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Clinical presentation of non-malignant diseases mimicking leukemia cutis: A report of two cases

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ABSTRACT

The infiltration of leukemia cells into the skin, known as leukemia cutis, is a rare presentation of this disease and accounts for a diagnostic challenge.

The main differential diagnoses include infections, other neoplastic diseases with skin involvement and histiocytic disorders, among others, as they entail different prognostic and therapeutic approaches.

Here we describe two patients who were initially diagnosed with leukemia cutis, whose final diagnosis was of non-malignant diseases.

Keywords: *skin disease; differential diagnosis; juvenile xanthogranuloma; histiocytosis.*

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INTRODUCTION

Leukemia cutis is a rare disease that may be associated with different types of leukemia. In acute myeloblastic leukemia (AML), 30% of cases develop extramedullary manifestations most frequently associated with the monoblastic variant (FAB M5), with or without associated marrow involvement.[1] Its incidence is higher in the neonatal population and during the first year of life: as much as 50% have this presentation, which is usually associated with genetic syndromes, such as trisomies 21, 13, and 9, and Bloom syndrome.[2] Skin lesions appear most frequently after hematological diagnosis and occur concomitantly in up to 30% of cases and prior to diagnosis in less than 10%.[3,4]

The cause for the migration of leukemia cells to the skin is unknown. One hypothesis proposes that migration is driven by cytokine receptor 4, which is aberrantly overexpressed in the blasts, attracting them to this site.[3] It is worth taking into account that leukemias in patients under 1 year of age usually present with hyperleukocytosis and extramedullary involvement, which manifests as organomegaly, skin and/or central nervous system (CNS) involvement.[5] The presence of skin involvement does not influence the prognosis of leukemia, which is unfavorable; according to the most representative series, survival rates reach 20–30%.[6,7] In addition, it has been reported that when skin involvement is observed, the incidence of CNS involvement is frequent, as an expression of disease dissemination.[3,7,8]

The main differential diagnoses include infections, other neoplastic diseases with skin involvement and histiocytic disorders, among others, as they entail different prognostic and therapeutic approaches.

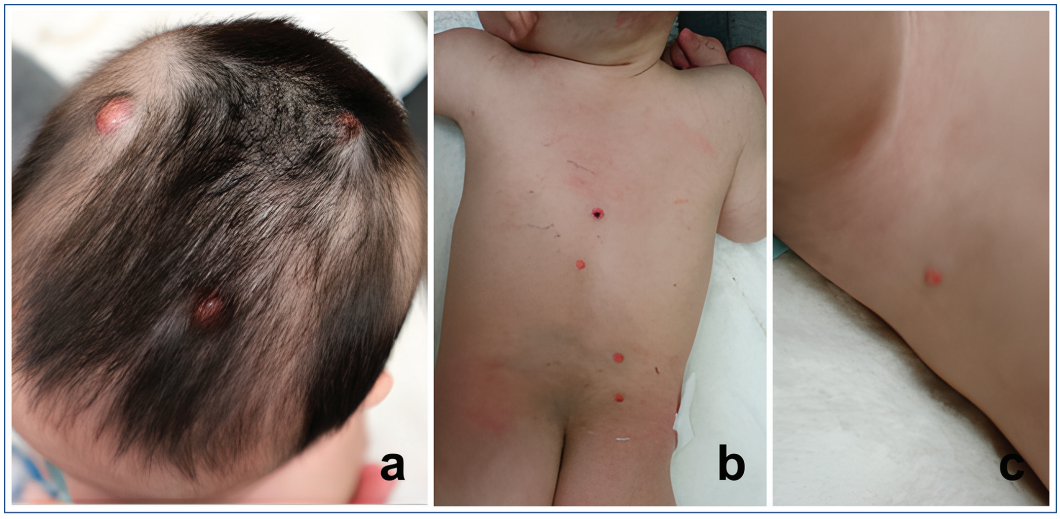
CASE REPORT 1

This was a 5-month-old, male patient with no relevant medical history, who consulted at the referring hospital for multiple, hard-elastic, pink, homogeneous, painless tumors and papules that measured 1–2 cm in diameter located on his scalp, face, back, and diaper area for the past 2 months (*Figure 1*).

