A case of intravascular large B-cell lymphoma of lung presenting with progressive multiple nodules on chest computed tomography

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ABSTRACT
A 71-year-old man was admitted to our hospital for dyspnea, which had worsened over a period of more than six months. He was previously diagnosed as having cryptogenic organizing pneumonia, and was treated with steroids in another hospital. He had complained of worsening dyspnea, despite the treatment. We performed video-assisted thoracoscopic surgery because of the high level of lactate dehydrogenase and inconsistency of the usual interstitial pneumonia pattern. Pathologic specimens showed atypical lymphocytes confined to the pulmonary capillaries. On immunohistochemical staining, tumor cells were found positive for CD20, without the T-cell marker. It was consistent with findings of intravascular large B-cell lymphoma. We report this case, which presented with progressive multiple nodules on chest computed tomography.

1. Introduction
Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal large B-cell lymphoma, according to the World Health Organization (WHO) [1]. It is characterized by the presence of tumor cells selectively within small vessels such as capillaries, with exception of larger arteries and veins. Clinical manifestations are variable because tumor cells can involve different systemic organs. Also, presenting symptoms at initial diagnosis of IVLBCL cases are quite different between Asian and European cohorts [2]. Of the Asian-variant IVLBCL, only 20% of patients have dyspnea at proper diagnosis [3]. Until now, chest computed tomography (CT) findings of these pulmonary IVLBCL cases are rare and nonspecific [4–6]. So, proper diagnosis is usually delayed and these patients have poor prognosis. The standard treatment is chemotherapy containing of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (R-CHOP) [2,3].

Here, we report a case of IVLBCL which was initially presented as dyspnea. A 71-year-old man had only suffering from dyspnea for more than three months. However, progressively, prominent superimposition of multiple nodules on background ground-glass opacities (GGOs) in the chest CT was recorded over three-month interval periods. This prompted the final diagnosis of IVLBCL by surgical lung biopsy (SLB), with the help of video-assisted thoracoscopic surgery (VATS). In addition, during the evaluation, significantly high level of serum lactate dehydrogenase (LDH) level caught our eyes. He achieved completely remission after 6 cycles of R-CHOP chemotherapy.

When the patient first visited us, we asked to ourselves a question. What made him suffering from dyspnea so long time? To cut to the point, our answers are an underestimation of the importance of SLB in a timely manner and an overlooking to check serum LDH level. Moreover, because of its scarcity, IVLBCL is mostly excluded from differential diagnosis. From this case, we want to share our experience as two lessons of the importance of timely SLB and the usefulness of serum LDH level for the diagnosis of IVLBCL.

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2. Case report

A 71-year-old man visited our hospital for a second opinion on his worsening dyspnea, recurrent for more than 6 months. 6 months ago, he had started to present dyspnea on exertion, which eventually worsened; he was admitted at a tertiary hospital. At the hospital, pulmonary function test results were normal except for the diffusing capacity for carbon monoxide, at 22.4 mL/mmHg/min (29%). Chest CT showed diffuse GGOs in the both lungs and consolidation at the left lower lobe (Fig. 1A). Echocardiography showed a mildly thickened left ventricle wall and moderate resting pulmonary hypertension (The maximal tricuspid regurgitation velocity 3.6m/sec). Heart biopsy was done to rule out amyloidosis, which came out negative. Bronchoscopic alveolar lavage (BAL) procedure was carried out; the fluid cell count included a total of 640 white blood cells, 64% alveolar macrophages, 12% neutrophils, and 24% lymphocytes. Additionally BAL culture provided no definite finding, as no pathogens were detected, including Mycobacterium tuberculosis and nontuberculosis mycobacteria. Transbronchial lung biopsy was not performed because of hypoxemia during the examination.

