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## Case report

# Long COVID presenting with intermittent fever after COVID-19 pneumonia ☆

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## ABSTRACT

A 72-year-old man presented to our hospital with a fever. Chest computed tomography showed typical coronavirus disease 2019 (COVID-19) pneumonia. The fever normalized after a few days, and the pneumonia was alleviated. However, the intermittent fever subsequently re-occurred and persisted for over a month. Various tests, including blood tests, culture tests, and image evaluations, were performed. However, the conclusion was that long COVID was the cause of the intermittent fever as an exclusion diagnosis. Many patients suffer from persistent symptoms of COVID-19, but the symptoms and their durations vary. Here we report a case of prolonged fever after COVID-19 pneumonia.

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## Introduction

Coronavirus disease 2019 (COVID-19) is prevalent worldwide. The common symptoms of COVID-19 include fever, cough, shortness of breath, fatigue, confusion, joint pains, sore throat, anosmia, chest pain, gastrointestinal symptoms, among others [1, 2]. Most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, can recover and regain normal health within 11 days. However, some patients may have symptoms that last for more than 2 weeks or even months after recovery from the acute illness [3]. This condition is known as 'long

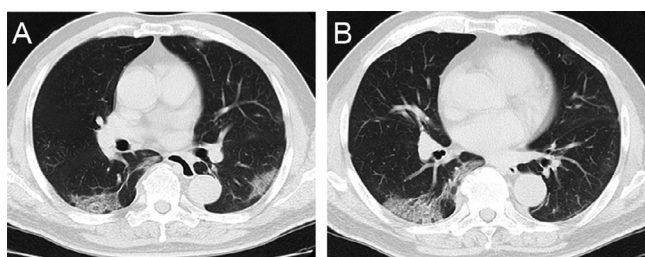
COVID' or the patients are called 'long haulers', and the condition occurs in approximately 10%-20% of COVID-19 patients [3-5].

The most reported long-term symptoms include fatigue, shortness of breath, cough, joint pain, and chest pain. Other reported long-term symptoms include difficulty with thinking and concentration, depression, muscle pain, headache, intermittent fever, and heart palpitations. However, few reports provide detailed laboratory data to rule out other diseases in patients with long COVID. Here we present the case of a 72-year-old man with prolonged intermittent fever, which lasted more than one-month after the initial symptoms, suspected to be long COVID.

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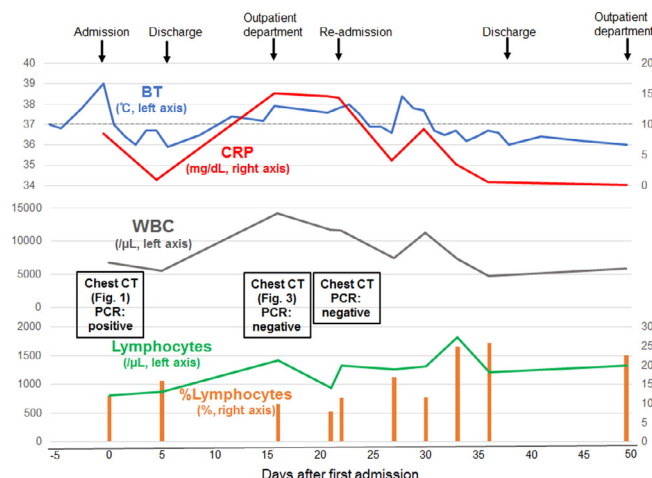
**Fig. 1 – Chest computed tomography (CT) showing pneumonia.**

Chest CT at the day of first admission revealed ground glass opacities (A) and “crazy-paving” pattern (B).

