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COVID-19 pathogenesis involving B cells and serum cytokines: A case report of hereditary bone marrow failure

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Abstract

In primary antibody deficiency (PAD) patients, the course of the coronavirus disease (COVID-19) varies from asymptomatic to fatal. Inflammatory cytokine level and B cell function influence the COVID-19 pathogenesis in PAD patients. Previous studies were often inadequate and did not demonstrate a clear relationship between PAD and COVID-19 severity. A 24-year-old man with inherited bone marrow failure due to germline tumor protein p53 (TP53) mutation developed COVID-19 during treatment for hypogammaglobulinemia and Diamond-Blackfan anemia. Serum inflammatory cytokines and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) antibody titers were measured. Additionally, the nasal viral load and shedding period were analyzed. The patient did not experience aggravated symptoms and was discharged on day 16 of hospitalization. Analysis of trends in various cytokines during hospitalization based on values 8 months after discharge showed no change. Production of anti-SARS-CoV-2 antibody IgM, but not IgG, was confirmed from the second week after onset. Virus levels were higher in the nasopharynx than in the anterior nasal site, and the period of viral shedding persisted until day 30 after illness onset. One reason patients with hypogammaglobulinemia due to TP53 mutations did not develop severe disease was related to low B cell counts before disease onset and low serum inflammatory cytokine levels early in the disease. The low B cell count resulted in inadequate SARS-CoV-2 antibody production, indicating a risk of re-infection. However, the virus elimination period was comparable to that of COVID-19 patients with normal immune function.

Keywords: COVID-19; Inflammatory cytokine; Primary antibody deficiency; SARS-CoV-2; Viral shedding.

Abbreviations: COVID-19, coronavirus disease; CRP, C-reactive protein; CVID, common variable immune deficiency; IL, interleukin; PAD, primary antibody deficiency; RT-PCR, real-time reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; WBC, white blood cell; XLA, X-linked agammaglobulinemia

Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a global public health problem. The clinical spectrum of COVID-19 in patients varies from asymptomatic infection to interstitial pneumonia and acute respiratory distress syndrome, often with multiple organ failures [1]. In patients with primary antibody deficiency (PAD), including X-linked agammaglobulinemia (XLA), common variable immune deficiency (CVID), and lack of specific humoral immune response, clinical disease outcome is highly heterogeneous [2,3]. Agammaglobulinemia and hypogammaglobulinemia in PAD occur at approximately 6 months of age, when the transfer of antibodies is low, and repeated bacterial and viral infections can be severe. The involvement of B cell function and inflammatory cytokines is currently reported as one of the factors involved in COVID-19 severity in agammaglobulinemia and hypogammaglobulinemia patients. Therefore, accumulating data regarding these factors is important for understanding COVID-19 in agammaglobulinemia and hypogammaglobulinemia patients [4]. This study reports a case of COVID-19 in a patient with hypogammaglobulinemia, one of the causes of PAD. We evaluated the B cell function and inflammatory cytokine levels in the patient and the duration of viral shedding from the nasal site during the course of SARS-CoV-2 infection.

