Letterer-Siwe disease associated with chronic myelomyonocytic leukemia: a fortuitous association?

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SUMMARY

Langerhans cell histiocytosis (LCH) and malignancy occurring in the same individual is unusual and has generally been the subject of isolated case reports. LCH is a rare condition in adults. Its cause is uncertain but, with the recent demonstration of clonality and its association with malignant disease, there has been a renewal of interest. We report a singular case of Letterer-Siwe disease associated with a chronic myelomonocytic leukemia developing in an elderly woman. The simultaneous occurrence of both malignant disorders supports the hypothesis of a common genetic origin.

KEY WORDS

Letterer-Siwe disease, chronic myelomonocytic leukemia

Introduction

Langerhans cell histiocytosis (LCH) is an uncommon clonal disorder. It is characterized by dysregulated growth, activity, and trafficking of Langerhans cells. It is generally considered a disease of childhood; however, late onset in adults is also found, particularly as multisystem disease. Letterer-Siwe disease (LSD) is the acute disseminated multisystemic form (1). The most common is primary or idiopathic LCH. The occurrence of LCH and malignancy in the same patient is uncommon (2). Here we report a singular case of late-onset LSD associated with chronic myelomonocytic leukemia (CML).

Case report

A 74-year-old woman was seen in our outpatient department of dermatology with a 1-month history of generalized pruritus, followed 2 weeks later by a slowly expanding eruption on her trunk and limbs. She had no other symptoms and felt well otherwise.

Clinical examination revealed an extensive reticular rash over the trunk and limbs confluent in the abdomen, flanks, flexures, and groin, consisting of crusted vesicles, papules, and pustules (Fig. 1). Purpuric papules on the limbs were also noted. A moderately enlarged, mobile lymph node was present in the right axilla. There was no hepatosplenomegaly.

Microscopic examination of the skin biopsy specimen showed a bandlike epidermotropic infiltrate in the superficial dermis. Numerous large cells were present with plentiful cytoplasm and

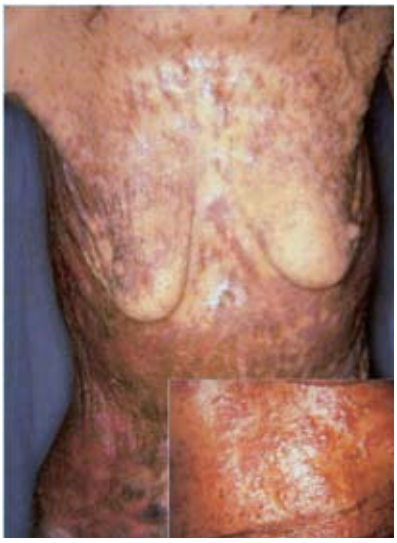

Figure 1. Pruritic papules disseminated on the trunk and limbs.

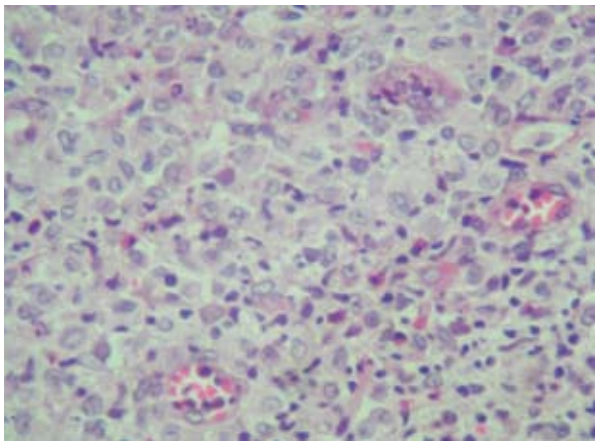

Figure 2. Numerous large cells with plentiful cytoplasm and reniform nuclei in the dermis.

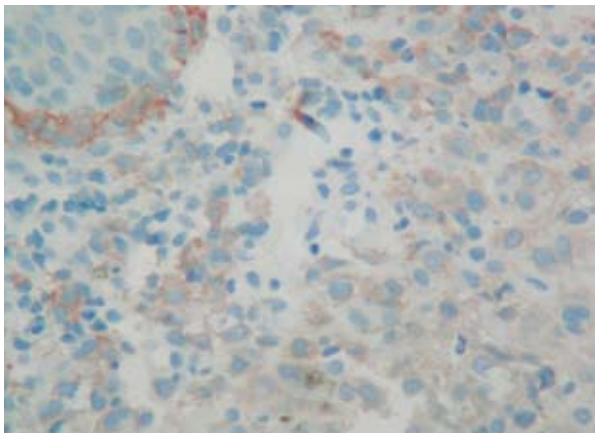

Figure 3. The infiltrate was strongly immunoreactive for CD1a.

reniform nuclei (Fig. 2). The infiltrate also included lymphocytes, plasmocytes, and eosinophils. The immunochemistry staining for CD1a, PS100, and CD3 was positive in the large cells (Fig. 3). These features indicated LCH. The hemoglobin was 6.8 g/dl; the monocyte count was 3,000/mm^3. The erythrocyte sedimentation rate was 79 ram/hr. The bone marrow aspirate demonstrated features of chronic myelomonocytic leukemia. Liver function tests were normal, as were the chest X-ray, cranial X-ray, and thoraco-abdominal tomography.

