Adult-onset Multisystemic Langerhans Cell Histiocytosis: A Case Presentation and Discussion

Shahrzad Akbary, BS,* Adam Sorensen, DO,** Richard Bernert, MD, FASDP,*** Joseph Machuzak, DO, FAOCD,**** Stephen Kessler, DO, FAOCD*****

*Medical student, 4th year, Midwestern University Arizona College of Osteopathic Medicine, Glendale, AZ
** Dermatology resident, 3rd year, Alta Dermatology/LECOMT, Mesa, AZ
*** Board-certified Dermatopathologist, Arizona Dermatopathology, Scottsdale, AZ
**** Board-certified Dermatologist, MacKenzie Dermatology, Prescott, AZ
*****Program Director, Dermatology Residency, Alta Dermatology/LECOMT, Mesa, AZ

Abstract

Langerhans cell histiocytosis (LCH) is a rare, systemic disease characterized by the clonal proliferation of bone-marrow-derived epidermal dendritic cells. Though more commonly a disease of the pediatric population, LCH can manifest at any age and involve any organ system. As signs and symptoms may mimic other disease processes, diagnosis is often delayed. Prognosis is variable and largely based on the severity of systemic involvement, with treatment being determined on a case-by-case basis. Herein, we present a case of adult-onset multisystemic LCH with high-risk organ involvement, followed by a brief discussion of its unique presentation and the management of this rare disease.

Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder characterized by the clonal proliferation and infiltration of CD207-positive (Langerin) dendritic cells in various organ systems.[1] Historically, LCH has been classified into several categories based on clinical presentation, including Letterer-Siwe disease, Hand-Schüller-Christian syndrome, eosinophilic granuloma, and Hashimoto-Pritzker disease. The current understanding, however, describes these entities merely as possible presentations on the spectrum of the LCH disease process.[2]

The etiology of LCH is incompletely understood. While the pathologic Langerhans cells in LCH are known to be clonal, there has long been a debate in the literature regarding whether LCH is a neoplastic or a reactive proliferation. However, the recent discovery in 2010 of oncogenic BRAF-V600E mutations in 57% of archived LCH specimens lends support to the idea that LCH may in fact be a neoplastic process and may respond to antineoplastic therapy such as BRAF-pathway inhibitors.[3]

Due to the rarity of the disease, much that is known about LCH is a result of individualized case studies. More commonly recognized in the pediatric population, LCH affects children at a rate of one in 200,000, usually occurring between 1 and 3 years of age.[4] In adults, the incidence is roughly one to two cases per million, predominantly affecting those between the ages of 20 and 35 years.[5] Here, we present a rare case of LCH presenting in a patient well outside the typical age of onset.

Case Presentation

A 60-year-old Caucasian male presented to the dermatology clinic with a chief complaint of a pruritic, mildly tender scalp along with flaking and scabbing of 10 years' duration. During that time, he had been evaluated by several physicians, including dermatologists, with diagnoses ranging from eczema and seborrheic dermatitis to folliculitis and alopecia.

Previous treatments had included use of clobetasol shampoo, oral minocycline, and betamethasone valerate cream off and on over many years, none of which had resulted in long-term relief of scalp changes. Past medical history was significant for long-standing central diabetes insipidus, type-II diabetes mellitus, hypertension, hyperlipidemia, low testosterone, iatrogenic hypothyroidism secondary to papillary carcinoma of the thyroid, anti-mitochondrial antibody (AMA)-negative primary biliary cirrhosis, and primary sclerosing cholangitis. Of note, the patient denied any history of smoking or pulmonary symptoms.

Physical exam showed multiple scattered, crusted papules and several vesicles over a nearly confluent erythematous, scaly base distributed diffusely over the scalp; there was also evidence of some follicular dropout and alopecia (**Figure 1**). Due to the progressive and prolonged nature of his disease as well as its refractoriness to prior treatments, two 4-mm punch biopsies of the left and right parietal regions were obtained. Differential diagnosis at the time included folliculitis decalvans and another cicatricial alopecia.

Figure 1. Multiple scattered papules and vesicles with accompanying yellow-tinged crusting on scalp; extensive flaking also evident.

Both biopsies revealed a neoplastic, folliculocentric, extensive Langerhans cell infiltrate diagnostic of Langerhans cell histiocytosis (**Figures 2, 3**). Extensive positivity for Langerin (CD-207), staining for CD-31, and lack of immunoreactivity for CD-83 further confirmed the diagnosis.

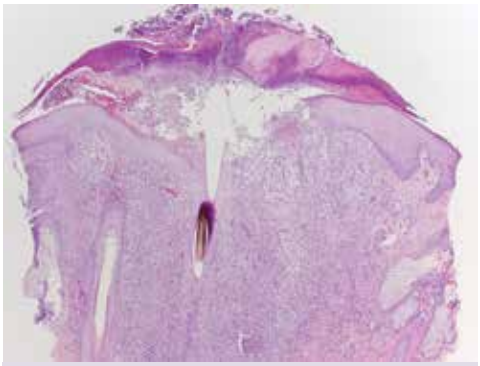

Figure 2. Dense mononuclear infiltrate positioned beneath a hemorrhagic, impetiginized scale, situated primarily within the papillary, perifollicular dermis.

