Intravascular Lymphomatosis of the T Cell Type Presenting as Interstitial Lung Disease - A Case Report -

Intravascular lymphomatosis (IL) is a rare and generally fatal disease characterized by proliferation of large lymphoma cells almost exclusively within the lumen of small blood vessels. The skin and central nervous systems are typically affected, but involvement of other organs, such as lung, has been described. Predominant lung involvement without cutaneous and neurologic manifestation is very rare and difficult to diagnose. Originally considered as an endothelial disorder, IL has recently been reclassified as lymphoma. Most of the cases reported are of B cell lineage with a few cases of T cell type. We describe a case of the T-cell type IL manifested clinically as an interstitial lung disease without involvement of skin and central nervous systems. Immunohistochemical studies showed the T-cell nature of the neoplastic cells in open lung biopsy sample. *(JKMS 1997; 12: 457~60)*

Key Words : *Lung diseases, Interstitial; Lymphoma, T-cell*

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INTRODUCTION

Intravascular lymphomatosis (IL) is a rare malignant disorder characterized by a massive proliferation of large pleomorphic cells within the lumens of capillaries, venules, and arterioles, usually in the absence of extravascular involvement. Since the first report in 1959 by Pfleger and Tappeiner under the designation "angioendotheliomatosis proliferans systemisata", over 120 cases have been documented in the literature (1). Various names, such as "malignant angioendotheliomatosis", "systemic angioendotheliomatosis", "neoplastic angioendotheliosis", "hemangioendotheliosis", "angiotrophic large cell lymphoma", has been used. The exact origin of the malignant cells was controversial, but considered as endothelial origin. In recent studies, however, lymphoid origin was confirmed primarily by immunohistochemical methods (2). Most IL has a B cell immunophenotype, but rare T cell type was reported (3~5).

Intravascular lymphomatosis is a systemic condition in which small blood vessel throughout the body are occluded by cytologically lymphomatous cells. Usually these lymphomatous cells are not found in peripheral blood and bone marrow, and produce a rare peripheral lymph node enlargement (3, 6). The disease primarily affects the skin and central nervous system, however, involvement of other organs has been reported with diverse clinical manifestations. Lung involvement can be demonstrated pathologically at autopsy in approximately 90% of cases (7), but prominent pulmonary symptom without cutaneous and neurologic manifestation is very rare at presentation (8~11).

We describe a case of the T cell type IL diagnosed by open lung biopsy and immunohistochemistry, presenting as interstitial lung disease with progressive exertional dyspnea and diffuse pulmonary infiltrates on chest radiographs.

CASE REPORT

A 54-year-old male, smoker (45 pack-year), was admitted to hospital because of progressive exertional dyspnea for two months. There were no complaints of fever, cough, sputum, weight loss, skin lesion, disorientation, or peripheral edema. He had no known history of hypertension. Physical examination revealed a blood pressure of 160/100 mmHg, a pulse rate of 88 beats/min and a respiratory rate of 25 breaths/min. He was mentally normal and had no focal neurologic deficits. Lung sound was clear and liver, spleen, and lymph nodes were not felt.

Laboratory examination revealed a hemoglobin of 16.1 g/dl, white blood cell count of 7,770/μl, platelet count of 81,000/μl, ESR of 13 mm/hr, BUN of 35.0 mg/dl, creatinine of 1.6 mg/dl. Arterial blood gas analysis show-

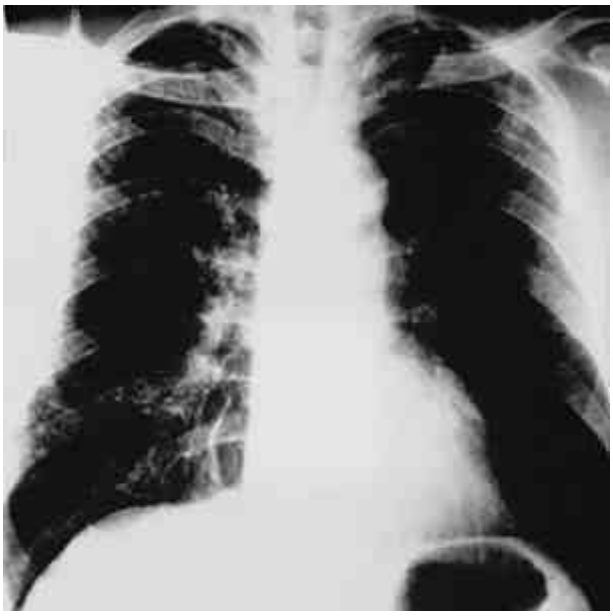

Fig. 1. Chest PA shows subpleural ground glass hazinesses and interstitial thickenings.

