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Journal

Dermatology Online Journal, 23(3)

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Publication Date

2017

DOI

10.5070/D3233034287

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Precursor-B-cell-ALL leukemia cutis resembling lipomas: an atypical presentation of a rare entity and a review of the literature

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Abstract:

Leukemia cutis (LC) is an extramedullary manifestation of leukemia owing to cutaneous infiltration of neoplastic cells resulting in characteristic firm, erythematous nodules. Most cases of LC occur in patients with acute myelogenous leukemia and chronic myelogenous leukemia. However in rare cases, LC has presented in patients with acute lymphoblastic leukemia (ALL). In these rare ALL-associated cases, only 10 cases of precursor-B-ALL (pre-B-ALL) have been described in the literature. We report a case of a 22-year-old man with relapsing pre-B-ALL who presented with a 4-day history of multiple asymptomatic, soft, dome-shaped, lipoma-like mounds on his scalp and chin, which exhibited cutaneous involvement by leukemic cells. To date, this is the first case of pre-B-ALL associated leukemia cutis presenting as soft, dome-shaped mounds resembling lipomas.

Keywords: leukemia cutis, precursor B-ALL, leukemia

Introduction

Leukemia cutis (LC) is an extramedullary manifestation of leukemia, defined as cutaneous infiltration by neoplastic leukemic cells resulting in clinically recognizable skin lesions [1, 2]. Leukemia cutis is distinct from other malignancy-associated cutaneous syndromes such as Sweet syndrome, erythema nodosum, and pyoderma gangrenosum, which are thought to represent reactive or paraneoplastic processes [3]. Morphologically, LC typically presents as firm erythematous nodules [2]. However, LC may

also present as violaceous or hemorrhagic papules, vesicles, bullae, or plaques of various sizes [1]. Sites classically involve locations of prior or ongoing inflammation such as the extremities, back, trunk, and face [1].

Leukemia cutis occurs more commonly in those with acute myelogenous leukemia (AML) or chronic myelogenous leukemia (CML) and rarely occurs in patients with acute lymphoblastic leukemia (ALL) [3]. Of note, LC occurring in a patient with precursor-B-cell acute lymphoblastic leukemia (Pre-B-ALL) is even more rare. To date, only 10 cases of pre-B-ALL associated LC have been reported (**Table 1**) [1, 3, 4, 6-12]. Herein we report a case of pre-B-ALL associated LC appearing during relapse as soft, dome-shaped mounds on the face and scalp and review the literature. To our knowledge, this is the first case that has presented with soft, dome-shaped mounds, resembling lipomas.

Case Synopsis

A 22-year-old man with history of pre-B-ALL presented to the dermatology clinic with 4 days of multiple asymptomatic soft mounds on his chin and scalp (**Figure 1** and **Figure 2**). He was diagnosed with pre-B-ALL 1 year prior. Bone marrow biopsy at that time revealed aggregates of blasts comprising >90% of the marrow elements. Flow cytometry analysis of bone marrow aspirate demonstrated that the blast population was positive for CD10, CD19, cCD22, CD34, and TdT, and negative for CD20, surface immunoglobulin λ and κ , and T-cell markers CD3 and CD5. This pattern was consistent with a diagnosis of pre-B-ALL. Additional surveillance

Authors (year)	Age	Sex	Part of relapse	Sites	Morphology	Treatment/ Outcome
Yen (1996)	2w	M	-	Scalp, face, extremity, trunk	Firm, tender, subcutaneous nodules with positive Darier sign	Remission with hyper CVAD, IVIG, IT MTX, cytarabine.
Sah (2005)	32y	F	-	Scalp, face, trunk, limbs	Firm, tender, erythematous nodules and plaques	Declined therapy, lost to follow up
Lee (2009)	20y	M	+	Site of previous catheter	Firm, dome-shaped erythematous nodule	Deceased 2 month after IFN- α , steroids, MP.
Anderson (2010)	5m	F	-	Scalp	Firm, non-tender, mobile, well-circumscribed nodule.	Remission after V, Ctx, D, P, L-asp chemotherapy
Yen (1996)	2w	M	-	Scalp, face, extremity, trunk	Firm, tender, subcutaneous nodules with positive Darier sign	Remission with hyper CVAD, IVIG, IT MTX, cytarabine.
Sah (2005)	32y	F	-	Scalp, face, trunk, limbs	Firm, tender, erythematous nodules and plaques	Declined therapy, lost to follow up
Lee (2009)	20y	M	+	Site of previous catheter	Firm, dome-shaped erythematous nodule	Deceased 2 month after IFN- α , steroids, MP.
Anderson (2010)	5m	F	-	Scalp	Firm, non-tender, mobile, well-circumscribed nodule.	Remission after V, Ctx, D, P, L-asp chemotherapy
Abruzzesse (2012)	67y	M	+	Scalp	Tender plaque with central ulceration	Remission after dasatanib during relapse. Initially allo-BMT
Nabhan (2012)	73y	F	-	Arm	Erythematous papules of different sizes	Unresponsive to hyper-CVAD chemotherapy, hospice care.

