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CASE STUDY

Intravascular lymphomatosis diagnosed by transbronchial lung biopsy

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ABSTRACT: Intravascular lymphomatosis is a rare lymphoma presenting a variety of symptoms due to proliferation of tumour cells within blood vessels in the brain, the skin and other organs. This disease is generally considered to be highly malignant, but to be relatively susceptible to combined chemotherapy, when diagnosed in the early stage.

We describe a case of intravascular lymphomatosis, presenting with diffuse interstitial shadows on chest radiographic image, which could be diagnosed by transbronchial lung biopsy. The patient showed a good response to combined chemotherapy.

We propose that transbronchial lung biopsy is a useful procedure for the diagnosis of intravascular lymphomatosis.

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Intravascular lymphomatosis (IVL) is a rare lymphoma, in which proliferation of tumour cells is limited to the inside of small arteries, veins and capillaries. The symptoms are caused by blood flow disturbances or embolisms due to massive proliferation of tumour cells within the lumina of the small vessels. IVL often involves the nervous system and/or the skin, with various clinical manifestations, but rarely the bone marrow, lymph nodes, liver or spleen, which are common targets of other lymphomas [1–5]. Antemortem diagnosis of IVL is often difficult, when skin lesions or neurological abnormalities are absent. We report a case with IVL presenting diffuse interstitial shadows on chest radiographic image, which could be diagnosed by transbronchial lung biopsy (TBLB) at an early stage and showed a good response to combined chemotherapy.

Case report

A 53 year old female, who had been complaining of persistent cough and high fever for a month, was admitted to a community hospital on May 6, 1994. Her chest roentgenogram showed slight interstitial changes in both lungs, and laboratory data revealed a highly elevated serum lactic dehydrogenase (LDH), level 3,858 IU·L^{-1}, (reference value 100–450 IU·L^{-1}). Although a diagnosis was not obtained, she was treated with prednisolone (30 mg·day^{-1}), and her symptoms and the level of serum LDH improved over the course of 1 month.

However, her symptoms relapsed as the dose of prednisolone was decreased over the next month, and additional complaints, such as headache and exertional dyspnoea, appeared. She was referred to our hospital on August 17, 1994.

On admission, the patient was physically unremarkable. There were no skin lesions or signs of neurological abnormality. Chest auscultation was normal. No lymphadenopathy or hepatosplenomegaly was detected. A white blood cell count was normal, and no malignant cells were observed in peripheral blood or in bone marrow aspiration. Laboratory tests indicated elevated LDH, 5,085 IU·L^{-1}, glutamic oxaloacetic transaminase (GOT) 113 IU·L^{-1} (reference value 5–35 IU·L^{-1}) and adenosine deaminase 50.5 IU·L^{-1} (reference value 8–20 IU·L^{-1}).

Arterial blood gas analysis showed moderate hypoxaemia (pH 7.42, arterial oxygen tension (P_{a,O_2}) 7.3 kPa (55 mmHg), arterial carbon dioxide tension (P_{a,CO_2}) 4.8 kPa (36 mmHg)), while the patient was breathing room air. Pulmonary function tests showed no restrictive or obstructive defects, but transfer factor for carbon monoxide was decreased to 50% of the predicted value. A chest radiographic image demonstrated bilateral diffuse interstitial changes, particularly in the bilateral lower lung fields and blunting of the right costophrenic sinus (fig. 1a). Computed tomography scans of the chest revealed diffuse ground-glass shadows in both lungs and a localized anterior medial peripheral wedge-like density in the right lung (fig. 2a), but there was no evidence of lymph node involvement or pleural fluid in the thorax.

TBLB specimens, from the right lower lobe documented the presence of atypical lymphocytes within small pulmonary arteries, veins and capillaries, but not outside the vessels (fig. 3). Those from the anterior medial peripheral wedge-like density revealed nonspecific old inflammatory changes. Furthermore, a magnetic resonance

