Infant acute lymphoblastic leukemia (MLL-AF) presenting as leukemia cutis with an isolated scalp nodule – A case report.

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Research Article

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Abstract

Background

Infant leukemia is a rare form of acute leukemia diagnosed prior to 1 year of age with an extremely poor prognosis, due to its poor response to current therapies. It comprises about 4% of childhood acute lymphoblastic leukemia (ALL). Isolated initial cutaneous involvement in ALL is very uncommon, and even more in infant ALL.

Case Presentation

Here we present a case of 2-month-old infant, presenting only nodular skin infiltrates on the scalp with the diagnosis of infant acute lymphoblastic leukemia (ALL), characterized by the immunophenotype of the most immature B-cell precursors (pro-B ALL) and chromosomal translocation t (9;11), associated with the rearrangement of KMTLA2 and AF9 genes, that is a negative prognostic factor. She underwent hematopoietic stem cell transplantation (HSCT) and she is still in remission.

Conclusions

This represents a peculiar case because isolated initial cutaneous involvement in ALL is rare. In fact, most reports of ALL leukemia cutis in literature are single cases. The novel treatment strategies, obtained from recent discoveries regarding the peculiar biology of these leukemias, are increasingly being incorporated into clinical trials and have the potential to improve the prognosis.

Background

Infant leukemia refers to acute leukemia diagnosed prior to 1 year of age and it is a rare aggressive type of leukemia, that comprises about 4% of childhood acute lymphoblastic leukemia (ALL). There is a slight predominance of lymphoid over myeloid cases within infant leukemia, and of the lymphoid cases, nearly all are B-lineage, with < 5% T-lineage [1]. Infant ALL is more often associated with very immature B-cell phenotype (pro-B ALL) without CD10 expression [2]. Compared with older children, infants with acute leukemia tend to present with more aggressive features, including high white blood cells (WBC) counts, hepatosplenomegaly, central nervous system (CNS) involvement, and skin infiltration, defined as leukemia cutis [3]. We present a case of 2-month-old infant, presenting only with nodular skin infiltrates on the scalp, in which we established the diagnosis of infant ALL, characterized by the immunophenotype of the most immature B-cell precursors (pro-B ALL) and chromosomal translocation t (9;11), associated with the rearrangement of KMTLA2 and AF9 genes. This represents a peculiar case because isolated initial cutaneous involvement in ALL is very uncommon, and even more in infant ALL. Moreover, the chromosomal translocation t (9;11) is mainly associated with acute myeloid leukemias and only in a small percentage of ALL. [4]
Case Presentation

A 2-month-old asymptomatic female infant visited our dermatological department, complaining of a steadily growing nodule located on the left mid-parietal scalp (Fig. 1). It appeared as a mobile, well-circumscribed, smooth, swelling, alopecic area, that measured approximately 3x3 cm. No dysmorphic features or other remarkable findings were observed. On suspecting malignancies, dermatologists performed a punch skin biopsy from the scalp nodule. Meanwhile, laboratory examination showed a white blood cell count of 21940/µL, haemoglobin 7.6 g/dL, platelets 38300/µL, and 45% circulating blasts. A bone marrow aspiration revealed 55% blast cells and the immunophenotype confirmed pro-B-cell ALL. The results of the biopsy showed monomorphic lymphoblasts diffusely infiltrating the dermis and subcutis, compatible with LC and cytogenetics detected the presence of KMT2A-rearrangement, with chromosomal translocation t(9;11) (p21;q23). The cerebrospinal uid analysis did not reveal leukemic infiltration of the central nervous system. The patient was subsequently treated according to protocol AIEOP BFM ALL 2017, HR pB-ALL and, after remission, she finally received allogeneic hematopoietic stem cell transplantation (HSCT) with an HLA identical matching donor hematopoietic stem cell transplantation. She is now 14-months old, and she is still in remission 6 months post-HSCT.

