Peripheral T-cell Lymphoma not Otherwise Specified (PTCL-NOS) in a Patient with Hypereosinophilic Syndrome Showing Multiple Nodules on Chest Computed Tomography

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Abstract

Hypereosinophilic syndrome (HES) encompasses both myeloproliferative and lymphoproliferative diseases. We encountered a rare case of lymphocytic HES followed by malignant T cell lymphoma, who was diagnosed as eosinophilic pneumonia upon the first visit. During the clinical course, the transition of the chest CT findings from bilateral multifocal ground-glass opacities and consolidations to bilateral scattered multiple small nodules was impressive and suggestive. Given the increased risk of developing T-cell lymphoma, patients with HES (especially lymphocytic-HES) should be monitored on a regular basis to detect this complication as early as possible.

Key words: hypereosinophilic syndrome, eosinophilic pneumonia, peripheral T-cell lymphoma


Introduction

Chusid et al originally defined hypereosinophilic syndrome (HES) in 1975 as (1) persistent eosinophilia of ≥ 1,500/mm³ eosinophils for over 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease; 2) absent evidence of parasites, allergies or other known causes of eosinophilia; and 3) presumptive signs and symptoms of organ involvement (1). Recently the diagnostic criteria of HES have been modified and improved (2). HES generally includes a heterogeneous group of rare disorders ranging from benign idiopathic eosinophilia to malignant diseases (3). The identification of specific HES entities with defined etiologies has facilitated confirmation of two pathogenic forms of HES, myeloproliferative and lymphocytic, each of which includes several clinically defined distinct HES disorders (2). Whereas the identification of the myeloproliferative HES rests upon the identification of clonal myeloid eosinophil and eosinophil precursor populations, especially those displaying the FIP1 L1-PDGFRA mutant gene, identification of the lymphocytic HES rests upon recognition of distinct helper T cell subsets and clonal overgrowth of specific cytokine-producing cells (4). Lymphocytic but not myeloproliferative HES may precede the development of overt T-cell lymphoma (5, 6). Given the increased risk of developing T-cell lymphoma, patients with HES should be monitored on a regular basis to detect this complication as early as possible. We report a rare case which was diagnosed as eosinophilic pneumonia upon the first visit, later revealed to be HES and finally developed into malignant lymphoma probably associated with HES.

Case Report

A 60-year-old woman with asthma and eosinophilia was admitted to our hospital for fever and malaise lasting 3-weeks. The patient was diagnosed with bronchial asthma 2 years before admission. At that time, she was admitted for respira-

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tory failure and an enlarged chest shadow. On physical examination at the first admission, chest auscultation revealed bilateral slight wheeze. Cardiac findings were normal. No skin lesions were found. A chest X-ray upon first admission showed ground glass opacities in the bilateral lower lung fields (Fig. 1A) and high-resolution chest CT revealed no pleural effusion nor pulmonary edema, but revealed bilateral multifocal ground-glass opacities and consolidations (Fig. 1B). Laboratory data revealed hypereosinophilia (white cell count, 5,300/μL, comprising 31.0% eosinophils, 42.0% neutrophils, and 23.0% lymphocytes) with IgE 2,533 IU/L. The patient was negative for antinuclear, anti-neutrophil cytoplasmic and anti-parasitic antibodies. A transbronchial lung biopsy (TBLB) and bronchoalveolar lavage (BAL) were performed on the left lower lobe. The white cell count in the BALF was 1,400/μL, comprising 56.0% lymphocytes, 41.0% eosinophils and 1.0% neutrophils. The T-cell subset in BALF analysed by flow cytometry was as follows: 4.0% CD3, 14% CD4, 13% CD8, CD4/CD8 ratio of 1.08, and 0.0% CD19. TBLB specimen showed the infiltration of eosinophils and lymphocytes into the alveolar spaces and alveolar walls. We administered corticosteroids (25 mg/day prednisolone) which resulted in immediate improvement and resolution of eosinophils and lymphocytes into the alveolar spaces and interstitium. These data suggested eosinophilic pneumonia; however, the chest CT findings differed from those when the eosinophilic pneumonia was first diagnosed. A video-assisted thoracoscopic surgery (VATS) biopsy of the

Figure 1. (A) Chest X-ray upon the first admission shows ground glass opacities in the bilateral lower lung fields. (B) High-resolution chest CT (lung windowing) upon the first admission shows bilateral subpleural multifocal ground-glass opacities, consolidations, reticulonodular pattern with intralobular interstitial thickening and no pleural effusions, nor pulmonary edema.
right S1 confirmed that small-to-medium lymphocytes that were immunohistochemically positive for T-cell-associated antigen (CD3, CD5), cytotoxic molecule (TIA-1) and negative for CD4, CD8, CD56, granzyme B, T-cell receptor α/β (beta-F1) and T-cell receptor γδ, had diffusely infiltrated the interstitium and formed nodules with a few histiocytes and eosinophils (Fig. 3). The neoplastic cells do not stain with CD20 and EBER-negative. From these immunophenotypic data, we diagnosed peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS); stage IV (lung, spleen).