A complete blood count was done; result showed a normal leukocyte count with lymphocyte predominance. A biopsy of a lesion on the back was performed, which showed mononuclear cell infiltration into the dermis, with Ki67 30–40% and immunohistochemistry (IHC) diagnostic of myelo-mononuclear proliferation. A flow cytometry was positive for HLA-DR, CD14, CD64, CD13, and CD11b, myelo-monocytic markers.

The initial suspicion was leukemia cutis, so the patient was referred to our hospital, where a bone marrow aspiration was performed and leukemic infiltration was ruled out. A reverse transcription polymerase chain reaction (RT-PCR) was done to rule out alterations in the *KMT2A* gene, which are frequent in patients under 1 year of age with acute leukemia; results were negative. The pathology block was reviewed; a new skin biopsy was performed, which showed

Figure 1. Case 1. Erythematous, orange-colored papules and tumors in the head (a), trunk (b), and armpit (c)



xanthomized histiocytes with multinucleated giant cells in the dermis and positive IHC for CD68 in the histiocytes. The diagnosis of disseminated juvenile xanthogranuloma (JXG) was confirmed (*Figure 2*).

Staging studies were performed and kidney, lung, and liver involvement were found as manifestations of disseminated JXG. The patient started receiving treatment according to the International Collaborative Treatment Protocol (LCH-IV) established by the Histiocyte Society. He is currently recovering, but his disease is active.

CASE REPORT 2

An 11-month-old, male patient with a history of atopic dermatitis consulted for fever and neutropenia associated with pink, painless subcutaneous nodules that measured 1 cm in diameter, located on his head and upper limbs for the past 5 months.

Previously, a biopsy of a lesion had been performed in another facility, which reported leukemia cutis. The review of the biopsy block showed myeloid proliferation in the dermis and hypodermis, with lysozyme expression and intense positivity for CD68 and CD43 (focal) (*Figure 3*). IHC determinations were also performed; HLA-DR and CD34 were negative, and this ruled out the diagnosis of leukemia, which was also ruled out by flow cytometry.

The histologic report of the bone marrow biopsies done simultaneously showed an increase in the reticulin structure, hemophagocytosis, and myeloid maturation arrest, without neoplastic cells. Molecular alterations associated with leukemia were ruled out by RT-PCR.

Given the decrease in myeloid precursors, a test for bone marrow failure was performed, which found iron and vitamins D and B12 deficiency. The sequencing of the *ELANE* and *SDBS* genes did not find gene alterations with phenotypic implications; the telomere length study was normal; the diepoxybutane test was negative; and the next-generation sequencing (NGS) did not show DNA variants compatible with the patient's condition. Immunodeficiencies were also ruled out.

The patient received colony-stimulating factor (GM-CSF), with adequate response. At present, he does not have neutropenia, and the skin lesions have resolved.

DISCUSSION

Here we described two cases for whom the initial diagnostic hypothesis was leukemia cutis, a rare disease associated with AML in this age group, with extramedullary manifestations associated with the FAB M5 variant present in 30–50% of patients.[1–4] Although both patients were in the age range of higher incidence of leukemia, it is important to take into account that leukemias in infants usually present with hyperleukocytosis, associated or not with leukostasis and extramedullary involvement, which is manifested by infiltration of the liver, spleen, skin, and CNS.[5–7] The histopathological examination shows a dense infiltrate of immature cells within collagen accumulations in the reticular dermis and vasculitis. Given these features, intravascular coagulation (IVC) is likely to be present, which has an impact on the general condition.[8]

In the cases described here, the clinical status

Figure 2. Pathological examination of case 1. (a) Dense cell proliferation is observed in the reticular dermis (hematoxylin and eosin staining, field objective). (b) Medium-sized cells with eosinophilic cytoplasm containing fine vacuoles (hematoxylin and eosin staining, 40X magnification) are observed, which are positive for CD163 (c) and evidence the histiocytic nature of the lesion

