Massive Pleural Effusion with Adenosine Deaminase (ADA) Test Positive and COVID-19 Confirmed: A Case Report

Dewintha Airene Novianti1, Puspa Wardhani 2,**

ABSTRACT
A 26-year-old man complained of shortness of breath for 3 days before the hospital admission. The patient had a history of coughing up blood and had consumed alcohol and drugs. Decreased vesicular auscultation and dull percussion in the left lateral palpation. Laboratory result showed increased neutrophil-lymphocyte ratio C-reactive protein, D-dimer, procalcitonin, ferritin, and decreased albumin level. Pleural fluid analysis indicated the presence of exudate, SARS-CoV-2 PCR positive, and increased ADA level to 43 U/L. Based on the examination results, we suspected that the etiology of the massive pleural effusion was tuberculous pleurisy, particularly due to increased ADA levels. The patient was diagnosed with COVID-19 pneumonia with massive pleural effusion and tuberculous pleurisy. Massive pleural effusion in SARS-CoV-2 infection is rare. Thus, laboratory modalities for massive pleural effusion diagnosis are needed to determine the etiology and effective treatment for the patient. ADA analysis could be considered as an initial examination in patients with pleural effusion during the wait for pleural fluid culture results.

Key words: Pneumonia, COVID-19, Pleural effusion, Tb pleuritis, ADA test, Infectious disease.

INTRODUCTION
A cluster of pneumonia cases of unknown cause was reported in Wuhan in early December 2019, in Hubei province, China. Early January 2020, it was found that the organism causing the severe acute respiratory syndrome is coronavirus 2 (SARS-CoV-2, previously known as 2019nCoV). SARS-CoV-2 infects human respiratory epithelial cells through interaction between viral protein S and angiotensin-converting enzyme 2 (ACE2) in human cells.1

Examination of the genetic material of SARS-CoV-2 using the viral nucleic acid real-time reverse transcription-polymerase chain reaction (RT-PCR) method is currently remains the gold standard for diagnosing COVID-19 pneumonia. Radiologic evaluation is a necessary supporting workup in the wait of the RT-PCR results2 In the early stage of COVID-19 pneumonia infection, common radiological findings observed included white patches and interstitial changes in the lung fields. Severe cases of SARS-CoV-2 pneumonia often manifested as consolidation, but pleural effusions are rare.3

The study by Lomoro et al.4 on 27 patients reported radiological findings of consolidation in 46.9% of the patients, GGO in 37.5% of the patients, and no finding of pleural effusion. Cozzi et al.5 observed that of 135 patients, pulmonary consolidation presented in 57.7% of the patients, GGO in 23.5% of the patients, and pleural effusions in merely 16.6% of the patients.5 Based on these data, it is known that pleural effusion in SARS-CoV-2 patients has a low prevalence.

In this report, we found a patient with confirmed SARS-CoV-2. The CXR radiograph of the patient showed a unilateral massive pleural effusion. This report was appointed to investigate the case of SARS-CoV-2 pneumonia with massive pleural effusion. We attempted to determine the etiology and effective treatment of the pleural effusion for the patient to result in a better outcome.

CASE REPORT
A 26-years-old man was admitted with a chief complaint of shortness of breath 3 days before the hospital admission. The complaint was accompanied by fever, cold, cough, sore throat, nausea and vomiting. There was a history of coughing up blood for 7 days, approximately, and a progressive weight loss. The patient also complained that his abdomen had become progressively bloated for the last 14 days and that he had diarrhea with a frequency of 3 times per day for the last 7 days. The patient has been held prisoner for 2 years. The patient disclosed a history of alcohol and drugs consumption. The patient has not been diagnosed with other diseases and denied any consumption of anti-tuberculosis drugs.

Physical examination
The patient was awake with the Glasgow Coma Scale of E4V5M6. The vital sign showed blood pressure of 130/90 mmHg, heart rate of 132 times per minute, respiratory rate of 29 times per minute, a body temperature of 37.2°C, and oxygen saturation of 87% without any respiratory support. The thorax expansion appeared to be asymmetrical on the inspection with reduced movements on the left side of the chest. Examination of the left lung presented a dull percussion on the left lateral and a decreased vesicular sound on auscultation. Other physical examinations were within normal limits.

Laboratory findings

The hematology analysis results showed an increased leukocyte count. Other parameters were within normal limits. The neutrophil-lymphocyte ratio (NLR) value was increased at the beginning of the admission then decreased towards the end of the treatment (Table 1). In clinical biochemistry and immunology examination, there was an increase in AST, ALT, and CRP levels and a decrease in albumin levels. There was also an increase in procalcitonin and ferritin levels (Table 1). Coagulation function examination revealed an increase in D-dimer levels during treatments. PPT, APTT, and fibrinogen were within normal limits (Table 1). The real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of SARS-CoV-2 presented a positive result and the SARS-COV-2 antibody test revealed a reactive IgG and IgM (Table 1).

