologic history was notable for a suspected exaggerated response to arthropod bites (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/wwxdg9x8z6.1) with associated lichen simplex chronicus.

Physical exam revealed well-demarcated 5 cm × 3 cm ulceration with satellite lesions on the right posterior labium majus (Fig 1). Biopsy revealed a mildly acanthotic epidermis and a mixed dermal lymphocytic infiltrate with B-cell predominance

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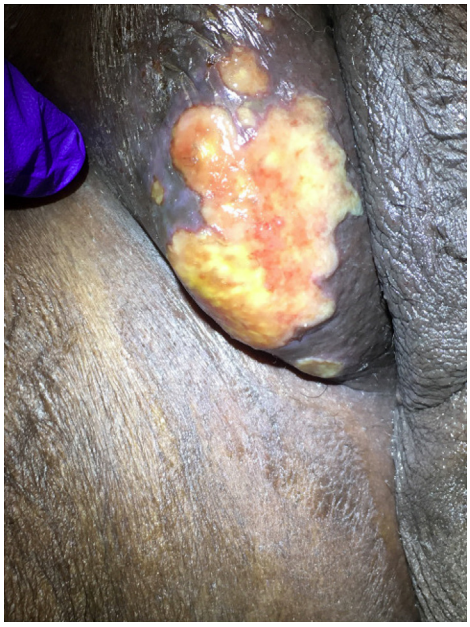

Fig 1. Well-circumscribed 5 cm × 3 cm ulceration with satellite lesions located on the right posterior labium majus.

(Fig 2, *A*). Immunohistochemical staining revealed CD20+/CD79a+ B-cells and CD3+ T-cells (Fig 2, *B*). B-cells also had strong CD5 co-expression and weak focal CD23 co-expression (Fig 2, *C*). Keratin 20, chromogranin, and synaptophysin were negative. Histologic findings were consistent with cutaneous CLL. Molecular genetics revealed BIRC3 and PIK3R1 mutations. BTK/PLC (Bruton tyrosine kinase/phospholipase) gamma mutations were negative.

Molecular testing of the peripheral blood was repeated, given concern for CLL progression. An increase in the proportion of ATM (11q22.3) deletion (97.5% from 68% at CLL diagnosis 5 years prior) and Trisomy 12 (89% from 65%) was identified. Subsequent ibrutinib resistance testing was negative. Positron emission tomography/computed tomography revealed supra- and infra-diaphragmatic lymphoma with areas of active pelvic disease, extranodal lymphoma involving the vulva and anterior abdominal wall, and diffuse nonfocal fluorodeoxyglucose avidity within the marrow. Given her disease progression on ibrutinib, she was switched to venetoclax 400 mg daily and received palliative radiation of the right labium majus (total dose 1000 cGY in 5 fractions). The patient achieved resolution of her vulvar ulceration (Fig 3) 1-2 months later and remains stable on venetoclax.

Her course was complicated by poor wound healing and drainage of an abdominal incision from an ileal resection the year prior. She had a focal draining ulcer with granulation tissue (Fig 4). Biopsy revealed scarring with a small, round, and low-grade B-cell infiltrate (CD79a+, Pax5+) and CD3+/CD5+ lymphocytic infiltrate at the dermo-epidermal junction, and throughout the dermis. The staining pattern was inconsistent with the cellular staining pattern on her vulvar biopsy. A follow-up 3 years after the initial presentation for her labial lesion revealed that the abdominal ulceration had still not fully healed.

In summary, this is a rare clinical presentation of LC manifesting as vaginal ulceration 5 years after CLL diagnosis, which was ultimately responsive to systemic chemotherapeutic and local radiation therapy.

