Successful Treatment of Adult Multisystemic Langerhans Cell Histiocytosis With Psoralen–UV-A, Prednisolone, Mercaptopurine, and Vinblastine

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Background: Langerhans cell histiocytosis (LCH) is a rare disease with a peak incidence in childhood. There is limited experience with treatment options for adult patients having multisystemic LCH involvement. We report successful treatment of a 70-year-old woman with adult onset of LCH and multisystem disease (diabetes insipidus centralis, bone marrow infiltration, and lung and skin involvement).

Observations: A 70-year-old woman with erythematous plaques and papules of the submammary and inguinal skin attended our outpatient clinic and was diagnosed as having LCH. Organ involvement was found in the infundibulum of the pituitary gland, associated with diabetes insipidus centralis, bone marrow infiltration, and several micronodules of the thoracic and lumbar spine and lungs. Based on the Histiocyte Society’s LCH-A1 study in adults, the patient was treated for 12 months with a combination of corticosteroids, vinblastine, and mercaptopurine. No major adverse effects were observed. The skin was also treated with a combination of psoralen–UV-A and local corticosteroids. Restaging revealed regression of all clinical symptoms (skin involvement and diabetes insipidus centralis) and regression of organ infiltration (pituitary gland, bone marrow, and lungs).

Conclusion: Effective treatment of adult multisystemic LCH disease was achieved using prednisolone, vinblastine, and mercaptopurine, which was well tolerated.

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LANGERHANS CELL HISTIOCYTOSIS (LCH) IS A RARE DISORDER CHARACTERIZED BY DYSREGULATED GROWTH, ACTIVITY, AND TRAFFICKING OF LANGERHANS CELLS.1,2 THESE ANTIGEN-PRESENTING CELLS REPRESENT AN IMMATURE STAGE OF DENDRITIC CELLS AND, ALONG WITH LYMPHOCYTES, EOSINO- PHILS, AND NEUTROPHILS, FORM TYPICAL INFILTRATES FOUND IN SKIN AND IN VARIOUS INTERNAL ORGANS. LANGERHANS CELL HISTIOCYTOSIS IS GENERALLY CONSIDERED TO BE A DISEASE OF CHILDHOOD (PEAK INCIDENCE, AGE 1-3 YEARS).3 THEREFORE, THE DISORDER HAS PRIMARILY BEEN STUDIED IN CHILDREN, AND MOST INFORMATION REGARDING CLINICAL FEATURES, PATHOGENESIS, AND TREATMENT OUTCOMES DERIVES FROM PEDIATRIC EXPERIENCES.3,5 HOWEVER, LATE ONSET IN ADULTS IS ALSO FOUND, PARTICULARLY AS MULTISYSTEM DISEASE.

Langerhans cell histiocytosis includes a wide range of clinical manifestations comprising clinical pictures of the historical terms eosinophilic granuloma, Hand-Schüller-Christian syndrome, and (Abt-) Letterer-Siwe disease.6 The current classification of LCH follows the guidelines of the Histiocytosis Society, incorporating study results from multicenter randomized trials in children.7 Depending on the organs involved, LCH has been categorized as a localized form (single-system disease) and as a disseminated form (multisystem disease). Multisystem disease is further subdivided into 2 risk categories (low and high) depending on the clinical course, response to treatment, and involvement of risk organs (lungs, liver, spleen, and hematopoietic system). Patients with disease that is localized (skin, bone, and lymph node) have a good prognosis and need minimal or no treatment.3,7 In contrast, multiorgan (multisystem) involvement, which is particularly common in children younger than 2 years but also occurs in adults, carries the risk of a poor outcome.3,7 The course of LCH is unpredictable, varying from spontaneous regression to rapid progression and death or to repeated recurrences and recrudescence with the risk of permanent consequences. Almost any part of the body can be involved. The organs most commonly affected include the skin, bones, lung, genitourinary tract, endocrine system, central nervous system, and lymphoreticular and gastrointestinal systems.3,4

Children with multisystem LCH benefit from treatment regimens with cytotoxic drugs or corticosteroids, alone or in combination.9,11 However, there is limited experience in adults because LCH is a rare disease and the incidence in adults is esti-
A 70-year-old, otherwise healthy, woman noticed the development of erythematous confluent papules and plaques in the submammary and inguinal regions (Figure 1A and B). Minor involvement of the axilla and the rima ani was also observed. The lesions grew in size and started to show erosions but did not disturb the patient otherwise. Biopsy specimens were obtained from the mammary and inguinal skin. Histologic examination revealed a parakeratotically thickened horny layer with acanthosis of the epidermis (Figure 2A). Several mitotic figures and cells positive for the proliferation marker MIB-1 were found (Figure 2C). On immunohistologic examination, the tumor cells reacted with S-100 (Figure 2D) and with CD1a (Figure 2E); therefore, the diagnosis of LCH was made.