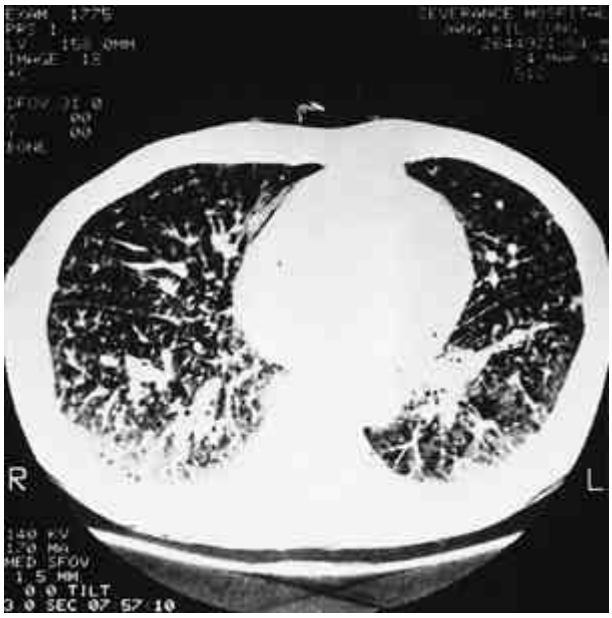

Fig. 2. Chest CT scan shows multifocal areas of increased patch densities predominantly on the subpleural area and diffuse bronchial wall thickenings on both lungs.

ed the following: pH 7.39, pCO_2 28.9 mmHg, pO_2 63.9 mmHg, bicarbonate 21 mmol/L, oxygen saturation 92.2% on room air. Urinalysis showed proteinuria and microscopic hematuria. A 24-hour collection of urine contained 2,990 mg of protein (2900 mg of albumin) and 1248 mg of creatinine, so creatinine clearance rate was 69.8 ml/min/1.73mm^3. Tests for antinuclear antibody, anti-DNA antibody, rheumatoid factor, and anti-platelet antibody were reported negative. Carcinoembryonic antigen (1.5 ng/ml) and α-fetoprotein (1.2 IU/L) were in normal range and serum protein electrophoresis showed no abnormal finding.

Pulmonary function test showed mild pulmonary insufficiency of obstructive type and severe decrease of diffusion capacity: FEV_1 of 2.8 L (78.1% of predicted), FVC of 4.06 L (90.7% of predicted), a residual volume of 3.53 L (116% of predicted), a total lung capacity 6.72 L (95.1% of predicted), and DLco of 2.35 mmol/min/kPa (23.2% of predicted). A chest radiographs showed subpleural ground glass haziness and interstitial thickening in both lung fields but no hilar lesions (Fig. 1). CT scanning of the chest revealed multifocal patchy increased densities in subpleural areas and diffuse bronchial wall thickening without enlarged hilar and mediastinal lymph nodes (Fig. 2).

An open lung biopsy was performed with a presumptive diagnosis of acute stage of usual interstitial pneumonia, which showed intraparenchymal small vessels diffusely filled with discohesive, large pleomorphic tumor