Little (2013)	10y	F	-	Cheek	Firm, tender, erythematous tumor	Remission after hyper-CVAD chemotherapy
Ansell (2013)	27y	M	+	Cheek, shoulder, chest, leg	Asymptomatic, dome-shaped erythematous nodule	Nodule resolved with RT, patient died 6 months later.
Novoa (2015)	65y	F	+	Trunk diffusely	Asymptomatic, erythroderma.	Unresponsive to hyper-CVAD therapy, hospice care.
Campuzano (2015)	46y	M	-	Nose, forehead, forearm	Firm, asymptomatic, dome-shaped, erythematous purplish nodule	Nonresponsive to hyper CVAD, lost to follow up
Current case (2016)	22y	M	+	Scalp, face	Soft, asymptomatic, dome-shaped nodules.	Undergoing hyper-CVAD chemotherapy.

Table 1. Previous documented cases of Pre-B-ALL associated LC. M, male; F, female; w, weeks; m, months; y, years; C, cyclophosphamide; V, vincristine; A, dexamethasone; D, doxorubicin; IVIG, Intravenous Immunoglobulin; IT, intrathecal; MTX, methotrexate; IFN, interferon; MP, mercaptopurine P, prednisone; L-asp, L-asparaginase; allo-BMT, allogeneic bone marrow transplant; RT, radiation therapy.

revealed CSF involvement by neoplastic cells with an immunophenotypic profile identical to the blast population of the bone marrow. CT scan revealed bilateral lymph node involvement superior and inferior to the diaphragm. The patient achieved minimal residual disease after therapy with hyper-CVAD protocol, which involves a course of cyclophosphamide, vincristine, doxorubicin, and dexamethasone followed by intrathecal methotrexate and cytarabine. However, he experienced multiple bone marrow and CSF relapses leading to 6 additional courses of hyper-CVAD over the span of a year. During his outpatient appointment with the oncology department a week prior to his eighth hyper-CVAD course, he was found to have new skin lesions and was referred to the dermatology clinic.

Physical examination revealed 5 skin-colored, 1 - 2 cm soft, dome-shaped mounds on his scalp and right chin without surface change or erythema. These mounds were non-tender. The oral cavity and remainder of his skin exam were unremarkable without lymphadenopathy or hepatosplenomegaly.

He endorsed on-going fatigue and weight loss from his disease and chemotherapy, but denied acute systemic symptoms.

A biopsy of the right chin lesions displayed diffuse dermal infiltrates by large immature cells (**Figure 3**). The infiltrate extended into the deep dermis, surrounding adnexal structures, and infiltrating the skeletal muscle (**Figure 4, Figure 5, Figure 6**). Mitotic figures and apoptotic bodies were identified in the background. Immunohistochemical stain for PAX-5, a B cell-lineage specific activator protein and a member of the paired box (PAX) family transcription factors, was diffusely and strongly positive in the nuclei of the neoplastic cells and suggests a B-cell origin (**Figure 7**). In addition, an immunohistochemical stain of terminal deoxynucleotidyl transferase (TdT), a specific nuclear DNA polymerase expressed in immature T or B cells, demonstrated diffuse and strong nuclear positivity in the neoplastic cells (**Figure 8**). These findings altogether supported the diagnosis of pre-B-ALL (Figures 3-8). Laboratory findings drawn at presentation included hemoglobin 8.9 g/dl; WBC



