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BRIEF REPORT

Self-limited cutaneous Langerhans Cell Histiocytosis: A case report

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KEYWORDS
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Abstract Blueberry muffin baby syndrome is a condition initially described in 1960 to classify the cutaneous manifestations of newborns with rubella. Subsequently, congenital diseases related to TORCH syndrome and blood dyscrasias have been included under this syndrome. Among the conditions associated with this syndrome is Langerhans Cell Histiocytosis, an uncommon condition with variable involvement of one or more organs, often affecting the skin. One of its forms of presentation is Hashimoto–Pritzker disease, a self-limited congenital Langerhans Cell Histiocytosis with exclusively skin involvement. First described in 1973 and with approximately 100 reported cases, its presentation as part of the Blueberry muffin baby syndrome is infrequent. Its prognosis is excellent, but long-term follow-up is required due to the possibility of relapses or subsequent visceral involvement.

PALABRAS CLAVE
Histiocitosis cutánea;
Histiocitosis de células de Langerhans;
Síndrome del bebé en magdalena de arándanos

Histiocitosis de células de Langerhans cutánea autolimitada: a propósito de un caso

Resumen El síndrome del bebé en magdalena de arándanos es una entidad descrita inicialmente en 1960 para clasificar las manifestaciones cutáneas en recién nacidos con rubeola. Posteriormente se han incluido enfermedades congénitas relacionadas con el síndrome TORCH y discrasias sanguíneas. Entre estas se encuentra la histiocitosis de células de Langerhans, una dolencia poco común que puede afectar de manera variable a uno o más órganos, con afectación frecuente de la piel. Una de sus formas de presentación es la enfermedad de Hashimoto-Pritzker,

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una histiocitosis de células de Langerhans congénita autolimitada que afecta exclusivamente a la piel. Descrita en 1973 y con aproximadamente 100 casos documentados, la presentación de esta enfermedad como parte del espectro del síndrome del bebé en magdalena de arándanos es poco frecuente. Su pronóstico es excelente, pero se requiere un seguimiento a largo plazo ante la posibilidad de recaídas o afectación visceral posterior.

Introduction

Langerhans Cell Histiocytosis is the most common histiocytic disorder, originating from myeloid progenitors and consisting of clonal macrophages. It is classified alongside other related conditions, such as juvenile xanthogranuloma and paediatric Erdheim–Chester disease. Several classification systems exist, the most significant being those provided by the World Health Organization and the Histiocyte Society. These disorders have a variable prognosis, which largely depends on the clinical presentation, ranging from solitary benign lesions to systemic involvement.[1–4] In this article, we present the case of an infant with self-limited cutaneous histiocytosis.

Case description

A 1-month-old male infant, born at term via emergency caesarean section, with no significant perinatal history, was referred from his primary care centre to our emergency department due to the presence of violaceous maculopapular lesions. The first lesion appeared on the back at 7 days of life, progressively extending to cover the entire body surface.

His mother was investigated due to two previous miscarriages and was diagnosed with antiphospholipid syndrome, currently under follow-up by the haematology department. During pregnancy, she has been treated with heparin (which continues postpartum) and acetylsalicylic acid. She is positive for lupus anticoagulant, with negative anti-Ro antibodies.

Upon examination, the infant presents with purpuric maculopapular lesions measuring 2–5 mm in diameter, with a violaceous colour. Some of these lesions exhibit central telangiectasia and are located on the dorsal region, chest, abdomen, upper and lower limbs, dorsum of the penis, as well as the right cervical and facial regions. A larger papular lesion, noted as the first to appear, is present on the right dorsal region. Additionally, a flat angioma was identified in the occipital region, along with a slight jaundice of the skin. No further abnormalities were noted on systemic physical examination, and an emergency blood test was performed, which evidenced no significant findings.

In the presence of a purpuric rash without associated abnormalities in the initial tests performed in the emergency department, the patient was referred to the outpatient paediatric rheumatology clinic for further investigation. A more comprehensive blood panel was carried out, which ruled out rheumatological disease. The case was discussed with the dermatology department, which diagnosed the patient with blueberry muffin syndrome. A biopsy of the largest lesion was subsequently performed. The histological findings were consistent with cutaneous Langerhans Cell Histiocytosis. Consequently, the case was discussed with the referral hospital, and the patient was scheduled for further assessment in the outpatient dermatology and paediatric oncohaematology clinics. The study extension showed no involvement of other organs. At 3 months, there was an improvement in the lesions, as seen in Fig. 1, with complete resolution of the skin manifestations by 9 months of age. The diagnosis of Hashimoto–Pritzker disease was confirmed, and the patient was discharged under the supervision of the local paediatrician.

