Congenital Self-healing Reticulohistiocytosis: An Underreported Entity

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PRACTICE **POINTS**

- Langerhans cell histiocytosis (LCH) is believed to occur in 1:200,000 children and tends to be underdiagnosed, as some patients may have no symptoms while others have symptoms that are misdiagnosed as other conditions.
- Patients with LCH usually should have long-term follow-up care to detect progression or complications of the disease or treatment.

Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a group of rare disorders characterized by the continuous replication of a particular white blood cell called Langerhans cells. These cells are derived from the bone marrow and are found in the epidermis, playing a large role in immune surveillance and the elimination of foreign substances from the body. Additionally, Langerhans cells are capable of migrating from the skin to lymph nodes, and in LCH, these cells begin to congregate on the bone, particularly in the head and neck region, causing a multitude of problems. Langerhans cell histiocytosis is classified into 4 variants: congenital self-healing reticulohistiocytosis (CSHR)(also known as Hashimoto-Pritzker disease), Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. Despite various clinical presentations and severity, all subtypes are pathologically caused by the proliferation of the Langerhans cell.

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Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a general term that describes a group of rare disorders characterized by the proliferation of Langerhans cells.[1] Central to immune surveillance and the elimination of foreign substances from the body, Langerhans cells are derived from bone marrow progenitor cells and found in the epidermis but are capable of migrating from the skin to the lymph nodes. In LCH, these cells congregate on bone tissue, particularly in the head and neck region, causing a multitude of problems.[2]

The spectrum of LCH includes 4 variants: congenital self-healing reticulohistiocytosis (CSHR) (also known as Hashimoto-Pritzker disease), Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma (also known as pulmonary histiocytosis X)(Table). Despite the various clinical presentations and levels of severity, all variants are caused by the proliferation of Langerhans cells. We present a case of CSHR in a 6-month-old male infant that was initially diagnosed as molluscum contagiosum. We believe the actual incidence of CSHR may be underreported due to its spontaneous regression and low rate of clinical recognition.

Case Report

A 6-month-old male infant was referred to our clinic by his pediatrician with a generalized cutaneous eruption of 3 weeks' duration. The eruption, which

Variants of Langerhans Cell Histiocytosis

Condition	Age of Onset	Skin Findings	Systemic/Other Manifestations	Histology	Prognosis
Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease)	At birth or during the neonatal period	Widespread, localized, or solitary lesions; typically reddish brown papules or papulovesicular lesions	Lesions typically resolve within several months; systemic involvement rarely occurs	Langerhans cells (reniform nuclei) with epidermotropism, mixed infiltrate; Birbeck granules on electron microscopy; stain positive for S-100, CD1a, and CD68 proteins	Benign
Letterer-Siwe disease	Early infancy, usually in children younger than 2 years	Multiple scaly papules in a seborrheic distribution on the scalp, face, trunk, and buttocks; lesions occur in crops and may be crusted or hemorrhagic	Visceral and bone lesions including the pulmonary system, liver, spleen, bone marrow, hypothalamus, gastrointestinal tract, and lymph nodes	Langerhans cells (reniform nuclei) with mixed infiltrate; Birbeck granules on electron microscopy; stain positive for S-100, CD1a, and CD68; more epidermotropism and fewer foamy cells than Hand-Schüller-Christian disease	With treatment, 5-year survival rate is 50%[3]
Hand-Schüller-Christian disease	Children aged 2 to 6 years	May resemble Letterer-Siwe disease or may present with papulonodular or granulomatous ulceration in intertriginous areas; xanthomatous appearance	Exophthalmos, diabetes inspidus, lytic bone lesions (typically of the skull), and mucocutaneous lesions	Langerhans cells (reniform nuclei) with mixed infiltrate; Birbeck granules on electron microscopy; stain positive for S-100, CD1a, and CD68; less epidermotropism, more foamy cells, more giant cells than Letterer-Siwe disease	Approximately 30% mortality rate[4]
Eosinophilic granuloma (pulmonary histiocytosis X)	Young adults (second and third decades of life), primarily in the third and fourth decades of life	Skin lesions are rare; noduloulcerative lesions in the mouth or perineal, perivulvar, or retroauricular regions	Primarily bone lesions, usually exhibits a benign course but may involve the cranium, ribs, vertebrae, pelvis, scapulae, and long bones	Langerhans cells (reniform nuclei) with mixed infiltrate; Birbeck granules on electron microscopy; stain positive for S-100, CD1a, and CD68; less epidermotropism, fewer foamy cells, and more diffuse infiltrate with eosinophils, histiocytes, and giant cells than Letterer-Siwe disease	Variable

