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Single Case

Pediatric Aleukemic Leukemia Cutis with Testicular Involvement: A Case Report

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Keywords
Leukemia cutis · Testicle · Childhood · Aleukemic leukemia cutis

Abstract
Introduction: Aleukemic leukemia cutis (ALC) is a rare condition and concerns less than 10% of leukemia cutis (LC) cases. LC is defined as a cutaneous infiltration of neoplastic myeloid or lymphoid blasts, which occurs in the absence of any prior bone marrow or peripheral blood involvement. ***Case Presentation:*** A pediatric case of B-cell ALL presenting as ALC is presented because of an exceptional testicular localization. ***Conclusion:*** B-cell acute lymphoblastic leukemia presenting as ALC is rarely described in the literature, and this case could be the first of childhood ALC with testicular involvement.

Introduction

Aleukemic leukemia cutis (ALC) is a rare condition defined as an infiltration of leukemic cells preceding or appearing in the absence of any prior blood and/or bone marrow involvement [1–3]. Most cases of leukemia cutis (LC) are diagnosed only after the diagnosis of systemic leukemia although, in less than 10% of all the cases, it can be isolated and hence termed as "ALC" or "primary extramedullary leukemia" [4]. The clinical appearance of LC is heterogeneous and therefore difficult to diagnose on a sole clinical base [1]. Usual sites are the trunk and extremities. LC is most frequently encountered in infants with congenital leukemia,

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in around 25% of the cases [1]. This report describes an exceptional case of a child presenting ALC associated with a blastic infiltration in one testicle, following an episode of severe thrombocytopenic purpura (TCP).

Case Presentation

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542377). A 10-month-old boy was referred to the dermatology department for a clinical suspicion of cutaneous mastocytosis. There were no particular medical, surgical, genetic nor allergic prior histories in the parents. The first skin lesions had appeared at the age of 5 months and presented as erythematous, slightly granular, indurated, infiltrated plaques on the trunk, face, shoulders, and thighs. At the age of 6 months, the patient had been hospitalized for a TCP. The workup, including blood tests, genetic analysis, and a bone marrow biopsy, was normal. The TCP was considered as a virus-triggered event. The severity of the thrombocytopenia required high doses of systemic corticosteroids, sirolimus, rituximab, intravenous immunoglobulins, and romiplostim. Eventually, both the purpura and the granular plaques resolved. However, after tapering of the immunosuppression the plaques recurred (Fig. 1a, b). A skin biopsy was performed, and histopathological analysis revealed a dense dermal infiltrate of immature blasts characterized by large vesiculated prominent nucleoli and a moderate amount of cytoplasm (Fig. 1c, 2). Immunohistochemistry demonstrated that the immature blastic cells expressed ki67, CD45, PAX5, CD79a, CD43, and CD34 whereas the malignant infiltrate was negative for terminal deoxynucleotidyl transferase (TdT) (Fig. 1d, e). The findings were suggestive of a cutaneous localization of a B-acute lymphoblastic leukemia (B-ALL). A complementary workup revealed a normal complete blood count, no evidence of malignancy or cytogenetic abnormalities in the bone marrow, and no malignant cells in the central nervous system. Chest X-ray, abdominal ultrasound, ophthalmologic examination, cardiac ultrasound, electrocardiogram, and cerebral magnetic resonance imaging showed no abnormalities. However, physical examination revealed an increased testicular volume, painful on palpation, indurated, prompting for a biopsy under general anesthesia. The testicular biopsy showed an infiltration by blast cells (Fig. 3) expressing CD19, CD34, CD45, but negative for CD20, CD3, TdT, again an immunohistochemical profile in favor of a B-cell lymphoblastic infiltrate. A MLL (KMT2A) rearrangement was evidenced in the testicle. The final diagnosis was an ALC with testicular involvement. The patient received induction and consolidation chemotherapy in accordance with the established protocols for type B lymphoblastic leukemia [1], without any serious adverse effects or unanticipated events. After 5 years, the child remains in complete remission.

Discussion

Pediatric LC is most frequently observed during acute myeloid leukemia followed by acute lymphoblastic leukemia (ALL). Usually, it presents concomitantly with systemic leukemia, particularly during initial leukemia episodes, rather than in relapsing leukemia [5]. In children, LC is often associated with a high leukemic tumor load and hepatosplenomegaly, however not encountered in our case [6].