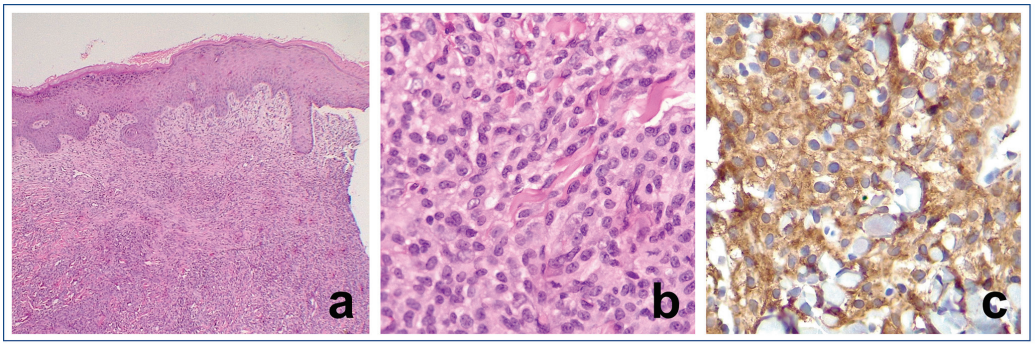
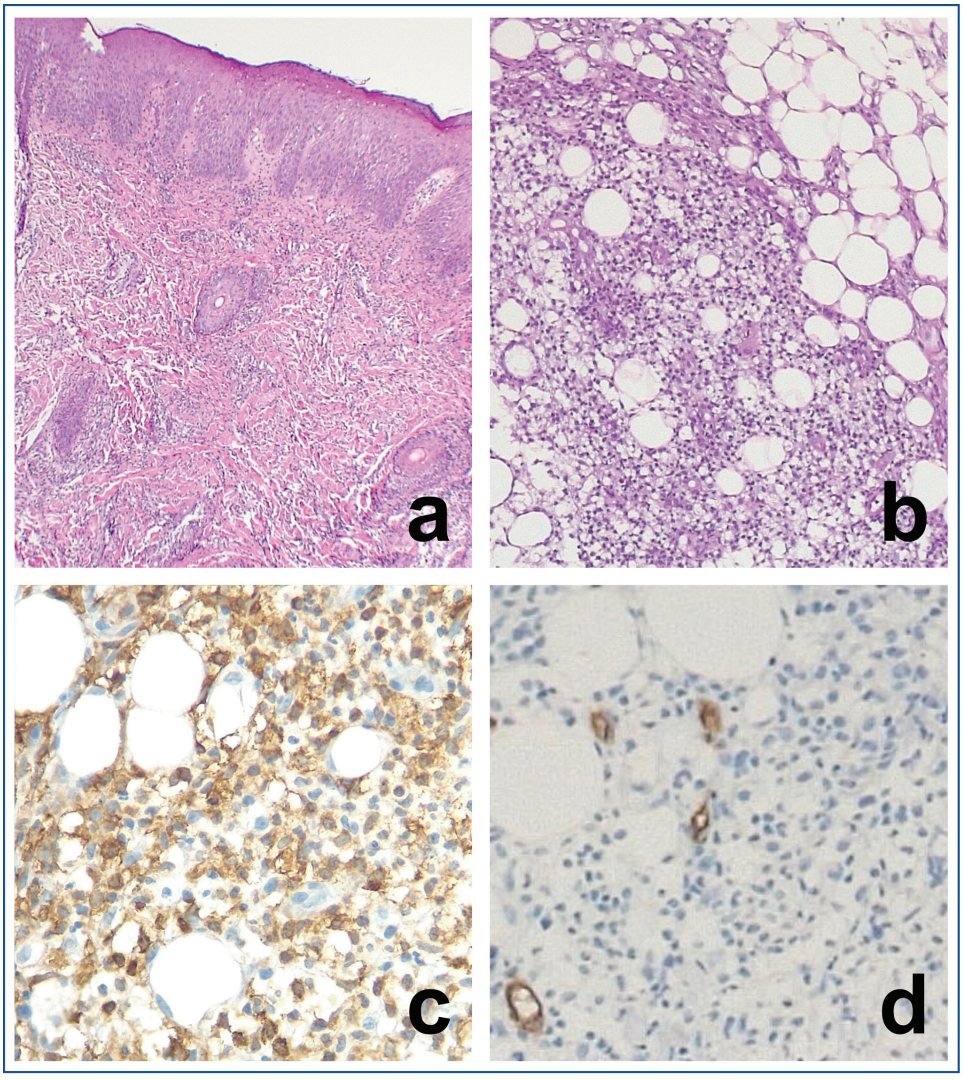