followed a recent viral upper respiratory tract infection, was characterized by multiple flesh-colored to erythematous, umbilicated papules distributed along the postauricular region, scalp (Figure 1A), abdomen (Figure 1B), and anterior aspect of the neck. Due to his recent illness, the patient was diagnosed with molluscum contagiosum by the referring pediatrician that was treated symptomatically with hydrocortisone lotion, Schamberg's cream formulated in our office (a compound mixture of zinc oxide,

menthol, calcium hydroxide solution, and olive oil), and pediatric diphenhydramine as needed. During a subsequent visit 2 weeks later, a more potent topical corticosteroid and a low-dose systemic corticosteroid was prescribed for 1 week due to development of new lesions and exacerbation of existing lesions. On follow-up 1 week later, the lesions on the trunk had improved, but the patient had developed new lesions on the scalp that differed from prior findings in that they were darker (more erythematous to brown) and firmer (papules and nodules).

A shave biopsy was obtained from the frontal scalp to rule out LCH. Histologic examination and culture of the biopsy specimen revealed an atypical cellular infiltrate effacing the dermoepidermal junction and extensive epidermotropism. Focal erosion of the epidermis and an acute inflammatory exudate were visible. The nuclei of the cellular infiltrate were enlarged and hyperchromatic with a characteristic reniform appearance and indistinct nucleoli (Figure 2). The cells were admixed with scattered eosinophils and extravasated red blood cells.

Immunohistochemical staining of the biopsy specimen was strongly positive for both CD1a and S-100 expression (Figure 3). Histopathologic findings were consistent with LCH. Clinicopathologic correlation strongly favored the diagnosis of CSHR.

Comment

Congenital self-healing reticulohistiocytosis is a rare, benign, congenital variant of LCH that spontaneously resolves with no systemic involvement. The more aggressive forms typically manifest at birth or during the first 2 months of life and regress within 3 to 4 months.[5] Since CSHR was first described in 1973 by Hashimoto and Pritzker,[5] more than 100 cases have been reported, but the true incidence is believed to be higher than reported given the high rate of spontaneous resolution and the low rate of clinical recognition.[2] The first reported case of CSHR occurred in a female infant who presented at birth with multiple, diffusely distributed, red-brown papules that were 2 to 4 mm in diameter. Although the patient received no treatment, the exanthem completely resolved within 3.5 months without recurrence at 14-year follow-up.[5] Most often, CSHR presents as multiple papules or nodules with occasional disseminated crusting and is followed within a few months by a dramatic and spontaneous regression. Lesions may heal with mild postinflammatory

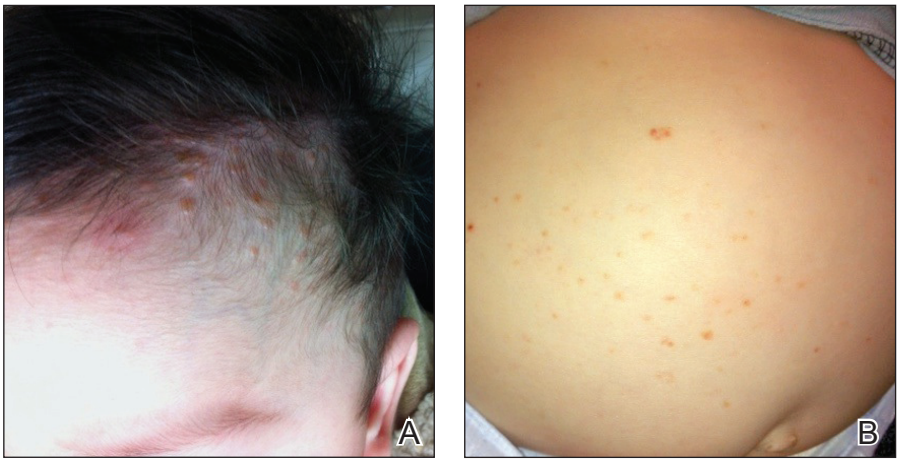

Figure 1. Multiple flesh-colored to erythematous, umbilicated papules on the frontal scalp (A) and erythematous papules on the abdomen (B).

