Diagnostic and therapeutic difficulties in the cutaneous form of Langerhans cell histiocytosis in infant

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ABSTRACT

Introduction: Langerhans cell histiocytosis is an uncommon inflammatory and neoplastic condition of myeloid dendritic cells. Langerhans cell histiocytosis presents with a wide spectrum of clinical manifestations, ranging from single-system involvement to disseminated disease involving multiple organs. Diagnosis is based on a combination of clinical features, radiological findings, and histopathological examination. Positive immunohistochemical staining of lesional cells for CD1a and S100 is necessary for definitive diagnosis of Langerhans cell histiocytosis.

Case report: Herein, we describe the case of a male infant who presented with multiple erythematous-papular lesions covered with yellow scales on the scalp, temples and face and oozing erythematous and erosive lesions mainly on the abdomen, upper chest, groins, gluteal cleft and armpits.

Conclusions: Further research is needed to unravel the underlying pathogenesis, develop standardized diagnostic criteria, and improve treatment strategies. Collaboration among various specialties, including dermatology, pediatrics, oncology, radiology, and pathology, is essential for optimal management and long-term follow-up of this complex entity.

Key words: infant, histiocytosis, Langerhans cells.

INTRODUCTION

Langerhans cells histocytosis (LCH) is an uncommon inflammatory and neoplastic condition of myeloid dendritic cells. LCH is characterized by the proliferation of abnormal dendritic antigen-presenting histiocytes. LCH may involve almost any organ. The clinical presentation of LCH therefore varies and is frequently misdiagnosed [1–3]. In the case of LCH, granulomatous lesions comprising langerin-positive (CD207+) histiocytes with accompanying inflammatory infiltrate can arise in virtually any organ system but have a particular affinity for bones, skin, the lungs, and the pituitary gland [4, 5]. Histiocytic diseases are rare diseases with a widely variable clinical presentation, ranging from single indolent lesions to explosive multisystem disease, pathogenesis of which is related to disorder of proliferation and differentiation of cells of the phagocytic system [6, 7]. The underlying cause of this disease is the clonal proliferation of histiocytes (Langerhans cells) immunohistochemically and morphologically resembling dendritic cells. The observed symptoms of the disease result from both the accumulation of these abnormal cells in tissues and organs, as well as the ongoing inflammatory process [8–12].

LCH is most common in children and adolescents. The annual incidence of LCH has been reported to be 4.6 cases per million children under 15 years of age per year, with a male-to-female ratio of 1.2 : 1 [13], which

means that approximately 20–25 new cases are diagnosed in Poland every year. Children up to 6 years of age are most often affected. The estimated incidence among adults is 1 to 2 cases per million, though LCH is probably underdiagnosed in this population [4, 14].

LCH can affect many organs and systems. In 77–80% of patients, the symptoms result from skeletal system involvement [12].

Skin lesions are common in LCH and affect about 40% of cases, although exclusive cutaneous involvement is rare (5%) [15]. It is reported that skin lesions are usually the first manifestation of LCH in 80% of patients [16]. 25–30% of children present skin involvement, 19% of children have lymphadenopathy in the course of LCH (most often with coexisting changes in the skeletal system), and mucosal involvement is found in 13%. Central nervous system (CNS) infiltrates occur in 6% [8–11].

According to the criteria established by the International Histiocyte Society, based on the clinical picture, LCH can be divided into a single system LCH (SS-LCH), in which one organ is affected and multisystem LCH (MS-LCH) involving at least two organs. The MS-LCH is subdivided into 'low-risk' and 'high-risk' ones. Low-risk patients have no involvement of 'high-risk' organs (liver, lungs, spleen, hematopoietic cells). High-risk patients have one or more of these organs involved [17]. Children with liver, spleen, or bone marrow involvement are at highest risk for death from LCH [5, 18].

Isolated skin lesions are relatively rare in adults compared to children. The most common initial skin changes are vesicles, papules and pustules, a rash resembling seborrheic dermatitis, changes in the mucous membranes (erosions, petechiae and granulomas), erythematous papules, nodular ulcerative lesions and generalized petechiae. LCH presents most often on the trunk, head and neck, followed by extremities, intertriginous sites, buttocks, and occasionally the oral mucosa. Most commonly involved mucosa is the oral and genital mucosa [9, 11, 19]. LCH can mimic seborrheic dermatitis, eczematous dermatitis, or manifest with solitary or grouped papules, nodules, or ulcerations. Pruritus is a common feature reported by patients [11].

CASE REPORT

A patient of 8 months of age was admitted to the Department of Dermatology for Children for the diagnosis and treatment of various types of skin lesions. Lesions were present from his 4 months of age. The skin lesions were previously considered as seborrheic dermatitis.

Dermatological examination revealed multiple erythematous-papular lesions covered with yellow scales on the scalp, temples and face and oozing erythematous and erosive lesions mainly over stomach, upper chest, groins, gluteal cleft and armpits (figs. 1 A, B).

The perinatal history was uncomplicated, the child had no chronic illnesses detected so far.