Discussion

Blueberry muffin syndrome is a rare, non-specific presentation that was initially used to describe the cutaneous manifestations of newborns with rubella in the 1960s. It has since been extended to include congenital conditions associated with the TORCH syndrome and various haematological disorders, with Langerhans Cell Histiocytosis being one of the conditions in which this presentation can be found.[5,6]

This condition, of poorly defined aetiology, involves the clonal proliferation of Langerhans cells within tissues, which can affect one or multiple organs.[6,7] Skin involvement is present in over 50% of cases,[6] although the bone is the most frequently affected organ in isolated cases.[8] It is the most common histiocytic disorder, characterised by the presence of cells that phenotypically express CD207.[9]

In the anatomical pathology study performed in our case, the images of which are shown in Fig. 2, dermal infiltration affecting the entire dermis was observed, characterised by a proliferation of medium-sized epithelioid cells with abundant cytoplasm. These were accompanied by giant cells with eosinophilic cytoplasm and coffee-bean-shaped nuclei with fine chromatin and inconspicuous nucleoli. The periphery showed abundant lymphoid cellularity, without a notable presence of eosinophils. Given the morphological suspicion of histiocytosis, a complementary immunohistochemical study was requested.

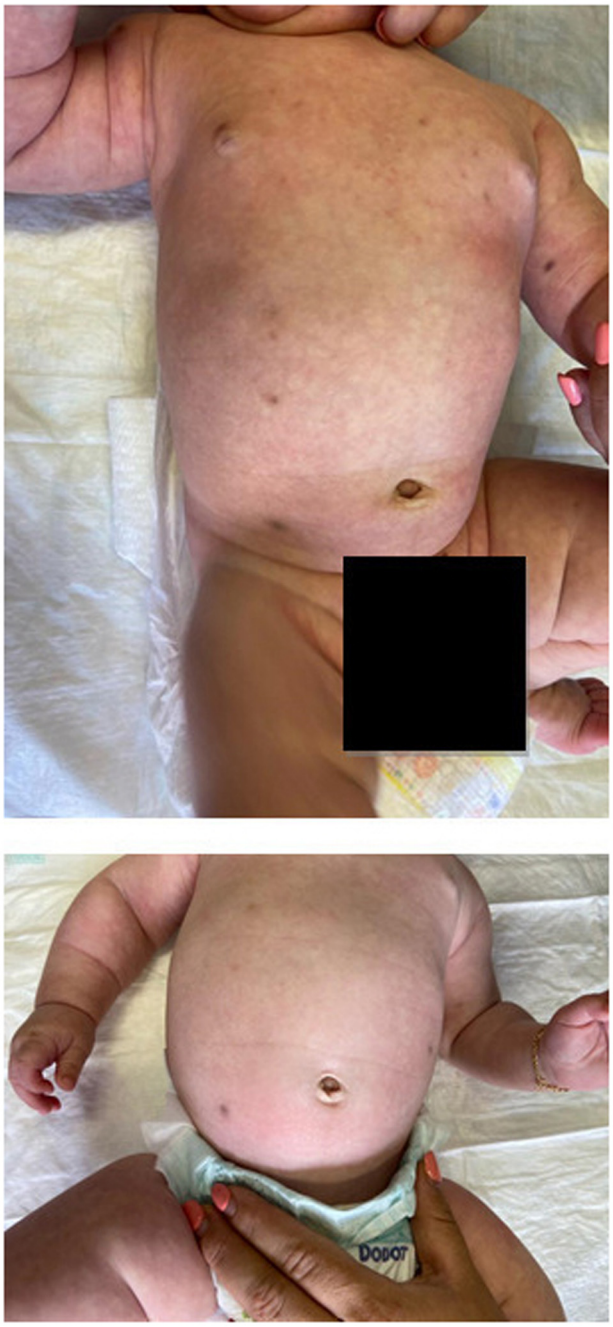

Figure 1 Maculopapular lesions, less than 1 cm in diameter, with a violaceous colour, located on the trunk and extremities at the first visit (above) and after 3 months (below).

The described cellularity showed expression of CD68, S100 protein, and CD1a, as well as Langerin (CD207), as seen in Fig. 2. No BRAF gene mutation was detected through molecular or immunohistochemical studies. Therefore, the diagnosis is Langerhans Cell Histiocytosis. This condition corresponds to group L in the classification proposed by the Histiocyte Society, where the diagnosis is based on the combination of clinical, radiological, and histopathological findings. Also included in this group are Erdheim–Chester disease, Indeterminate Cell Histiocytosis, and a mixed pattern between Langerhans Cell Histiocytosis and Erdheim–Chester disease. Within the family of histiocytosis, group C corresponds to cutaneous and mucocutaneous histiocytoses, which includes juvenile xanthogranuloma. Group R includes familial Rosai–Dorfman Disease, group M encompasses malignant histiocytoses, and group H corresponds to haemophagocytic lymphohistiocytosis and macrophage activation syndrome.[4] Table 1 shows the classification of the different types of histiocytosis and their potential skin involvement.

