Introduction: Prior reports of Langerhans cell histiocytosis (LCH) suggest that isolated skin involvement is rare and often progresses to systemic disease. More rapid access to pediatric subspecialty care has likely led to more frequent representation of this condition. The purpose of this study is to characterize the natural history of skin-limited LCH in an era of increased access to pediatric subspecialty care.

Materials and Methods: A retrospective chart review was performed on all patients newly diagnosed with LCH between 2001 and 2012 at the Children’s Hospital of Wisconsin. Extensive review of laboratory, physical examination, and imaging reports was performed and data collected for patients with biopsy-proven skin LCH.

Results: Sixteen individuals with skin-limited LCH were identified. The median age at onset of skin eruption was birth (range, birth to 6 mos), and median duration of follow-up was 19.5 months (range, 2 wk to 10 y) from diagnosis. One patient (6%) developed pituitary disease and 1 patient (6%) had refractory skin involvement. All others experienced complete resolution. For patients without progressive or refractory disease, resolution of skin findings occurred within 7 months from onset.

Discussion: Progression of skin-limited to multisystem LCH likely may be less frequent than previously described.

Key Words: Langerhans cell histiocytosis, skin limited, multisystem

Langerhans cell histiocytosis (LCH) is a rare disorder1,2 believed to result from the proliferation and accumulation of clonal dendritic cells called Langerhans cells.3,4 Manifestations vary widely, from single system to disseminated disease involving essentially any organ. Despite the potential for multisystem involvement, two thirds of patients have only single-system involvement, primarily of bones, skin, and lymph nodes.5-7 Although nearly half of all cases will eventually involve the skin, only 7% to 13% of patients have disease confined to the skin at diagnosis.6,7 Skin findings are variable; however, an erythematous, scaly dermatitis involving the scalp, posterior auricular regions, perineum, and/or axillae is typical of LCH. Additional characteristic findings include erythematous, red-brown papules with or without secondary erosion, hemorrhage, or crusting commonly seen in the scalp, conchal bowls, palms, soles, and/or flexural regions.8

An historical distinction has been made between the congenital, self-healing presentation of skin involvement (Hashimoto-Pritzker disease or congenital self-healing LCH) and those skin-limited presentations that often require treatment. On the basis of this nomenclature, an estimated 8% to 13% of cases with the congenital, self-healing phenotype later experience multisystem relapse.9,11 As both entities may demonstrate either spontaneous resolution or progression, they are now felt to represent a broader continuum of the same disease.9,12

The largest series (ranging from 9 to 19 patients) evaluating the entire spectrum of skin-limited presentations report progressive disease in 21% to 56% of patients and refractory skin involvement in an additional 11%.6,7,13 These estimates were derived from patients primarily treated between 1980 and 2000 outside of the United States.6,13 We hypothesized that improved access to pediatric subspecialty care14-16 and subsequent increases in pediatric subspecialty referral rates7,18 have led to earlier and more complete recognition of both self-resolving and progressive skin-limited LCH. The objective of this study was to estimate the rate of progression from skin-limited to multisystem LCH in a cohort spanning an era of increased provider awareness and access to pediatric subspecialty care.

MATERIALS AND METHODS

Subjects

This retrospective chart review was approved by the Institutional Review Board at the Children’s Hospital of Wisconsin (CHW). Consecutive patients seen at CHW between January 1, 2001 and November 2, 2012 carrying International Classification of Diseases, Ninth Revision (ICD-9)19 codes consistent with LCH were identified and independently evaluated for eligibility by 2 authors (M.J.E. and S.R.H.). This study period coincides with a single electronic medical record at CHW and subsequently allows for more accurate data capture. During this period, there were 2 to 8 pediatric dermatologists and 3 to 7 pediatric oncologists at CHW. Subjects were included if they were...
diagnosed within the study interval at CHW with biopsy-proven, skin-limited LCH as defined by the criteria set forth by the Histiocyte Society. Subjects were excluded if: (1) they had multisystem LCH at diagnosis (evidenced by computed tomography, skeletal survey, bone scan, or laboratory aberrations); (2) the diagnosis was made outside of CHW or the designated study period; and (3) the primary diagnosis as coded by ICD-9 was inconsistent with LCH.

Chart Review

Electronic medical records of eligible subjects were reviewed and the following details were collected: sex, race (self-identified), age at onset of lesions, age at diagnosis, physical examination findings, description of skin lesions, pathology results, laboratory results, imaging results, treatment, time to resolution or progression, outcome, and duration of follow-up. Radiologic diagnoses were abstracted from the medical records and did not undergo additional central review. Local reference ranges were utilized for comparison of laboratory values. Time to disease resolution, progression, or last follow-up was determined from documented evaluations by dermatology or oncology providers.

Biostatistics

Descriptive statistics were generated to characterize median age of onset, median age at diagnosis, median duration of follow-up, and rates of both progressive and refractory disease. Patients lacking adequate follow-up documentation were omitted from median and range calculations.

RESULTS

Ninety-three patients were diagnosed with LCH at CHW between January 2001 and November 2012. Sixteen individuals (17%) with skin-limited LCH were identified (Fig. 1). Skin biopsies demonstrated characteristic histologic features and CD1a-positive lesional cells. All patients had a skeletal survey and 15 of the 16 received recommended laboratory evaluation for systemic involvement as recommended by the Histiocyte Society. Patients were followed clinically for evidence of disease progression and additional evaluation was dictated by the individual clinical course. Patient characteristics for subjects with skin-limited LCH are summarized in Table 1. Eight were male and 8 were female patients; 87% were white. The median age at onset of skin eruption was birth (range, birth to 6 mo), whereas the median time from onset to diagnosis was 18 days (range, 1 d to 12 mo). The median duration of follow-up was 19.5 months (range, 2 wk to 10 y) from diagnosis. All patients were alive at last follow-up.