Laboratory tests were performed: complete blood count with a manual smear, urinalysis, glucose concentration, electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, DPA-Dx (component-resolved diagnostics of the most common childhood allergies) and abdom-

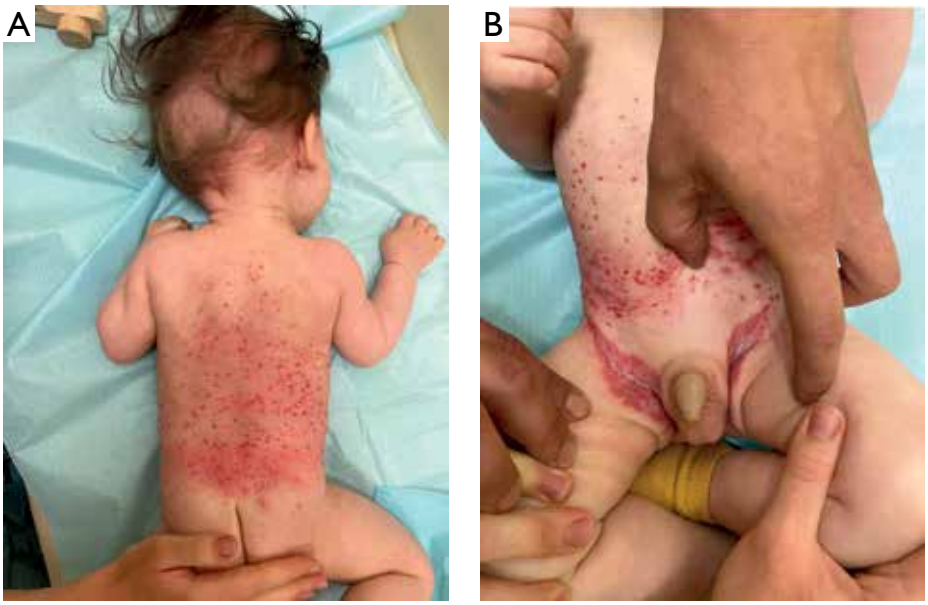

Figure 1. A, B – Clinical presentation before the treatment: multiple erythematous-papular lesions covered with yellow scales on the scalp, temples and face and oozing erythematous and erosive lesions mainly over the stomach, on the upper chest, groins, gluteal cleft and armpits

inal ultrasound examination. There were no abnormalities in laboratory and imaging studies detected.

The patient was consulted by a gastroenterologist due to inhibition of the infant's weight gain, and lactation counseling was performed.

The patient was consulted by ophthalmologist, and no abnormalities were found in the examination.

A biopsy from the skin lesion was taken for histopathological examination. Histopathology revealed inflammatory infiltrate in the dermis of cells expressing S-100 protein, CD1a, Langerin protein (CD207) and CD 68/PGM1. The microscopic presentation and immunohistochemical tests confirmed the diagnosis of Langerhans cell histiocytosis (LCH).

Reduction in the severity of skin lesions occurred after topical treatment, using a solution of gentian violet, fusidic acid and betamethasone.

The patient was transferred to the children hematology department. Currently, he is under the care of the tertiary referral hospital. Oncologic examination, including complete blood count, comprehensive metabolic panel, skeletal survey, and non-contrast head computed tomography did not reveal any systemic involvement. In the case of our patient, it was decided not to start chemotherapy due to the exclusion of histiocytosis of internal organs.

During follow-up, routine imaging revealed lytic bone changes, X-ray and positron emission tomography/computed tomography (PET/CT) exhibited penetration or osteolytic bone destruction, but involvement of other internal organs was excluded. In our patient's case, LCH was classified as low-risk multisystem disease. Systemic chemotherapy regimen involving the combination of vinblastine and prednisone was administered.

The patient responded well to treatment, partial regression of lytic bone lesions was observed.

DISCUSSION

LCH is a rare disorder characterized by the accumulation and proliferation of abnormal Langerhans cells in various tissues and organs. The exact pathogenesis of LCH is not fully understood, but there are several proposed genetic, immunologic, and environmental mechanisms that may contribute to its development [20].

Key aspects of the pathogenesis of LCH include the following:

- Clonal proliferation: LCH is thought to arise from a clonal proliferation of abnormal Langerhans cells. Clonality suggests that these cells are derived from a single precursor cell that underwent genetic mutations, leading to uncontrolled growth and survival. In LCH, these cells become abnormal and lose their normal immune-regulatory functions. Instead, they become proliferative and can infiltrate various organs, forming characteristic granulomas. The uncontrolled proliferation of Langerhans cells may occur in response to various stimuli, including infections or inflammatory signals [1, 3, 4, 15].
- Genetic mutations: Genetic studies have revealed that some cases of LCH have been associated with specific genetic mutations. The most common genetic mutation identified in LCH is the BRAF V600E mutation, which is present in approximately 50–60% of cases. This mutation leads to the activation of the MAPK/ERK signaling pathway, contributing to uncontrolled cell growth and survival [6, 15, 21, 22].
- Dysregulated immune response: There is evidence to suggest that LCH may result from an abnormal immune response to various triggers, such as infections or environmental exposures. The precise triggers remain unclear, but they could lead to the activation of Langerhans cells and subsequent uncontrolled proliferation. However, the specific triggers have not been definitively identified [15].
- Inflammatory cytokines: The LCH patients had significantly higher serum levels of IL-1Ra, IL-3, IL-6, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, TNF-α, G-CSF, M-CSF, MIF, HGF, VEGF, CCL2, CCL3, CCL7, CXCL1, and CXCL9 than the controls by univariate analysis. Of these, IL-9, IL-15 and MIF were significant by multivariate analysis; but not differed between MS and SS diseases. The LCH patients with the *BRAF* V600E mutation had higher serum levels of CCL7. These cytokines can promote the recruitment and activation of immune cells, contributing to the formation of granulomas [12, 15, 23].