Discussion And Conclusions

Leukemia cutis (LC) describes the localized or disseminated infiltration of the epidermis and/or dermis by leukemic cells. [5] Recent molecular analyses suggest the involvement of various chemokines, influencing cell-cell interaction and adhesion molecules to mediate the migration of leukemic cells via skin-selective homing processes. [6]

We reported this unusual case because LC is usually seen in acute myeloid leukaemia (AML), while there are few reported cases of cutaneous involvement in children with ALL, and even fewer in infant ALL [1], which refers to an aggressive type of acute leukaemia diagnosed prior to 1 year of age. [7] The frequency of leukemia cutis is 10–15% in AML and only about 1% in ALL [6]. Bone marrow infiltration and peripheral blood involvement generally develop prior to the appearance of cutaneous lesions but, rarely, LC may be the primary manifestation of leukaemia, preceding the systemic symptoms by months. [5].

Bontoux reported that in 31% of children in their cohort of 38 patients affected by ALL with LC, skin lesions appeared before the ALL diagnosis, suggesting that cutaneous manifestations may help to anticipate the diagnosis. [8]

That case series also confirmed that, although LC lesions of may have highly variable clinical presentation, the most common manifestations are erythematous or violaceous nodules, involving the head, principally. This unusual scalp location has been already reported by Millot in the largest series of children with ALL presenting with cutaneous involvement. [9] Therefore, not only multiple nodules but also solitary scalp masses in paediatric patients should be treated as suspicious for malignancy and a skin biopsy should be performed to optimize differential diagnosis. [10] (Table 1)
However, the lesions associated with leukemia cutis may have highly variable clinical presentation. Other primary lesions described include macules, ulcers, and wheals, in addition to nonspecific skin involvement resulting from bone marrow failure, such as petechiae, purpura and ecchymoses.

Generally, the clinical manifestation of skin lesions in not correlated to a particular type of leukaemia, except for gingival hypertrophy, mostly associated with AML and chloroma, which presents as a firm nodule with a greenish colour, that is a peculiarity of acute myelogenous leukaemia [11].

Another peculiarity of our case is the detection of the translocation t(9;11)(p22;q23 involving histone lysine methyltransferase 2A gene (KMT2A), formerly known as mixed lineage leukemia (MLL), mainly associated with AML and extremely rare in ALL.

A high proportion of infant leukemias are characterized cytogenetically by balanced chromosomal translocations involving KMT2A/MLL gene at chromosome 11q23. To better understand the pathogenetic role of MLL in malignant hematopoiesis, Hess et al. generated an MLL knock-out mouse and found defective yolk sac hematopoiesis in MLL-null mice and a block in hematopoietic differentiation in MLL-null embryonic stem cells have been observed. These observations support the pivotal role of KMT2A/MLL gene in the regulation of hematopoietic differentiation and in leukemogenesis as well [12]. Also, KMT2A/MLL gene rearrangements can be detected in blood samples at birth in most infant leukemia patients, suggesting a prenatal origin of leukemic cells in infant leukemia. [13, 14] The different chromosomal rearrangements involving KMT2A/MLL gene are associated with a specific leukemia type. For example, the translocation t(4;11) (q21;q23), which generates the –AF4 fusion, is found predominantly in acute lymphoblastic leukemias [15], suggesting that the AF4 segment has a role in controlling of the lineage. On the other hand, the translocation t(9;11) (p22;q23) is mainly associated with acute myeloid leukemias and fuses AF9 to MLL, suggesting a role for AF9 in myeloid disease. [16, 17] Chen et al, showed a direct relationship between cell-specific transformation susceptibility and oncogene dosage effects in progenitor cells. The expression of the fusion gene MLL-AF9 in common lymphoid progenitors (CLP) rather than in GMP results in a more aggressive disease associated with distinct origin-related gene-expression profiles [19]. Thus, this translocation, without any other cytogenetic anomalies, is not a significant risk factor in infant AML, while it is clearly associated with poorer outcome in infant ALL, such as higher WBC at diagnosis and skin involvement. [18] Although our patient presented several of these risk factors (cutaneous involvement and chromosomal translocation), she had a good outcome and she remained in complete remission at 12 months from the start of chemotherapy. This case demonstrated that early recognition of suspicious sign of leukaemia may allow us to achieve early diagnosis and start therapies earlier, thus improving prognoses in children. We also highlight the important of novel treatment strategies, obtained from recent discoveries regarding the peculiar biology of leukemias, which reduce both relapse rates and treatment-related toxicities.

