CLINICAL VIGNETTE

18-Month-Old Infant with a Persistent Rash

Thomas Jacob, MD

Case Presentation

An 18-month-old female infant presents to primary care with a persistent scalp rash. She had scalp rashes since birth. They were initially small bumps with occasional scaling and diagnosed as seborrheic dermatitis with improvement with coconut oil application and brushing. The scaling had significantly worsened over 6 months with yellowish crusting without bleeding or discharge. Fluocinonide 0.01% was added to coconut oil and exfoliation for one month without significant improvement.

Parents report prior eczematous rashes along her axilla, antecubital and popliteal fossa which resolved with skin moisturization. They noted two small raised erythematous lesions in her inguinal region present for months, which have not increased in size. Her past medical history is significant for multiple prior ear infections, with one ear infection requiring antibiotic therapy in the prior month. Birth history includes birth at 34 weeks gestation, followed by a 2-week hospital stay for feeding difficulty and hyperbilirubinemia requiring phototherapy. There is no family history of atopy or other skin disorders.

On a physical exam, the patient has thick scaly yellowish lesions diffusely across the scalp. There were also raised erythematous patches in areas of the scalp without scaling. Given worsening of symptoms with poor response to steroid therapy, the patient was referred to dermatology. Scalp skin biopsy showed:

> *"band-like inflammatory infiltrate composed of lymphocytes, histiocytes and scattered eosinophils. The histiocytes are characterized by large, ovoid mononuclear cells with folded nucleus, small nucleolus and moderate amount of mildly eosinophilic cytoplasm. The nucleus exhibited a retiform or coffee-bean shaped pattern. Overlying epidermis exhibited mild hyperkeratosis with focal parakeratosis. Stains are positive for langerin, CD1a, S100."*

Given the diagnosis of Langerhans cell histiocytosis, skeletal survey and chest x-ray showed a sclerotic lesion in the left pubic bone. Complete blood count showed white blood count of 12.2 x10E3/uL, Hemoglobin of 11.6 g/dL, Hematocrit of 36.7%, platelets of 521 x 10E3/ul (elevated). The differential showed 35% neutrophils, 56% lymphocytes (elevated), 5% monocytes, 1% eosinophils, and 1% basophils. Renal and liver function tests were normal, including coagulation studies. Lactate Dehydrogenase was 234 IU/L (normal) and uric acid was 2.8 mg/dL (normal). C-reactive protein was elevated at 16.9 mg/L, however, erythrocyte sedimentation rate was normal at 15mm/hr.

Discussion

Langerhans Cell Histiocytosis (LCH) is a rare myeloproliferative disorder characterized by the accumulation of pathologic dendritic (Langerhan) cells along with an inflammatory infiltrate. The finding of tennis racquet shaped Birbeck granules on electron microscopy is considered pathognomonic of the disease.[1] Approximately 2-9 cases per million children are reported per year. The incidence of LCH peaks between the ages of 1-4 years in children.[2]

There is significant variability in clinical presentation, which makes diagnosis of LCH quite challenging. Skin manifestations are the most common initial presentation, noted in 80% of cases. However, other presenting symptoms may include diabetes insipidus, gait abnormalities, conductive hearing loss, respiratory distress, failure to thrive, hepatosplenomegaly or cytopenias. Central diabetes insipidus is the most common endocrine manifestation in LCH as a result of pituitary gland involvement, noted in 25% of patients overall. Generally, patient with isolated bone lesions typically present between 5-15 years of age, whereas multisystem LCH tends to present before 5 years of age.[3] Most common organ involvement is bone (79%) or skin involvement (36%). Liver, bone marrow or splenic involvement as well as failure to treatment with first line therapy is associated with poorer prognosis.[4]

Once LCH is on the differential, the clinician should consider a skin biopsy. Lesions have a characteristic appearance on hematoxylin and cosin (H&E) stain, including pathologic dendritic "Langerhans" cells along with inflammatory infiltrate that include eosinophils, lymphocytes or macrophages. Diagnosis of LCH may be confirmed with specific immunohistochemical staining for antigen markers CD207 (Langerin) and/or CD1a.

At a minimum, patients with confirmed LCH should have a complete blood count, liver function testing, electrolyte assess-

ment, coagulation studies, skeletal survey, chest radiography, and ultrasonography of the liver and spleen.[5] An early morning urine specimen for specific gravity and osmolality should be ordered if diabetes insipidus is suspected. Performing BRAF mutation analysis is now the standard of care, however, it is not universally available.[3]

Treatment of LCH is dictated by the severity and extent of involvement. For mild, skin limited disease, topical corticosteroids are considered first line therapy, followed by tacrolimus, imiquimod, topical nitrogen mustard and phototherapy.[6] Solitary bone lesions may be treated with curettage and corticosteroid injection. Multi-system LCH requires oral prednisone and IV vinblastine as first line therapy. Distinguishing between self-limited disease and systemic LCH is crucial as systemic LCH can become aggressive and require chemotherapy.[7]

Testing for BRAF mutations is now included in the evaluation of LCH since the literature suggests that BRAF V600E mutations may play a role in its pathogenesis. BRAF V600E mutation was found in 50% of LCH cases. This oncogene is part of the extracellular signal-regulated kinase (ERK) or mitogen-activated protein kinase pathway (MAPK). Patients who fail first line therapy may benefit from targeted therapies such as vemurafenib (a BRAF V600E inhibitor), trametinib and cobimetinib (MEK inhibitors). Patients treated with BRAF and MEK inhibitors have shown a significant and sustained response in early-phase trials.[2,3,6]

Although LCH is currently acknowledged as an inflammatory hematopoietic neoplasm, it is not a typical malignancy. Apart from BRAF mutation association, there are limited genetic changes or chromosomal abnormalities currently identified. There are additional immunological studies that hypothesize viruses as a trigger for the inflammatory processes that leads to driver mutations noted in LCH. Early experience is encouraging with good clinical responses seen with kinase inhibitors for both children and adults, however, recurrence occurs when therapy is stopped. Treatment-free remission has remained elusive.[4,8]

The overall prognosis for single lesion skin limited LCH, also known as Hashimoto-Pritzker disease, is excellent and most lesions spontaneously resolve within 4-18 weeks.[7] It is important for clinicians to know that regression of cutaneous disease cannot rule out future dissemination and close long-term follow-up with a multidisciplinary team is necessary.[9] The prognosis is worst in children under 2 years of age with disseminated multisystem LCH and organ dysfunction.[5]

Conclusion

Langerhans cell histiocytosis should be on a differential for patients with persistent eczema or seborrheic dermatitis with poor response to escalating therapy. Median time from first symptoms to diagnosis is 5 months, however, some patients go undiagnosed for years.[1]

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