DISCUSSION

LC is a rare manifestation of B-lymphocyte CLL, especially when initially presenting on the external genitalia.[3] The mechanism for LC is not clear. It is suspected integrin and chemokine receptor expression direct leukemic cells to the skin in a process called 'skin selective homing.'[2]

We believe this is the fourth report of vulvar LC associated with CLL (Table I). Of these reports, all presented with a vulvar ulceration in the setting of B-cell CLL. The most common cytometric aspects reported included CD20+/CD5+/CD23+. All reported clinical improvement, despite different treatment regimens, likely pointing to the treatable nature of this condition. The incidence of vulvar LC is likely higher than it appears, as relevant symptoms may be underreported or may fail to come to clinician attention due to resolution with chemotherapy. Finally, clinicians may be unaware of LC potentially involving the external genitalia.

Two notable parts of this case remain unexplained. The first is the occurrence of clonal evolution versus the co-occurrence of a distinct B-cell proliferative neoplasm,[7] as revealed by the different immunophenotypic features present in this patient's known CLL and the infiltrate in the abdominal ulcer. While there are data to suggest an increased risk for additional B-cell malignancies amongst CLL patients, the distinction between the risks of clonal transformation versus formation of an unrelated B-cell neoplasm is limited.[7] Increased risk for additional B-cell malignancies may be secondary to immune dysfunction, therapy-associated genotoxicity, and/or genetic predisposition.[7] Despite reported cases of biclonal CLL,[8] initial discovery via biclonal LC remains unique. While variations in surface phenotype, as seen in this case, suggest 2 independent clonal populations, additional molecular testing is needed to distinguish true biclonal disease from clonal evolution.[8]

The second notable feature of this case is her suspected history of hypersensitivity to arthropod bites (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/wwxdg9x8z6.1). In previous