List Of Abbreviations
Acute lymphoblastic leukemia (ALL)
Hematopoietic stem cell transplantation (HSCT)
High white blood cells (WBC)
Central nervous system (CNS)
Leukaemia cutis (LC)
Acute myeloid leukaemia (AML)
Mixed lineage leukemia (MLL)
Common lymphoid progenitors (CLP)
Histone lysine methyltransferase 2A gene (KMT2A)

**Declarations**

**Ethics approval and consent to participate**

All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics approval was obtained by Hospital Scientific Direction. Written informed consent was obtained from a parent and/or legal guardian.

**Consent for publication**

Written informed consent was obtained from a parent and/or legal guardian for publication of this case report and accompanying images.

**Data availability statement**

Data available on request due to privacy/ethical restrictions.

**Competing interests**

The authors declare that they have no competing interests.

**Funding sources**

The authors disclosed no financial association or funding source.

**Authors’ contributions**

Study conception and design: FP, FF, EB, PC, MS, NB; collection and interpretation of data: FP, FF, EB, PC, MS, NB; statistical analysis: N/A; manuscript drafting: FP; manuscript editing: FP, FF, EB, PC, MS, NB;
approval to submit: All authors read and approved the final manuscript.

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The patient's guardians in this manuscript have given written informed consent to the publication of their case details.

References


Table 1
“Differential diagnosis of Scalp Nodules in Infancy”

<table>
<thead>
<tr>
<th>Nodule</th>
<th>Clinical characteristics</th>
</tr>
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<tbody>
<tr>
<td>Congenital Hemangioma</td>
<td>Vascular lesions that are fully formed at birth and remains stable. Usually round or oval, raised, and warm to the touch, with parenchymatous consistency. They are dark pink to blue or purple in color.</td>
</tr>
<tr>
<td>Deep Infantile Hemangioma</td>
<td>Vascular lesions that appear in the first weeks of life. They manifest as partially compressible, subcutaneous, bluish vascular swellings. They have a rapid proliferative phase in infancy which is followed by a gradual involutional phase over the next several years of life. Doppler ultrasound study usually shows high vascular flow.</td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>A growth of normal tissue enclosed in a pocket of cells called a sac. It appears as compressible, subcutaneous nodule, with variable mobility, commonly on superolateral orbit rim.</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>It is the mildest form of Langerhans cell histiocytosis. The lesions are typically raised, clearly defined, and yellowish-pink in color. Pain and swelling in the region of involved bone is the most common presenting symptom</td>
</tr>
<tr>
<td>Juvenile Xanthogranuloma</td>
<td>It is a non-Langerhans cell histiocytosis that is usually benign and self-limiting. The lesions present as smooth, round, firm papules that change from red-brown to yellow.</td>
</tr>
<tr>
<td>Leukemia cutis</td>
<td>Pink/red to tan nodules or plaques (with petechiae or purpura associated, according to bone marrow involvement)</td>
</tr>
<tr>
<td>Nevus psiloliparus</td>
<td>A rare fatty tissue nevus often described as a smoothly surfaced, irregularly shaped, circumscribed hairless lesion involving the scalp.</td>
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Figures
Figure 1

“Patient at 2 months of age with primary isolated scalp nodule”.

Supplementary Files

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