

□ 증 례 □

A Case of T-cell Primary Pulmonary Lymphoma Diagnosed by TCR γ gene rearrangement

Young Mee Choi, M.D., Seung Joon Kim, M.D., Soon Seog Kwon, M.D.,
Young Kyoan Kim, M.D., Kwan Hyung Kim, M.D., Hwa Sik Moon, M.D.,
Sung Hak Park, M.D. and Jeong Sup Song, M.D.

Department of Internal Medicine, Catholic University Medical College, Seoul, Korea

= 초 록 =

TCR γ 유전자 재배열로 진단된 T세포 원발성 폐림프종 1예

가톨릭대학교 의과대학 내과학 교실

최영미, 김승준, 권순석, 김영균, 김관형, 문화식, 박성학, 송정섭

반복되는 흉막염 및 폐렴을 주소로 내원한 30세 남자환자에서 경기관지 폐생검과 흉수 내 림프구에 대한 유세포 분석 및 T세포 수용체 유전자 재배열 분석을 실시하였다. 경기관지 폐생검 조직의 면역조직화학 염색상 대부분의 림프구가 T세포 표식자인 UCHL1에 대해 강하게 염색되었고, B세포 표식자인 L26에 대해서는 거의 염색되지 않았다. 흉수에서 추출한 림프구의 유세포 분석상 CD3양성, CD2양성인 T림프구가 대부분이었고, 이들 림프구에 대해 중합효소연쇄반응을 이용한 T세포 수용체 유전자 재배열 분석을 하였더니 TCR γ 유전자 재배열과 클론성을 관찰할 수 있었다. T세포 원발성 폐림프종으로 진단하였고, 문헌고찰과 함께 보고하는 바이다.

Key Words : Lung, Lymphoma, T-Cell, Polymerase chain reaction

Extranodal involvement in non-Hodgkin's lymphoma is very rare but is a relatively common phenomenon than one in Hodgkin's lymphoma (1).

Most cases of non-Hodgkin's lymphoma occur in the skin, gastrointestinal tract, nasal cavity, salivary gland, ocular adnexal tissues, and Waldeyer's ring,

while cases involving the lung are rare. Lung parenchymal involvement of non-Hodgkin's lymphoma, including primary pulmonary lymphoma, causes a variety of radiographic findings and clinical manifestations. Frequently, malignant lymphomas of the lung are so similar to other benign lymphoproliferative

* 본 논문은 1996년도 가톨릭 중앙의료원 임상연구비의 보조로 이루어졌음

ferative diseases in pathologic findings that they are often misdiagnosed. Recently, new-developed techniques of gene rearrangement analysis have been used sometimes in the diagnosis of lymphoproliferative diseases, especially in the cases of minimal residual diseases.

We present a case of T-cell lymphoma involving lung and pleural fluid in which a monoclonal T-cell population of lymphoid cells in pleural effusion was detected by gene rearrangement analysis through the PCR.

Case Report

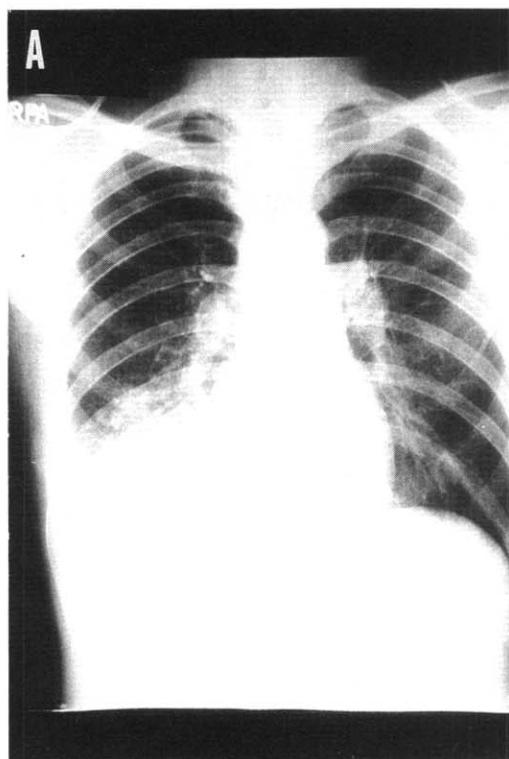
A 30-yr-old man was referred to Youido St. Mary's Hospital for about one year history of recurrent pleural effusion. During the last 10 months, he was treated with anti-tuberculous chemotherapy at local clinic under the impression of tuberculous pleurisy because tuberculosis is still quite prevalent in Korea. However, there was no improvement of pleural effusion and rather progressed. On admission, he presented with right chest discomfort and mild fever. The temperature was 37.2°C. There was no superficial lymphadenopathy or hepatosplenomegaly.