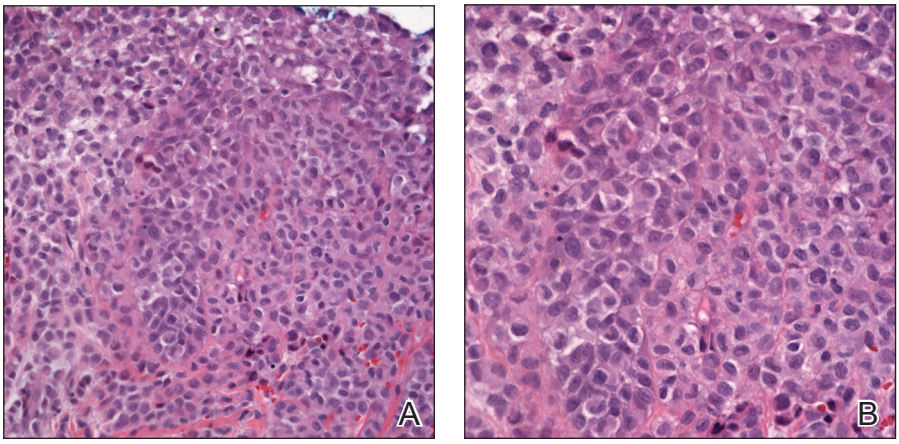

Figure 2. Low-power view of dermal mononuclear cells with reniform nuclei (A)(H&E, original magnification ×100), and high-power view of enlarged and hyperchromatic nuclei with a characteristic reniform appearance admixed with eosinophils and extravasated red blood cells (B) (H&E, original magnification ×400).

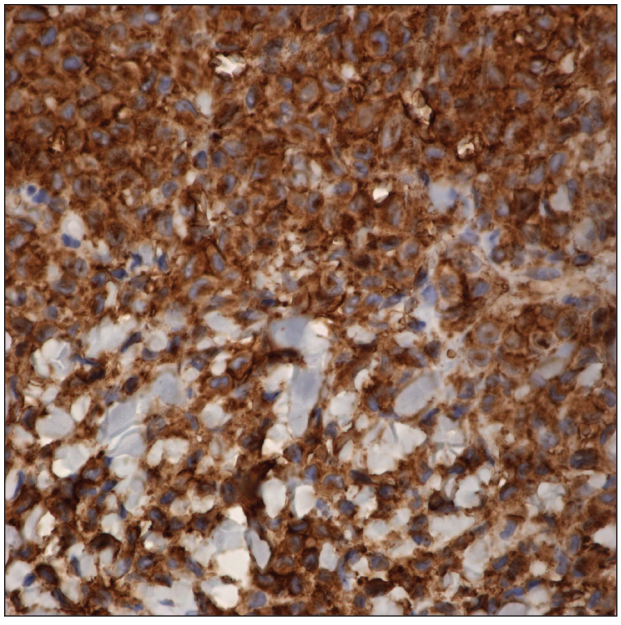

Figure 3. Immunohistochemical staining of the biopsy specimen was strongly positive for CD1a and S-100 expression (original magnification ×400).

hyperpigmentation. Pseudo-Darier sign, the propensity to urticate from physical manipulation, has been reported in some lesions with an increased number of mast cells.[6] Extensive superficial nasal and oral mucosal erosions have been reported in 2 cases.[7] Solitary lesions have been reported in 25% of cases.[8]

The etiology of CSHR remains unknown, though neoplastic, viral, and immunologic origins have been suggested. There have been reports that human herpesvirus 6 may contribute to the development of LCH.[9] It may be postulated that our patient's presentation of CSHR was potentiated by his recent upper respiratory tract illness. In the literature, CSHR is distributed equally among males and females. Prevalence is higher in the white population than in other racial groups.[5]

Although CSHR is a benign cutaneous variant of LCH, there have been reports of patients with disseminated and extracutaneous involvement. In 1 rare case, CSHR reportedly involved the eyes, producing multiple, bilateral, well-circumscribed, diffuse, yellow-white lesions of the retinal pigment epithelium throughout the posterior pole of the eyes.[10] The retinal lesions spontaneously regressed along with the skin manifestations. Additionally, it was reported that a neonate in Thailand presented with CSHR at birth and 1 month later developed multiple lung cysts that had completely regressed 11 months later.[11] One study reported that initial diagnoses of LCH in 18 patients with only cutaneous involvement eventually progressed to systemic LCH, requiring further management.[12] When LCH is suspected, a thorough physical examination, including hematologic and coagulation evaluation, liver function tests, musculoskeletal examination, and consultation with specialists if necessary, is recommended.[13]

