


CASE REPORT

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Multiple lung abscesses and cold agglutinin syndrome following coronavirus disease 2019: a case report

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Abstract

Background Cold agglutination syndrome is a subtype of autoimmune hemolytic anemia. The condition is referred to as “cold” because the antibodies become active and induce hemolysis at cold temperatures, typically 3–4 °C, which is not always the case in other kinds of autoimmune hemolytic anemia. Whereas primary cold agglutination syndrome may occur in the absence of underlying conditions, secondary cold agglutination syndrome is associated with the presence of underlying infections, including coronavirus disease 2019.

Case presentation We report the case of a 69-year-old Japanese woman with periodontitis who was referred to our hospital with complaints of brown-colored urine and chest pain. Her hemoglobin level was 6.1 g/dL. Computed tomography revealed multiple lung abscesses. Her direct antibody test results were positive (2+) for anti-complement direct antiglobulin and negative for immunoglobulin G, and her cold agglutinin titer was elevated at 1:4096. Workup for anemia revealed a positive result for cold agglutination syndrome. The patient had received the fourth dose of coronavirus disease 2019 vaccination. Nasopharyngeal swab test for detecting severe acute respiratory syndrome coronavirus 2 using a real-time reverse-transcription polymerase chain reaction gave a cycle threshold value of 42.3, and the level of virus-specific immunoglobulin G was elevated at 7.71 S/C (normal range –1.4 S/C).

Conclusion A decrease in hemoglobin in patients with coronavirus disease 2019 may be associated with secondary cold agglutination syndrome. The patient was hypothesized to have developed multiple lung abscesses with secondary cold agglutination syndrome following coronavirus disease 2019. Thus, following coronavirus disease 2019, patients can develop secondary cold agglutination syndrome, which could worsen owing to associated bloodstream bacterial infections.

Keywords Coronavirus disease 2019, Lung abscess, Secondary cold agglutinin syndrome

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Background

Cold agglutination syndrome (CAS) is a form of autoimmune hemolytic anemia (AIHA). This condition is characterized by the presence of autoantibodies, known as cold agglutinins, which cause agglutination, with an optimum temperature of 3–4 °C, when the red blood cells circulate in cooler parts of the body [1]. Primary CAS may occur in the absence of underlying conditions. In contrast, secondary CAS is associated with the presence of underlying infections such as *Mycoplasma pneumoniae* pneumonia and Epstein–Barr virus infection, autoimmune disorders, and lymphoid malignancies [2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent responsible for coronavirus disease 2019 (COVID-19), can induce many hematological abnormalities. Furthermore, several case reports and case series have suggested that AIHA, including secondary CAS, may be associated with COVID-19 [3–6]. Herein, we report a case of multiple lung abscesses with secondary CAS following COVID-19.

Case presentation

A 69-year-old Japanese woman with hypertension, dyslipidemia, and periodontitis under dental care complained of brown-colored urine and chest pain. She had visited her primary care physician 5 days prior to visiting our hospital and was prescribed amoxicillin, which did not improve her symptoms. She was referred to our hospital with elevated bilirubin levels and multiple lung mass shadows observed on computed tomography (CT). The patient had no history of smoking or

alcohol consumption. She had received the fourth dose of COVID-19 vaccination, with the Pfizer-BioNTech BNT16B2b2 mRNA vaccine, 7 months prior to presentation. The patient’s temperature was 36.7 °C, heart rate was 98 beats per minute, blood pressure was 115/75 mmHg, respiratory rate was 24 breaths per minute, and oxygen saturation was 90% on ambient air. On physical examination, there was no evidence of hepatomegaly or lymphadenopathy; however, reduced bilateral breath sounds and jaundice throughout the patient’s body were noted.

