A 52-year-old male with fever and rapidly progressive dyspnea.
What is your Diagnosis?

A 52-yr-old male with fever and rapidly progressive dyspnea

Shigeki Nakamura¹), #Katsunori Yanagihara¹)²), Koichi Izumikawa¹),

Masafumi Seki¹), Hiroshi Kakeya¹), Yoshihiro Yamamoto¹), and Shigeru Kohno¹)³)

¹)Second Department of Internal Medicine, ²)Department of Laboratory Medicine, and

³)Division of Molecular & Clinical Microbiology, Department of Molecular Microbiology & Immunology, Nagasaki University Graduate School of Medical Science, Nagasaki, Japan

*Corresponding author: Katsunori Yanagihara

Department of Laboratory Medicine, Nagasaki University School of Medicine

1–7–1 Sakamoto, Nagasaki 852-8501, Japan

Tel: +81 – 95 – 819 – 7276; Fax: +81 – 95 – 849 – 7285

E-mail: k-yanagi@nagasaki-u.ac.jp
Case report

A 52-year-old man who had never smoked was admitted to our hospital because of severe hypoxemia of unknown origin. He had a history of high fever (about 39°C) and dyspnea for several days. He had no prior history of lung disease and no exposure to occupational dust or animal hazards. The patient had no peripheral lymphadenopathy, no skin lesions, and no neurological deficits. On abdominal examination, the liver and spleen tip were not palpable. Laboratory examination showed an anaemia (Hb, 7.6 g/dl), a decreased platelet count (3.6×10^4/mm^3), and a normal white blood cell count. The serum C-reactive protein (CRP) level was elevated (14.3 mg/dl), and the erythrocyte sedimentation rate was increased (24 mm/h). Other laboratory results included: total protein, 6.0 g/dl; serum albumin, 3.5 g/dl; serum creatinine, 1.4 mg/dl; blood urea nitrogen, 11.0 mg/dl; serum lactate dehydrogenase, 781 IU/l (markedly elevated); serum glucose concentration, normal; liver function tests, normal; and the serum complement prothrombin time was 53%. Arterial blood gases drawn on 4L O2 given nasally were: PaO2, 48.8 Torr; PaCO2, 31.8 Torr; pH, 7.48; HCO3, 24.1 mmol/L; BE 1.3 mmol/L. Antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies were not detected. Repeated blood, sputum, urine, and stool cultures were negative for possible pathogens. The urine was negative for Legionella antigen, and the Mycoplasma
pneumoniae antigen was negative. Chest radiography and high-resolution computed tomography (HRCT) were taken (Fig. 1A and Fig. 1B). Chest radiography on admission (Fig. 1A) showed slightly diffuse interstitial shadows in both lung fields. Chest HRCT revealed a bilateral ground-glass appearance involving predominantly the upper and middle lobes (Fig. 1B). An angio-CT scan showed no signs of pulmonary thromboembolism or lymphadenopathy in the chest and abdomen. There were no abnormalities on echocardiographic examination. Bronchoscopy could not be done because of his hypoxemia and thrombocytopenia. The respiratory disturbance and pulmonary interstitial shadow progressed rapidly for several days from admission (Fig.2A and Fig.2B). Diffuse interstitial shadow progressed rapidly with pleural effusion on chest CT (Fig. 2C).

What is your diagnosis?
Clinical course

Key words: intravascular lymphoma, interstitial shadow, early diagnosis

Since the differential diagnosis initially included atypical pneumonia, AIP, and CVD, the patient was treated with antibiotics and steroid pulse therapy. His clinical status improved temporarily, and the diffuse interstitial infiltrates on both lung fields responded well to treatment with steroid pulse therapy (Fig. 2C), but he deteriorated when the steroid dose was reduced. His bicytopenia did not improve despite therapy. In order to characterize the blood disorder, bone marrow biopsy was performed, and many lymphoma cells were detected (Fig. 3). Flow cytometry studies demonstrated that the tumor cells were enhanced CD20-, CD5-, and CD22-positive B cells, and soluble IL-2 receptor levels were very high (8701). In addition, the marrow cells showed monoclonality (99% sIgλ). Thus, based on the patient’s clinical characteristics and the immunohistochemical reactions, a diagnosis of pulmonary invasion of intravascular large B-cell lymphoma was made, and combination chemotherapy was begun. After combined chemotherapy clinical symptoms, laboratory and radiological findings were markedly improved.