Breathing sound was decreased at the right lower lung field. The hematocrit was 38.6, the white-cell count was 4,400/mm³, the platelet count was 94,000/mm³, and the erythrocyte sedimentation rate was 90mm/h. The aspartate aminotransferase (AST) was 71IU/L, the alanine aminotransferase (ALT) was 54IU/L, the total bilirubin was 0.5mg/dl, the alkaline phosphatase was 867IU/L, the lactate dehydrogenase was 838IU/L, and the prothrombin time was 100%.

Viral markers such as hepatitis B surface antigen

(HBsAg), hepatitis B surface antibody (HBsAb) and anti-hepatitis C virus (anti-HCV) were also negative.

Serum IgG and IgE markedly increased to 4190mg/dl and 1510IU/ml, respectively. Chest roentgenogram and computed tomographic (CT) scans of the chest showed pleural effusion combined with consolidation and partial atelectasis in the right lower lung field and moderate hepatosplenomegaly (Fig 1).



Specifically, cervical, mediastinal or retroperitoneal lymphadenopathy were not found. Thoracentesis revealed an exudative fluid with a lactate dehydrogenase 654unit/L and a total protein of 7.2gm/dl. Pleural fluid cytology and cell block were nondiagnostic. Bronchoscopy showed pus-like discharge at the right lower lobe bronchus without endobronchial lesion. The transbronchial lung biopsy (TBLB)

