CASE REPORT

Primary extranodal NK/T-cell lymphoma of the lung: Mimicking bronchogenic carcinoma

Chia-Hsin Liu¹, Hong-Hau Wang², Cherng-Lih Perng^{3,4}, Chung-Kan Peng¹, Chih-Feng Chian¹ & Chih-Hao Shen¹

1 Division of Pulmonary and Critical Care, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

2 Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

3 Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, Taipei, Taiwan

4 Graduate Institute of Pathology, National Defense Medical Center, Taipei, Taiwan

Keywords

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Correspondence

Chih-Hao Shen, Division of Pulmonary and Critical Care, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Cheng-Gung Road, Nei-Hu Dist. 114, Taipei, Taiwan.

Tel: +886 2 87927208

Fax: +886 2 87927209

Email: arron1218@ndmctsgh.edu.tw

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Abstract

Primary extranodal natural killer/T-cell lymphoma, nasal type (NK/TCL) in the lung is extremely rare and associated with Epstein-Barr virus (EBV) infection. An 80-year-old male presented with hemoptysis, which had lasted three days. Physical examination revealed inspiratory crackles at the left lung base and massive splenomegaly. Chest radiograph shows a mass-like lesion in the left lower lung but no active lesion six months earlier. Computed tomography demonstrated a soft tissue mass (size: 6.6 × 5.1 cm) with increased ground-glass opacities in the left lower lobe, several pulmonary nodules, and mediastinal lymphadenopathy. Transthoracic needle biopsy of the left-lower-lobe lung mass was performed. The pathology revealed atypical lymphoid cell infiltration, which is immunoreactive for cytoplasmic CD3, CD30 and CD56, but not reactive for CK and CD20. EBV-encoded RNA (EBER) was also detected in these atypical lymphoid cells. The serum EBV DNA level was 7.03×10^6 copies/mL and subtype 1 EBV was identified. No evidence of lymphoma involvement was found in the extrathoracic site. Primary pulmonary lymphoma showing nasal-type NK/T-cell subtype was diagnosed. Chemotherapy with cyclophosphamide and prednisolone was initiated immediately but the patient deteriorated and died three weeks later. In conclusion, patients presenting with rapidly growing lung mass and massive splenomegaly raise the possibility of aggressive pulmonary lymphoma. Extranodal NK/T-cell lymphoma with high baseline plasma EBV DNA levels signifies poor prognosis. Identifying young high-risk patients may have benefits for early aggressive and successful treatment.

Introduction

Primary pulmonary lymphoma is a rare disorder, and represents only 0.5–1% of all primary pulmonary malignancies, less than 1% of all cases of non-Hodgkin's lymphoma and 3–4% of all extranodal manifestations of this disease.¹ The most frequent form of primary pulmonary lymphoma is low-grade B-cell type that originates from mucosa-associated lymphoid tissue.² Extranodal natural killer/T-cell lymphoma, nasal type (NK/TCL) in the lung is extremely rare and strongly associated with Epstein-Barr virus (EBV). We present a case of primary extranodal NK/TCL presenting

with rapidly growing lung mass and massive splenomegaly mimicking bronchogenic carcinoma.

Case report

An 80-year-old man who was an ex-smoker presented with a cough and blood-streaked sputum lasting for three days. No fever, weight loss or night sweats were identified. Physical examination revealed inspiratory crackles at the left lung base, massive splenomegaly (spleen palpable 8 cm below the costal margin), and no other peripheral lymphadenopathy. Laboratory results were as follows: white blood cell count,

Figure 1 (a) Posteroanterior chest radiograph shows no active lesion six months earlier. (b) Posteroanterior chest radiograph shows a mass-like lesion in the left lower lung. (c) Axial non-enhanced computed tomography (CT) scan shows a CT halo sign (peritumoral ground-glass attenuation). (d) Medias-tinal lymphadenopathy in the pretracheal retrocaval region.

6100/uL; neutrophil/lymphocyte ratio, 88.4/7.8; hemoglobin, 12.4 g/dL; platelet count, 161000/uL; and LDH, 271 U/L. Chest radiography revealed a mass-like lesion in the left lower lung zone and no active lesion six months earlier (Fig 1a,b). A chest computed tomography (CT) scan revealed a soft tissue mass (6.6×5.1 cm) with ground-glass attenuation in the left lower lobe, several pulmonary nodules, and mediastinal lymphadenopathy (Fig 1c,d). Percutaneous transthoracic needle biopsy of the left-lower-lobe mass was performed and the pathology revealed monotonous, medium-sized cells infiltrating the lung tissue. These cells have high nuclear cytoplasmic ratio and inconspicuous nucleoli (Fig 2a). Coagulative necrosis and mitotic figures were easily found. Immunohistochemical stains revealed reactivity for cytoplasmic CD3, CD56 and CD30, but no reactivity for CK and CD20 (Fig 2b,c). In situ hybridization for EBV-encoded RNA (EBER) showed a positive reaction in these lymphoid cells (Fig 2d). The serum EBV DNA level was 7.03×10^6 copies/mL and subtype 1 EBV was identified. After serial studies including nasopharyngoscopy, abdominal sonography, and bone marrow biopsy, no evidence of lymphoma involvement was found in the extrapulmonary site. Extranodal NK/TCL

primary in the lung was diagnosed. The patient only received induction chemotherapy with cyclophosphamide and prednisolone, not a standard cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone (CHOP) regimen, in consideration of his advanced age and Eastern Cooperative Oncology Group Performance (ECOG) Status 2. Nevertheless, he died three weeks after chemotherapy as a result of disease progression with increasing tumor size following respiratory failure.