Based on these clinical, biological, and histological features, the diagnosis of LSD associated with CML was made. The patient received systemic corticosteroids (0.5 mg/kg/day). The clinical course was partially favorable. We attempted intralesional infiltration of lesions using Caryolysine 2 mg/day. The patient presented with hypotension after the injection. We decided to withdraw the treatment. The patient was lost to follow-up after 2 years.

Discussion

LCH occurs worldwide and most commonly develops in children, although the disease can develop at any age. An annual incidence of at least five per million has been reported for LCH in childhood, with the adult incidence believed to be less than one-third that of children (3). We report a singular case of LSD associated with CML in an elderly woman. The occurrence of LCH and leukemia in the same individual has generally been the subject of isolated case reports (2). It supports the concept of a Langerhans cell–mononuclear phagocytic system lineage disorder. The simultaneous presentation of a chronic monocytic leukemic process and Letterer-Siwe disease is exceptional (2, 4, 5). Several authors have described patients with either LSD or histiocytic medullary reticulosis associated with acute monocytic leukemia (AML) (6, 7). Egeler et al. (6) reviewed LCH cases from 1960 to 1993; among the 91 patients enrolled in this study, 22 patients presented an association of LCH with leukemia; 16 (73%) cases were associated with acute myeloid leukemia (AML) and only 2 patients were over 60 years old. In a review of 274 adults from 13 countries (1) with biopsy-proven adult LCH, registered with the International Histiocyte Society Registry, 17 (6.2%) of them had been diagnosed with various types of cancer of the following types: non-Hodgkin's lymphoma (n = 5), skin carcinoma (n = 2), and chronic lymphocytic leukemia, acute lymphoblastic leukemia, breast cancer, prostate cancer, endometrial carcinoma, "malignant histiocytoma," or other undefined (n = 4).

Several hypotheses have been proposed to explain the mechanisms of this association. The temporal patterns of the LCH/acute lymphoid leukemia (ALL) and LCH/AML associations are distinct, with ALL usually preceding the diagnosis of LCH (6, 8) and AML succeeding it (9). Egeler et al. (6) have offered a number of hypotheses, including that LCH and ALL are different manifestations of the same disease, that LCH is a "reaction" to ALL, and/or that the chemotherapy used to treat ALL unmasks LCH in some genetically predisposed children. Finally, it has been suggested that ALL may serve as a "co-factor" with immunosuppressive agents for the initiation of LCH.

The latency of AML after the diagnosis of LCH was suggestive of a therapy-related process (6, 8). In fact, chemotherapy might kill all cells with lymphoblastic differentiation, whereas cells of the same clone that preferentially show histiocytic differentiation might be more chemoresistant and survive to present later as histiocytic neoplasms (10).

In our case report, the simultaneous occurrence of CML and LCH excludes a therapy-related process and favors the hypothesis of a genetic origin rather than a reactional origin for LCH. Both malignant disorders might have resulted from a common abnormality in a precursor cell. Moreover, a case of a dermal Langerhans' cell tumor representing the first clinical manifestation of chronic myelomonocytic leukemia in a 71-year-old male has been reported (5). Writers support the hypothesis that Langerhans cells are of myeloid origin and that the neoplastic blood monocytes could be the precursors of the dermal Langerhans cells. This differentiation does not take place in the bone marrow, but only in the dermis, where Langerhans cells occur under non-neoplastic conditions (i.e., "homing") (5).

LSD is usually observed in children and presents the most severe disease manifestation of LCH, typically involving the abdominal viscera (11, 12). Our case is also unusual because LCH involved only the skin in an elderly patient. In a review of the literature, of a total of 1,350 reports of LCH, only 55 document the disease in the elderly and only 13 had disease limited to the skin (13). Chevrant-Breton found that 15 of 23 adult cases of LSD presented with cutaneous lesions, but all 23 had skin lesions during the course of the disease (14). Vollum observed that the characteristic seborrheic dermatitis-like skin lesions preceded systemic disease and terminal illness by up to 9 years. However, she noted no relation between the extent or duration of the skin eruption and the prognosis, and concluded that the prognosis of the disease depends on the extent of systemic rather than cutaneous involvement (15). Our patient presented a generalized cutaneous eruption without systemic involvement as the first manifestation of LCH. She was then lost to follow-up, and so we were unable to predict disease evolution.

In adult patients with LCH, various treatment strategies have been used depending on organ involvement and clinical course. Therapeutic options include local treatment, radiation therapy, chemotherapy, immunomodulation, and liver, lung, and stem cell transplantation in advanced-stage disease (16). Our patient did not respond to systemic corticotherapy and did not tolerate intralesional infiltration with Caryolysine. In cases of association of LCH and AL, both diseases should be treated separately. In a review of a total of 26 patients with AML after LCH, it is suggested that AML has a poor prognosis and allogeneic bone marrow transplantation seems to be the treatment of choice (8).

In conclusion, this case obviously suggests an interrelation between myeloproliferative disease and the focal accumulation of LC in the dermis. The simultaneous occurrence of both diseases in the same patient provides further evidence favoring the hypothesis of a genetic origin rather than a reactional origin for LCH. Because Langerhans cells and monocytes have the same medullary origin, it was tempting to interpret this case as a demonstration of a unique disorder of the Langerhans cells. Further molecular studies of both neoplasms should be pursued in such cases to characterize the association with the original leukemia. Here we describe a new case of LCH associated with chronic myelomonocytic leukemia. LCH needs to be considered in the differential diagnosis in patients with underlying hematopoietic diseases. Conversely, unusual presentations of LCH in adults may warrant a hematologic evaluation for possible underlying hematopoietic diseases.

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