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Subcutaneous Nodules Revealing Acute Lymphoblastic Leukemia in an Infant: A Case Report and Literature Review

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ABSTRACT

Background: Cutaneous involvement at the onset of acute lymphoblastic leukemia (ALL) is uncommon in children and may delay diagnosis, as such lesions are frequently mistaken for benign or infectious processes. Leukemia cutis is particularly rare in pediatric B-ALL, and reports describing subcutaneous nodules as the initial presentation remain limited. Case Presentation: We report the case of a 12-month-old girl who presented with a four-month history of progressively appearing, firm, painless subcutaneous nodules involving the scalp, trunk, and face. Initial laboratory tests revealed bicytopenia without circulating blasts. Biopsy of one nodule showed an undifferentiated small round cell proliferation with immunohistochemical expression of CD45, CD79a, Pax5, CD99, focal CD10, and a high Ki-67 index, consistent with cutaneous infiltration by lymphoblasts. Bone marrow aspiration demonstrated 95% blasts, confirming pro-B acute lymphoblastic leukemia. Cytogenetic analysis identified a pseudodiploid clone with a t(X;10)(p10;p10) translocation. Imaging studies showed diffuse subcutaneous nodular lesions. The patient was treated according to the Marall 2005 high-risk protocol, with rapid regression of the nodules by day 30 of induction and achievement of complete clinical and hematologic remission. Conclusion: This case highlights that persistent, painless subcutaneous nodules in infants may represent an early manifestation of ALL, even when classical hematologic abnormalities are subtle or absent. Early skin biopsy plays a crucial role in accelerating diagnosis and preventing therapeutic delay. Recognizing leukemia cutis as a possible presenting feature of pediatric B-ALL is essential, as timely systemic therapy generally leads to excellent clinical response.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant hematologic disorder in children. Its typical presentation includes signs of bone marrow failure—such as anemia, thrombocytopenia, and neutropenia—along with bone marrow infiltration by leukemic blasts and, in some cases, extramedullary involvement of the liver, spleen, or lymph nodes. Cutaneous manifestations at disease onset, including subcutaneous nodules or masses, are uncommon in ALL and are more frequently described in acute myeloid leukemia. Nevertheless, several reports have shown that the skin may occasionally represent the initial site of leukemic infiltration, making early diagnosis particularly challenging. We report the case of a 12-month-old infant with pro-B ALL whose initial presentation consisted of atypical subcutaneous lesions. We also discuss this presentation in light of current literature.

Case Report

A 12-month-old girl, previously hospitalized at 7 months for septic shock secondary to pneumonia, presented with a four-month history of progressively appearing, firm, painless subcutaneous nodules. The lesions were located on the scalp, trunk, and face, measuring between 0.5 and 4 cm, and showed no overlying inflammatory changes (Figure 1). Physical examination revealed marked pallor without fever or bleeding manifestations.

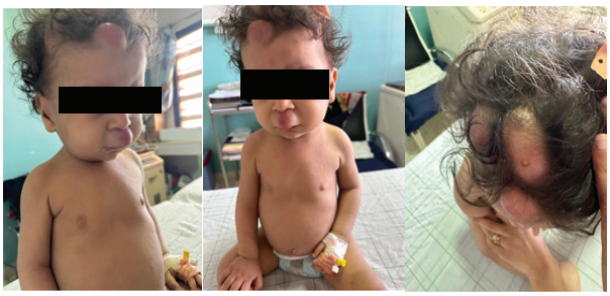

Figure 1: Subcutaneous nodules in a 12-month-old infant.

Initial differential diagnoses included deep infectious lesions, histiocytosis, and rare cutaneous tumors.

Laboratory evaluation revealed bicytopenia:

- Hemoglobin: 4.6 g/dL
- MCV: 79.7 fL; MCHC: 32
- White blood cells: 5,280/mm^3 (ANC 180/mm^3; lymphocytes 4,860/mm^3)

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- Platelets: 171,000/mm^3
- No blasts were detected on the peripheral blood smear.

