Title page

Case report

COVID-19-related pneumonia with a predominant lymphocyte fraction in bronchoalveolar lavage fluid

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Key Clinical Message

A woman was clinically diagnosed with COVID-19-related pneumonia because of a positive antibody test. Her BALF contained an elevated lymphocyte fraction, which might explain why steroids are effective against COVID-19-related pneumonia.

Keywords：
COVID-19
Dexamethasone
BAL
organizing pneumonia
RT-PCR
antibody testing

(1) Text

Introduction:

Steroid treatment, such as dexamethasone, is currently considered effective for coronavirus disease 2019 (COVID-19)[1] [2]. However, evidence of the effect of steroids in COVID-19-associated pneumonia remains unclear. We performed bronchoalveolar lavage (BAL) in a patient with mild pulmonary inflammation diagnosed with COVID-19-related pneumonia by antibody testing and confirmed the elevation of lymphocytes in the leukocyte fraction. This is considered the reason for the effectiveness of steroids in treating early COVID-19-related pneumonia.

(2) Case Report:

A 48-year-old woman, considered a close contact of her husband who was diagnosed with COVID-19-related pneumonia, visited our hospital. She was asymptomatic. A plain chest x-ray showed a nodular shadow on the margin of her right middle lung field (Figure 1A), and simple chest computed tomography (CT) showed segmental ground-glass opacities in the lower right lobe of her lung (Figure 1B). Reverse transcription-polymerase chain reaction (RT-PCR) on her nasopharyngeal swab was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, after returning home, she became febrile and experienced dysgeusia, fatigue, and headaches. RT-PCR tests for SARS-CoV-2 were repeated on nasopharyngeal swabs on days 3 and 6 but remained negative. Because the symptoms did not improve, she returned to our hospital on day 9 of the illness. Chest CT showed exacerbation of the ground-glass shadow on the lower right lobe. However, RT-PCR with an additional nasopharyngeal swab was still negative. Because the symptoms did not subsequently improve, she was

hospitalized 2 days later to investigate the cause. RT-PCR on a nasopharyngeal swab was performed again on admission but was negative. Laboratory test results showed no leukocyte elevation, and C-reactive protein was only slightly elevated (Table 1). Chest x-ray showed the appearance of a ground-glass shadow in the lower right lung field (Figure 1C), and chest CT showed the appearance of a mobile ground-glass shadow (Figure 1D) in the lower right lobe. Because COVID-19 could not be diagnosed via a nasopharyngeal swab, a differential disease was suspected, such as organizing pneumonia, or other diseases, such as tuberculosis. Bronchoscopy was performed on day 12 of the illness to investigate the cause. BAL of the lower right lobe was performed by injecting saline (50 mL) into the bronchi and then recovering it. This was repeated three times (total injected: 150 mL), and a total of 35 mL was recovered (recovery rate: approximately 23%). The leukocyte fraction of the bronchoalveolar lavage fluid (BALF) was lymphocyte-dominant (52.0%), and the culture results were negative. SARS-CoV-2 RT-PCR of the BALF was negative (Table 1), and the $CD4^+/CD8^+$ ratio was not measured. Thus, no diagnosis could be made from the BALF results. Therefore, an additional COVID-19 antibody test for research use only (RUO; Elecsys Anti-SARS-CoV-2) was performed on a peripheral blood sample, and a positive result was obtained. Because of the presence of a ground-glass shadow characteristic of COVID-19-related pneumonia in the lower right lobe as well as fever and dysgeusia, she was clinically diagnosed with COVID-19-related pneumonia. The fever disappeared after admission and without treatment. Because the BALF was lymphocyte-dominant, steroid treatment was administered. The lung field shadow improved over the course of the disease. She was eventually discharged on day 17.

(3) Discussion:

There are few reports on the leukocyte fraction of BALF for COVID-19-related pneumonia, and a literature search found only one report of an elevated leukocyte fraction in BALF in COVID-19-related pneumonia[3]. Our case of COVID-19-related pneumonia showed an elevated level of lymphocytes in the leukocyte fraction of the BALF.

In cases of viral pneumonia, the elevation of the leukocyte fraction of BALF occurs because of infection with new influenza or parainfluenza virus[4] [5]. Organizing

pneumonia has also been reported in cases of parainfluenza virus infection. Generally, organizing pneumonia includes idiopathic organizing pneumonia of unknown etiology and organizing pneumonia that is secondary to infectious diseases (bacteria, viruses, parasites, fungi, and various pathogens), drug-induced collagen disease, malignant disease, and irradiation treatment[6]. In idiopathic organizing pneumonia of unknown cause, lymphocytes in the leukocyte fraction of BALF are often elevated[7], as is the case in secondary organizing pneumonia[8]. Thus, it is thought that the lymphocytes in BALF are elevated because of secondary organizing pneumonia in viral pneumonia caused by infection with new influenza or parainfluenza virus. Our case also revealed an elevated lymphocyte fraction of the leucocytes in the BALF. Additionally, the ground-glass shadow was mobile.