Laboratory tests at admission revealed a white blood cell count of 20.3×10^3 cells/ μ L, hemoglobin (Hb) level of 6.1 g/dL, and platelet count of 519×10^3 / μ L. Other biochemical tests showed an elevation of bilirubin (total bilirubin, 6.1 mg/dL; direct bilirubin, 1.5 mg/dL) and C-reactive protein (31.7 mg/dL) (laboratory data are summarized in Table 1). The workup for acute anemia revealed serum iron levels of 135 μ g/dL (normal range 40–188 μ g/dL), ferritin level of 6,218 μ g/dL (normal range 4.63–204 μ g/dL), and iron saturation of 91.8% (normal range 20–55%). The reticulocyte index was 1.9% (normal range 0.5–2.5%). The lactate dehydrogenase level was 445 U/L (normal range 124–222 U/L), and the D-dimer concentration was 8.94 μ g/mL (normal range <1.0 μ g/mL). Haptoglobin levels had decreased beyond the detection sensitivity. Her direct antibody test results were positive (2+) for anti-complement direct antiglobulin and negative for immunoglobulin (Ig)G, and her cold agglutinin titer was elevated at 1:4096. Serum protein electrophoresis did not detect monoclonal gammopathy, including IgM, and flow cytometry of the peripheral

Table 1 Laboratory data during the course of the disease

Variable	Reference range (adult)	Day 1	Day 2	Day 4	Day 7	Day 14	Week 4	Week 8
Hemoglobin (g/dL)	11.6–14.8	6.1	4.4	6.4	7.5	8.5	10.6	12.7
Hematocrit (%)	35.1–44.4	18.3	13.5	18.5	22.8	26.7	34.2	40.4
White blood cell count ($\times 10^3$ / μ L)	3.3–8.6	20.3	17	23.2	14.9	5.9	5.6	6.1
Platelet count ($\times 10^3$ / μ L)	158–348	519	540	494	641	1085	462	311
RBC (10^6 / μ L)	3.86–4.92	2.02	1.5	2.11	2.46	2.71	3.39	4.17
MCV (fL)	83.6–89.2	90.6	90	87.7	92.7	98.5	100.9	96.9
ALP (U/L)	38–113	172	148	127	106	105	126	107
Bilirubin (mg/dL)								
Total	0.4–1.5	6.1	4.1	2.2	0.8	0.5	0.5	0.4
Direct	0.0–0.5	1.5	1.1	0.5	0.2	0.1	0.1	0
AST (U/L)	13–30	34	30	28	41	24	18	18
ALT (U/L)	7–23	62	45	36	60	47	20	19
LDH (U/L)	124–222	445	486	384	291	179	187	179
C-reactive protein (mg/dL)	<0.14	31.7	28.3	17.4	8.9	1.7	0.3	0
Cold agglutinin titers	<256		4096				1024	256

RBC red blood cell, MCV mean corpuscular volume, ALP alkaline phosphatase, AST aspartate aminotransferase, ALT alanine transaminase, LDH lactate dehydrogenase

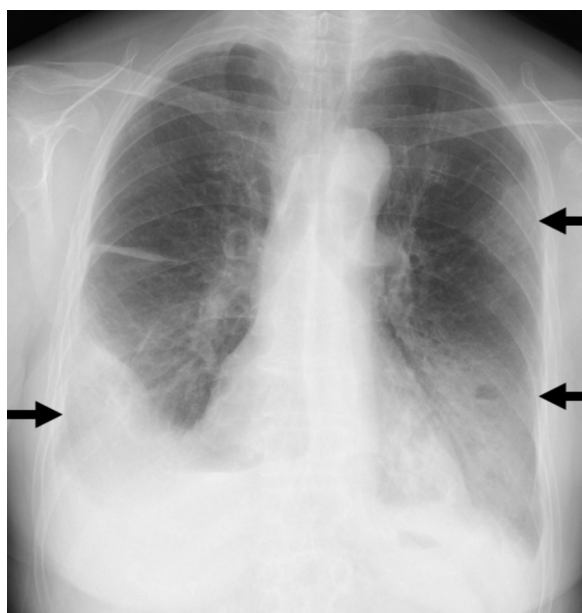


Fig. 1 Chest radiograph at presentation revealing bilateral consolidation with an air–fluid level (black arrows)