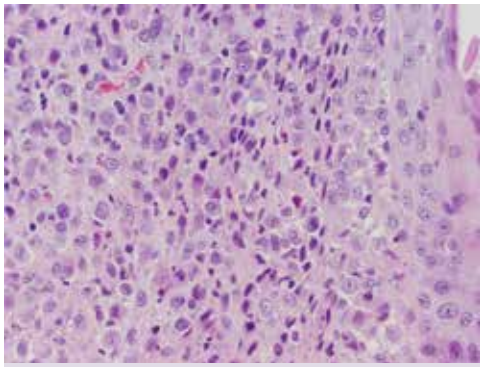

Figure 3. Infiltrate consisting mostly of large, rather monomorphic histiocytic cells with high nuclear-to-cytoplasmic ratios, conspicuous nucleoli, and irregular nuclear profiles with ridges and grooves; few eosinophils distributed unevenly.

Multisystemic Work-up

In light of the patient's history of central diabetes insipidus and hepatobiliary disease, we suspected multisystemic LCH. Systemic work-up revealed normal CBC and CMP with the

Table 1. Clinical Classification of LCH[6]

Type	Involvement
Single-system LCH (one organ/system involved, uni- or multifocal)	Bone: unifocal (single bone) or multifocal (>1 bone)
	Skin
	Lymph node (not the draining lymph node of another LCH lesion)
	Lungs
	Hypothalamic-pituitary/central nervous system
	Other (e.g., thyroid, thymus)
Multisystem LCH (two or more organs/systems involved)	With or without involvement of "risk organs" (hematopoietic, liver, spleen, lung)

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exception of known and chronically elevated alkaline phosphatase and transaminases. A chest radiograph concerning for bibasilar changes prompted a high-resolution chest CT without contrast to be ordered. This revealed severe coalescing fibrotic and cystic lung disease in bilateral lower lobes with mild centrilobular emphysema and bilateral upper-lobar pulmonary fibrosis. Tiny calcified and uncalcified nodules were also noted throughout. A skeletal radiographic survey showed several tiny punctate lucencies scattered in the right and left humeral heads as well as the humeral shafts. As these findings were consistent with multisystemic Langerhans cell histiocytosis with involvement of high-risk organs, the patient was referred to the Mayo Clinic in Scottsdale, Arizona for further evaluation and treatment. There, a follow-up bone-marrow biopsy and PET scan were not found to be consistent with hematologic malignancy.

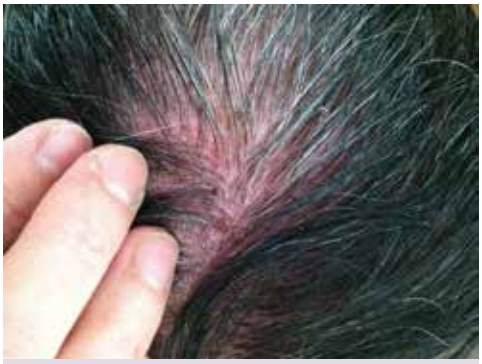

Figure 4. Scalp after one month of treatment with 0.05% clobetasol spray; note near-resolution of papules and vesicles, persistent erythema.

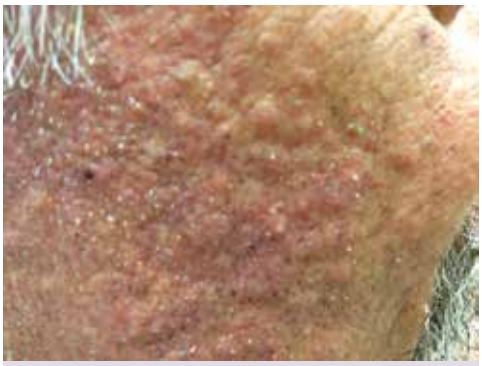

Figure 5. Erythematous papules on right cheek presenting seven months after initial diagnosis; biopsy consistent with Langerhans cell histiocytosis.

Treatment

For scalp symptoms, the patient was prescribed 0.05% clobetasol spray and instructed to use it twice daily. After one month, he reported significant improvement in symptoms (**Figure 4**). However, seven months after initial presentation the patient presented with new, scattered erythematous papules on bilateral cheeks and jawline; these were biopsied and found to be consistent with LCH (**Figure 5**). It is interesting and gratifying to note that despite the above multisystemic findings, the patient insists he feels healthy and is not experiencing any shortness of breath, bone pain, or a lessened quality of life other than his skin complaints. However, due to the severe findings on imaging and persistent skin lesions, the patient was initiated on a regimen of methotrexate at Mayo Clinic, Scottsdale, where treatment is ongoing.

Discussion

In order to better classify LCH, the Histiocyte Society stratifies disease based the number of organ systems involved (single-system versus multi-system) and whether or not disease activity is unifocal or multifocal in each organ system (**Table 1**). They also classify disease based on involvement of high-risk organs, defined as the hematopoietic system, liver, spleen, and lungs.