Overall, LCH is a complex disease with multiple potential factors contributing to its development. Ongoing research aims to uncover the precise mechanisms underlying LCH pathogenesis, which may lead to improved diagnostic and therapeutic approaches for this condition.

First-line treatment for skin-confined LCH requires watchful waiting, as the lesions may resolve spontaneously, especially when the disease is limited and causing minimal symptoms, a "watch and wait" approach may be adopted [5, 12]. This involves close monitoring of the disease's progression without immediate intervention. Medium to high-potency topical glucocorticosteroids are considered as a first-line treatment for LCH. They help to reduce inflammation and can be effective in controlling symptoms. The appropriate therapy for refractory cases remains controversial [9, 10, 12, 24]. Other topical options include nitrogen mustard and tacrolimus [25]. Photochemotherapy with psoralen plus ultraviolet A (UVA) or UVB light can be effective, but the child's ability to

participate in therapy and the potential for late cutaneous malignancy limit its use [10, 15, 25]. Oral treatment options include methotrexate and thalidomide, both of which have been used to treat severe or recalcitrant LCH [26, 27]. For more extensive or severe cases of LCH, chemotherapy agents like vinblastine may be used [15]. These drugs target and kill the abnormal cells responsible for the disease. The choice of chemotherapeutic agents will depend on the specific circumstances and the patient's age. In recent years, targeted therapies have shown promise in treating LCH. The discovery of *BRAF* and *MAP2K1* mutations in LCH has led to utilizing of therapies acting upon the RAS/RAF/MEK/ERK pathway [1, 2]. Drugs like vemurafenib and dabrafenib, for patients with LCH involving the BRAF V600E mutation, have been used in certain situations. Small series and anecdotal case reports of refractory and relapsed LCH have shown responses to the BRAF inhibitors, vemurafenib and dabrafenib [21, 22]. Lack of pediatric long-term safety data may raise questions about using these drugs in children with LCH. The optimal design of therapy is unknown, given that 75% of adults with histiocytosis relapse after discontinuation of BRAF inhibitors [28], indicating that therapy is not a permanent cure. Consequently, in children with LCH, a study of BRAF or MEK inhibitors, rigorously controlled and carefully noting potential acute and late toxicities, optimal duration and cost, is needed [1]. In very severe or refractory cases, hematopoietic stem cell transplantation may be considered as a potential treatment option. This involves replacing the patient's bone marrow with healthy stem cells from a donor. Medications that modulate the immune system, such as interferon-α, may be prescribed to control the disease and reduce its impact on affected organs [15, 20]. In certain instances, surgical excision of isolated skin lesions may be considered, especially if they are causing significant symptoms or if there is concern about malignancy.

Taverna *et al.* [29], O'Kane *et al.* [30] and Dodd *et al.* [24] each reported a case of adult cutaneous LCH treated with imiquimod. Patients experienced rapid clearance of lesions with minimal adverse effects, since LCH may be confined to the skin and is often a benign disease. It is important to rule out visceral involvement and monitor progression to systemic LCH over time.

All patients should undergo a thorough history and physical examination to assess the extent of the disease. Attention is directed to the skin, lymph nodes, ears, oral cavity and mucosa, skeletal system, lungs, thyroid, liver, spleen and central nervous system. Constitutional symptoms (fevers, chills, fatigue, weight loss, and lymphadenopathy) are sought and may indicate bone marrow or lymph node involvement. Polyuria or polydipsia could suggest pituitary involvement, while headaches, nystagmus, tinnitus might indicate cranial infiltration affecting ocular or auricular structures. A complete blood count, comprehensive metabolic panel, skeletal survey, chest radiography and sonography of the liver and spleen are recommended [5, 11]. It is crucial to appropriately screen all patients diagnosed with cutaneous LCH for internal organ involvement as this can affect management and overall prognosis. The authors aim to highlight the need for further investigations to ultimately dictate standardized management and treatment for isolated cutaneous LCH in the child population.

CONCLUSIONS

The clinical presentation of cutaneous LCH might be confusing since it resembles other entities, making the diagnosis difficult. The aim of the article was to present the case of a boy with a skin-confined LCH and discuss the pathophysiology and differential diagnosis of this group of proliferative diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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