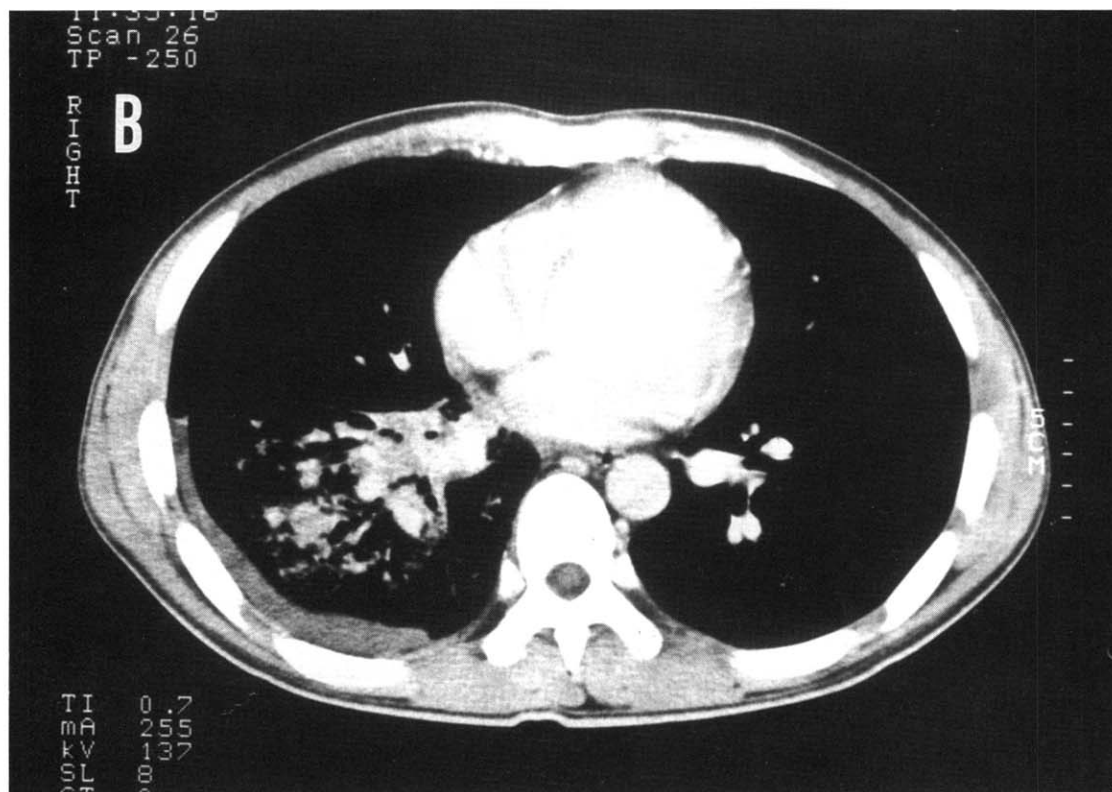


Fig. 1. PA chest radiograph(A) and computed tomography scan of the chest(B) demonstrating pleural effusion combined with consolidation and partial atelectasis on right lower lung field.

specimen from the right lower lobe bronchial tree showed a diffuse, small, pleomorphic lymphoid infiltrate without germ centers. Invasion of the abnormal lymphoid cells was noted in the bronchial smooth muscle(Fig 2).

Immunohistochemical studies with monoclonal antibodies revealed that the abnormal lymphoid cells reacted with the T-cell marker UCHL1(Fig 3), while only a few reacted with the B-cell marker L26 (Fig 4).

The laparoscopic liver biopsy specimen showed irregular infiltration of a small lymphoid cells that destruct normal liver architecture. Immunohistochemical studies with monoclonal antibodies revealed

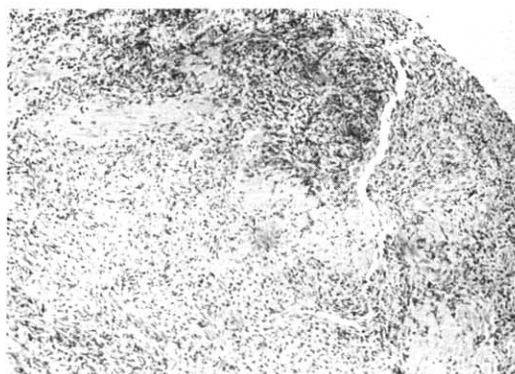


Fig. 2. Transbronchial lung biopsy specimen showing infiltration of abnormal lymphoid cells destroying normal architectures of alveoli and invading to smooth muscle (hematoxylin-eosin stain ; original magnification : $\times 100$)

that small lymphoid cells reacted with the T-cell marker UCHL1, while none reacted with the B-cell marker L26. T-cell and B-cell partition studies were also carried out by flow cytometry on lymphocytes obtained from pleural fluid, revealing that 83.7% of lymphocytes were CD3-positive and 92.0% were CD2-positive, demonstrating that the major component of the lymphocytes was T cells. These results were consistent with the immunohistochemical study of transbronchial lung biopsy (TBLB) specimen. PCR with primers corresponding to the consensus sequences of variable and joining segments flanking the CDR3 of Ig heavy chain and consensus primers of TCR γ gene was performed on lymphocytes of the pleural fluid obtained from the repeated thoracentesis. The results also showed TCR γ gene rearrangement and clonality (Fig 5). A bone marrow examination for staging showed no specific findings.

We diagnosed this tumor as T-cell primary pulmonary lymphoma invading the pleura and the liver.