The most common cutaneous findings were crusted papules involving the groin, axillae, head, neck, trunk, and/or extremities. Papules were described as pink, red-brown, or violaceous and ranged in size from 1 to 4 mm in most subjects. Two patients had solitary lesions, 13 had multiple skin lesions, and 1 lacked documentation of skin findings. Consistent with the diagnosis of skin-limited LCH, no patients had lymphadenopathy or hepatosplenomegaly.

Subject 2 experienced relapsing and remitting skin exacerbations predominantly of the inguinal folds and scalp despite topical corticosteroids. At 12 months of age, 6 months following diagnosis, lack of linear growth prompted evaluation of pituitary function. Thyroid-stimulating hormone, free thyroxine, IGF-1, IGF-binding protein 3, and cortisol levels remained normal. Magnetic resonance imaging of the brain demonstrated pituitary stalk thickening and concurrent loss of the characteristic pituitary “bright spot.” Skeletal survey and computed tomography of the chest, abdomen, and pelvis showed no other organ involvement. Pituitary progression and subsequent diabetes insipidus coincided with resolution of skin involvement. The patient is currently being treated with monthly cytarabine for pituitary LCH without clinical or radiographic evidence of further disease progression. Diabetes insipidus is controlled with desmopressin.

Subject 1 was diagnosed at 17 months of age with a 1-year history of skin rash. Initial therapy included topical corticosteroids and 2 separate courses of oral prednisone. Vinblastine was added to prednisone for persistent disease at 3 years of age, 1.5 years following diagnosis. Response varied with the intensity of therapy. At 5 years of age, 3.5 years following diagnosis, biopsy-proven nail-bed involvement complicated by a fungal nail infection prompted treatment with cytarabine. Six months later, vinblastine and prednisone were restarted for refractory skin and nail-bed involvement.

FIGURE 1. Patient selection process. CHW indicates Children’s Hospital of Wisconsin; ICD-9, International Classification of Diseases, Ninth Revision; LCH, Langerhans cell histiocytosis.
We believe that improved access to pediatric care has led to increased representation of those with resolving disease in tertiary centers.\(^\text{14-16}\) Therefore, the decreased rate of progression of skin-limited LCH in our study may better represent that seen in modern practices.

Alternatively, our selection process may have excluded patients with primary skin-limited disease who presented after the development of multisystem LCH. We identified 10 patients with multisystem LCH at diagnosis, 9 of which reported preceding skin eruptions. If we consider these 9 patients to have had skin-limited disease at onset, the rate of progression to multisystem LCH in our cohort increases to 38%. Conversely, exclusion of children with self-resolving skin-limited presentations not referred for tertiary evaluation overestimates the true rate of progression. As it was impossible to determine the extent of disease at onset in these 9 patients, we have excluded them from the overall analysis.

Pituitary progression in subject 2 coincided with skin resolution 17 months after initial diagnosis. This sharply contrasts the 14 patients with remitting disease who each experienced skin resolution within 7 months of diagnosis. Although reliable clinical and dermatological findings to predict progression have not been identified, prolonged duration of a primary skin eruption may suggest those at higher risk and merits future investigation. In the absence of reliable predictors, patients continue to require follow-up for progressive disease.

**DISCUSSION**

Our findings demonstrate progression from skin-limited to multisystem LCH in only 1 patient (6%). This rate of progression is similar to that reported by Ng et al\(^\text{22}\) (0 of the 6 patients) in a similar era. Both are strikingly lower than previously reported rates of progression ranging from 61\% to 56\% in patients diagnosed between 1980 and 2000.\(^\text{5,7,13}\) We believe that improved access to pediatric subspecialty care has led to increased representation of those with resolving disease in tertiary centers.\(^\text{14-16}\) Therefore, the decreased rate of progression of skin-limited LCH in our study may better represent that seen in modern practices.

One patient (6\%) developed refractory skin disease. Refractory skin-limited disease is unusual and can be challenging to treat.\(^\text{23}\) With increasing referrals, we anticipated increased recognition of individuals with self-resolving skin-limited disease. However, we did not expect changes in referral patterns for those with recalcitrant or progressive disease. The incidence of recalcitrant disease in our cohort was similar to the 11\% previously reported by Titgemeyer et al\(^\text{6}\) and supports the likelihood that referral rates for those with refractory or progressive disease have remained unchanged despite increasing access to pediatric subspecialty care.

This is the largest and most recent cohort of patients with skin-limited LCH described within the United States health care system. However, several limitations of this study are recognized. First, our hypothesis regarding increasing tertiary referrals for skin LCH may be incorrect. However, 17\% of our newly diagnosed patients had skin-limited LCH. The same incidence (16.7\%) has been demonstrated by Kwon et al\(^\text{24}\) in a similar diagnostic era. These higher than historically reported incidences support improved recognition and referral in the modern era.\(^\text{6,7,13}\) Second, we cannot exclude late progression in patients no longer followed at CHW. In particular, 5 patients were followed for < 6 months before being lost to follow-up. As the tertiary referral center, it is reassuring that these patients have not returned to CHW with progressive LCH; however, we cannot exclude presentation to another institution. Finally, this study represents a single institution’s experience and therefore limits the generalizability of our findings.

Skin-limited LCH remains a disease with an excellent overall prognosis. Our study suggests that most patients with skin-limited LCH in a tertiary center will have resolution of disease without progression or recurrence. Prospective confirmation of these findings is an aim of the ongoing LCH-IV study and may add clarity to this rare condition. Patients continue to require close evaluation for progressive disease in the early follow-up period; however, prognosis may be improved from previous estimates.
REFERENCES