There are 3 additional variants of LCH. Letterer-Siwe disease is an acute form of LCH that accounts for 10% of all LCH cases and typically presents in children younger than 2 years. It involves multiple organs, including the bones, lungs, liver, and lymph nodes.[14] Affected patients usually present with fever; hepatosplenomegaly; anemia; lymphadenopathy; extensive lytic skull lesions; and a generalized cutaneous eruption, appearing as a maculopapular scaling rash with underlying purpura on the scalp, neck, axilla, and trunk.[3] Letterer-Siwe disease is inherited in an autosomal-recessive pattern. Diagnosis is confirmed by skin biopsy demonstrating a thinning of the epidermis and a collection of reticulum cells in the dermis.[3] Letterer-Siwe disease is treated with radiation and chemotherapy; if left untreated, the disease is fatal.[4]

Hand-Schüller-Christian disease, a chronic form of LCH, is most commonly seen in children aged 2 to 6 years and accounts for 15% to 20% of all LCH cases. This LCH variant presents with a classic triad of diabetes insipidus (resulting from erosion into the sella turcica), lytic bone lesions, and exophthalmos.[15] Hand-Schüller-Christian disease also affects the oral cavity, producing nodular ulcerations of the hard palate, trouble swallowing, and halitosis.[4] The involvement of lytic bone lesions of the mastoid process and petrous portions of the temporal bones may cause recurrent or chronic otitis media and otitis externa. Hand-Schüller-Christian disease is treated with a combination of chemotherapy, radiation, and surgical excision. The mortality rate is 30%.[4]

Eosinophilic granuloma is the most prevalent variant of LCH, accounting for 60% to 80% of all cases. Characterized by Langerhans cell granulomatous infiltration of the lungs and painful cystic bone lesions, eosinophilic granuloma primarily presents in the third or fourth decades of life.[16] Some studies suggest an epidemiologic association with tobacco use.[17] In the preliminary stages of this disease, Langerhans cells, eosinophils, lymphocytes, and fibroblasts infiltrate and form nodules on the terminal bronchioles in the upper and middle lung zones, damaging the airway walls.[18] Fibrotic scarring progresses, ultimately resulting in alveolar destruction.[10] The common signs and symptoms of eosinophilic granuloma are a nonproductive cough, dyspnea, weight loss, spontaneous pneumothorax, fever, peripheral edema, and a tricuspid regurgitation murmur.[14] The prognosis of eosinophilic granuloma is variable. Although some patients progress

to end-stage fibrotic lung disease requiring lung transplant, there have been reports of complete remission following cessation of cigarette smoking.[17]

Langerhans cells travel from the bone marrow to the epidermis where they express the CD1a protein on the surface of the antigen-presenting cell. Elevated levels of cytokines, such as tumor necrosis factor α, IFN-γ, granulocyte-macrophage colony-stimulating factor, and interleukins have been seen in patients with LCH.[1] Their role in the pathogenesis of this disease remains unknown, but the elevated levels of cytokines may indicate the lack of an efficient immune system.

Histologically, hematoxylin and eosin–stained sections demonstrate an infiltrate of histiocytes, neutrophils, eosinophils, and an increased number of mast cells involving the papillary and reticular dermis. Infiltrating Langerhans cells have concave reniform nuclei[18] and stain positive for CD1a, S-100, and CD68 antigens.[15] In 10% to 30% of CSHR cases, Birbeck granules can be seen on electron microscopy and tend to transform into laminated dense bodies, signifying the degenerative changes seen in CSHR.[15] The various forms of LCH exhibit no significant differences in the expression of the epithelial cadherin, the phosphorylated histone H3, and the Ki-67 proteins, indicating that they are simply different forms of the same disease represented on a spectrum.[15]

Conclusion

The actual incidence of CSHR may be notably underreported due to its spontaneous regression and low rate of clinical recognition. A subtype of LCH, CSHR is a diagnosis of exclusion. Although CSHR generally follows a benign clinical course, a thorough workup and evaluation for systemic disease with close follow-up is recommended after diagnosis due to the potential of LCH to involve multiple organs and to relapse at a later date after apparent regression.

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