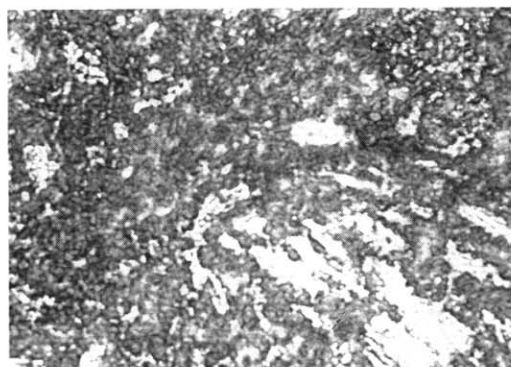


Fig. 3. Transbronchial lung biopsy specimen shows that abnormal lymphoid cells react with the T-cell marker UCHL1 (Immunohistochemical stain using UCHL1; original magnification: $\times 400$)

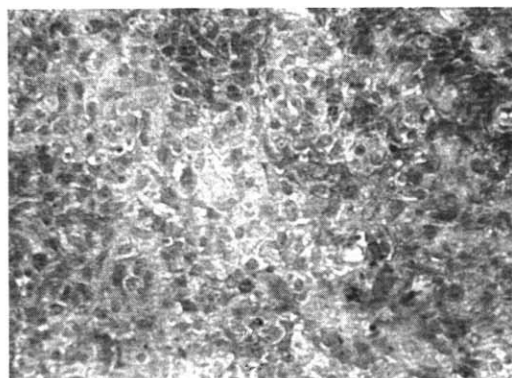


Fig. 4. Transbronchial biopsy specimen shows that only a few reactive lymphocytes react with B-cell marker L26 (Immunohistochemical stain using L26; original magnification: $\times 400$)

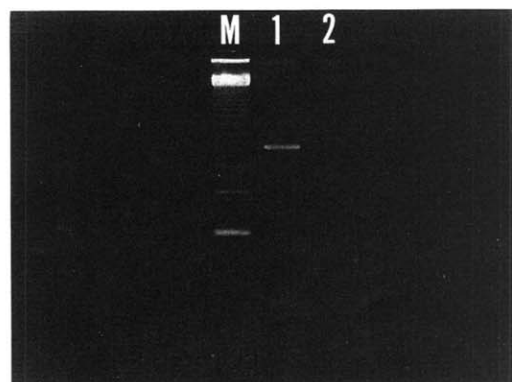


Fig. 5. PCR with primers corresponding to the consensus sequences of variable and joining segments flanking the CDR3 of Ig heavy chain and consensus primers of TCR γ gene performed on lymphocytes of the pleural fluid shows TCR γ gene rearrangement.

M : 123 bp marker

Lane 1 : T cell line of patient

Lane 2 : B cell line of patient

Discussion

Malignant lymphoma can involve the lung as primary or dissemination or direct extension from the adjacent site such as mediastinum (14). The criteria defining PPL presented by Saltzstein are as follows: There is no evidence of dissemination from extrapulmonary lymphoma at the time of the diagnosis or for 3 months after the diagnosis (4). Weiss et al, however, thought that Saltzstein's criteria is too rigid to be used clinically. They proposed a more practical definition of primary pulmonary lymphomas, i.e., those lymphomas that clinically present in the lung (15). In this case, the patient was asymptomatic before the development of progressive pleural effusion. The hepatosplenomegaly was discovered by chance on admission. Although malignant lymphoid cells were detected both in the lung and the liver, we could find neither lymphadenopathy nor marrow invasion. Based upon Weiss' criteria, we regarded this pulmonary lymphoma as primary. In pulmonary lymphoma, dominant cell lineage is usually B cell (5-6). T-cell lymphomas are known to occur usually in the thymus, skin, or nasal cavity(1) and its incidence in the lung is very low. For example, Weiss et al, Herbert et al, Hansmann et al, have reported 2 cases in 19, none in 9, 2 cases in 62, respectively (1,15,16,17). In pulmonary lymphoma, the patterns of pulmonary involvement are diverse, i.e., areas of diffuse nodular or round infiltration, areas of consolidation, pleural effusion, and occasionally endobronchial lesion can be seen (1,14,18). It sometimes seems pathologically benign. Saltzstein differentiated pulmonary lymphoma from other benign lymphoproliferative diseases with abse-

