Non-Hodgkin’s Lymphoma with Pulmonary Infiltrates Mimicking Miliary Tuberculosis

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Miliary infiltrates observed on chest films in non-Hodgkin’s lymphoma are extremely rare. We report a case with pulmonary infiltrates mimicking miliary tuberculosis associated with prominent eosinophilia and elevated IgE levels. The levels of circulating eosinophils correlated with disease activity as they transiently returned to normal after effective chemotherapy in a short period. However, the patient developed acute respiratory failure due to the rapid progression of the disease even with intensive chemotherapy. We emphasize that small nodular shadows appear to be a sign of the rapid progression of the disease and a poor prognosis.

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Key words: T-cell lymphoma, small lymphocytic type, miliary infiltrates, eosinophilia

Introduction

The lung parenchyma contains a relatively large number of lymphoid cells, which appear as either isolated cells within the interstitium or unencapsulated clusters or aggregates referred to as bronchus-associated lymphoid tissue (1, 2). Pulmonary involvement of malignant lymphoma is occasionally present in some cases. Filly et al (3) reported that intrathoracic lesions are present in 43% of patients with untreated non-Hodgkin’s lymphoma (NHL) and that the most common manifestation of intrathoracic lesion was mediastinal and/or hilar lymphadenopathy and pleural effusion. Only about 4 percent of the lesions are located in lung parenchyma (3). Miliary infiltrates on a chest film in non-Hodgkin’s lymphoma are extremely uncommon and are always accompanied with other intrathoracic lesions in the end stage of the disease. We report a case of NHL with small pulmonary nodules mimicking miliary tuberculosis with marked eosinophilia and elevated IgE levels.

Case Report

A 60-year-old man was referred to Tokyo National Chest Hospital on June 9, 1992 for further evaluation of abnormal shadows on chest films. He had been well until May 15, 1992, when he started complaining of wheezing at night. He consulted a physician and his complaints disappeared soon after taking theophylline and tulobuterol hydrochloride. A chest X-ray film taken on the first visit showed diffuse bilateral nodular infiltrates with bilateral hilar and mediastinal lymphadenopathy (Fig. 1). Past history revealed bronchial asthma in childhood. On physical examination, no lymphadenopathy was found and the lungs were clear. The white cell count was 22,600/mm³ with 47% eosinophils. Serum lactic dehydrogenase (LDH) was also increased (649 IU/l, normal: 207 to 399). Serum IgE was 4,060 IU/ml and IgE RAST proved to be positive for mites and house dusts. Mild hypoxemia (PaO₂ 79.5 Torr) was observed. A computed tomographic (CT) scan revealed centrilobular miliary nodular shadows located in the inner to mid-portion throughout the lung, and mediastinal and hilar lymphadenopathy (Fig. 2). Specimens obtained by transbronchial lung biopsy via a fiberoptic bronchoscope disclosed alveolitis with mild infiltration of mature lymphocytes and eosinophils. Bronchoalveolar lavage in the right middle lobe was performed and lavage fluids revealed that the total cell count was 12.3x10⁷ cells with 61.4% eosinophils, 30.8% macrophages, and 7.8% lymphocytes; no acid-fast bacilli was seen. T lymphocyte subpopulations in lavage fluids disclosed that CD3⁺ was 48.4%, CD4⁺ 27.1%, and CD8⁺ 37.0%. Ga scintigram disclosed diffuse accumulation of ⁶⁷Ga citrate in both lung fields with no accumulation in generalized lymph nodes. An open lung biopsy was performed on June 25, 1992 when eosinophilia and the pulmonary infiltrates increased, and lymphadenopathy at bilateral inguinal and axilla was observed. Biopsy specimen disclosed that small nodules of less than 2 mm in diameter were scattered throughout the lung parenchyma and the perivascular and peribronchiolar infiltration of predominantly lymphocytes, with reduced num-
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Figure 1. Chest X-ray film on admission showing bilateral hilar lymphadenopathy and diffuse nodular infiltrates.

Figure 2. CT film on admission showing bilateral nodular infiltrates predominantly in the middle portion of lung.

Figure 3. a) Low power view of the open lung biopsy showing small nodules around small vessels and bronchioles consisting of predominantly lymphocytes and also eosinophils (HE stain, ×2). b) High power view of the open lung biopsy showing lymphoma cells (HE stain, ×40).