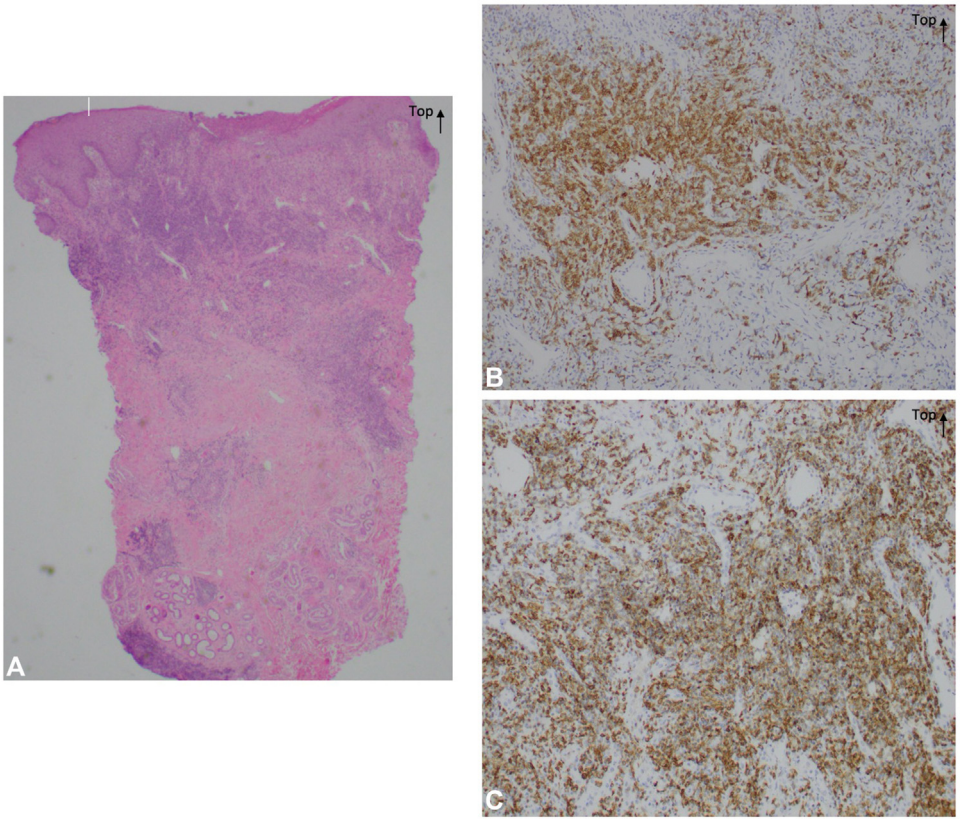

Fig 2. A, Hematoxylin and eosin stain of the right posterior labium majus revealed a dense atypical B-cell lymphocytic infiltrate consistent with her previously diagnosed chronic lymphocytic leukemia. The epidermis is mildly acanthotic. At the dermis there is a dense infiltrate of small round lymphocytes with extensive crush artifact (2×). **B,** Immunocytochemical stains show that the infiltrate is a mixture of both T and B cells (CD20, CD79a, and CD3) with a predominant B-cell population (10×). **C,** Immunocytochemical stain showing that the B-cell co-express CD5 (strong) and CD23 (weak and focal), consistent with chronic lymphocytic leukemia (10×).

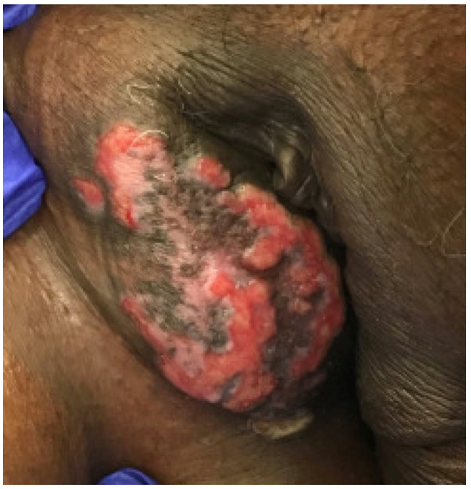

Fig 3. Resolving, well-circumscribed, and ulcerative right vulvar lesion with visible *pink* granulation tissue after receiving chemotherapy and palliative radiation.

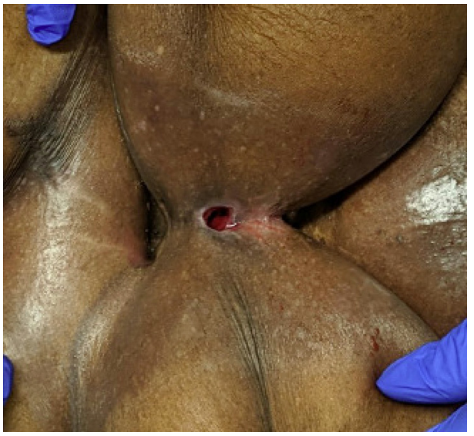

Fig 4. Draining ulcer with *pink* granulation tissue on the anterior abdomen at the site of a previous surgical incision.

literature, CLL patients have been reported to have an "exaggerated response to insect bites" or "arthropod bite-like lesions" that are histologically similar.[9] More recently, it is suspected insect bites do not precipitate these lesions, and such clinical and histologic findings are now referred to as eosinophilic dermatosis of hematologic malignancy.[9] Although pathogenesis and prognostic implications remain unclear,[10] it is

Table I. Reported cases of vulvar leukemia cutis associated with chronic lymphocytic leukemia[4-6]