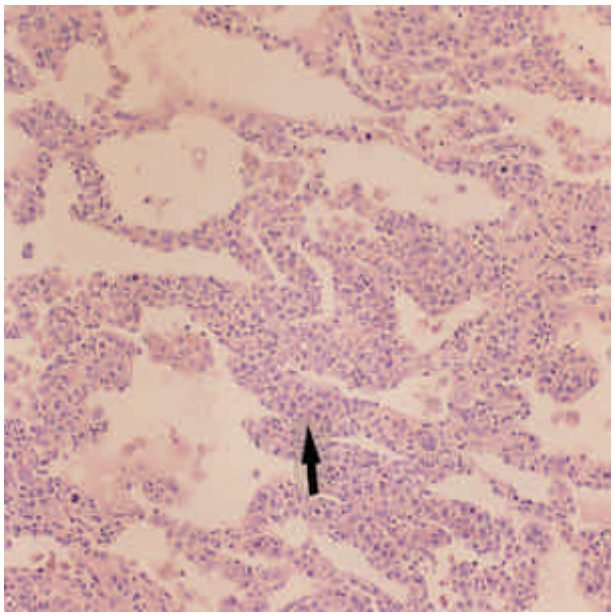

Fig. 3. Open lung biopsy findings show intraparenchymal small vessels (arrow) filled with discohesive and large pleomorphic tumor cells.

cells (Fig. 3). Immunohistochemical stains for cytokeratin, factor VIII related antigen were negative, but leukocyte common antigen and T cell markers (CD3, UCHL) were positive (Fig. 4). A bone marrow aspiration specimen was negative for malignant cells. The histopathology of the

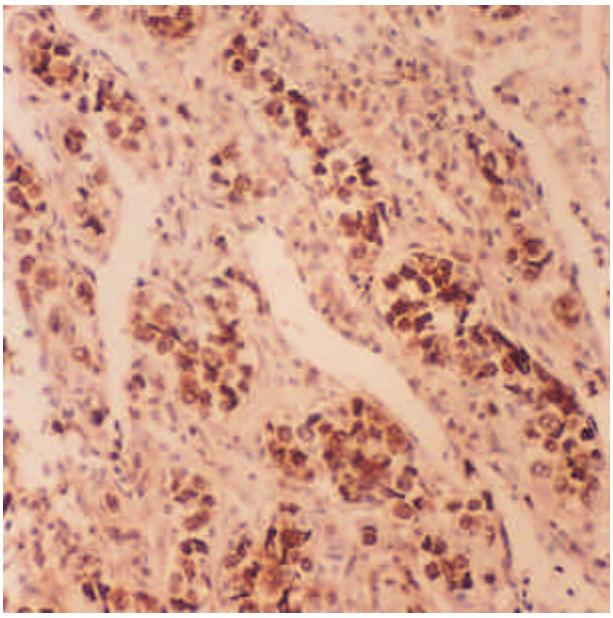

Fig. 4. Immunohistochemical stain for T cell marker (CD3) shows strong positivity in the tumor cells.

lung tissue and immunohistochemical results were consistent with the diagnosis of intravascular lymphomatosis of the T cell type.

The patient received a combination chemotherapy of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). After the second course of CHOP chemotherapy he was readmitted for worsening dyspnea. He died of respiratory failure after 3 months from the diagnosis.

DISCUSSION

Intravascular lymphomatosis was first described as unusual cutaneous small vessel neoplasms in 1959 (12). In the earlier literature, many investigators have concluded that the neoplastic cells are of endothelial origin, based on the intravascular distribution of the neoplastic cells. The ultrastructural findings such as Weibel-Palade bodies, presence of cytoplasmic filament, small amount of rough endoplasmic reticulum, and well-developed Golgi bodies, and the immunohistochemical reactivity of the neoplastic cells with antibody to factor VIII-related antigen appeared to provide further evidence for the possible endothelial origin (13, 14).

Following ultrastructural studies, however, it has been shown that hyperplastic endothelial cells may extend cytoplasmic processes around intraluminal neoplastic cells, and that neoplastic cells entrapped in fibrin-platelet thrombi could absorb platelet-derived factor VIII, both of which could lead to spurious staining for factor VIII (2, 7). Furthermore, cells with the documented Weibel-Palade bodies were interpreted ultimately as reactive endothelial cells (10, 15).