The differential diagnosis was conducted with the other two conditions in group L. Erdheim–Chester disease is characterised histopathologically by small, CD1a-negative foamy mononuclear histiocytes, in contrast to Langerhans Cell Histiocytosis. On the other hand, indeterminate Cell Histiocytosis, described in 1985, shows expression of CD1a and S100, with a notable absence of Langerin.[4,9] This distinction was necessary due to the similar clinical presentation of indeterminate Cell Histiocytosis with the Hashimoto–Pritzker disease presented in our case. The presentation of the former tends to be exclusively cutaneous, although multiorgan involvement has occasionally been reported.[12] The presence of Langerin is definitive for the differential diagnosis.

Clinically, the presentation exhibited by the patient could resemble histiocytic entities from groups other than Langerhans, particularly juvenile xanthogranuloma. However, histological examination confirmed that the condition presented falls within the spectrum of group L.[4] Furthermore, at the molecular level, alterations related to the MAP kinase pathway can be observed in three out of four cases in this group. Additionally, in 50% of paediatric patients with Langerhans Cell Histiocytosis, a mutation in the BRAF gene can be detected, with the most common mutation being $BRAF^{V600E}$, which was absent in our case, followed by alterations in exons 2 and 3 of MAP2K1 In the analysis conducted on a sample of paediatric patients from the French national histiocytosis registry, the most frequently detected alterations in patients with Langerhans Cell Histiocytosis, where no BRAF gene mutations were found, were those related to MAP2K1. The presence of these mutations not only aids in diagnosis but also has clinical, prognostic, and therapeutic implications. For instance, there is a higher likelihood of skin involvement and the risk of permanent sequelae, particularly neurodegenerative clinical manifestations, when the $BRAF^{V600E}$ mutation is present compared to when it is not detected. In contrast, MAP2K1 mutations were associated with less skin involvement and a lower risk of permanent sequelae compared to the absence of observed mutations. This highlights the importance of molecular analysis in such patients.[13]

The presentations of Langerhans Cell Histiocytosis include congenital self-healing Langerhans Cell Histiocytosis, also known as Hashimoto–Pritzker disease, which was described in 1973. This is a rare variant characterised by skin lesions not involving other organs, with a tendency for spontaneous resolution within weeks or months.[14,15] Approximately 100 cases have been described in the literature,[8] although the incidence is likely underestimated due to its exclusive cutaneous presentation and the resolution of the condition within weeks or months.[7,8] The onset of the disease is typically congenital or neonatal,[8,14]