Case report

A 24-year-old man with SARS-CoV-2 delta strain infection visited Jichi Children's Medical Center in Tochigi, Japan in May 2021, with a low-grade fever (approximately 37.8^{0}C) and increased sputum production since the previous day. The patient had an inherited bone marrow failure syndrome phenotype due to a tumor protein p53 (TP53) germline mutation [5]. This rare de novo mutation causes bone marrow failure due to an activated p53 protein produced by a mutated TP53 gene. Complicated Diamond-Blackfan anemia and hypogammaglobulinemia were treated with regular transfusion and gammaglobulin replacement therapies. Over the past decade, white blood cell (WBC) counts in the peripheral blood were in the range of 4,000−13,000/μL, although they varied with bacterial and viral infections, and the WBC fraction was maintained at 45−90% for neutrophils and 10−47% for lymphocytes. Flow cytometry analysis performed when the patient was aged 14 and 21 years for T cell and B cell ratio showed that CD3-positive T cell and CD19-positive B cell levels were 97.5−99.1% and 0.4−0.6%, respectively, indicating a sustained decrease in B cell count. At age 23, the year before the onset of COVID-19, CD19-positive B cells were low at 0.3%. Particularly, blood tests performed during an influenza infection at the age of 11 showed no increase in B cell count, although the WBC increased from the normal range to 11,500/μL. The clinical manifestations were mild. At age 14, the lymphocyte blastoid transformation test in T cell function analysis induced by phytohemagglutinin and concanavalin A were 16,100 cpm (normal: 20,500−56,800 cpm) and 14,800 cpm (normal: 20,300−65,700 cpm), respectively, confirming that both CD4 and CD8 activity were low. He continuously received gamma globulin replacement therapy every 2 months to maintain the IgG levels above 600 mg/dL, and the latest replacement therapy was performed 45 days before COVID-19 onset. The last red blood cell transfusion was performed at age 14, and anemia was not observed to date.

After the COVID-19 onset, the patient's general condition did not deteriorate; however, he was admitted to our hospital on the third day of onset, considering the exacerbation of the general condition due to the underlying disease. On admission, heart rate was 83 beats/min, blood pressure was 120/89 mmHg, and oxygenation was 98% in room air. His body temperature was 37.8^{o}C and he was afebrile the next day. Chest breath sounds were normal, and there was no cyanosis or coldness in the peripheral extremities. A blood exam showed a WBC count of 6,700/μL (neutrophils 48%, lymphocytes 45%, monocytes 10%), hemoglobin 14.2 g/dL, platelets 12.4 × 10^3/μL, C-reactive protein (CRP) 2.3 mg/dL, negative procalcitonin, aspartate aminotransferase 42 U/L, alanine aminotransferase 61 U/L, lactate dehydrogenase 268 U/L (no change from results of the regular visit), and no other abnormalities in renal function or electrolytes (Table 1). Serum gamma globulin was IgG 730 mg/dL (45 days after the most recent immunoglobulin replacement), IgM 5 mg/dL, and IgA was below the detection limit. After admission, sputum production temporarily increased; however, he required neither oxygen therapy, antiviral agents, neutralizing antibody therapy, nor corticosteroids. On day 12 after admission, his blood exam showed that CRP and coagulation levels had normalized, and liver function parameters had not worsened. Chest radiographs taken on admission and day 2 after admission showed no abnormal shadows. No worsening of the respiratory condition was noted during hospitalization, and he was discharged on day 16 after admission. No gamma globulin replacement therapy was administered during hospitalization.

Serum cytokines of interleukin-1a (IL-1a), IL-1b, IL-2, IL-6, IL-15, IL-18, TNF-α, and IFN-γ were analyzed in the acute phase and recovery phase 8 months after onset with the Bio-Plex suspension array system (Bio-Rad Laboratories, Hercules, CA, USA), as described previously [6]. However, cytokines levels were not altered by COVID-19. Antibodies against SARS-CoV-2 spike viral surface protein were investigated using the chemiluminescent immunoassay method. IgM antibody titer was 4.7 AU/mL at 4 weeks after onset, followed by a negative result 3 months after onset. IgG remained negative during infection until 8 months after onset. Nasal swab specimens were collected from the nasopharyngeal site from the time of admission until discharge from the outpatient clinic (42 days after onset of illness) and analyzed for the duration of viral shedding (Figure 1). To evaluate the distribution of the virus in the nasal cavity, samples from the anterior nasal and nasopharyngeal regions were collected at the same time. SARS-CoV-2 RNA was detected using real-time reverse-transcription polymerase chain reaction (RT-PCR) until day 30 of disease onset. The amount of viral RNA in nasopharyngeal swabs at this time was 2.2 × 10^6 copies/mL. The viral load of all anterior nasal specimens was lower than that of the nasopharyngeal specimens.