Pleural fluid analysis showed an increase in glucose, protein, and LDH levels which indicated the presence of exudate fluid (Table 2). The first CXR during the patient admission indicated a milliary lung tuberculosis with bilateral pleural effusion. The effusion was more massive on the left side (Figure 1). We attempted to determine the etiology of the pleural effusion. Thus, an ADA analysis was performed on the pleural fluid. The analysis showed increased ADA levels of the pleural fluid (Table 2).

The patient was treated with a mix of intravenous fluids of 0.9% NaCl and aminofluid with a 1:1 ratio. The mix was administered per 24 hours. Other medication regimens included multivitamins tablets once daily, N-acetyl cysteine tablet 200 mg thrice daily, Curcuma tablet thrice daily, vipalbumin 2 capsules thrice daily, Arixtra intravenous 5 mg once daily, ceftriaxone intravenous 1 g twice daily, fluconazole intravenous 400 mg once daily. Based on the results of the ADA analysis, an anti-tuberculosis treatment regimen was planned to be administered.

DISCUSSION

Diagnosis of COVID-19 pneumonia is established based on clinical presentations that could be obtained from history taking, physical examination, and workup studies. According to WHO, the severity of COVID-19 is classified into mild, moderate and severe. Diagnosis criteria for severe COVID-19 include fever, cough, shortness of breath, increased respiratory rate to more than 30 times per minute, and SpO₂ <90% in room air. This patient was presented with shortness of breath, fever, cough, loss of appetite, and diarrhea. Therefore, this patient was qualified for severe COVID-19 diagnosis.³ WHO recommends RT-PCR analysis for all patients with suspected COVID-19 via nasopharynx and oropharynx specimens.³ The RT-PCR analysis in this patient resulted as SARS-CoV-2 positive. Routine examinations for COVID-19 patients include complete blood counts, coagulation function (PT, APTT, and D-dimer), and related inflammatory parameters (ESR, CRP, ferritin, and procalcitonin).

Lymphopenia is a common finding in COVID-19 due to SARS-CoV-2 attachment to the angiotensin-converting enzyme 2 (ACE2) receptor. This attachment triggers immune responses that would cause a decrease in T CD4⁺, T CD8⁺, NK cells, and B cells, thus presented as lymphopenia.

Table 1: Laboratory result.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Result</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10³/µl)</td>
<td>13.33⁴</td>
<td>3.37-10</td>
</tr>
<tr>
<td>% Neutrophil</td>
<td>85.2</td>
<td>39.8-70.5</td>
</tr>
<tr>
<td>% Lymphocyte</td>
<td>5.7</td>
<td>23.1-49.9</td>
</tr>
<tr>
<td>NLR</td>
<td>14.9⁴</td>
<td>3.13</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>96⁴</td>
<td>0-50</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>121⁴</td>
<td>0-50</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.8</td>
<td>3.4-5.0</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>8.7</td>
<td>0-1</td>
</tr>
<tr>
<td>Procalcitonine (ng/ml)</td>
<td>1.47⁴</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Test Ferritin (ng/ml)</td>
<td>2906.7⁴</td>
<td>M: 22-323</td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>12</td>
<td>9-12</td>
</tr>
<tr>
<td>aPTT (seconds)</td>
<td>27.3</td>
<td>23-33</td>
</tr>
<tr>
<td>D-Dimer (mg/dL)</td>
<td>1320⁴</td>
<td>&lt;400</td>
</tr>
<tr>
<td>Antibody IgG/IgM</td>
<td>Reactive</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>PCR SARS-CoV-2</td>
<td>Positive⁴</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Non-reactive

Table 2: Pleural fluid analysis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Result</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>86.0⁴</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td>4.1⁴</td>
<td>Exudate: &gt;50% serum levels</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>653⁴</td>
<td>Exudate: &gt;60% serum levels</td>
</tr>
<tr>
<td>Number of cells (10³/µl)</td>
<td>0.346</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine deaminase (ADA) of the pleural fluid</td>
<td>43 U/L</td>
<td>≤30 U/L</td>
</tr>
</tbody>
</table>

pH, power of hydrogen; LDH, lactate dehydrogenase; WBC-BF, total white blood cell count; RBC-BF, total red blood cell count; MN#, monocytes count; PMN#, polymorphonuclear cells count; MN%, monocytes percentage; PMN%, polymorphonuclear cells percentage.

*abnormal results

Figures

Figure 1: AP thorax radiograph presented a left massive pleural effusion.
with relative neutrophilia or increased NLR.\(^6,7\) This patient showed an increase in NLR to 14.9. An increased NLR to more than 3.13 had been indicated to be a predictor of a worsening prognosis. NLR is thought to be a cost-effective marker. It could be assessed from routine peripheral blood tests and could be associated with the progression and prognosis of COVID-19. A meta-analysis study has reported that patients with severe COVID-19 infections had a higher NLR than those with non-severe COVID-19 infections.\(^7-10\)