blood did not show B-cell clonality. Transthoracic echocardiography revealed no evidence of valvular disease or vegetation. Chest radiography revealed bilateral consolidation with an air–fluid level (Fig. 1). Whole-body CT revealed multiple masses or nodule consolidation at the air–fluid interface of the lung and no signs of active bleeding, thrombosis, hepatomegaly, or lymphadenopathy (Fig. 2). A nasopharyngeal swab test for detecting SARS-CoV-2 using real-time reverse-transcription polymerase chain reaction (RT-PCR) yielded a cycle threshold (Ct) value of 42.3, and the level of virus-specific immunoglobulin G (IgG) was elevated at 7.71 S/C (normal range <1.4 S/C).

Antibacterial treatment with piperacillin/tazobactam (4.5 g, three times a day) was started. She did not receive any specific treatment for COVID-19 because she was thought to have contracted the disease some time ago based on the high Ct value of the RT-PCR test and elevated IgG for SARS-CoV-2-specific IgG. On the second day of admission, her Hb level dropped to 4.4 g/dL, and she was transfused with 4 units of blood. On the third day of admission, chest radiography revealed bilateral pleural effusions. The thoracentesis fluid showed an exudative pleural effusion with neutrophil predominance; however, chest drainage could not be performed because the amount of pleural effusion was small. Sputum cultures revealed normal flora, and thoracentesis fluid and blood cultures revealed no pathogens. The patient improved clinically, her Hb level stabilized to 9.0 g/dL during the 3 weeks of hospital stay, and cold agglutinin

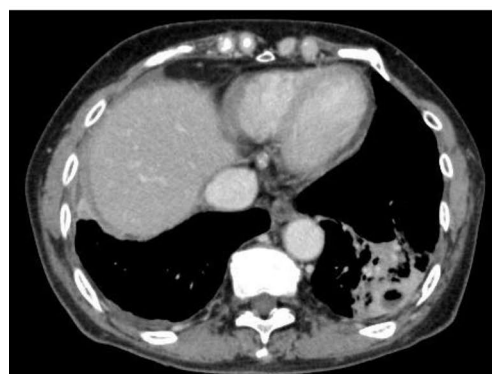
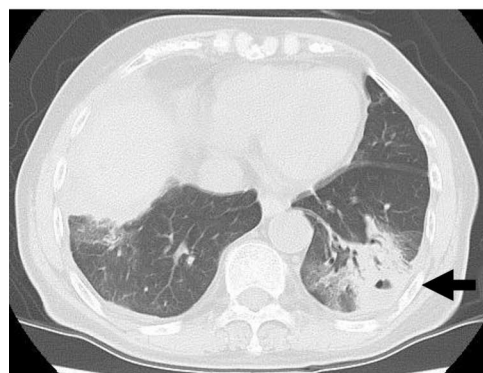
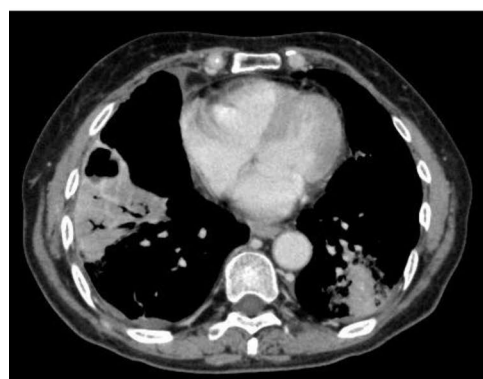
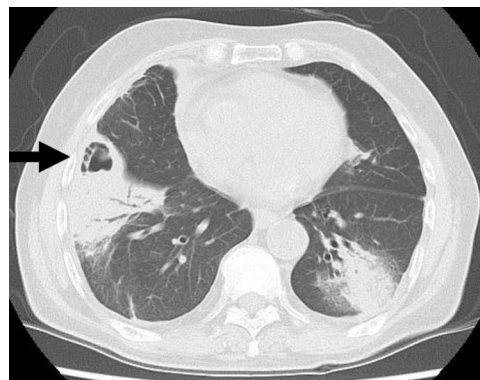


Fig. 2 Computed tomography at presentation showing multiple lung abscesses (black arrows)

titers gradually decreased. Eight weeks after presentation, cold agglutinin titers normalized, and chest radiography showed only slight shadows. There were no treatment-related adverse effects.