The initial differential diagnosis of this patient included atypical pneumonia, AIP, CVD, drug-induced pneumonia, and lymphoproliferative disease since the patient
responded to steroid therapy temporarily. Furthermore, the diffuse interstitial shadows in both lung fields deteriorated while steroid therapy was tapered. The patient was finally diagnosed as having diffuse large B-cell lymphoma based on bone marrow biopsy, and the fact that steroid therapy had a temporary effect suggests that the hypoxemia and the radiological changes were caused by lymphoma, since lymphoma is well known to be sensitive to steroid therapy. This type of lymphoma includes pyothorax-related lymphoma, mediastinal large cell lymphoma, and intravascular large cell lymphoma; it accounts for half of adult non-Hodgkin lymphoma cases. In the present case, there was no lymph node swelling, but the patient presented with a high fever, acute dyspnea, and bicytopenia. Although the patient was given antibiotics no improvement was seen. There was no evidence of a clear focus of lymphoma other than the lung infiltration, so that a diagnosis of intravascular large B-cell lymphoma (IVL) was made. IVL is a rare, distinctive form of malignant lymphoma, and accounts for \( \leq 1\% \) of adult non-Hodgkin lymphoma cases \([1]\). It has been previously reported that IVL is characterized by CNS and skin lesions and is not accompanied by lymph node enlargement \([2]\). It is difficult to make an early diagnosis since the tumour grows primarily in small arteries, small veins, and capillary vessels, without enlarged lymph nodes or tumour formation. But recent reports have suggested that complete remission
and long-term disease-free survival may be achieved with early therapeutic intervention [3]. One of the particular aspects of this case is chest radiographic manifestation. Although IVL is frequently found in the lung at autopsy, there are a few reports about pulmonary manifestation. The majority of cases with lung involvement showed diffuse interstitial infiltrates on chest radiographs [4-9] (Table1). The mechanism of this radiographic change and hypoxemia in the present case was assumed to be the result of diffuse invasion of lymphoma cells into pulmonary small vessels, resulting in a ventilation-perfusion mismatch due to lymphoma cell accumulation within the pulmonary blood vessels, as well as a diffusion disturbance due to invasion of lymphoma cells into the pulmonary interstitial space. Especially, lung pathologic lesion, respiratory disturbance and rapidly progressive clinical course were frequently shown in AIVL. The patient in this case presented with bicytopenia and rapid deterioration of the respiratory symptoms but not CNS and skin lesions; such a clinical course is similar to that described for AIVL, which has been reported in many Asian countries, including Japan [10]. In the present case, diffuse ground glass opacity with septal thickening and perivascular spaces on high resolution (HR) CT was seen. Yamagata et al. reported that almost 75% of 16 cases of IVL pulmonary involvement showed diffuse pulmonary shadow such as bilateral reticular shadow, reticulonodular shadow, ground-glass opacity
There are a few reports about the lung radiographic manifestations of IVL, so the analysis and accumulation of radiologic information about IVL may be able to play an important role in leading to a prompt diagnosis and an appropriate therapy for clinicians.

In conclusion, IVL should be suspected in patients with a fever of unknown origin, hypoxaemia, and a high LDH level. Even though IVL is a blood disorder, patients may present with a clinical picture suggestive of pneumonia, as in the present case. Thus, in patients with pneumonia who do not respond to antibacterial therapy but have an atypical clinical course with diffuse ground glass opacity on high resolution (HR) CT, it is important to consider the possibility of IVL early to improve the mortality rate.

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References

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Pulmonary intravascular lymphomatosis presentation with dyspnea and air trapping.


Figure legend

Fig. 1A
Chest radiography on admission showed slightly diffuse interstitial shadows in both lung fields.

Fig. 1B
Chest high-resolution computed topography (HRCT) on admission revealed a bilateral ground-glass appearance involving predominantly the upper and middle lobes.

Fig. 2A
Chest radiography after 6 days from admission showed diffuse interstitial shadow progressed rapidly on chest radiography.

Fig. 2B
Chest CT after 6 days from admission showed diffuse interstitial shadow progressed rapidly with pleural effusion.

Fig. 2C
The infiltrations on both lung fields were improved after steroid pulse therapy.

Fig. 3.
Bone marrow biopsy was performed. Microscopically, the numerous neoplastic cells have large and round nuclei (H&E, ×400).
Fig. 2
Fig. 3
<table>
<thead>
<tr>
<th>Reference</th>
<th>Presentation</th>
<th>Chest Xp or/and chest CT findings</th>
<th>outcome</th>
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<tbody>
<tr>
<td>Yousem et al[4].</td>
<td>Shortness of breath, fever, weight loss</td>
<td>diffuse interstitial infiltrates (Chest Xp)</td>
<td>died</td>
</tr>
<tr>
<td>Walls et al.[5]</td>
<td>Dyspnea, fever, dry cough</td>
<td>mosaic attenuation consistent with air trapping (HRCT)</td>
<td>survive</td>
</tr>
<tr>
<td>Tan et al.[6]</td>
<td>Fever, exertional dyspnea</td>
<td>diffuse interstitial shadow without hilar enlargement (Chest Xp)</td>
<td>survive</td>
</tr>
<tr>
<td>Jang et al.[7]</td>
<td>General weakness, dyspnea</td>
<td>bilateral patchy areas of ground-glass opacity with subpleural prominence and mild thickening of the interlobular septa (HRCT)</td>
<td>died</td>
</tr>
<tr>
<td>Nakamura et al (current report)</td>
<td>High fever, dyspnea</td>
<td>bilateral ground-glass opacity with subpleural prominence and thickening of the interlobular septa (HRCT)</td>
<td>survive</td>
</tr>
<tr>
<td>Ko et al.[8]</td>
<td>Fever, dyspnea, headache</td>
<td>diffuse reticulonodular shadow (Chest Xp)</td>
<td>died</td>
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<tr>
<td>Paassen et al. [9]</td>
<td>Dyspnea, cough</td>
<td>diffuse interstitial change, ground glass opacity (Chest CT)</td>
<td>died</td>
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Table 1  previous intravascular lymphoma cases with interstitial shadow