Numbers of eosinophils, was observed (Fig. 3a, b). The high percentage of eosinophils in bronchoalveolar lavage (BAL) fluid as compared with biopsy specimen suggested the presence of eosinophils on bronchial and bronchiolar wall. An immunohistological study revealed the infiltration of predominantly HLA-DR positive, CD3 positive, CD4 positive, CD5 positive, and CD8 negative T lymphocytes leading to the diagnosis of malignant lymphoma (non-Hodgkin’s lymphoma, NHL, diffuse small lymphocytic type). Chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) resulted in improvement of eosinophilia and pulmonary infiltrates. After three consecutive chemotherapies, the abnormal lung infiltrates nearly disappeared and peripheral lymphadenopathy reduced in size to red beans or smaller, and the number of peripheral eosinophils returned to normal levels although the concentration of IgE was still elevated (2,981 IU/ml). The patient was
discharged on Sept. 30. However the infiltrates on a film with eosinophilia and systemic lymphadenopathy re-appeared and he was re-admitted to the hospital on Oct. 23, 1992. Laboratory data on re-admission revealed severe hypoxemia (PaO₂ 32.8 Torr) and eosinophilia (1,500/mm³) and elevated IgE (1,705 IU/ml). An alternate treatment with 1-asparaginase, vindesine, mitoxantrone, and methyl prednisolone was started. Although transient improvement of lung shadow was observed, bilateral diffuse patchy shadow appeared in his end stage and he died on Dec. 27, 1992 of respiratory failure (Fig. 4). Autopsy revealed the presence of malignant lymphoma cells in lungs, peripheral lymph nodes including cervical, axillary and inguinal portion, thymus, liver, spleen and skin, but bone marrow involvement was not observed. Accompanied with lymphoma cells, cytomegalic inclusion bodies were found in various organs including lungs.

**Discussion**

The pulmonary involvement of NHL can be classified as nodular type, bronchovascular-lymphangitic type, pneumonic-alveolar type, and miliary-hematogenous type (4). The most common manifestation of NHL is a bronchovascular-lymphangitic pattern (4, 5). The miliary-hematogenous infiltrates observed in the present case are uncommon and have been described often in the end stage of the disease (6). Balikian and Herman reported that the miliary hematogenous pattern was observed in 6.1% of NHL with pulmonary involvement in 27 patients (4). In contrast, our review of intrathoracic involvement in NHL at our hospital from 1987 to 1994 disclosed that approximately 50% of 87 patients had abnormal shadows on chest films and miliary shadows were not observed in this series suggesting that the miliary-hematogenous shadows are extremely uncommon.

The centrilobular small nodular shadows in the present case became increased in size and Kerley’s B line appeared in a short period of time. This type of pulmonary infiltrate might implicate the rapid spreading of lymphoma cells via lymphatic and vascular pathways.

Another interesting finding of this patient was eosinophilia and an elevation of IgE. The patient had bronchial asthma and elevated specific IgE antibodies to mites and house dusts, which might be responsible for eosinophilia and elevated IgE levels. However, no episodes of asthma occurred during his admission and eosinophilia was correlated with the severity of NHL, suggesting an association between eosinophilia and NHL.

Eosinophilia can be associated with various lymphoid malignancies although the association with Hodgkin’s disease is best-known. A blood eosinophil excess has been rarely described in association with B-cell malignancies. In contrast, eosinophilia is frequently observed in T cell malignancies, and T cell proliferation associated with eosinophilia is generally characterized by cells with a mature phenotype and most often belong to the helper (CD4⁺) subset of mature T cells (7). In the present case, the levels of circulating eosinophils correlated with disease activity, suggesting the release of cytokines from lymphoma cells which stimulates the production of eosinophils. The association of eosinophilia with the prognosis of malignant lymphoma is unclear, although Samoszuk et al reported that eosinophil peroxidase might make lymphoma cells less suscep-
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tible to killing by antineoplastic therapy via glucose oxidase (8). In contrast, IgE was consistently elevated. This discrepancy cannot be explained by clearance of IgE as its half life is approximately two or three days. There is a possibility that prednisolone reduces the number of eosinophils within a short period, but it requires more time to suppress IgE production. In conclusion, we propose that miliary infiltrates of NHL might represent a rapid progression of lymphoma cells and may be a poor prognostic sign. Further, in cases of NHL with eosinophilia, the number of eosinophils might be a good indicator of therapeutic effects.

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References