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Single Case

Multisystem Langerhans Cell Histiocytosis following Treatment of Initially Presumed Atopic Dermatitis with Dupilumab: A Case Report of an Extremely Confusing Scenario

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Atopic dermatitis · Dupilumab · Langerhans cell histiocytosis · Case report

Abstract
Introduction: Atopic dermatitis (AD) is a common chronic, recurrent, and non-infectious inflammatory skin disease. Dupilumab is a human monoclonal antibody with clinical efficacy in severe AD and has a good safety profile. ***Case Presentation:*** We hereby describe a previously unreported case of multisystem Langerhans cell histiocytosis (MS-LCH) that is associated with a history of AD treatment using dupilumab. ***Conclusion:*** A single case of MS-LCH with a history of dupilumab treatment for AD was described for the first time. This case highlights that given its susceptibility to skin involvement, LCH needs to be considered as a differential diagnosis for skin lesions that are not improved by established therapies.

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, and non-infectious inflammatory skin disease that is clinically characterized by dry skin, an eczema-like rash, and severe itching [1]. Dupilumab is a human monoclonal antibody with clinical efficacy in severe AD and has a good

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safety profile [1]. Langerhans cell histiocytosis (LCH) is an inflammatory myeloid tumor of unknown etiology [2]. Because of the lack of specific clinical manifestations in the early stage of LCH, it is easy to miss the diagnosis and misdiagnosis. In this paper, we describe a previously unreported case of multisystem LCH (MS-LCH) that is associated with a history of AD treatment using dupilumab.

Case Report

A 62-year-old Chinese woman was hospitalized for a generalized severe rash, accompanied by fever. The patient reported a 2-year history of diffuse erythematous, pruritic, and sometimes squamous lesions. She consulted with dermatologists in several hospitals. Repeated hematological examinations showed elevated levels of eosinophils and immunoglobulin E. Based on a history of allergic rhinitis that stretched back to childhood, all doctors diagnosed the patient with AD. In addition, all the results of three biopsies of different body parts and in varying periods suggested the pathological changes of subacute or chronic eczema, which is consistent with AD. The patient received various traditional therapeutic regimens for AD, with all of them exhibiting poor efficacy. Seven months before hospitalization, dupilumab was introduced according to guidelines and standard protocol, as advised by a dermatologist. Only the symptoms of pruritus slightly improved, while no overall relief of the rash was observed.

Six months after starting dupilumab, which was a month before hospitalization, the patient began to develop recurrent fever, with more obvious systemic erythema and scales, accompanied by increased itching. The patient presented to our hospital. Results from physical examination after hospitalization showed extensive and scaly erythema, reddish papules, and nodules on the face, trunk, and limbs (Fig. 1). The swollen lymph nodes could be touched in the bilateral supraclavicular fossa, axilla, and groin.

Hematological examination revealed a white blood cell count of 2.5×10^9/L (normal range $4\sim10 \times 10^9$/L), lymphocyte count of 8.7% (normal range 20~40%), eosinophilic granulocyte count of 22.2% (normal range 0.4~8%), hemoglobin levels of 75 g/L (normal range 115~150 g/L), platelet count of 59×10^9/L (normal range $100\sim300 \times 10^9$/L), immunoglobulin E level of 718 IU/mL (normal range <100 IU/mL), and C-reactive protein levels of 34.4 mg/L (normal range 0~10 mg/L). Chest and abdominal computed tomography and magnetic resonance imaging of the skull showed no significant abnormalities.

Bone marrow biopsy revealed active myeloid hyperplasia and increased eosinophilia. Positron emission tomography-computed tomography showed multiple hypermetabolic lymph nodes in the bilateral supraclavicular area, bilateral axilla, retroperitoneal large vessels, iliac vascular walking area on both sides of the pelvis, and bilateral inguinal area. The biopsy of the right axillary lymph node indicated that tumor cells were diffuse in the interfollicular region and para-cortex, S100+, CD1a+ (Fig. 2). Genetic tests showed positive and negative results for BRAFV600E and MAPK2K1, respectively. The BRAFV600E mutation was found to be absent in lymph nodes and skin biopsy samples. The skin pathological examination was repeated. Biopsy specimens of two lesions on the right upper arm and abdomen showed parakeratosis and infiltration of lymphocytes around small vessels in the dermis. Immunohistochemical staining showed that there were no Langerhans cells that invaded the skin. The final diagnosis was MS-LCH. After systemic therapy with the vincristine + prednisone chemotherapy regimen, the skin lesions were significantly relieved at first, but this progressively took longer with time.