Discussion

We report the first case of multiple lung abscesses complicated with secondary CAS following COVID-19. This case demonstrates two crucial issues. First, patients can develop secondary CAS, which could worsen owing to bacterial infections after COVID-19. Second, COVID-19, even without hospitalization, might increase the risk of bloodstream infections.

Although the precise mechanism by which COVID-19 induces CAS is yet to be determined, molecular mimicry has been considered to account for the induction of SARS-CoV-2-induced autoimmune phenomena, including AIHA [7]. A systematic review conducted in 2021 reported that 50 patients were diagnosed with AIHA, including CAS, secondary to SARS-CoV-2 infection or vaccination [3]. Our patient presented with multiple lung abscesses simultaneously with secondary CAS, with no radiographic evidence of COVID-19 pneumonia. Since there have been no reports of secondary CAS being triggered by lung abscesses alone, we could not explain the elevated cold agglutinin levels caused by the lung abscesses. However, the secondary CAS and lung abscesses in this patient improved spontaneously without any COVID-19-specific treatment. Therefore, although COVID-19 is thought to play a central role, bacterial infection might be an exacerbating factor.

Lung abscesses are classified as primary or secondary depending on the etiology [8]. Primary lung abscesses result from aspiration of oropharyngeal secretions, and secondary lung abscesses occur when there is a predisposing condition such as bronchial obstruction, hematogenous spread, or an immunocompromised status. Several studies have reported that periodontitis causes septic pulmonary embolism, which could lead to secondary lung abscesses [9, 10]. Blood, thoracentesis fluid, and sputum cultures showed no pathogens; therefore, whether her radiographic abnormalities were induced by bacterial infection was unknown. However, it was likely that bloodstream infections from periodontitis caused secondary lung abscesses in this patient because there were multiple shadows, the distribution of the shadows was peripheral dominant, thoracentesis was neutrophil predominant, and her condition improved clinically only with antibiotics. Only 8.1% of periodontal disease-associated septic pulmonary embolism cases have reported positive blood culture [10]. A systematic review revealed that

the rate of occurrence of bloodstream infections was 7.3% [95% confidence interval (CI) 4.7–11.0%] in hospitalized patients with COVID-19 [11], which is higher than that for patients without COVID-19 (odds ratio 2.77; 95% CI 1.53–5.02). The present case suggests that COVID-19 might be related to bloodstream infections even without hospitalization. Lung abscesses as a complication of COVID-19 have been reported earlier in nonintubated COVID-19 cases [12, 13]. However, in each of these cases, only a single cavitory lesion was found. Hence, bloodstream infection due to periodontitis was more likely to be the suspected etiology for this case.

Conclusions

This case report describes a patient who developed multiple lung abscesses with secondary CAS following COVID-19. The patient's Hb level stabilized, and cold agglutinin titers slowly decreased with clinical improvement of the lung abscesses without COVID-19 treatment. The abrupt drop in Hb levels observed in patients with COVID-19 may be associated with secondary CAS, and clinicians should remain alert for such complications. This is the first report of lung abscess complicated with secondary CAS after COVID-19. However, there is a need for continuous observation to evaluate whether COVID-19, even when it does not require hospitalization, is related to the development of secondary infections. In addition, more case reports are needed to establish the association of lung abscess with secondary CAS.

Abbreviations

AIHA	Autoimmune hemolytic anemia
CAS	Cold agglutination syndrome
COVID-19	Coronavirus disease 2019
CT	Computed tomography
RT-PCR	Real-time reverse-transcription polymerase chain reaction.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Author contributions

MA and SM devised the project and the main conceptual ideas. MA drafted the manuscript and designed the figures. All authors provided critical feedback and helped shape the manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Informed consent has been obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

All authors declare that they have no conflicts of interest.

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