nance of germinal center, infiltration of immature cells, and involvement of lymph nodes. Several recent reports, however, show that polymorphous benign cells often infiltrate, occasionally accompany germinal centers, and they sometimes overshadow the neoplastic cells (16,19). Secondary parenchymal changes such as accumulation of alveolar macrophages, interstitial infiltration of lymphocytes and plasma cells, metaplasia of alveolar lining cells, and bronchiolitis obliterans may be seen. These secondary changes can occur in the pulmonary lymphomas themselves, showing extensive necrosis which sometimes obscure neoplastic infiltration. These findings of pulmonary lymphomas could lead to misdiagnosing them as benign diseases. Especially, a variety of lymphoproliferative diseases of the lung such as lymphocytic interstitial pneumonitis, pseudolymphoma, and lymphomatoid granulomatosis should be differentiated since these diseases have similar morphologic features and often progress to malignant lymphoma (14,15,19). Thus, the diagnosis of pulmonary lymphoma based upon only pathology itself may not be reliable, especially in T-cell pulmonary lymphoma, which have more polymorphous reactive cells and are more easily misdiagnosed as benign disease. In the past, clinically aggressive behavior was regarded as a feature of malignancy.

However, there have been several reports that benign lymphoproliferative diseases may progress to malignant lymphoma and that malignant lymphoma may be stable for a long period of time. Recently, the concept of monoclonal proliferation has been accepted as a feature of malignant lymphoid cells (3,19). Recent advances in immunology and molecular biology have allowed better definition of type,

maturation, and clonality of lymphoma cells. With the novel application of immunophenotypic or gene rearrangement analysis, discrimination of B-and T-lineage and identification of clonality in lymphoproliferative diseases are possible (8-10). There have been several reports of pulmonary lymphoma diagnosed by gene rearrangement analysis using the Southern blotting or immunophenotypical analysis in pleural effusion or bronchoalveolar lavage fluid (BALF) (2,5,12,13,20-21). This gene rearrangement analysis has been usually performed with the Southern blot hybridization. But the molecular analysis technique using PCR is faster, simpler, and inexpensive than the one using the Southern blot.

Although in this case the T-cell malignant lymphoma was very likely judging from the pathologic result of TBLB specimen it self, we carried out the gene rearrangement analysis using PCR in pleural effusion to detect monoclonality and specificity of T cell. As a result, we detected TCR γ gene rearrangement in pleural fluid lymphocytes. This report demonstrates gene rearrangement's usefulness in pulmonary lymphoma through PCR instead of Southern blotting.