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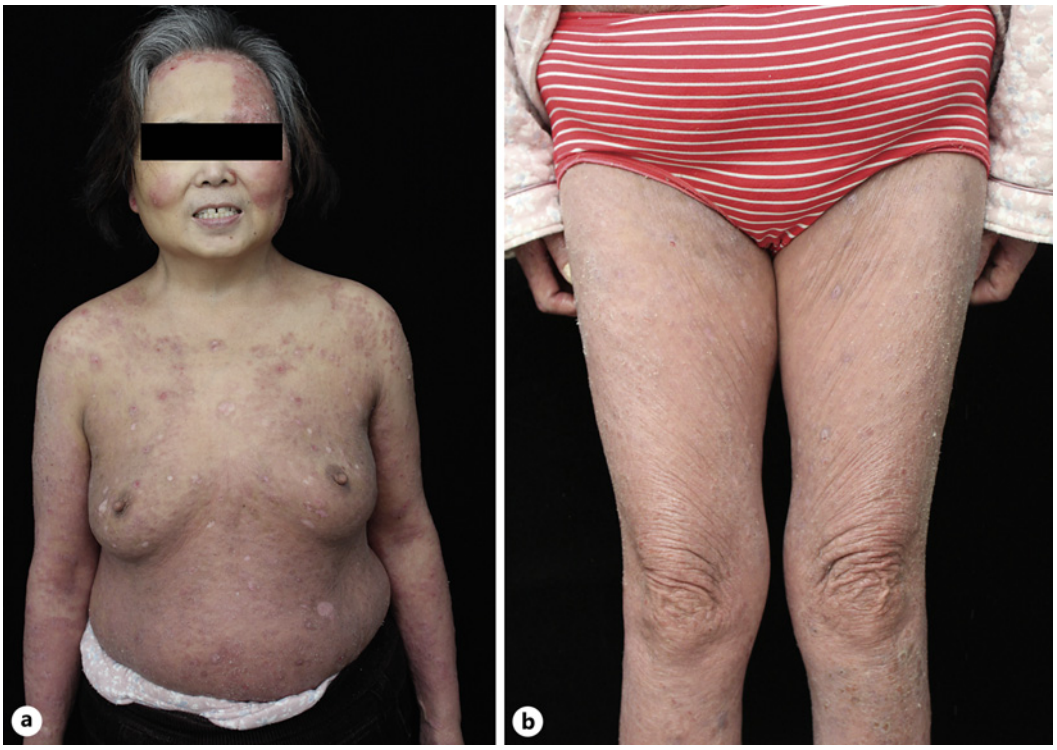

Fig. 1. Clinical findings. Extensive and scaly erythema, reddish papules, and nodules, on the face, trunk, arms (**a**) and legs (**b**).

Discussion

LCH is an inflammatory myeloid tumor of unknown etiology, and it is characterized by the abnormal clonal proliferation of CD1a+/CD207+ dendritic cells [2, 3]. LCH exists in various clinical forms and has been further classified into two groups. First, there is a single-system group, which is based on single- or multiple-site involvement. Second, there is the multifocal multisystem group, which is based on whether or not the risk organ (liver, spleen, or bone marrow) is involved [4]. Still worse, the process from spontaneous regression to multisystem involvement is unpredictable [5]. On the other hand, the early diagnosis of LCH is relatively difficult in clinical practice because of the absence of typical specific symptoms. This is especially true if the LCH involves multiple systems. In its early stage, LCH may show the symptoms of a single system. When visiting the corresponding department, patients are often subjected to symptomatic treatment, which ignores the inference of the cause. For example, the patient we reported first went to the dermatology department because of itchy erythema on her skin, and no evidence of Langerhans cell invasion were found in multiple skin biopsies. She was diagnosed with AD and received dupilumab treatment.

The case presented in this article arouses many questions. Did this patient have LCH which was initially misdiagnosed as AD? Could it be that she had LCH with AD? Could it be that dupilumab induced LCH while the patient was undergoing AD treatment? Therefore, it is recommended that AD be determined according to the diagnostic criteria for AD in Chinese adults [6]. It is also puzzling to note that the multiple traditional treatments for AD, and even dupilumab, did not reduce the skin lesions and itching. We speculate that such resistance to treatment is attributed to LCH. In addition, dupilumab-induced lymphoma has been reported before [7–9]. However, LCH as a myeloid tumor has not been reported to be related to

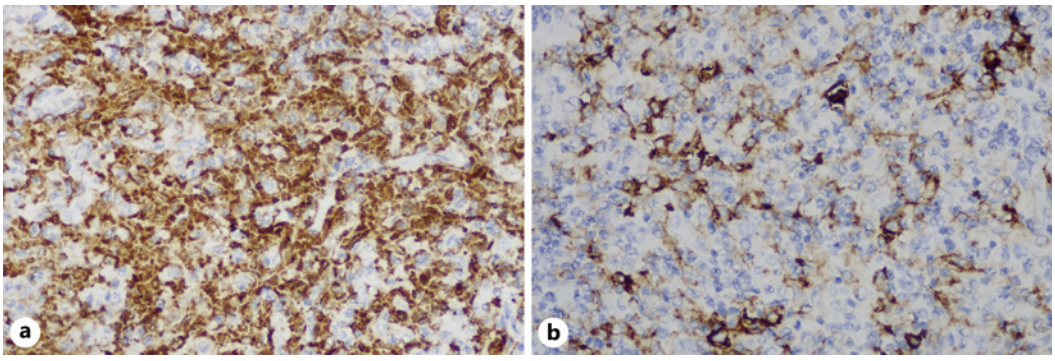

Fig. 2. Histopathological findings. Immunohistochemistry of the right axillary lymph node: S100 is strongly positive; original magnification (×400) (**a**). **b** CD1a is strongly positive; original magnification (×400).

dupilumab. At present, we could not determine whether dupilumab was involved in the onset of LCH in this case. Further research into the factors that explain the relationship between dupilumab and LCH should be conducted.

Conclusion

In conclusion, a single case of MS-LCH with a history of dupilumab treatment for AD was described for the first time. This case highlights that LCH remains highly prone to missed diagnosis or misdiagnosis. Given its susceptibility to skin involvement, LCH needs to be considered as a differential diagnosis for skin lesions that are not improved by established therapies. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539704).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and all accompanying images. Ethical approval is not required for this single case report in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Wenhao Cheng collected the clinical data and wrote the initial manuscript. Hong Ren contributed to literature review, writing, and reviewing the manuscript. Wenlong Hu was the primary author and contributed to manuscript revising and supervision.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study. Further inquiries can be directed to the corresponding author.

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