A biopsy of one of the subcutaneous nodules revealed an undifferentiated small round cell proliferation. Immunohistochemistry demonstrated diffuse expression of CD45 (LCA), CD79a, Pax5, and CD99; focal expression of CD10; and a high Ki-67 index (~100%). These findings were consistent with cutaneous involvement by a B-lymphoblastic lymphoma or B-cell acute lymphoblastic leukemia.

Bone marrow aspiration revealed **95% blasts**, confirming the diagnosis of ALL. Immunophenotyping identified a **pro-B lymphoblastic lineage**.

Cytogenetic analysis demonstrated a pseudodiploid clone with a structural abnormality: a reciprocal translocation **t(X;10)(p10;p10)** observed in 15 metaphases. Cerebrospinal fluid examination was unremarkable.

A thoraco-abdominal-pelvic CT scan showed diffuse subcutaneous nodular formations.

The patient was treated according to the **Marall 2005 high-risk protocol**. The subcutaneous nodules regressed rapidly by day 30 of induction therapy. She achieved complete clinical and hematologic remission, with post-induction bone marrow blasts <5%, and is currently undergoing re-induction (Re-induction 5) per the high-risk protocol.

Discussion

Cutaneous or subcutaneous involvement as an initial manifestation of ALL is rare in the pediatric population. ALL typically presents with bone marrow failure, lymphadenopathy, or organomegaly. A presentation dominated by painless subcutaneous nodules may therefore contribute to diagnostic delay, as illustrated by this case.

Early data from Millot et al. (1997), in a cohort of 26 children with ALL or lymphoblastic lymphoma, reported cutaneous manifestations in fewer than 3% of cases, with highly variable clinical presentations ranging from papules to deep, non-inflammatory nodules [1]. This rarity explains why such lesions are frequently mistaken for benign dermatologic or infectious processes.

Several reports highlight that skin lesions may constitute the first clinical sign of ALL. Jiang et al. described a case of B-ALL presenting with firm, painless nodules on the trunk and limbs prior to any significant hematologic abnormalities [2]. The clinical characteristics reported—multiple, painless, subacute nodules—closely resemble the presentation in our patient.

Similarly, Cerqueira et al. (Cureus, 2024) reported a child whose infiltrated cutaneous lesions led to the diagnosis of ALL, emphasizing the importance of early skin biopsy when leukemia cutis is suspected [3]. In our case, early biopsy significantly accelerated diagnosis.

Aleukemic presentations have also been described, in which cutaneous lesions precede detectable bone marrow or peripheral blood involvement. Atay et al. reported an infant with leukemia cutis despite normal initial marrow findings and absence of circulating blasts, illustrating the capacity of lymphoblasts to infiltrate the skin at a very early stage [4]. Although our patient had bicytopenia at presentation, the dissociation between cutaneous and marrow involvement is essential to recognize, as it directly impacts diagnostic timing.

A broader review by Godínez-Chaparro et al. (2021) estimated that dermatologic manifestations occur in approximately 10% of pediatric leukemia cases, while true leukemia cutis—histologically confirmed leukemic infiltration—remains much less common and is often associated with aggressive disease. However, data are limited, and no specific prognostic factor has been clearly established for pediatric B-ALL [5].

In the present case, the subcutaneous nodules occurred in the context of high-risk ALL due to the pro-B phenotype and the patient's age. Notably, the patient exhibited rapid clinical improvement during induction, with complete regression of the nodules—consistent with most reported cases of leukemia cutis associated with pre-B ALL. The literature suggests that, unlike acute myeloid leukemia, where cutaneous involvement may indicate poorer prognosis, leukemia cutis in pediatric ALL does not appear to significantly alter overall prognosis, and response to systemic therapy is typically excellent.

Conclusion

Cutaneous presentation of ALL, although rare, should be recognized as a potential early manifestation. Persistent, firm, painless subcutaneous nodules in infants should prompt consideration of malignant hematologic disorders, even in the absence of overt hematologic abnormalities. Skin biopsy, blood cytology and immunophenotyping, and bone marrow examination remain essential to avoid delays in diagnosis and treatment initiation.

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