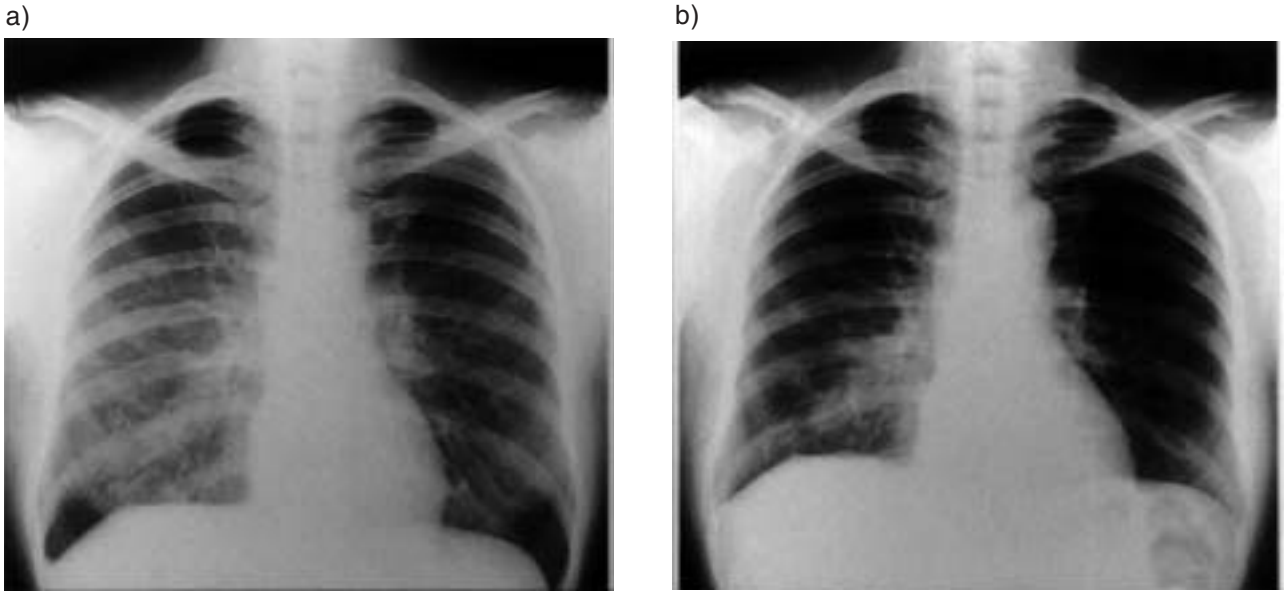

Fig. 1. – a) Chest posteroanterior radiographic image on admission, showing interstitial changes in the bilateral lower lung fields without hilar enlargement. b) After CHOP therapy, these changes improved appreciably. CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone combined chemotherapy.

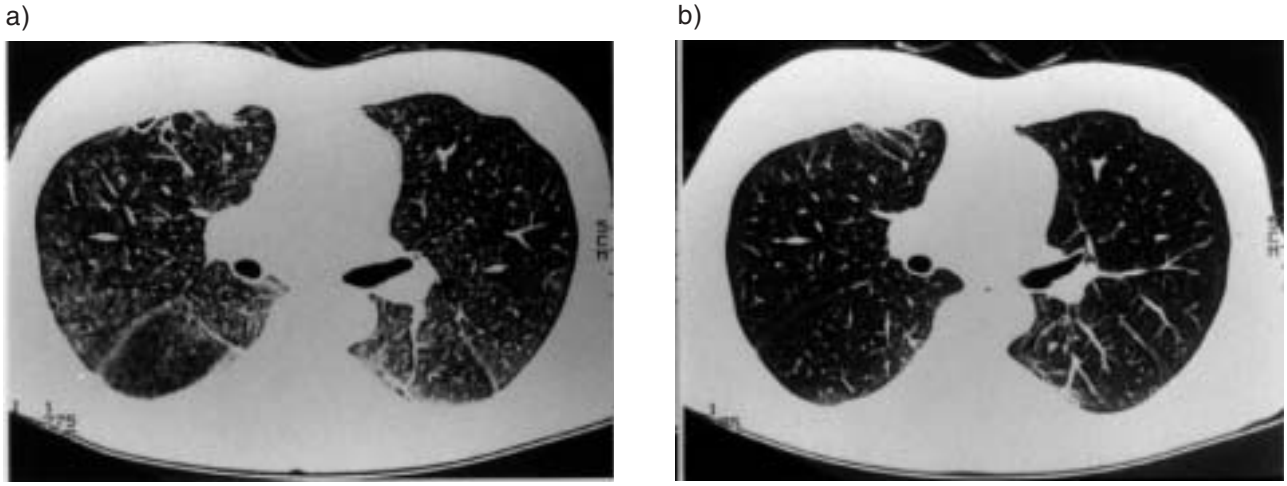

Fig. 2. – a) Computed tomography scan of the lung, showing ground-glass shadows in both lungs. b) After therapy, these shadows almost disappeared.