These results, supplemented by others, prompted his attending physician at that hospital to explain to the patient that he was diagnosed as having suspected cryptogenic organizing pneumonia. Thus, the attending physician decided to treat him with 50 mg of intravenous methylprednisolone, as an empirical therapy. Initially, therapy was effective; however, upon gradual tapering of the steroid, recurrence of dyspnea on exertion occurred. Upon conducting a follow-up chest CT scan, newly developed multiple nodules were found to have been superimposed on GGOs in the both lungs (Fig. 1B). Subsequently, the patient visited our hospital for further evaluation and management of the worsening dyspnea.

The patient had type 2 diabetes mellitus, dyslipidemia, a duodenal ulcer, and benign prostatic hyperplasia. The patient stated that before the dyspnea occurred, he had smoked 15 cigarettes per day for 50 years, totally 37.5 pack years. His family history and alcohol history were nonspecific.

His vital signs showed blood pressure of 110 mmHg over 70 mmHg, heart rate of 93 beats per minute, respiratory rate of 22 breaths per minute, and body temperature of 36.4 °C. His lung sounds were diffusely coarse in both sides. He had no cervical neck vein engorgement, organomegaly, or palpable mass.

In laboratory examinations, he had a white blood cell count of 5990/mm³ of blood (neutrophil 80.9%), hemoglobin concentration of 11.8 g/dL, platelet count of 71,000/mm³, 306 mOsm/kg serum osmolarity, 128 mEq/L sodium, 4.1 mEq/L potassium, 97 mEq/L chloride, 3.6 g/dL total protein, 2.1 g/dL albumin, 566 mg/dL glucose, 0.5 mg/dL total bilirubin, 28 mg/dL blood urea nitrogen, 1.4 mg/dL creatinine, 32 IU/L aspartate aminotransferase, 31 IU/L alanine transaminase, 1.9 mg/L c-reactive protein, and 1707 IU/L LDH. Blood gas analysis showed pH 7.41, PaCO2 25 mmHg, PaO2 61 mmHg, and oxygen saturation level was 96% at receiving oxygen 3L/min via nasal prong.

Upon review of sequential chest CT at the previous hospital (Fig. 1) and high LDH level, we decided to perform SLB through VATS. On hematoxylin and eosin staining, pulmonary interstitium was filled with several atypical lymphocytes, as an empirical therapy. Initially, therapy was effective; however, upon gradual tapering of the steroid, recurrence of dyspnea on exertion occurred. Upon conducting a follow-up chest CT scan, newly developed multiple nodules were found to have been superimposed on GGOs in the both lungs (Fig. 1B). Subsequently, the patient visited our hospital for further evaluation and management of the worsening dyspnea.

Fig. 1. The sequential chest computed tomography (CT) axial images, with an interval period of three months. (A) shows multifocal patchy distributed ground glass opacities (GGOs) in the both lungs and consolidation at the left lower lobe; (B) shows newly developed multiple nodules superimposed on GGOs in the both lungs, only three months later.
avid lesion (Fig. 4). Thus, we could confirm him as IVLBCL of lung without any other organic involvement. He was treated with R-CHOP chemotherapy for six cycles.

One month later, he came back to the outpatient clinic of the hematology of Seoul St. Mary’s hospital after completion of the chemotherapy. He said that he could climb mountain just like a few years ago and had no dyspnea at all. His lung sounds were clear without crackles. In laboratory examinations, he had a white blood cell count of 15,770/mm$^3$ of blood (neutrophil 81.0%), hemoglobin concentration of 10.2 g/dL, platelet count of 281,000/mm$^3$, 26.0 mg/dL blood urea nitrogen, 1.24 mg/dL creatinine, and 726 IU/L LDH. In radiologic findings, the comparison of sequential chest CT images before and after R-CHOP treatment were also compatible with complete remission of IVLBCL (Fig. 5). He went back home looking forward to his next visit to the hospital.