Figure 1: Soft, dome-shaped mound on right chin



Figure 2. Two soft, dome-shaped mounds on right scalp

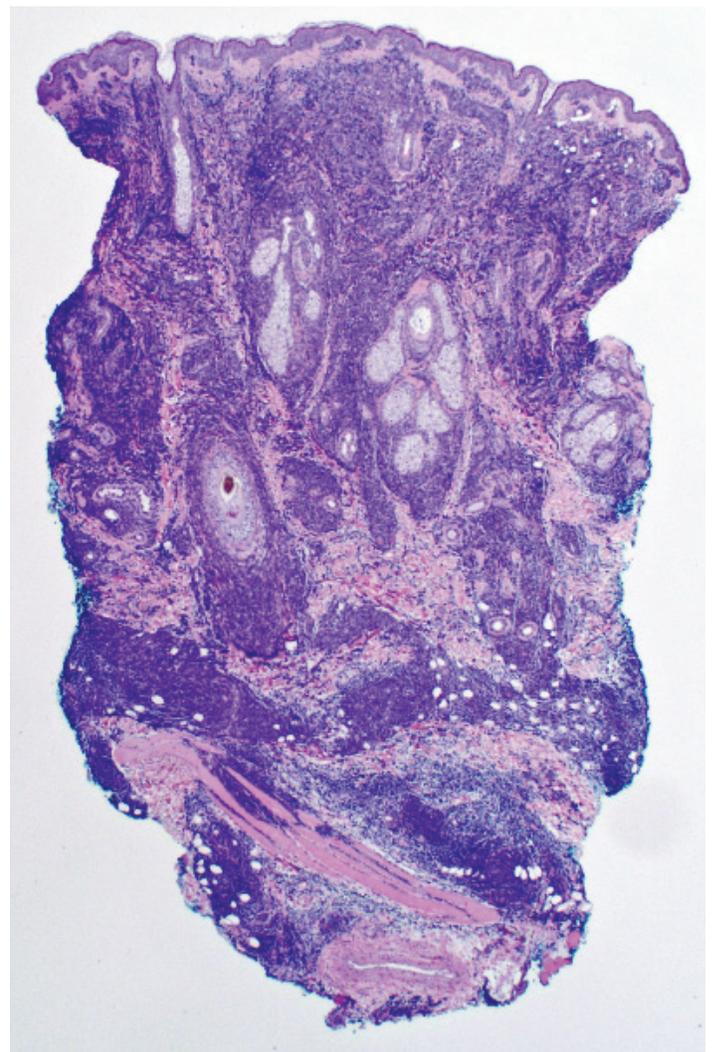


Figure 3. Section shows skin with a dermal proliferation of large immature cells spanning the entire thickness of the tissue sample, surrounding adnexal structures and infiltrating the skeletal muscle (hematoxylin and eosin stain; original magnification x20)

1.6 x 10³/μL with 85% polymorphonuclear cells; 11% lymphocytes, 4% monocytes, 0% eosinophils, 0% basophils, and platelet count of 18 x 10³/μL. A follow-up peripheral blood smear one week later revealed 6% blasts. Bone marrow aspirate showed 5% blasts and was non-diagnostic. However, lumbar puncture revealed blasts with histomorphological and immunophenotypic features consistent with residual or recurrent pre-B-ALL. The patient was admitted and is now undergoing his eighth course of hyper-CVAD therapy.

Case Discussion

Pre-B-ALL is a rare variant of leukemia, accounting for approximately 2% of all acute leukemia. It occurs more frequently in childhood, but can also occur in adults with a median onset age of 40 years. Up to half

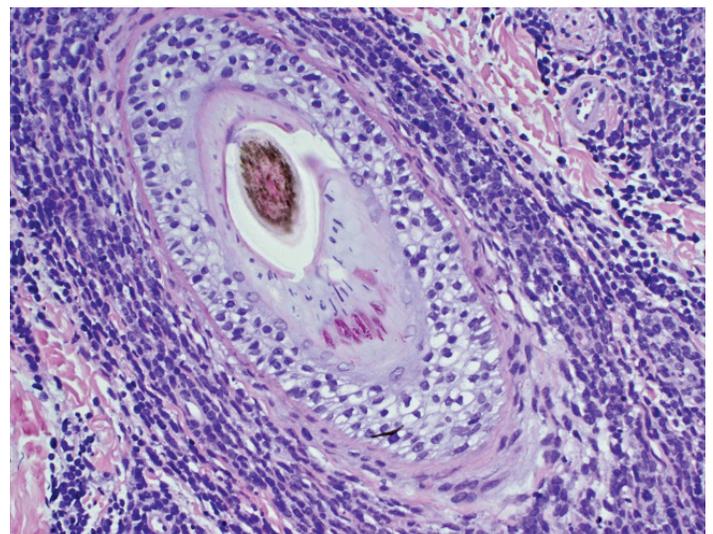


Figure 4. Section shows a hair follicle, blood vessel and nerve bundle surrounded by large immature cells, apoptotic debris and scattered lymphocytes (hematoxylin and eosin stain; original magnification x200)