## Case report

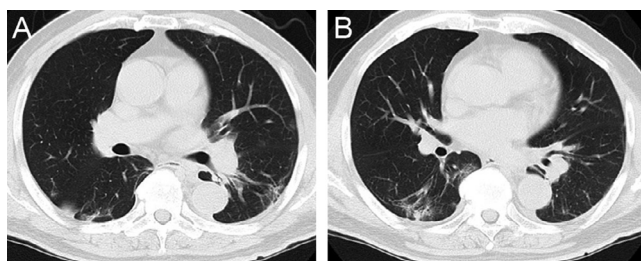
A 72-year-old man with hypertension and dyslipidemia controlled on valsartan 80 mg, amlodipine 5 mg and atorvastatin 5 mg, presented to our hospital with fever of 5 days' duration. On physical examination, at rest, his body temperature, blood pressure, heart rate, and peripheral oxygen saturation were 39.0°C, 132/82 mm Hg, 86 bpm, and 96% in room air, respectively. His lungs were clear on auscultation, and there was no abnormal heart murmur. The C-reactive protein level was elevated at 8.55 mg/dL; the white blood cell count was 6800/ $\mu$ L, although the lymphocyte count was low at 816/ $\mu$ L (12% of the white blood cell count). Chest computed tomography revealed ground glass opacities and ‘crazy-paving’ pattern bilaterally in the lower lobes (Fig. 1 A, B). The result of the reverse transcription-polymerase chain reaction (RT-PCR) test of the sputum was positive for SARS-CoV-2. The patient was hospitalized and quarantined. Ceftriaxone sodium hydrate was administered because of undeniable complications of urinary tract infection. Two days after admission, the patient's body temperature dropped below 37°C, and he was discharged on the sixth day (Fig. 2). At discharge, his C-reactive protein level had decreased to 0.94 mg/dL, white blood cell count was 5500/ $\mu$ L, and lymphocyte count was 880/ $\mu$ L (16% of the white blood cell count).

A few days after discharge, the patient developed a fever of about 37°C and returned to the outpatient department. C-reactive protein had increased again to 15.19 mg/dL, the white blood cell count was 14,200/ $\mu$ L and lymphocyte count was 1,420/ $\mu$ L (10% of the white blood cell count). Repeat chest computed tomography, compared to the initial one performed at hospitalization, had improved (Fig. 3 A, B) and RT-PCR for SARS-CoV-2 then became negative. Levofloxacin was prescribed because of suspected bacterial infection. However, the intermittent fever did not improve even after several days, and the patient was readmitted to investigate the cause of the fever (Fig. 2). At readmission, his body temperature, C-reactive protein level, white blood cell count, and lymphocyte count were 37.6°C, 14.69 mg/dL, 11,700/ $\mu$ L, and 936/ $\mu$ L (8% of the white blood cell count), respectively. Results of the RT-PCR test for SARS-CoV-2 remained negative. Influenza A/B viral antigens, HIV antigen/antibody, cytomegalovirus antigenemia, Epstein-Barr virus VCA IgM and interferon- $\gamma$  re-



**Fig. 2 – Clinical course.**

After the first admission, the fever had normalised, but a few days later, intermittent fever was observed. It continued until the 30th day. CRP levels and WBC counts were rising and falling along with the intermittent fever. The proportion of lymphocyte count was low when fever persisted, but increased when the fever normalised. BT, body temperature; CRP, C-reactive protein; CT, computed tomography; PCR, polymerase chain reaction; WBC, white blood cell; %lymphocytes = lymphocytes/WBC\*100



**Fig. 3 – Chest computed tomography (CT) showing healed of pneumonia.**

Chest CT improved with scars at 15 days after first admission (A, B).

lease assay were also negative. Serum procalcitonin and  $\beta$ -D-glucan levels were not elevated, and blood, urine, and sputum cultures for bacteria were negative. Pneumonia, which was detected on chest computed tomography images, further improved, and abdominal computed tomography showed no lesions that could have caused the fever. A few days after readmission, his fever subsided (Fig. 2), C-reactive protein level decreased to 4.13 mg/dL, white blood cell count was 7400/ $\mu$ L, and lymphocyte count was 1258/ $\mu$ L (17% of the white blood cell count). However, the body temperature, which had normalized, rose 7 days after readmission and C-reactive protein level and white blood cell count were again elevated to 9.24 mg/dL and 11,300/ $\mu$ L, respectively (Fig. 2). At this time, Gallium scintigraphy showed no abnormal accumulation. Contrast-enhanced chest and abdominal computed tomography did not reveal any malignant tumors or