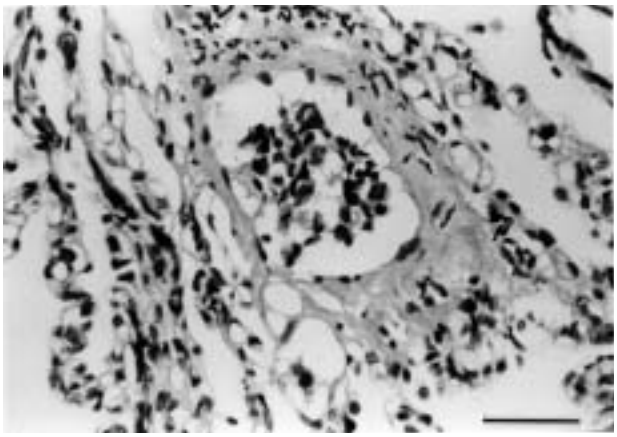

Fig. 3. – A biopsy specimen of the lung. Atypical lymphocytes are seen within small pulmonary arteries, veins and capillaries, but not outside the vessels. Expansion of the alveolar septa due to atypical lymphocytes within the capillaries is also visible. (Haematoxylin and eosin (H&E) staining; internal scale bar=5 μM).

image of the brain demonstrated bilateral subdural hydroma and herniation of the cerebellar tonsil, which were considered to be the cause of the symptoms of intractable headache. Biopsy specimens of the dura revealed the same findings as in the lungs, where atypical lymphocytes were detected only within small vessels. Atypical cells observed in the frozen specimens from the lung and the dura were positive for L-26 (CD20), CD19, CD22 and CD45 which were B-cell markers, but were negative for CD45RO, CD3 and CD4 which were T-cell markers.

The patient was, thus, diagnosed as having IVL with pulmonary and dural involvement. She received systemic chemotherapy, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). Her chest radiographic image (fig. 1b), computed tomography scans (fig. 2b), laboratory data, and symptoms markedly improved within 1 month. Since the anterior medial peripheral wedge-like density in the right lung showed no perceptible change during the chemotherapy, it was

considered to be an old inflammatory change. However, in December 1995, 1 month after completing the ninth cycle of CHOP therapy, serum LDH was again found to be 2,466 IU·L^{-1}. The appearance of atypical lymphocytes in peripheral blood confirmed a relapse. The patient is receiving another chemotherapy regimen, with vincristine, cyclophosphamide, prednisolone and doxorubicin, with a good initial response at the present time.

Discussion

IVL was first described by PFLEGER and TAPPEINER [6] in 1959 as "cutaneous small vessel neoplasm", and was considered to be an endothelial neoplasm. However, subsequent reports have provided evidence that it should be considered a subtype of B-cell lymphoma, in which proliferation of tumour cells is limited to the inside of small arteries, veins and capillaries [7, 8]. The symptoms are caused by blood flow disturbances or embolisms due to massive proliferation of tumour cells within the lumina of the small vessels. IVL often involves the nervous system and/or the skin, with some clinical manifestations, but rarely involves the bone marrow, lymph nodes, liver or spleen, which are common targets of other lymphomas [1–5].

Antemortem diagnosis of this disease is often difficult, when skin lesions or neurological abnormalities are absent. Although the involvement of the lung has frequently been found in IVL at autopsy [2], there have been few reports presenting it as a primary lung disease [4, 5, 9–13]. In most cases, clinical signs and symptoms do not prompt the physician to consider a biopsy of the lung for differential diagnosis, so that the patients may not, unfortunately, receive appropriate therapy at an early stage. There have been a few cases diagnosed by open lung biopsy [4, 10], but only one case diagnosed by TBLB [5].

This is the second report, to our knowledge, demonstrating that TBLB is a useful procedure for the diagnosis of this disease. In general, IVL is thought to be highly malignant. In a review of 73 cases, the overall mortality was over 80%, with a survival time ranging 2–48 months after diagnosis (median 6 months, mean 10 months) [1]. However, IVL presenting only lung involvement often shows a good response to combined chemotherapy [5, 10] and, moreover, 9 year survival was reported in a case with successful treatment [4]. In the present case, thanks to diagnosis at an early stage, when the patient complained of headache but had no neurological abnormalities, the patient has shown a good response to chemotherapy and has so far survived for over 2 yrs. Our experience and those of others suggest that early diagnosis is of great importance for better prognosis in IVL.

In conclusion, we propose that intravascular lymphomatosis should be included in the differential diagnosis when diffuse interstitial shadows are seen on chest radiographic image associated with a marked elevation of serum lactate dehydrogenase. Of particular note is the fact that transbronchial lung biopsy is a useful procedure for the early diagnosis of intravascular lymphomatosis, and may contribute to a relatively good prognosis.

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