Once a biopsy-proven diagnosis of cutaneous LCH is made, investigation into multisystemic manifestations is of utmost importance to determine prognosis and guide treatment.[7] Guidelines for diagnosis and treatment are well established for the pediatric population;[8] however, the approach to management for adult patients is less well defined. In 2009, the Histiocyte Society published guidelines for recommended baseline laboratory and radiographic evaluation (**Table 2**). This proposed work-up investigates the hematopoietic system, liver, bone, lung, and endocrine system.

While Langerhans cell histiocytosis can affect any organ system, the skin is often the first identifiable manifestation of disease. In adults, cutaneous involvement is extremely variable in presentation.[10] Lesions may present as small papules, pustules, and/or vesicles with accompanying yellow crusting and erythema; these classically occur in intertriginous areas or, as with our patient, on the scalp.[7,10] On examination, the cutaneous manifestations can be easily mistaken for common dermatologic conditions such as eczema, seborrheic dermatitis,

Table 2: Recommended baseline evaluation upon diagnosis/reactivation of LCH[9]

Full blood count
Hemoglobin, white-blood-cell and differential count, platelet count
Blood chemistry
Total protein, albumin, bilirubin, ALT, AST, alkaline phosphatase, GGT
BUN, creatinine, electrolytes
Ferritin
Coagulation studies
INR/PT, APTT/PTT, fibrinogen
Early-morning urine sample
Specific gravity and osmolality
Abdominal ultrasound
Size and structure of liver and spleen
Chest radiograph (CXR)
Skeletal radiograph survey*

*Functional imaging such as bone scan is optional and can be performed in addition to skeletal survey. PET scan has proven to be the most sensitive functional test used in the identification of LCH lesions and in evaluating patient response to therapy. However, PET scan is currently expensive and not widely available.

dermatophytosis, and folliculitis. This mimicry, coupled with the rarity of adult LCH, often leads to a delay in biopsy and diagnosis.

Central diabetes insipidus (DI) is the most common endocrine manifestation of LCH and is caused by Langerhans cells infiltrating the posterior pituitary. A retrospective analysis by Arico et al. reported DI to occur in 29.6% of patients;[5] however, incidence as high as 40% in adult patients has been reported.[7] Magnetic resonance imaging (MRI) is the most sensitive diagnostic tool for LCH-associated DI and will often show thickening of the pituitary stalk with "loss of bright spot," which corresponds to loss of antidiuretic hormone (ADH)-containing granules.[11] Once this infiltration occurs, it results in the irreversible sequelae of central DI, and patients must receive lifelong supplementation with desmopressin acetate. Diabetes insipidus presents with polydipsia and polyuria and may predate the diagnosis of LCH or develop subsequently.[7] Our patient exemplifies this, as he was diagnosed with central DI in 1994 and insists his scalp changes did not occur until the early 2000s.

In adults, pulmonary LCH is more commonly seen as an isolated disease rather than a manifestation of multisystemic LCH, and it is strongly associated with smoking.[7] When the lungs are affected in adult multisystemic LCH, as in our patient, the disease is classified as high-risk.[6] The pathogenesis of pulmonary LCH is thought to be the infiltration and excessive activation of Langerhans cells in the lung parenchyma. While definitive diagnosis cannot be established without a biopsy demonstrating these abnormal Langerhans cells, imaging modalities can be highly suggestive of disease in the proper clinical context. Presence of nodules, cystic changes, and honeycombing on high-resolution CT are signs of advanced disease and increase the risk of pneumothorax, which occurs in up to 15% of patients.[12] Dyspnea and a non-productive cough may also occur; however, as in our case, many patients may be asymptomatic, making imaging and subsequent pulmonary-function testing vital for patient prognosis and monitoring.

As exemplified in our case, hepatobiliary and splenic involvement in Langerhans cell histiocytosis is not uncommon, occurring in up to 20% of patients. As Langerhans cells progressively infiltrate these organs, they cause bile-duct destruction and can lead to sclerosing cholangitis, biliary cirrhosis, and subsequent portal hypertension.[13] Therefore, a metabolic panel with work-up of any abnormalities is always warranted in this patient population.

Treatment for adult LCH is variable and depends largely on the extent of disease and its impact on the patient's quality of life. Typically, patients with skin-limited disease will respond to high-potency topical steroids and require no further treatment. However, in patients with multisystemic disease, approach considerations may include a combination of systemic steroids along with a single-agent chemotherapeutic -- either vincristine or vinblastine. For these patients, response during the six-week induction phase with these therapies has been shown to be the single most important long-term prognostic indicator.[14]

Conclusion

Adult multisystemic Langerhans cell histiocytosis is a rare, though likely under-recognized, disease that requires a high index of clinical suspicion to diagnose. LCH should be considered in adults with refractory lesions on the scalp. Once diagnosed, it requires an appropriate multisystemic work-up both for risk stratification and to guide subsequent therapeutic decision-making. While patients often first present to the dermatologist, adults with multisystemic LCH require a multidisciplinary approach to manage disease manifestations and guide treatment.

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Correspondence: Shahrzad Akbary, BS; sakbary81@midwestern.edu