Non-Hodgkin’s Lymphoma Accompanied by Pulmonary Involvement with Diffuse Ground-Glass Opacity on Chest CT: A Report of 2 Cases

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Abstract

We report 2 rare cases of non-Hodgkin’s lymphoma accompanied by pulmonary involvement with diffuse ground-glass opacity. Histological examination of the lung revealed a diffuse large B-cell-type lymphoma within the bronchiolar wall and alveolar septum. Although this is a rare occurrence, diffuse large B-cell-type non-Hodgkin’s lymphoma should be considered in the differential diagnosis of pulmonary diffuse ground-glass opacity in the chest CT scan.

Key words: non-Hodgkin’s lymphoma, ground-glass opacity

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Introduction

Malignant lymphoma involving the lung occurs less frequently in non-Hodgkin’s lymphoma than in Hodgkin’s disease (1). By using CT, Lewis et al categorized the lung involvement in 16 patients with recurrent or secondary non-Hodgkin’s lymphoma into nodules, masses, alveolar or interstitial infiltrates, masses of pleural origin, and peribronchial or perivascular thickening (2). However, these lesions were localized to a part of the lung parenchyma. Diffuse ground-glass opacity of whole lung fields in the chest CT scan is extremely rare in diffuse large B-cell non-Hodgkin’s lymphoma. We report 2 cases of diffuse large B-cell non-Hodgkin’s lymphoma accompanied by pulmonary involvement with diffuse ground-glass opacity observed in the chest CT scan.

Case Report

Case 1

An abnormal shadow was observed in the chest roentgenogram of a 59-year-old man who was suffering from progressive dyspnea for 2 months. He was admitted to our hospital in November 2006 for further medical examination. He was a nonsmoker and had no history of occupational exposure. Physical examination revealed that he had no skin lesions or neurological abnormalities. There was no peripheral lymphadenopathy in the cervical, axillary, or inguinal region. Chest auscultation showed no abnormal findings. Laboratory investigations revealed a total leukocyte count of 6,800 cells/mm³, comprising 78% neutrophils, 12.5% lymphocytes, 6% monocytes, 1% basophils, and 2.5% eosinophils. The level of C-reactive protein was slightly elevated to 2.39 mg/dL. The serum lactate dehydrogenase level had

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increased to 1,461 U/L (normal, 110-230 U/L). The soluble interleukin-2 receptor (sIL-2R) had increased to 1,248 U/mL (normal, 127-582 U/mL). Hypoxemia (percutaneous oxygen saturation [SpO2], 90%) was observed while breathing room air. Pulmonary function studies were within normal limits except for a mild reduction in the diffusing capacity (DLco 78% of the predicted value). The chest roentgenogram and CT scan revealed diffuse bilateral ground-glass opacity in the whole lung (Figs. 1, 2). There was no radiographic evidence of cardiomegaly, pleural effusions, or significant lymphadenopathy. CT scan of the head was unremarkable. Histological examination of the specimen by transbronchial lung biopsy specimens from the right lower lobe demonstrated a thickened bronchiolar wall and alveolar septum with invading neoplastic cells that had accumulated in the small vessels of the lung (Fig. 3). Immunohistochemical examination revealed that the atypical lymphocytes observed in the frozen specimens obtained from the lung were positive for the B-cell marker CD20, but negative for the T-cell marker CD3. The patient was treated with 4 cycles of systemic chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) from December 2006. His chest radiographs, chest CT scans, laboratory data, and symptoms markedly improved within 1 month. However, in April 2007, he presented to our hospital with sudden onset of unsteadiness on feet. Magnetic resonance imaging (MRI) revealed multiple masses compatible with brain metastases of a malignant lymphoma. He was treated with 3 cycles of high-dose methotrexate (MTX) and intrathecal MTX twice, and the brain tumors slightly reduced in size on MRI. In June 2007, he became acutely febrile and developed progressive weakness and anorexia, which led to his death from multiple organ failure. Consent for autopsy was not obtained.

**Case 2**

An abnormal shadow was observed in a chest roentgenogram of a 74-year-old man who presented with a persistent dry cough and slight fever for 2 weeks. He was admitted to our hospital in January 2008 for further medical examination. He had been receiving insulin treatment for diabetes mellitus since 2000 and underwent a coronary artery bypass graft surgery in 2002. He was a smoker (1 pack a day for 54 years) and had no history of occupational exposure. Physical examination revealed that he had no skin lesions or neurological abnormalities. There was no peripheral lymphadenopathy in the cervical, axillary, or inguinal region. Chest auscultation showed no abnormal findings. Laboratory investigations revealed a hemoglobin level of 12.8 g/dL, and a total leukocyte count of 9,600 cells/mm³, with 93% neutrophiles, 2% lymphocytes, 2% monocytes, and 0% eosionphils. The level of C-reactive protein was ele-
Activated to 8.83 mg/dL. The findings of the liver biochemistry tests were mildly abnormal: aspartate aminotransferase, 51 IU/L (normal, 11-34 IU/L); alanine aminotransferase, 19 IU/L (normal, 7-34 IU/L); alkaline phosphatase, 374 IU/L (normal, 110-230 U/L); lactate dehydrogenase, 665 U/L (normal, 110-230 U/L); and total bilirubin concentration, 2.1 mg/dL (normal, 0.3-1.3 mg/dL). The albumin level had decreased to 2.1 g/dL. Soluble interleukin-2 receptor (sIL-2R) had increased to 8,981 U/mL (normal, 127-582 U/mL). Hypoxemia (arterial oxygen tension [PaO₂], 53.3 torr) was observed. The chest roentgenogram and CT scan revealed diffuse bilateral ground-glass opacity in the whole lung (Figs. 1, 2). There was no radiographic evidence of cardiomegaly, pleural effusions, or significant lymphadenopathy. An abdominal CT scan showed splenomegaly. Further, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography imaging demonstrated intense FDG activity in the liver and spleen and a slight accumulation in the lung fields. Histological examination of transbronchial lung biopsy specimens from the right middle lobe revealed neoplastic cells within the bronchiolar wall and alveolar septum that resulted in a diffuse thickening (Fig. 3). In addition, lymphoma cells were seen within some vessels. Immunohistochemical examination revealed that the atypical lymphocytes observed in the frozen specimens obtained from the lung were positive for the B-cell marker CD20, but negative for the T-cell marker CD3. At 14 d after admission, the patient died due to the progression of hepatic insufficiency, presumably due to hepatic infiltration by lymphoma cells and no chemotherapy was administered.