References

- 1) Maejima S, Kitano K, Ichikawa S, Kaneko T, Saito H, Kiyosawa K, and Furuta S. T-Cell Non-Hodgkin's Lymphoma of the Lung. *Internal Medicine* 32 : 403-407, 1993
- 2) Betsuyaku T, Munakata M, Yamaguchi E, Ohe S, Hizawa N, Sukoh N, Yamashiro K, Mikuni C, and Kawakami Y. Establishing Diagnosis of Pulmonary Malignant Lymphoma by Gene Rearrangement Analysis of Lymphocytes in Bronchoalveolar Lavage Fluid. *Am J Respir Crit Care Med* 149 : 526-9, 1994
- 3) Knowles DM, Halper JP, and Jakobiec FA. The immunologic characterization of 40 extranodal lymphoid infiltrates. *Cancer* 49 : 2321-2335, 1982
- 4) Saltzstein SL. Pulmonary malignant lymphomas and pseudolymphomas : classification, therapy, and prognosis. *Cancer* 16 : 928-955, 1963
- 5) Davis WB, and Gadek JE. Detection of Pulmonary Lymphoma by Bronchoalveolar Lavage. *Chest* 91 : 787-790, 1987
- 6) Small JH, Round A, Simpson RHW, Ferguson AD. Wegener's granulomatosis simulated by a T cell lymphoma of the lung. *Thorax* 46 : 465-466, 1991
- 7) Picker LJ, Weiss LM, Medeiros LJ, Wood GS, and Warnke RA. Immunophenotypic criteria for the diagnosis of Non-Hodgkin's lymphoma. *Am J Pathol* 128 : 181-201, 1987
- 8) Bertness V, Kirsch I, Hollis G, Johnson B, and Bunn PA. T-cell receptor gene rearrangement as clinical markers of human T-cell lymphomas. *N Engl J Med* 313 : 534-538, 1985
- 9) Waldmann TA, Davis MM, Bongiovanni KF, and Korsmeyer SJ. Rearrangement of genes for the antigen receptor on T cells as markers of lineage and clonality in human lymphoid neoplasms. *N Engl J Med* 313 : 776-783, 1985
- 10) Trainor KJ, Brisco MJ, Wan JH, Neoh S, Grist S, and Morley AA. Gene rearrangement in B- and T-Lymphoproliferative disease detected by the polymerase chain reaction. *Blood* 78 : 192-196, 1991

- 11) Schwaiger A, Prior C, Weyrer K, Umlauf F, Gattringer C, Grunewald K. Non-Hodgkin's lymphoma of the lung diagnosed by gene rearrangement from bronchoalveolar lavage fluid : a fast and noninvasive method. *Blood* **77** : 2538-2544, 1991
- 12) Kavuru MS, Tubbs R, Miller ML, and Wiedemann HP. Immunocytometry and gene rearrangement analysis in the diagnosis of lymphoma in an idiopathic pleural effusion. *Am Rev Respir Dis* **145** : 209-211, 1992
- 13) Keicho N, Oka T, Takeuchi K, Yamane A, Yazki Y, and Yotsumoto H. Detection of lymphomatous involvement of the lung by bronchoalveolar lavage. *Chest* **105** : 458-62, 1994
- 14) Kennedy JL, Nathwani BN, Burke JS, Hill LR, and Rappaport H. Pulmonary lymphomas and other pulmonary lymphoid lesions. *Cancer* **56** : 539-552, 1985
- 15) Weiss LM, Yousem SA, Warnke RA. Non-Hodgkin's lymphomas of the lung. *Am J Surg Pathol* **9** : 480-490, 1985
- 16) Herbert A, Wright DH, Isaacson PG, and Smith JL. Primary malignant lymphoma of the lung : Histopathologic and immunologic evaluation of nine cases. *Hum Pathol* **15** : 415-422, 1984
- 17) Hansmann ML, Zwingers T, Lennert K. Primary lymphoma of the lung : Morphological, immunohistochemical and clinical features. *Histopathology* **16** : 519, 1990
- 18) Kilgore TL, and Chasen MH. Endobronchial Non-Hodgkin's lymphoma. *Chest* **84** : 58-61, 1983
- 19) Colby YV, and Carrington CB. Pulmonary lymphomas : Current concepts. *Hum Pathol* **14** : 884-887, 1983.
- 20) Eliasson AH, Rajagopal KR, and Dow NS. Respiratory failure in rapidly progressing pulmonary lymphoma. *Am Rev Respir Dis* **141** : 231-234, 1990
- 21) Oka M, Kawano K, Kanda T, and Hara K. Bronchoalveolar lavage in primary lymphoma with monoclonal gammopathy. *Am Rev Respir Dis* **137** : 957-959, 1988