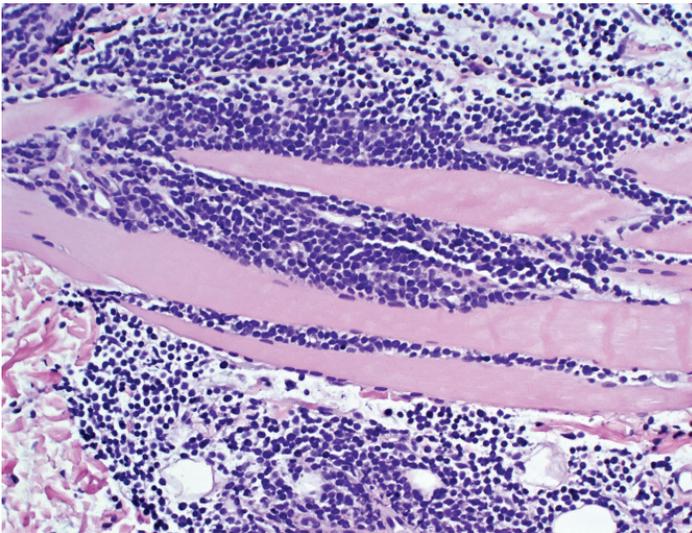


Figure 5. Section shows large immature cells infiltrating skeletal muscle bundles (hematoxylin and eosin stain; original magnification x200)

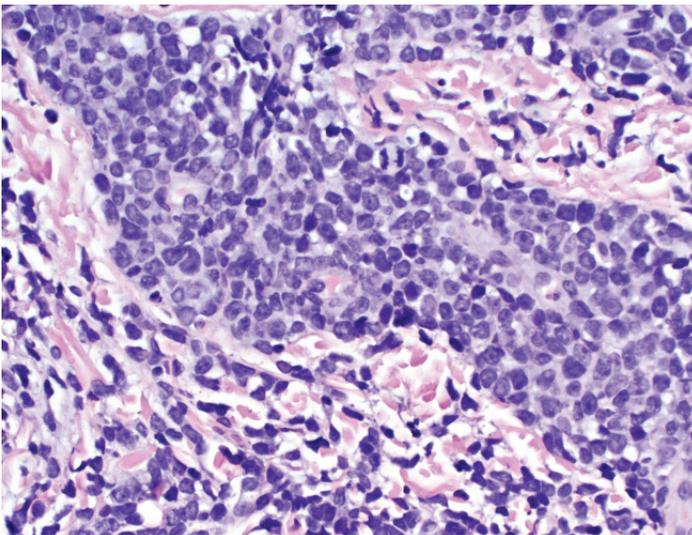


Figure 6. Section shows a dermal infiltrate of immature cells with high nuclear to cytoplasmic ratio, irregular nuclear contours, fine to vesicular chromatin and one or more small nucleoli. Mitotic figures and apoptotic bodies are identified in the background (hematoxylin and eosin stain; original magnification x400)

of cases present with hepatomegaly, splenomegaly, or lymphadenopathy [1]. In this variant, the central nervous system is the most common extramedullary site involved [1]. Pre-B-ALL is usually more aggressive compared to mature B-ALL, with a median survival rate of 14 months after diagnosis [1].

Leukemia cutis occurs more commonly in those with AML or CML and is seen in 10-15% of AML and 4-20% of CML patients. Leukemia cutis rarely occurs in patients with ALL, affecting only 1-3% of these patients [3]. The incidence of LC in adult T-cell versus B-cell ALL has yet to be fully elucidated. However, a