Discussion

Extranodal NK/TCL represents a distinct clinicopathological entity characterized by the presence of lymphoma cell involvement, ulcerative mucosa, and angiodestructive growth pattern. The tumor cells mostly expressed CD56 and EBV in the great majority of cases.³ This disorder is rare in the United States and Europe, but common in Asia, South and Central America, and Mexico.³ Sinonasal disease is a usual finding, although skin and aerodigestive mucosae are commonly involved, but rare in the lung.⁴

Figure 2 (a) Percutaneous transthoracic needle biopsy specimen revealed monotonous, medium-sized cells infiltrating the lung tissue. Tumor cells have high nuclear cytoplasmic ratio and inconspicuous nucleoli (Hematoxylin & Eosin [H&E] staining, magnification, 200 $\times$). (b,c) Immunohistochemical stains revealed reactivity for cytoplasmic CD3, CD56 (magnification, 200 $\times$). (d) In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) showed positive reaction in tumor cells (magnification, 200 $\times$).

Only a few cases have been reported for primary extranodal NK/TCL of the lung. Most of the cases presented with fever, cough, and dyspnea.⁵ Radiographic findings may present multiple nodular lesions,^{5,6} mass or mass-like consolidation,^{5,6} consolidation with cavitation,⁵ consolidation with airbronchogram,^{5,6} halo sign (ground-glass attenuation surrounding a pulmonary nodule),⁶ pleural effusion,^{5,6} and absence of hilar or mediastinal lymphadenopathy.^{5,6} Most cases were also associated with EBV, including positive EBER in the tumor cells or EBV viremia.^{5,6} Extranodal NK/TCL, nasal type is associated with EBV. Circulating EBV DNA levels are related to a tumor burden and can serve as an invaluable tumor marker for assessing treatment response, monitoring disease progress, and as strongly predicting outcomes.⁷ Patients with high baseline plasma EBV DNA levels (≥ 600 copies/mL) had a significantly poorer overall survival expectancy than those with low levels (< 600 copies/mL).⁷

The present case was an ex-smoker with a rapidly growing lung mass, pulmonary nodules, and mediastinal lymphadenopathy, giving the first impression of bronchogenic carcinoma. Nevertheless, splenomegaly is not a usual presentation in lung cancer and might be a diagnostic clue for malignant lymphoma. The differential diagnostic possibilities are much fewer when the spleen is massively enlarged; that is, it is palpable more than 8 cm below the left costal margin or its weight exceeds 1000 g. The vast majority of such patients will have non-Hodgkin's lymphoma, chronic lymphocytic

leukemia, hairy cell leukemia, chronic myelogenous leukemia, myelofibrosis with myeloid metaplasia, or polycythemia vera.⁸ In addition, a very rapidly growing lung tumor suggests infection, infarction, small cell lung cancer, aggressive lymphoma⁹ or a fast-growing metastasis from tumors, such as germ cell tumors and certain sarcomas.¹⁰ Therefore, rapid growth of a lung tumor in six months with massive splenomegaly, as in our patient, indicates aggressive pulmonary lymphoma.

The diagnosis of extranodal NK/TCL is based on histopathology, immunophenotype and EBV status in conjunction with the anatomic site of presentation. Histopathological examination usually reveals: lymphoma cells with a broad cytologic spectrum; small, large or anaplastic in appearance; nucleoli are generally inconspicuous or small; and an angiodestructive growth pattern is frequently present.¹¹ The immunophenotypic profile of the tumor cells bear CD2, and CD56 cytoplasmic CD3, while surface CD3 is usually absent.¹² In addition, clonal Epstein-Barr virus (EBV) genomes are virtually always present. In situ hybridization for EBER is the preferred method of demonstrating the presence of EBV.¹³

There is no recommended treatment at present because of the extreme rarity of these cases. CHOP-based chemotherapy and surgical resection have been reported in the literature.¹⁴ Other treatment strategies, including combined field radiotherapy and chemotherapy, autologous bone marrow

transplantation, and L-asparaginase treatment in relapsed cases,^{15,16} have been used in extranodal NK/TCL, but it remains difficult to cure.¹⁷ The five-year survival rate in extranodal NK/TCL is less than 50% and the median survival for advanced stage disease is only six to 12 months.¹⁷

In our case, positive EBER in tumor cells confirmed the positive correlation between lymphoma and EBV. Subtype 1 EBV identified from serum was compatible with its predominant geographic distribution in Asia. The patient didn't receive chemotherapy with the standard CHOP regimen because of advanced age and performance status. In conclusion, patients presenting with rapidly growing lung mass and massive splenomegaly may have aggressive pulmonary lymphoma. High circulating EBV DNA in extranodal natural killer/T-cell lymphoma would mean a poor prognosis. Identifying young high-risk patients may have benefits for early aggressive and successful treatment.

Disclosure

No authors report any conflict of interest.

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