LC presents as firm, indurated, violaceous, red, brown, or hemorrhagic papules, nodules, and plaques of different sizes [7]. Erythematous papules and nodules are the most common clinical features [8]. Macules, ulcers, bullae, and palpable purpura are more exceptional. The

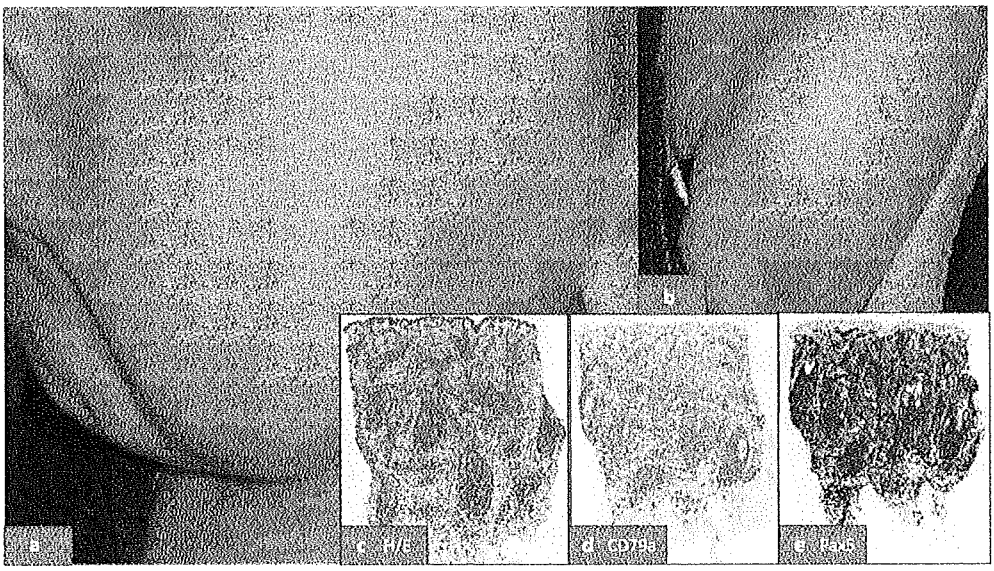

Fig. 1. LC lesion on the cheek (**a**), on the shoulder/upper arm (**b**). **c** Histology (H/E). **d** CD79a immunostaining. **e** PAX5 immunostaining.

lesions can be small and solitary, but large and multiple lesions can be observed [1–3]. Preferential sites are the legs and the head followed by the arms, back, chest, and the scalp [5].

LC is to be distinguished from non-leukemic cutaneous disorders occurring in patients with leukemia such as pyoderma gangrenosum, vasculitis, acute febrile neutrophilic dermatosis, mast cell disorders, drug-induced reaction, infectious illnesses, all kind of tumors, and erythema nodosum [7]. A skin biopsy is required to differentiate LC from other conditions. The malignant cells are centered in the dermis but can also be present in the subcutaneous tissue, or infiltrate the vessels and the adnexal structures. Epidermotropism is usually absent. Immunohistochemistry permits to characterize the immature blast cells. Immunostainings for CD117, CD45, CD79a, PAX5n, CD33, CD34, TdT, CD68, CD117, CD43, CD14, and lysozyme allow to categorize most subtypes [9, 10]. While TdT positivity is a common marker for B-ALL, it is important to note that approximately 2% of B-ALL cases can be TdT-negative [11]. In this case, the diagnosis of B-ALL was confirmed through the co-expression of B-lineage markers (PAX5 and CD79a) and markers of immaturity (CD34), consistent with established diagnostic criteria. TdT-negative B-ALL has been reported by some authors as having distinct clinical and genetic features, including younger age at diagnosis and higher white blood cell counts. The lack of TdT expression in this case aligns with the documented variability in TdT expression and does not exclude the diagnosis of B-ALL [12].

The pathophysiology of ALC is not well elucidated. It remains unclear whether the malignant cells originated in the skin or were disseminated from the bone marrow, whereas in individuals with systemic leukemia, LC is commonly a sign of bone marrow relapse. The cutaneous blasts represent a nidus from which new neoplastic cells can proliferate, spread, and secondarily repopulate the bone marrow and other organs [1].