inflammatory findings, and no deep vein thrombosis or pulmonary embolism was found. A head computed tomography also showed no abnormalities. The levels of various tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, and prostate specific antigen, were not elevated, and the test results for antinuclear antibodies, rheumatoid factor, myeloperoxidase-anti-neutrophil cytoplasmic antibody, serine proteinase3-anti-neutrophil cytoplasmic antibody and anti-cyclic citrullinated peptide antibody were negative. Results of drug-induced lymphocyte stimulation tests for valsartan, amlodipine, and atorvastatin were negative. In addition, no abnormal findings were found on upper and lower endoscopy. Ten days after readmission, the patient's fever fully resolved, and he was discharged on the 17th day after readmission.

Eleven days after discharge, the patient visited our outpatient department, there was no recurrence of fever during this period, and no increase in C-reactive protein level or white blood cell count were noted (Fig. 2).

## Discussion

Prolonged symptoms after COVID-19 have been reported, and it is also a social concern. The prolongation period varies depending on the report from 2 weeks to 60 days or more [6–8]. Several symptoms, including cough, shortness of breath, fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, after COVID-19, are being reported by increasing numbers of patients [9]. Intermittent fever is also reported as one of the long COVID symptoms [3, 6]. However, these previous reports did not completely rule out the causes of fever, other than the prolongation of COVID-19. Therefore, we decided to investigate the cause of intermittent fever in a hospitalized patient after COVID-19 pneumonia. The cumulative number of COVID-19 patients at the time of our case was 99,000, which was 0.08% of the total population of Japan. In addition, there were no reports of mutant strains at that time, and vaccinations had not started.

After the first hospitalization for COVID-19 pneumonia, the patient's chest computed tomography showed improvement in pneumonia; however, his body temperature rose intermittently, along with the C-reactive protein level and white blood cell count. Initially, bacterial infection was suspected and levofloxacin was administered, but this was completely ineffective. Therefore, various tests were performed in the hospital to investigate the origin of the fever. While investigating the cause of fever, we referred to the detailed examinations of the causes of fever of unknown origin [10]. Bacterial infections were ruled out because blood culture results were negative, and procalcitonin and  $\beta$ -D-glucan levels were not elevated. In addition, urine and sputum cultures were negative and Mycobacterium tuberculosis PCR was also negative. Test results for hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, influenza virus, and human immunodeficiency virus were also negative. Regarding autoimmune diseases, there was no increase in the levels of antinuclear antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibody. Complement level was not elevated. In addition,

no rash or arthralgia, which are characteristics of collagen disease, was observed. Regarding malignant tumors, there was no increase in various tumor marker levels. No tumor or inflammation was observed on contrast-enhanced chest and abdominal and plain head computed tomography. Moreover, no abnormal accumulation was noted on Gallium scintigraphy. In addition, no abnormal findings were noted on upper and lower endoscopy. Deep vein thrombosis or pulmonary embolism was not observed. The patient's drug-induced lymphocyte stimulation tests for the medications also yielded negative results, and drug fever was ruled out. Based on these results, we concluded that prolonged intermittent fever is a sequela of COVID-19.

The reason for the persistence of intermittent fever remains unclear, but it may be due to the proportion of lymphocytes (Fig. 2). Interestingly, intermittent fever recurred, except when the ratio of lymphocyte count to white blood cell count improved. Before the second discharge, the lymphocyte count recovered to 20% or more of the total white blood cell count, and no fever was observed thereafter.

In a previous report, the number of lymphocyte subsets exhibited a significantly negative correlation with biochemical indices related to organ injury, in COVID-19 patients [11]. In another report, compared to healthy controls, COVID-19 patients had a significantly lower total lymphocyte count [12]. Based on these results, COVID-19 may be prolonged without the recovery of the lymphocyte count or ratio and subset. Further research is warranted to understand the mechanism of long COVID [13].

## Patients consent

Informed written consent was obtained from the patient for publication of the Case Report and all imaging studies. Consent form on record.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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