Coagulopathy in COVID-19 patients is manifested as prolonged PT and APTT, increased D-dimer, fibrinogen, and fibrin degradation products (FDP), and decreased antithrombin III. In this patient, fibrinogen and D-dimer levels were elevated in initial assessments during admission.\(^7,11-13\) D-dimer is a product of fibrin breakdown and could be utilized as a marker of fibrinolytic activity. This patient had an increased D-dimer level. The increase of D-dimer levels was predicted to be due to the involvement of pro-inflammatory cytokines during endothelial injury that triggers coagulation activation and fibrinolysis inhibition.\(^11-15\) Elevated D-dimer levels at initial assessment could predict impending bleeding complications, thrombotic complications, critical illness, and death. An elevated D-dimer has a more pronounced association as inflammatory markers rather than coagulation parameters. Yu et al.\(^11\) reported that any abnormalities in conventional coagulation tests, specifically elevated D-dimer and FDP levels during hospitalization, were associated with poor prognosis in COVID-19 patients.\(^11-15\)

Elevations in AST and ALT levels are estimated due to the direct bond between SARS-CoV-2 and ACE2 receptors in cholangiocytes. This attachment would cause cholangiocyte dysfunction and systemic inflammation that induces liver damage. A reduction in albumin levels is as well as a consequence of COVID-19 with severe features exhibited as a hyper-inflammation state that would trigger a cytokine storm. A cytokine storm is defined as an uncontrolled inflammatory response due to the release of numerous pro-inflammatory cytokines. The cytokine releases are triggered by the activation of innate and cellular immunity. Elevated levels of inflammatory biomarkers, including IL-6, IL-2, IL-7, TNF-α, interferon (IFN)-γ, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, granulocyte-colony stimulating factor (G-CSF), CRP, procalcitonin (PCT), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and ferritin, have been commonly reported in COVID-19 patients. CRP, ferritin, and procalcitonin elevations were found in our patient.\(^7,11-13,21\)

Chest radiograph in COVID-19 patients in the early stages would show small white patches and interstitial changes that are more pronounced in the peripheral zone of the lung. When COVID-19 pneumonia endures, the radiograph would advance to ground-glass opacities (GGO) and infiltration in both lung fields. Radiograph appearance could even represent consolidation in severe COVID-19 pneumonia. Findings of pleural effusion are very rare, yet this patient presented with a massive pleural effusion. This finding does not correspond with the predominant representation of COVID-19 pneumonia. Therefore, finding the etiology of the pleural effusion is much needed for diagnosis and prompt treatment.\(^1,2,4\)

According to Light’s criteria,\(^22\) a pleural effusion is an exudate if at least one of the following criteria is met: (1) pleural total protein/serum total protein ratio >0.5, (2) pleural LDH/serum LDH ratio >0.6, (3) pleural LDH level >23 upper limit of the laboratory’s reference range of serum LDH or >200 IU. In this patient, the pleural fluid analysis indicated a presence of exudate due to a qualified increase in protein and LDH levels. Exudate finding in the pleural fluid analysis was suspected due to the presence of parapneumonic, i.e., coinciding community-acquired pneumonia, hospital-acquired pneumonia, empyema, or tuberculosis.\(^5,23,24\) The patient was assessed for the adenosine deaminase (ADA) analysis. ADA analysis is a test used to establish the diagnosis of TB pleurisy, with an accuracy and sensitivity of 92% and a specificity of 90%.\(^26,27\) ADA consists of 2 isoenzymes: ADA1 and ADA2. ADA1, a ubiquitous enzyme that is produced by many different cell types, including neutrophils, accounts for most cases of false positivity in non-TB effusions. In contrast, ADA2 is secreted only by monocytes and macrophages and is the dominant isoenzyme that accounts for 85% of tuberculous effusion. Keng et al.\(^28\) reported that patients with TB pleurisy have significantly higher levels of pleural ADA, ADA2, and IFN-γ than those with non-TB pleurisy. This finding is parallel with the results of a preceding meta-analysis. The study presented that pleural ADA and IFN-γ are both sensitive and specific markers for diagnosing TB pleurisy.\(^23,24,26-29\) Previous studies further demonstrated that ADA2 can improve the efficiency of ADA in the diagnosis of TB pleurisy and that IFN-γ is slightly more accurate than ADA. An ADA level of above 35 U/l could suggest a TB pleurisy. In this patient, the ADA level was 43 U/l. Thus, it can be concluded that the etiology of the pleural effusion is indeed attributable to TB pleurisy.

**CONCLUSION**

Cases of severe COVID-19 pneumonia with persistent pleural effusion and tuberculous pleurisy are rare. Diagnosis of severe pneumonia is established based on various clinical presentations such as shortness of breath, decreased lung sounds, decreased lymphocyte count, and increased NLR, CRP, D-dimer, ferritin, and procalcitonin. Hyperinflammatory state was found to be the basis of the processes in COVID-19 patients. On the contrary, TB pleurisy is diagnosed based on the results of radiological examinations, pleural fluid analysis, and ADA analysis. The rare incidence of pleural effusion in COVID-19 patients requires holistic thinking and proper investigations. The ADA analysis could be considered as an initial assessment in patients with pleural effusion, during the wait for the culture results. Thus, appropriate treatment could be achieved for the patients.

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**DISCLOSURE STATEMENT**

The authors have declared that no competing interests exist.

**REFERENCES**


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