Figure 3. Pathological examination of case 2. (a) and (b) show dense cell infiltration into the skin, which is more evident in the hypodermis, and includes mature and maturing lymphocytes (hematoxylin and eosin staining, field objective). (c) Infiltrating cells are positive for myeloperoxidase, but negative for CD34 (d). The positive marking in (d) corresponds to vascular endothelium



of both patients was adequate, with no elevated white blood cell count, organomegaly, or signs of IVC.

The presence of skin involvement does not influence the prognosis of leukemia, which is unfavorable; according to the most representative series, survival rates reach 20–30%.[6,7] In addition, when skin involvement is observed, the incidence of CNS involvement is frequent.[7,8] The gold standard diagnostic method is a biopsy of the lesions with IHC and molecular biology tests to look for rearrangements of the *KMT2A* gene (previously called *MLL* gene), which translocates with the *MLLT3* gene thus causing the *KMT2A-MLLT3*/t(9;11)(p21.3;q23.3) fusion transcript, and is associated with *de novo* AML-M5 in children under 1 year of age, which results in an unfavorable prognosis, with a mortality of 80% 1 year after diagnosis.[7,8]

The biopsies of both patients showed mononuclear infiltrates with negative IHC, multiparameter flow cytometry, and molecular biology tests.

It is important to consider diseases whose

clinical characteristics are similar to those of leukemia cutis: in case 1, the diagnosis was JXG, a histiocytic disorder included in group C histiocytosis (skin involvement only) or group L histiocytosis (involvement of other organs). The histologic characteristics are identical: xanthomized histiocytes and Touton and foreign-body giant cells are observed. The origin of these cells is unknown, although it has been proposed that they share characteristics with dermal macrophages, since they express factor XIIIa. The IHC shows that histiocytes express CD68 (100%), vimentin, factor XIIIa (99%), and lysozyme and are negative for CD34, smooth muscle actin, S-100, CD1a, and langerin. Molecular findings found in pediatric patients include activating mutations of the mitogen-activated protein (MAP) kinase pathway (*BRAF V600*), *NTRK 1* fusions, and mutations in the *MAP2K1* and *CSF1R* genes.[9]

Clinically, JXG presents as a single or multiple, pink or yellowish, asymptomatic, papulo-nodular lesion located in any region of the body in patients between 6 months and 2 years of age.[10] The disseminated form of the disease is very rare; the anterior chamber of the eye is the most frequent extracutaneous site, followed by the lung, liver, meninges, spleen, and testis.[11] It is a benign disease and, in general, does not require treatment; however, if systemic involvement is present, treatment with corticosteroids and vinblastine may be indicated.[12]

In case 2, the patient had associated neutropenia. Based on this, secondary causes were initially looked for, such as infections, mainly of the TORCH group, which manifest as hepatosplenomegaly, anemia, thrombocytopenia, and the blueberry muffin syndrome appearance with bluish subcutaneous nodules.[13] Another differential diagnosis in infants with skin involvement and blood count alterations is neuroblastoma, a malignant tumor that may present with skin involvement in 2% and may be associated with bone marrow involvement when occurring congenitally and up to 18 months of age.[14] However, another important characteristic of JXG is liver involvement due to infiltration, a situation that frequently generates restrictive respiratory distress and impairs the patient's general condition, which in this case was good.

Finally, in relation to skin involvement in inborn errors of immunity, the presence of cold nodules associated with common variable immunodeficiency, severe combined immunodeficiency, and chronic granulomatous syndrome has been rarely described.[15] In this child, the history of atopic dermatitis and neutropenia made it necessary to rule out this disease. In addition, the study of myeloid bone marrow failure was carried out using tests of increasing complexity, from the search for malabsorption, poisoning, and immunodeficiency to genomic sequencing.

In both patients, the interdisciplinary approach was critical to reach an adequate diagnosis, which in both cases resulted in different scenarios in terms of treatment and prognosis. ■

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