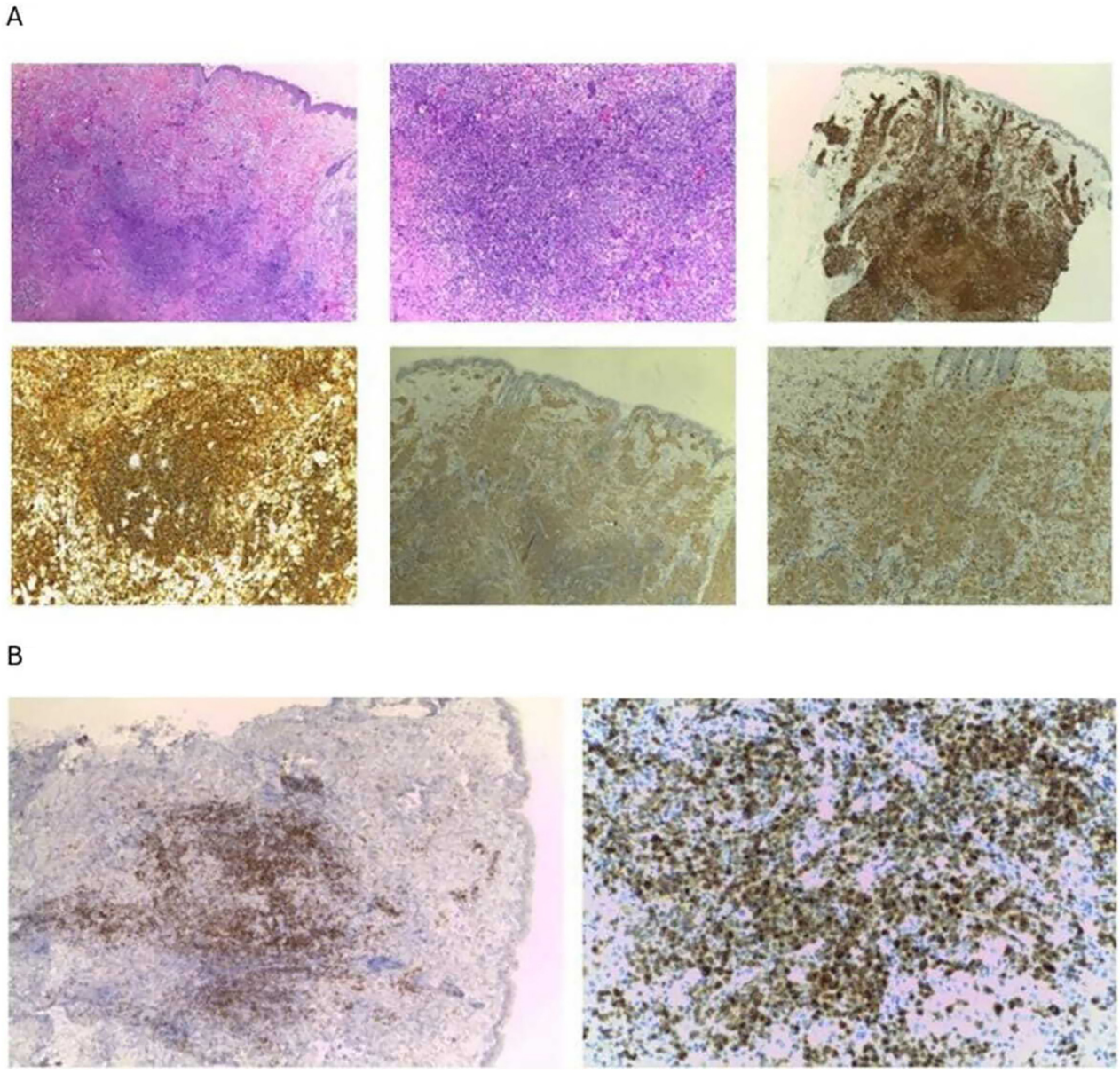

Figure 2 Anatomical pathology study: (A) A richly cellular diffuse dermal infiltrate is observed, consisting of abundant macrophages surrounded by lymphocytes. Eosinophils are not present. (B) Immunohistochemical profile: The described histiocytes showed expression of CD68, CD1a, and Langerin.

and less frequently occurs in early childhood. It is uncommon for the presentation to be considered part of the spectrum of blueberry muffin syndrome.[8]

The diagnosis is clinical and histological, but the diagnosis of Hashimoto–Pritzker disease can only be made retrospectively after excluding involvement of other organs.[15] Long-term follow-up is recommended due to the unpredictable course of Langerhans Cell Histiocytosis, as relapses of cutaneous manifestations or subsequent visceral involvement have been reported.[8]

Specific treatment is not necessary; topical treatment of the skin lesions can be performed, with the most common sequela being hyper- or hypopigmentation following inflammation.[8] The prognosis is excellent.[14]

Ethical considerations

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Table 1 Classification of the types of histiocytosis according to the Histiocyte Society classification and associated skin involvement.[4,10,11]

Group	Diseases	Skin involvement
L (Langerhans)	Langerhans Cell Histiocytosis	Involvement in 33% in paediatric patients, lower frequency in adults. The lesions can vary from papules to ulcers
	Indeterminate Cell Histiocytosis	Tendency for exclusive cutaneous involvement, usually manifesting as papules or nodules.
	Erdheim–Chester disease	Cutaneous involvement is uncommon, mainly xanthelasma in adults
C (cutaneous and mucocutaneous histiocytosis)	Xanthogranuloma family Non-xanthogranuloma family	Cutaneous-mucosal involvement in both families and varied presentation
M (malignant histiocytosis)	Primary malignant histiocytosis Secondary malignant histiocytosis	It can be associated with vasculitis, including lesions such as palpable purpura, nodules or ulcers
R (Rosai–Dorfman disease and other non-cutaneous histiocytoses, non-Langerhans cells)	Familial Rosai–Dorfman disease Classic Rosai–Dorfman disease Extranodal Rosai–Dorfman disease Rosai–Dorfman disease associated with neoplasia Rosai–Dorfman disease associated with immune disease Other histiocytoses not included in groups C, L, M, H	Skin is affected in 10% of the patients and may present as macules or plaques, with the malar regions or the eyelids being the most affected areas. However, its main characteristic is bilateral cervical adenopathies
H (Hemophagocytic lymphohistiocytosis and macrophage activation syndrome)	Primary hemophagocytic lymphohistiocytosis Secondary hemophagocytic lymphohistiocytosis	Cutaneous involvement is uncommon

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Conflict of interest

The authors declare that they have no conflicts of interest.

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