**Discussion**

In Japan, according to the World Health Organization classification there were 3,025 cases (94.71%) of non-Hodgkin’s lymphoma (68.53%; B-cell lymphoma) and the incidence of the largest subtype of non-Hodgkin’s lymphoma was 33.34% for diffuse large B-cell lymphoma (3). The present patients were diagnosed with right diffuse large B-cell lymphoma by transbronchial lung biopsies.

Reports of the involvement of the pulmonary parenchyma in non-Hodgkin’s lymphoma at the time of initial diagnosis are relatively rare. The ground-glass opacity observed in the chest CT scans of our non-Hodgkin’s lymphoma patients is an extremely rare finding. Filly et al reviewed a series of 300 patients with untreated malignant lymphoma with lymphomatous involvement of the lung parenchyma as demonstrated by plain chest radiographs and tomograms, and they reported that the lung involvement was 11.6% in the case of patients with Hodgkin’s disease and 3.7% in the case of patients with non-Hodgkin’s lymphoma (1). Castellino et al noted pulmonary parenchymal involvement in 24 (13%) of 181 patients with untreated non-Hodgkin’s lymphoma (4). Lewis et al reviewed a series of 31 patients with recurrent...
and secondary lymphoma with lymphomatous involvement of the lung parenchyma as demonstrated by CT scanning; the most common finding [21 of 31 patients (68%)] was a mass or mass-like consolidation (2). The present patients showed bilateral diffuse ground-glass opacity with peripheral predominance at the back, without peribronchovascular interstitial thickening and interlobular septal thickening on chest CT. Moreover, there was no loss of lung volume. We found only one Japanese case of pulmonary involvement of diffuse large B-cell lymphoma with diffuse ground-glass opacity in both lungs (5), and this report showed that the ground-glass opacity reflected the infiltration of lymphoma cells into the pulmonary interstitial spaces.

Pulmonary lymphoma mostly spreads via the lymphatics (6, 7) and hematogenous spread is believed to be rare (8). However, some reports suggest a hematogenous spread in non-Hodgkin’s lymphoma (9-11). Paladugu et al reviewed an autopsy series of 7 patients with non-Hodgkin’s testicular lymphoma and reported the high incidence of vascular invasion (41%) and noncontiguous lung involvement (86%), suggesting a hematogenous spread (9). In our patients, lymphoma cells mainly infiltrated into the bronchiolar walls and alveolar septa of the lungs, but not in the alveolar spaces. In addition, lymphoma cells were seen within some vessels. These microscopic findings may be the evidence of hematogenous spread of lymphoma cells into certain parts of the lungs. Moreover, on the lung images of our patients, there was no remarkable peribronchovascular interstitial thickening and interlobular septal thickening, which occurs as a result of spread of lymphoma cells via lymphatic pathways. Thickenig of the alveolar walls due to invasion by lymphoma cells, without involvement of the lymphatics, was also noted. The above findings suggest that the pathological mechanism underlying bilateral diffuse ground-glass opacity on chest CT is the spread of lymphoma cells mainly via the vascular rather than lymphatic pathways.

Intravascular lymphomatosis (IVL) is a rare type of lymphoma, which is characterized by proliferation of tumor cells within the vascular lumina (12). Yamagata et al reported a case of IVL, showing bilateral ground-glass opacity in a part of the lungs or wedge-shaped subpleural opacities in the chest CT scan (13). In this report, they reviewed chest radiographic images of 16 IVL cases; a bilateral reticular shadow was observed in 25% of the cases, reticulonodular shadow in 25%, ground-glass opacity in 25%, and wedge-shaped subpleural opacities in 19%. Thus, pulmonary imaging of IVL often shows patchy areas of ground-glass opacity. Pathologically, areas of ground-glass opacity can be correlated with expanded alveolar septa and perivascular spaces due to distended septal capillaries, venules, and arterioles, filled with neoplastic cells, and to alveolar congestion and hemorrhage (14). These features of typical IVL are different from what was seen in the present patients. In 2001, the World Health Organization classified IVL as a rare subtype of diffuse large B-cell lymphoma characterized by the presence of lymphoma cells only in the lumen of small vessels. The mechanism underlying the selective intravascular growth of this neoplasm was suggested to be an abnormality in the adhesion molecules involved in lymphocyte and endothelial adhesion phenomena (15, 16). However, Petito et al showed prominent perivascular infiltration of lymphoma cells in progressive diseases by postmortem examination (17). Because there were lymphoma cells mainly within the bronchiolar walls and alveolar septum and there were no particular intravascular or perivascular lesions in the present patients, a definite diagnosis of diffuse large B-cell lymphoma was made.

Although various CT findings are noted in non-Hodgkin’s lymphoma involving the lung parenchyma (2), diffuse ground-glass opacity in both whole lung fields on a chest CT scan is extremely rare. Diffuse large B-cell lymphoma should be included in the differential diagnosis when diffuse ground-glass opacity is seen in the chest radiograph.

References