More recently, numerous immunohistologic studies have confirmed the lymphomatous nature of this disorder since immunohistochemical stains of the tumor cells showed positivity for leukocyte common antigen and lymphocyte antigens (2, 3, 7). Regarding the lymphoid differentiation of the neoplastic cells, the vast majority of reported cases are of B cell lineage. Intravascular lymphomatosis of the T cell type is very rare, there being only several cases reported in English literature confirmed by immunohistochemical stain with monoclonal antibodies (1, 3, 5) or monoclonal rearrangement of T cell receptor β sequences (4).

The restriction of these neoplastic cells to the intravascular compartment without involvement of lymphoid tissue may relate to alterations in the Hermes 3 homing receptor antigen, a receptor on lymphocytes for high endothelial venules (15). It has been hypothesized that the lack of expression of this antigen by the cells of IL may impair their ability to exit blood vessels and reach interstitial tissues (10).

Intravascular lymphomatosis occurs in man and woman with equal frequency, and the mean age at onset is between 50 and 70 years (7). The physiologic consequences are related to vascular occlusion by intravascular thrombosis of neoplastic cells. Most reports have focused on the neurological complications, particularly dementia, transient ischemic episodes, and progressive spinal cord involvement with nerve root damage (1). Cutaneous disease with vascular involvement results in indurated erythematous plaques with patchy coagulative necrosis (16). Clinical presentation with other organ involvement, such as lung, kidney, adrenal gland, and pituitary gland, was rare (17). But autopsy findings showed multiple organ involvement in over 90% of the cases. Characteristically lymph node, spleen, and bone marrow were not affected.

Although the disease often spreads to the lung and other internal organs, predominant involvement of the lung without cutaneous or neurologic manifestations is very rare. Pulmonary intravascular lymphomatosis is clinically manifested with exertional dyspnea, nonproductive cough, and hypoxemia. Radiologically diffuse infiltrative lesions appear as interstitial lung disease on chest radiographs. Pulmonary function test shows disturbance of diffusion capacity and arterial blood gas analysis reveals hypoxemia. Open lung biopsy with immunohistochemical study is necessary for confirming the diagnosis. Pathologic findings show extensive microembolization within pulmonary arterioles and alveolar

capillaries which can cause acute cor pulmonale and hypoxia when diffusely involving more than 40% of microvessels (18). Nephrologic manifestations, such as proteinuria, hematuria, hypertension, and nephrotic syndrome, are also considered to be rare (19, 20).

In this case, the patient was admitted with the complaint of progressive exertional dyspnea for 2 months. Chest films and pulmonary function test strongly supported accelerated interstitial lung disease prompting an open lung biopsy to confirm the diagnosis. The histologic and immunohistochemical findings are compatible with the T cell type IL. Nonnephrotic range proteinuria (about 3 gram/day), microscopic hematuria, and hypertension of acute onset were considered as evidences of renal involvement but renal biopsy was not performed.

Intravascular lymphomatosis is high grade malignant lymphoma with very poor prognosis. In a review of 73 cases (16), the overall mortality was above 80% with a survival time ranging from two to 48 months after the diagnosis. A wide range of anti-neoplastic therapies have been used, but most of them have proved ineffective. Complete remission and improved survival have, however, been achieved by use of combination chemotherapies including steroids (3, 8, 20). Our patient received two cycles of the combination chemotherapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, but he died after 3 months from the diagnosis.

In conclusion, to our knowledge, this is the first case of T cell type IL presenting as interstitial lung disease without cutaneous and neurologic manifestations. We suggest that IL, albeit rare, should be included in the differential diagnosis of interstitial lung disease.