Testicular involvement is frequent in pediatric ALL and is encountered in 1.1% to 2.4% of boys at the time of diagnosis [13–15], but has never, as far as we are aware of, been reported in childhood ALC. Increased size, irregular swelling, and/or firm consistency orientate toward testicular involvement.

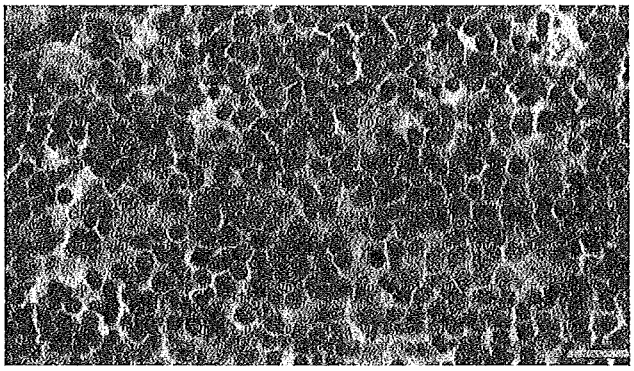

Fig. 2. Higher magnification of the blastoid population revealing intermediate-sized cells characterized by immature chromatin, scant cytoplasm, and inconspicuous nucleoli (H&E, ×800).

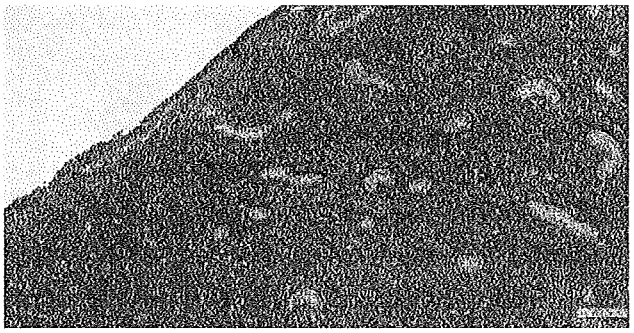

Fig. 3. Extensive infiltration of blastoid cells within the testicular parenchyma, with scattered residual seminiferous tubules (H&E, ×50).

The management of ALC remains controversial. The prognosis is poor. Most authors agree that a diagnostic workup including bone marrow studies, FISH, and cytogenetics should be performed before initiating a treatment. They suppose that a large number of patients would develop a systemic disease if they were not treated. However, spontaneous regression has been reported in the literature although they all seem to concern congenital ALC [16, 17]. The management of ALC is usually identical as for acute leukemia, i.e., induction and consolidation chemotherapy following recommended protocols [9]. Combination chemotherapies penetrating the blood-testis barrier have significantly decreased the morbidity of ALC. Although overt testicular involvement seems not to be a negative prognostic factor in children with ALL (15), its significance in ALC is not clear.

Conclusion

ALC is a rare condition, and the diagnosis is challenging. The management remains controversial, although early diagnosis and early treatment probably offer a better prognosis. A skin biopsy should always be performed with immunophenotyping as well as an examination of peripheral blood smears and bone marrow aspirates.

B-cell ALL presenting as ALC is rarely described in the literature, and this case could be the first of childhood ALC with testicular involvement. Given the lack of detailed information in the literature describing presentation and outcomes in pediatric patients with ALC, further studies are still required.

Statement of Ethics

Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. In addition, this study was reviewed and the need for approval was waived by EC CHU Liège (Accreditation number: 707, Liège, Belgium).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design of study and acquisition of data – Sophie Bailleux, Sandrine Cao, and Arjen F. Nikkels. Analysis and/or interpretation of data: Sophie Bailleux, Sandrine Cao, Bita Dezfoulian, Patrick Collins, Jaon Somja, Sophie Gatineau, Julie Longton, and Arjen F. Nikkels. Drafting the manuscript – Sophie Bailleux, Sandrine Cao, Joan Somja, and Arjen F. Nikkels. Approval of the version of the manuscript to be published – Sophie Bailleux, Sandrine Cao, Bita Dezfoulian, Patrick Collins, Joan Somja Sophie Gatineau, Julie Longton, and Arjen F. Nikkels.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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