No.	Reference	Age and Gender	Systemic disease staging	Clinical presentation	Histology	Molecular pathology	Therapy and response
1	Mikhail et al[4]	74	In remission	Postmenopausal bleeding with ulcerated clitoris and atrophic vagina	Cervical biopsy: immature lymphocytes, lymphocytes with plasmacytoid features, and mature plasma cells. Clitoral biopsy: focal dense collections of monomorphic small lymphocytes	N/A	Responded to vincristine, Adriamycin, VP-16, and bleomycin, subsequently lost to follow-up
2	Udupa et al[5]	55	N/A	Swelling and ulcerative lesion of the vulva present for 8 months	Sheets of mature appearing lymphocytes	CD5+ CD20+ CD23+ LCA+ CD79α+ CD43+	Two cycles of bendamustine, responded well to treatment with reduced vulvar swelling
3	Lim et al[6]	82	Rai stage IV/Binet C	Nontender, firm left labial lump	Small lymphoid infiltrate in a diffuse pattern	CD5+ CD20+ CD23+	Six cycles of obinutuzumab and chlorambucil chemotherapy with complete resolution of the labial lesion.
4	This case	67	Rai stage I	Labial ulceration with yellow malodorous drainage	Mildly acanthotic epidermis and a mixed dermal lymphocytic infiltrate with B-cell predominance	CD20+ CD79a+ CD3+ CD5+ CD25+	Progressed on ibrutinib and switched to venetoclax with targeted radiation therapy, with notable improvement

N/A, Not applicable.

possible this patient's findings were the first indication of her leukemic progression.

Clinicians must pay special attention to cutaneous lesions and vulvovaginal symptoms in patients with hematological malignancy and should have a low threshold to biopsy atypical vulvovaginal ulcerations. From the sparse cases available in the literature, it appears that vulvar involvement of LC associated with CLL can resolve with appropriate chemotherapy for the systemic disease and regional radiation therapy.

Conflicts of interest

None disclosed.

REFERENCES

1. Ratnam K, Khor C, Su W. Leukemia cutis. *Dermatol Clin*. 1994;12(2):419-431.
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(1):27-36. https://doi.org/10.1111/j.1610-0387.2011.07842.x
3. Martínez-Leboráns L, Victoria-Martínez AM, Torregrosa-Calatayud JL, Alegre de Miquel V. Leukemia cutis: a report of 17 cases and a review of the literature. *Actas Dermosifiliogr*. 2016;107(9):e65-e69. https://doi.org/10.1016/j.adengl.2016.08.014
4. Mikhail MS, Runowicz CD, Kadish AS, Romney SL. Colposcopic and cytologic detection of chronic lymphocytic leukemia. *Gynecol Oncol*. 1989;34(1):106-108. https://doi.org/10.1016/0090-8258(89)90118-2
5. Udupa K, Ganesan P, Majhi U, Sagar TG. Unusual involvement of cervix and vulva in a case of chronic lymphocytic leukemia. *J Gynecol Oncol*. 2012;23(3):205-206. https://doi.org/10.3802/jgo.2012.23.3.205
6. Lim HW, Collins SAB, Resneck JS, et al. The burden of skin disease in the United States. *J Am Acad Dermatol*. 2017;76(5):958-972.e2. https://doi.org/10.1016/j.jaad.2016.12.043
7. Parikh SA, Meacham PJ, Zent CS, Evans AG. Multiple B cell malignancies in patients with chronic lymphocytic leukemia: epidemiology, pathology, and clinical implications. *Leuk Lymphoma*. 2020;61(5):1037-1051. https://doi.org/10.1080/10428194.2019.1709830
8. González-Campos J, Ríos-Herranz E, Blas-Orlando JMD, Martín-Noya A, Parody-Ruiz-Berdejo R, Rodríguez-Fernández JM. Chronic lymphocytic leukemia with two cellular populations: a biphenotypic or biclonal disease. *Ann Hematol*. 1997;74(5):243-246. https://doi.org/10.1007/s002770050292
9. Heymann WR. Eosinophilic dermatosis of hematologic malignancy: reality bites. *J Am Acad Dermatol*. 2019;81(1):74-75. https://doi.org/10.1016/jjaad.2019.04.059
10. Lucas-Truyols S, Rodrigo-Nicolás B, Lloret-Ruiz C, Quecedo-Estébanez E. Eosinophilic dermatosis of hematologic malignancy. *Actas Dermosifiliogr*. 2017;108(6):e39-e44. https://doi.org/10.1016/j.ad.2016.10.021