After the diagnosis, she was initially treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).
Figure 3. Low magnification lung biopsy [Hematoxylin and Eosin staining ×10 (A)] shows randomly scattered small nodules. High-power field of nodule periphery [Hematoxylin and Eosin staining ×200(B) ×400(C)] shows diffuse infiltration by monotonous small-to-medium lymphocytes, eosinophils and histiocytes. High endothelial venules are increased.

for the PTCL-NOS, which improved the pulmonary infiltration and splenomegaly, while tumor cells were detected de novo in bone marrow and tumor-related fever continued after this regimen. We also administered DeVIC (dexamethasone, etoposide, ifomide, and carboplatin), CHASE (cyclophosphamide, high-dose cytarabine, dexamethasone, and etoposide) and high-dose methotrexate, but the response to these salvage therapies was poor. The patient died of tumor progression 7 months after the diagnosis of PTCL, NOS.

Discussion

Hypereosinophilic syndrome generally describes a heterogeneous group of rare disorders ranging from benign idiopathic eosinophilia to malignant diseases (3). Therefore, the necessary diagnostic studies, including blood work and imaging studies of affected tissues must proceed before initiating therapy. Non-specific lung involvement in 40% of patients with HES can include pleural effusion, cough and pulmonary opacities on chest CT (interstitial infiltrates, ground-glass attenuation, small nodules), which should be distinguished from pulmonary edema resulting from cardiac involvement (2, 7).

Lymphocytic HES (L-HES) was recently introduced to distinguish this proportionally significant pathogenic subgroup from idiopathic HES (8), furthermore L-HES has been defined as a primitive lymphocytic disorder characterized by non-malignant expansion of a T-cell population producing IL-5 in patients with HES (5, 9). Most reports indicate that T-cell populations associated with L-HES bear the intriguing CD3<sup>-</sup>CD4<sup>+</sup> surface phenotype (10), but several other phenotypically abnormal T-cell subsets have been identified in small patient subgroups (5, 11, 12). Several investigators have also reported the protracted development of T-cell lymphoma in patients with L-HES (6, 13). The presence of CD3<sup>-</sup>CD4<sup>+</sup> Th2-like lymphocytes in patients with HES has the prognostic implication of the protracted development of T-cell lymphoma. In clinical routine practice, a diagnosis of L-HES is laborious, and may be stalled by the inability to interpret the results of flow cytometry or T-cell receptor gene rearrangement patterns, or a lack of equipment or expertise to culture T cells and assess cytokine production. A retrospective analysis of BALF from the present patient revealed a discrepancy between the CD3 count and the CD4 plus CD8 count, though the clinical role of the flow cytometric immunophenotyping of BALF was not confirmed. Furthermore, high levels of serum IL-5 were detected upon the second admission. We could not prove the clonality of abnormal T-cell lymphocytes and evaluate T-cell receptor gene rearrangement patterns, however this data sug-
gested a clonal population of CD3^+CD4^-Th2-like lymphocytes. This case may have been L-HES. We performed lymphocyte phenotyping on whole blood by flow cytometry, but no aberrant CD3^+CD4^-Th2-like lymphocyte subset was detected. Unfortunately, we could not obtain the BALF specimen and re-analyse the BAL cells at the second admission to examine for the presence of CD3^+CD4^-Th2-like lymphocyte subset.

Upon the first admission, the clinical course of the patient and TBLB results were compatible with eosinophilic pneumonia and a VATS biopsy was not performed. Since it cannot be diagnosed from TBLB specimens, malignant lymphoma might already have been present at the time of the first admission. However, chest CT upon the first admission, when eosinophilic pneumonia was diagnosed, showed bilateral multifocal ground-glass opacities and consolidations, whereas those at the time of the diagnosis of PTCL-NOS were small multiple scattered nodules. The change in the chest CT findings between the first and second admissions is considered to represent the different entities between eosinophilic pneumonia and PTCL-NOS. Malignant T-cell formation might have influenced these changes, and the variations in chest imaging findings indicated that malignant T-cell lymphoma was probably absent at the time of the first admission. The timing of aberrant T-cell transformation into malignant T-cell lymphoma was unclear. Given the increased risk of developing T-cell lymphoma, patients with HES (especially L-HES) should be monitored on a regular basis to detect this complication as early as possible (14).

We encountered an extremely rare case which was diagnosed as eosinophilic pneumonia upon first visit, and later revealed to be HES and finally developed into malignant lymphoma probably associated with HES. During the clinical course, the transition of the chest CT findings from bilateral multifocal ground-glass opacities and consolidations to bilateral scattered multiple small nodules was impressive and suggestive. Respiriologists should pay attention to HES behind eosinophilic lung diseases because HES (especially L-HES) has the increased risk of developing T-cell lymphoma as in the present case.

The authors state that they have no Conflict of Interest (COI).

References