DIAGNOSTIC INVESTIGATIONS

The results of laboratory investigations were as follows: potassium, 3.3 mEq/L (reference range, 3.6-4.8 mEq/L); antidiuretic hormone, 2.6 pg/mL (normal level, <8 pg/mL); serum osmolality, 312 mOsm/kg (reference range, 280-300 mOsm/kg); and C-reactive protein, 22 mg/L (normal level, <5 mg/L) (to convert potassium level to millimoles per liter, multiply by 1.0; to convert antidiuretic hormone level to picomoles per liter, multiply by 0.923; to convert serum osmolality level to millimoles per kilogram, multiply by 1.0; to convert C-reactive protein level to nanomoles per liter, multiply by 9.524). The following other laboratory findings were normal: thyroid levels, complete blood count, renal variables (urea, electrolytes, and creatinine levels), cholesterol levels (total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), and hepatic variables (bilirubin, alkaline phosphatase, aspartate aminotransferase, and glutamic pyruvic transaminase).

The following diagnostic investigations were performed, which showed no abnormalities: gastroscopy, electrocardiogram, pulmonary function, abdominal and lymph node ultrasonography, and radiography of the head, thorax, large bones, and pelvis. A bone marrow sample was obtained, which on pathologic examination showed nodular infiltration with Langerhans cells (Figure 3A and B). Multifocal bone edema of the vertebral bodies of the thoracic and lumbar portions of the spine was observed on magnetic resonance imaging (Figure 3D); no other bone involvement was found on radiographs of the arms, legs, and pelvis.

An endocrinologic examination revealed that the patient had previously unrecognized polyuria (3-4 L/d) and increased thirst. The infundibular area of the pituitary gland was enlarged based on magnetic resonance imaging (Figure 4A and B). In addition, multifocal hyperplasia of the adrenal gland was observed on computed tomography of the abdomen. Administration of dexamethasone did not induce a sufficient decline of the serum cortisol level, suggesting subclinical Cushing syndrome. Ultrasonography and scintigraphy of the thyroid gland demonstrated nodular structures with normal thyroid function; biopsy specimens revealed no suspicious findings.

Computed tomography of the lungs showed diffuse infiltration of the lung parenchyma with micronodules and an area of opacity in the right upper lobe (Figure 4E). On cardiologic examination, mild hypertensive heart disease with coronary sclerosis was seen, and antihypertensive medication was started. In summary, the patient was diagnosed as having multisystem LCH. Involvement of the skin, bones, bone marrow, lung (micronodules), and pituitary gland (partial diabetes insipidus centralis) was noted.

TREATMENT

Because of multisystem involvement, chemotherapy based on the regimen used in adults in the LCH-A1 trial was started. The patient received 12 months of therapy. During treatment initiation (6-week course), the patient was treated with vinblastine (6 mg/m² intravenously) once a week and oral prednisone daily (1 mg/kg/d [60 mg total]) for 4 weeks. Corticosteroids were then tapered for an additional 2 weeks (1 week at 40 mg and 1 week at 20 mg). Therapy was continued in 3-week cycles of prednisone (60 mg) on days 1 through 5, together with vinblastine (6 mg/m²) on day 1. During continuation therapy, mercaptopurine (30 mg/m²) was administered orally every day. No grade 2 or 4 hematologic toxic effects were observed during treatment. The patient experienced no...
severe adverse effects (eg, infections). Occasional emerg-
ing nausea was improved by treatment with metoclop-
ramide hydrochloride.

Zoledronic acid (4 mg intravenously) was given every
4 weeks to treat bone osteolysis. Diabetes insipidus cen-
tralis was treated with desmopressin acetate (0.2 mg/d),
which normalized thirst, serum levels, and urine pro-
duction within several weeks. Skin involvement was
treated locally with methylprednisolone aceponate (0.1%)
cream once daily, supported by psoralen–UV-A expo-
sure (2.5 J/cm²).

FOLLOW-UP EXAMINATIONS

After 9 months of therapy, marked reduction in the sig-
nal intensity of the osteolysis was observed, as well as
regression of swelling and infundibulum enhancement
of the pituitary gland (Figure 4C and D). Skin manifesta-
tions were significantly reduced (compare Figure 1D–F)
over time. Histopathologically, bone marrow infiltra-
tion was no longer detectable 4 months after treatment
initiation (Figure 3C). Lung involvement was im-
proved, and micronodules were no longer seen. In con-
clusion, a near-complete remission was observed dur-
ing a follow-up duration of 1 year.

COMMENT

Langerhans cell histiocytosis ranges in severity from cur-
able solitary lytic bone lesions to a fatal leukemialike dis-
order. Intermediate forms demonstrate variable courses
characterized by diabetes insipidus centralis, varying de-
grees of organ dysfunction, and bone, skin, and mucous
membrane involvement. The clinical picture, treatment
planning, and prognosis depend on the extent of the dis-
ease and the age of the patient at the time of onset.