Our findings suggested secondary organized pneumonia due to COVID-19-related pneumonia, which is similar to other viral pneumonia. There are currently various reports on the treatment of COVID-19, including the use of antiviral drugs. Steroid treatment, such as methylprednisolone and dexamethasone, has been reported as effective[1] [2]. However, few reports have substantiated the reason for steroid use.

It is believed that there are two phases of COVID-19 infection. In the early stage, there is a reaction to the viral infection. This is followed by an acute inflammatory reaction phase where the host develops acute respiratory distress syndrome (ARDS) because of severe respiratory failure[9]. A four-case report of the cellular composition of BAL in cases of ARDS due to COVID-19 infection reported neutrophil dominance[10]. Generally, BALF in cases of ARDS is predominantly neutrophilic[11]. Furthermore, steroid administration does not significantly reduce the mortality rate in the acute phase of ARDS[12], and the effectiveness of steroid treatment is reduced in cases of ARDS where COVID-19 infection has already occurred. On the other hand, if the COVID-19-related early mild pneumonia does not develop into ARDS, as in our case, it is considered to be secondary organized pneumonia due to the viral reaction in the early stage of infection. Since it has been reported that secondary organized pneumonia is improved by steroid treatment as well as organic pneumonia[13]. Therefore, it is considered to be the basis for the use of steroid treatment in COVID-19-related pneumonia.

In our case, testing for SARS-CoV-2 via RT-PCR using a nasopharyngeal swab was performed five times and was negative in all instances. The standard diagnostic method currently used for COVID-19 involves RT-PCR, which detects viral nucleotides from specimens obtained from oropharyngeal and nasopharyngeal swabs. However, the sensitivity of RT-PCR has been reported as 60%–71%[14], which may be the reason for the negative results obtained in our case. Our patient was RT-PCR-negative using both nasopharyngeal swab samples and BALF. Regarding the concordance rate between RT-PCR for nasopharyngeal swabs and BALF, a higher positive rate was reported for RT-PCR for BALF than for nasopharyngeal swabs[15]. Vannucci et al. assessed 81 cases of BALF with interstitial shadows in the lungs and suspected COVID-19, where the nasopharyngeal swabs were negative. Of them, three cases (3.7%) were positive. All three cases later became positive in the nasopharynx, which has been reported as an effective test for patients in the gray zone[16].There is one case report where the nasopharyngeal swab sample was negative, but the BALF sample was positive[17]. On the other hand, it was reported that if the nasopharyngeal swab is negative, the BALF is also likely to be negative[18]. In our case, RT-PCR of BALF was also negative. Also, in our case, interstitial pneumonia, including other collagen diseases, was excluded, and infectious diseases that could be differentiated from others were also excluded. In our case, bronchoscopy was performed on day 12 of the illness. It was considered that one of the reasons why the RT-PCR test was negative for both the nasopharyngeal swabs and BALF was the relatively long period that had elapsed since the disease onset.

Our case was not diagnosed by RT-PCR. Instead, a serum antibody test for the presence of IgM/IgG antibodies against SARS-CoV-2 by immunochromatography was positive. According to the National Institute of Infectious Diseases in japan, the IgG antibody positivity rate in patients who tested positive for RT-PCR was reported as 96.9% at 13 days after disease onset[19]. Thus, it has been suggested that IgG levels may be useful in cases where it is difficult to diagnose by RT-PCR after a long time has elapsed from the disease onset. Our case was positive on day 12 after the disease onset. It is believed that the measurement should be performed at the time when the antibody test is at its most reliable. The antibody test that we used was an Elecsys Anti-SARS-CoV-2 (RUO) kit, which has sensitivity to RT-PCR-positive cases of 99.5% and a specificity of

99.8%[20]. Because there was no previous episode of COVID-19 infection in our patient, this case was clinically diagnosed as a COVID-19 infection.

In summary, this case was clinically diagnosed as COVID-19 because the antibody test was positive. Furthermore, there were imaging findings of mild pneumonia without respiratory failure. Lymphocyte elevation was observed in the leukocyte fraction of the BALF. This may be one of the reasons why steroids are as useful as in general viral pneumonia in early COVID-19-related pneumonia that has not progressed to ARDS. Our findings suggest that steroids should be administered early in cases of COVID-19-related pneumonia.

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(5) Figure legends

Figure 1. A: Chest X-ray on day 1 of the illness showing a nodular shadow on the margin of the right middle lung field.
B: Chest computed tomography on day 1 of the illness showing segmental ground-glass opacities in the lower right lobe of the lung.
C: Chest x-ray on day 11 of the illness showing the appearance of a ground-glass shadow in the lower right lung field.
D: Chest computed tomography on day 11 of the illness showing the appearance of a mobile ground-glass shadow in the lower right lobe.