3. Discussion

IVLBCL is a disease characterized by the presence of tumor cells almost exclusively within the lumina of small vessels [4]. The tumor cells can involve any systemic organs; thus vague and nonspecific symptoms make it challenging to diagnose the condition accurately in patients, and in a timely manner [2]. For these reasons, IVLBCL is known as an aggressive lymphoma with poor prognosis [2]. However, after rituximab was added to the CHOP chemotherapy treatment, there has been a great improvement in the IVLBCL treatment results. For example, a retrospective analysis of 106 IVLBCL patients who were treated either with rituximab or without rituximab, in Japan, reported in favor of the use of rituximab in CHOP chemotherapy. This was because, two years after diagnosis, the rituximab-containing group presented a significantly higher progression-free survival rate and overall survival rates [3]. Currently, the treatment of choice of IVLBCL is R-CHOP chemotherapy [2,3].

There are two important lessons in our case. First, SLB should be performed in case an inconsistency is noted, with usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT), especially, when the nodules are well defined with pulmonary infiltrates [5,7]. The nodular pattern is a distinctively important finding because it may be created by thrombi which may have originated from the invasion of the vessels by atypical cells [5]. Second, a high serum LDH level is frequently found in human malignancies [8].

According to the evidence-based guidelines for the diagnosis and management of idiopathic pulmonary fibrosis (IPF) published by the American Thoracic Society, the European Respiratory
both lungs, compatible with complete remission of intravascular lymphoma of the lung (IVLBCL).

Fig. 5. The sequential chest CT axial images, before (A) and after (B) the rituximab, cyclophosphamide, hydroxydaunorubicin, vincristin, and prednisolone (R-CHOP) chemotherapy. (A) shows multiple nodules superimposed on multifocal patchy distributed GGOs in the both lungs; (B) shows regression of diffuse fine nodules and multifocal patchy GGOs in the both lungs, compatible with complete remission of intravascular lymphoma of the lung (IVLBCL).

Society, the Japanese Respiratory Society, and the Latin American Thoracic Association in 2011, the diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease and the presence of a UIP pattern on HRCT in patients not subjected to SLB, or specific combinations of the HRCT and SLB pattern, in patients subjected to SLB [7]. This guideline recommends that patients who present possible UIP pattern or are inconsistent with UIP pattern on HRCT, should be subjected to SLB [7]. In the case of our patient, his sequential chest CT images demonstrated progressive prominence of multiple nodules superimposed on background GGOs, which is relevant to one of the seven inconsistencies in the UIP patterns [7]. Indeed, even though rare, there was a quite similar case to ours. Katayama et al. [5] reported a case of IVLBCL of lung started from GGO progressed to nodular shadow in chest CT. We suggest that an SLB should be done earlier, especially in an event where definitive diagnosis is not possible [4]. As the sequential chest CT images changed rapidly and the progressive nodular pattern was inconsistent with the UIP pattern, it could have been more helpful for our patient suffering from dyspnea for six months if an SLB had been performed in a timely manner.

Miao et al. [8] suggested that high serum LDH levels are significant in the clinical diagnosis and prognosis of cancer. Serum LDH level may be a potential diagnostic marker for cancer, as well as a useful prognostic indicator of life expectancy, or even a predictive marker for tumor sensitivity to therapy. Although further studies are needed, the authors proposed LDHA, one of the five active isoenzymes in the human tissue, as a new target for inhibition of cancer cell proliferation and invasion.

The usefulness of PET-CT as a diagnostic tool of IVLBCL has been a matter of debate [2,4,5,9]. Indeed, in our case, PET-CT showed no FDG avid lesion at all. We think this could be possible because the number of tumor cells per volume might be lower for IVLBCL to be detected. As mentioned above, the distinct feature of IVLBCL which is characterized by selective growth of tumor cells in the lumina of small vessels in whole bodies makes the density of tumor cells low, so that the accuracy of the PET-CT low [2,9].

In conclusion, although rare, progressive nodules superimposed on GGOs in chest CT could be seen in IVLBCL. Hence, when these patterns are detected, it is recommended to perform SLB if indicated, test serum LDH as a tumor marker and be aware of IVLBCL as a candidate of differential diagnosis.

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