In adult patients with LCH, different treatment strate-
gies have been used depending on organ involvement
and clinical course. Therapeutic options include local
treatment, radiation therapy, chemotherapy, immuno-
modulation, and liver, lung, and stem cell transplanta-
tion in advanced-stage disease. Chemotherapy op-
tions for multisystem disease include combined treatment
with vinblastine, etoposide, mercaptopurine, corticoste-
roids, azathioprine, cyclophosphamide, chlorodeoxy-
adenosine, and cytosine arabinoside. Patients with limited disease have an excellent prognosis, usually without need for systemic therapy. In contrast, patients with multifocal skeletal involvement, refractory cutaneous lesions, and disseminated or recurrent organ disease will almost always benefit from systemic treatment. However, the optimal treatment strategy for adult patients with LCH remains to be defined.

Adults with multisystem LCH have a disease course similar to that in children with multiorgan LCH. Evidence accumulated by pediatric trials demonstrated success in treating multisystem LCH. The standard chemotherapy regimen for multisystem LCH in children is a combination of vinblastine and prednisolone administered during 12 months. As demonstrated by systemic studies in children (DAL-HX 83 and 90, LCH I, and LCH II), the standard etoposide regimen has not shown additional benefit for response, survival, or reactivation frequency as monotherapy or in combination with vinblastine and prednisolone. Therefore, etoposide was not included in the treatment schedule of LCH III/LCH-A1 because of its potential leukemogenicity.

According to the LCH-A1 study, launched in 2004 by the Histiocyte Society, and to confirm the efficacy of the standard chemotherapy in adult patients, we applied this scheme in our patient with multiorgan adult LCH who was (because of her age) ineligible to be enrolled in this study. In the LCH-A1 study, patients with multisystem disease receive prednisolone and weekly infusions of vinblastine for 6 weeks, followed by continuation treatment with vinblastine, prednisolone, and mercaptopurine for 6 months (arm A) or for 12 months (arm B).

In our patient, the LCH-A1 therapy was combined with topical corticosteroid treatment and psoralen–UV-A irradiation of the skin. This treatment schedule allowed not only significant clinical improvement of the affected skin but also normalization of multisystem LCH (including bone, lung, and pituitary gland) within several months. The therapy was well tolerated, no grade 2 to 4 hematologic toxic effects were observed, and the only adverse effects were rare occurrences of nausea. Follow-up evaluation revealed complete response within 1 year.

As reported by the Histiocyte Society, multisystem disease represents more than two-thirds (68.6%) of the total cases among adult patients with LCH, with skin and pul-
monary involvement representing 51% and 62% of cases, respectively.19 Pulmonary involvement occurs as part of multisystem disease or as isolated pulmonary LCH, a distinct disease entity accounting for approximately 20% of adult cases of LCH. Most adult patients have a good prognosis with an indolent disease course, but pulmonary LCH may progress to end-stage pulmonary fibrosis and to honeycomb lung.20,21 In the study18 by the Histiocyte Society, patients with single-system disease had 5-year event-free survival of 100%, patients with isolated pulmonary manifestations had 87.8% survival, and patients with multisystem disease had 91.7% survival. According to results from systemic studies12-15 in children (LCH I, LCH II, LCH III still open), risk organ involvement and poor response to initial 6-week treatment emerged as important independent prognostic factors. For severe refractory multisystem cases, high-dose chemotherapy followed by allogeneic stem cell transplantation may be considered.22 Innovative treatment approaches include the development of monoclonal antibodies directed against CD1a and the use of immunomodulatory agents (eg, thalidomide, the kinase inhibitor imatinib mesylate, and the monoclonal anti-CD52 alemtuzumab).23-27 Despite the good prognosis of patients under effective treatment regimens, the quality of life among adult patients may be impaired by long-term sequelae, including deafness, neurologic defects, orthopedic problems, pituitary insufficiency, and impaired lung and liver function.

In summary, LCH should be included in the differential diagnosis for adults with disseminated or localized disease involving not only bone, skin, and mucous membranes but also lung and endocrine and central nervous systems. The standard therapeutic approach to adult LCH has not yet been established, but treatment in most patients should follow the guidelines of ongoing trials. As demonstrated herein, treatment based on the LCH-A1 study12 of the Histiocyte Society in a 70-year-old woman with multisystem disease (including skin, lung, bone marrow, and pituitary gland) with prednisolone, vinblastine, and mercaptopurine in combination with topical corticosteroids and psoralen–UV–A irradiation is a successful and well-tolerated therapeutic strategy, leading to long-term remission of adult multisystem LCH.

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Author Contributions: Dr von Stebut had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: von Stebut, Doberauer, and Steinbrink. Acquisition of data: von Stebut, Schmadmand-Fischer, Kreft, and Steinbrink. Analysis and interpretation of data: von Stebut, Brauning, Kreft, and Steinbrink. Drafting of the manuscript: von Stebut. Critical revision of the manuscript for important intellectual content: von Stebut, Schmadmand-Fischer, Brauning, Kreft, Doberauer, and Steinbrink. Administrative, technical, and material support: Schmadmand-Fischer. Study supervision: Doberauer.

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