REFERENCES

1. Glass J, Hochberg FH, Miller DC. *Intravascular lymphomatosis. A systemic disease with neurologic manifestations. Cancer 1993; 71: 3156-64.*
2. Wrotnowski U, Mills SE, Cooper PH. *Malignant angioendotheliomatosis: An angiotropic lymphoma? Am J Clin Pathol 1985; 83: 244-8.*
3. Sheibani K, Battifora H, Winberg CD, Burke JS, Ben-Ezra J, Ellinger GM, Quigley NJ, Fernandez BB, Morrow D, Rappaprot H. *Fruther evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med 1986; 314: 943-8.*
4. Sepp N, Schuler G, Romani N, Geissler D, Gattringer C, Burg G, Bartram CR, Fritsch P. *"Intravascular Lymphomatosis" (Angioendotheliomatosis): Evidence for a T-cell origin in two cases. Hum Pathol 1990; 21: 1051-58.*
5. Tateyama H, EimotoT, Tada T, Kamiya M, Fujiyoshi Y, Kajiura S. *Congenital angiotropic lymphoma (intravascular lymphomatosis) of the T-cell type. Cancer 1991; 67: 2131-6.*
6. Ansell J, Bhawan J, Cohen S, Sullivan J, Sherman D. *Histiocytic lymphoma and malignant angioendotheliomatosis: one disease or two? Cancer 1982; 50: 1506-12.*
7. Wick MR, Mills SE, Scheithauer BW, Cooper PH, Davitz MA, Parkinson K. *Reassessment of malignant "angioendotheliomatosis": evidence in favor of its reclassification as "intravascular lymphomatosis". Am J Surg Pathol 1986; 10: 112-23.*
8. Tan TB, Spaander PJ, Blaisse M, Gerritzen FM. *Angiotropic large cell lymphoma presenting as interstitial lung disease. Thorax 1988; 43: 578-9.*
9. Snyder LS, Harmon KR, Estensen RD. *Intravascular lymphomatosis (malignant angioendotheliomatosis) presenting as pulmonary hypertension. Chest 1989; 96: 1199-200.*
10. Yousem SA, Colby TV. *Intravascular lymphomatosis presenting in the lung. Cancer 1990; 65: 349-53.*
11. Kamesaki H, Matsui Y, Ohno Y, Amano H, Imanaka T, Takahashi Y, Kobashi Y, Kawakami K, Kita K. *Angiocentric lymphoma with histologic features of neoplastic angioendotheliomatosis presenting with predominant respiratory and hematologic manifestations: Report of a case and review of the literature. Am J Clin Pathol 1990; 94: 768-72.*
12. Pfleger L, Tappeiner J. *Zur Kenntnis systemisierten Endotheliomatose der cutanen Blutgefasse. Hautarzt 1959; 99: 359-63.*
13. Fulling KH, Gersell DJ. *Neoplastic Angioendotheliomatosis: Histologic, immunohistochemical, and ultrastructural findings in two cases. Cancer 1983; 51: 1107-8.*
14. Kitagawa M, Matsubara O, Song SY, Kurashima C, Okeda R, Kasuga T. *Neoplastic Angioendotheliosis: Immunohistochemical and electron microscopic findings in three cases. Cancer 1985; 56: 1134-43.*
15. Ferry JA, Harris NL, Picker LJ, Weinberg DS, Rosales RK, Tapia J, Richardson EP. *Intravascular lymphomatosis (malignant angioendotheliomatosis): A B-cell neoplasm expressing surface homing receptors. Modern Pathol 1988; 1: 444-51.*
16. Gupta AK, Lipa M, Haberman HF. *Proliferating angioendotheliomatosis: Case with long survival and review of literature. Arch Dermatol 1986; 122: 314-9.*
17. Domizio P, Hall PA, Cotter F, Amiel S, Tucker J, Besser GM, Levison DA. *Angiotrophic large cell lymphoma (ALCL): Morphological, immunohistochemical and genotypic studies with analysis of previous reports. Hematol Oncol 1989; 7: 195-206.*
18. Abbondanzo SL, Klappenbach RS, Tsou E. *Tumor cell embolism to pulmonary alveolar capillaries: cause of sudden cor pulmonale. Arch Pathol Lab Med 1986; 110: 1197-8.*
19. D'agati V, Sablay LB, Knowles DM, Walter L. *Angiotrophic large cell lymphoma (intracellular malignant lymphomatosis) of the kidney: Presentation as minimal change disease. Hum Pathol 1989; 20: 263-8.*
20. Nishikawa K, Sekiyama S, Suzuki T, Ito Y, Matsukawa W, Tamai H, Yoshida F, Fukatsu A, Matsuo S, Shigematsu H. *A case of angiotrophic large cell lymphoma manifesting nephrotic syndrome and treated successfully with combination chemotherapy. Nephron 1991; 58: 479-82.*