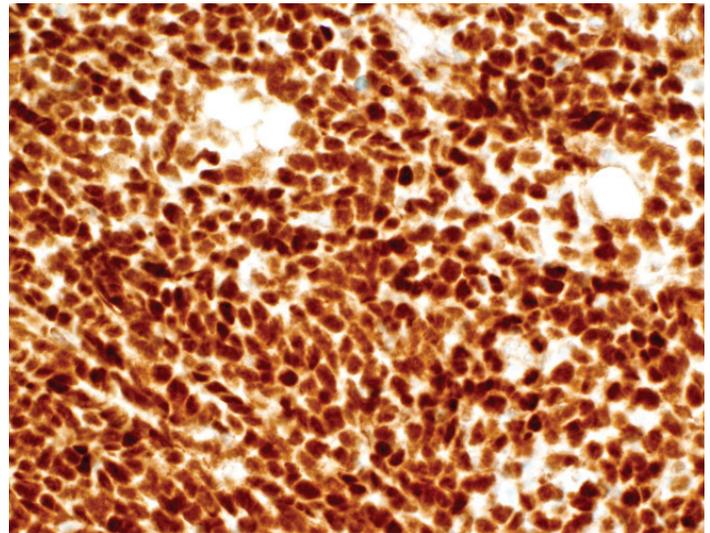


Figure 7. PAX5 immunohistochemical stain. Section shows strong and diffuse nuclear staining of the neoplastic cells (Original magnification x400)

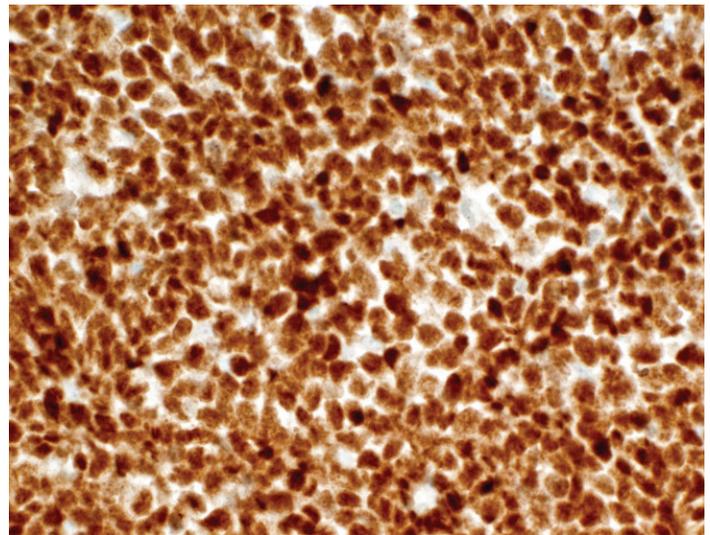


Figure 8. TdT immunohistochemical stain. Section shows strong and diffuse nuclear staining of the neoplastic cells (Original magnification x400)

review of literature by Nabhan et al. revealed that most of the published cases are of T-cell lineage. [4] Most cases of LC occur in the setting of established systemic leukemia, but in rare occasions LC may precede observable peripheral blood or bone marrow involvement. This condition is known as aleukemic leukemia cutis (ALC) [2, 3].

Leukemia cutis of pre-B-ALL is believed to be an under-reported entity, with only 10 previously described cases in literature (**Table 1**). Of the total 11 cases including the presenting one, 6 (54.5%) occurred in female patients and 8 (72.7%) occurred in adults. Five cases (45%) occurred during disease

relapse as opposed to initial leukemia presentation. Six cases (54.5%) described firm lesions whereas four cases (36.4%) did not comment on whether the lesions were firm or soft. To our knowledge, the current case is the only one that described a soft, as opposed to firm, lesion. Thus, it is crucial to include extramedullary leukemia in the differential for a soft, skin-colored mound in order to establish early diagnosis and treatment.

Leukemia cutis in adults typically predicts accelerated disease with worse prognosis [1]. In a study by Su et al., 37 of 42 (88%) patients with LC of any underlying leukemia variant died within 1 year [5]. The treatment involves conventional anti-leukemic chemotherapy, sometimes followed by allogeneic hematopoietic stem cell transplant (HCT) [2]. Small, local lesions may be treated with surgical removal or local radiotherapy [6]. Of the 10 previously reported pre-B-ALL LC cases, 4 (40%) were unresponsive to chemotherapy and passed within 6 months; however, 4 (40%) achieved remission. The remaining 2 (20%) were lost to follow up.

Conclusion

Leukemia cutis is an extramedullary condition most commonly associated with AML and CML. The presence of LC often portends a poor prognosis. It typically presents as asymptomatic firm erythematous nodules. Leukemia cutis rarely occurs in patients with ALL and is even rarer in patients with pre-B-ALL. Previously, LC in patients with pre-B-ALL has been reported only in cases. We report the first case of pre-B-ALL associated LC presenting as soft, lipoma-like mounds. Given its prognostic implications, LC should be considered in the differential diagnosis of rapidly growing soft mounds. Suspicion and early biopsy by a dermatologist and subsequent collaboration with hematologists and oncologists are crucial for timely management.

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