Discussion

To the best of our knowledge, this is the first report of simultaneous and longitudinal analysis of the immune response and nasal viral dynamics in the development of COVID-19 in a hypogammaglobulinemic state. PAD patients are equally vulnerable to most bacterial infections because antibodies are important in blocking infectivity and preventing diseases [7]. PADs are listed

Table 1: Changes in blood analysis including antibody titers and cytokines after onset

			2 days	12 days	1 month	3 months	8 months
	Normal range						
WBC (Neut%, Lymph%)	3,000-11,000	(/μL)	6,700 (48%, 45%)	6,000 (42%,46%)	4,600 (32%,61%)	7,100 (46%,44%)	6,000 (43%, 45%)
CRP	<0.05	(mg/dL)	2.3	OOR<	OOR<	0.08	OOR<
AST	26-35	(IU/mL)	42	48	61	54	59
ALT	18-32	(IU/mL)	61	72	81	55	67
LDH	180-290	(IU/mL)	268	280	320	251	336
D-dimer	<0.1	(μg/mL)	0.4	0.2	NA	NA	NA
IL-1α		(pg/mL)	2.9	5.6	5.8	7.2	4.7
IL-1β		(pg/mL)	2.5	2.6	2.7	2.4	2.7
IL-2		(pg/mL)	OOR<	OOR<	OOR<	OOR<	OOR<
IL-6		(pg/mL)	OOR<	OOR<	OOR<	OOR<	OOR<
IL-15		(pg/mL)	OOR<	OOR<	OOR<	OOR<	OOR<
IL-18		(pg/mL)	59.3	56.0	59.5	57.6	67.3
TNFα		(pg/mL)	19.2	21.6	19.6	18.8	15.5
IFNγ		(pg/mL)	3.9	4.1	3.7	4.3	3.5
SARS CoV-2 IgM	<1.0	(AU/mL)	OOR<	1.4	4.7	OOR<	OOR<
SARS-CoV-2 IgG	<1.0	(AU/mL)	OOR<	OOR<	OOR<	OOR<	OOR<

OOR <, out of range below; NA, not applied; WBC, white blood cell; CRP, C-reactive protein; IL, interleukin; SARS CoV-2, severe acute respiratory syndrome coronavirus type 2

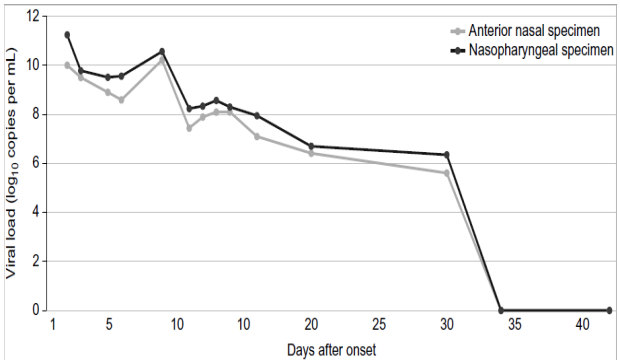

Figure 1: Viral dynamics of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in the nasal cavity after the coronavirus disease onset.
Specimens were collected simultaneously from the nasopharyngeal and anterior nasal sites on multiple occasions from day 2 to day 42 of onset. A real-time reverse transcription-polymerase chain reaction (RT-PCR) assay, which targets SARS-CoV-2 nucleotide 2 gene-specific primers, was performed according to the National Institute of Infectious Disease protocols [2019-nCoV20200319.pdf (niid.go.jp)]. SARS-CoV-2 was confirmed in specimens up to day 30 of onset. Viral load was higher in all nasopharyngeal specimens than in anterior nasal specimens.

by the Centers for Disease Control and Prevention as risk factors for severe COVID-19 [8]. However, the evidence on the actual impact of different PADs on COVID-19 is limited. For example, the clinical course differs between patients with XLA and those with CVID, with the former reported as mild and the latter as severe [9]. B lymphocytes may enhance the inflammatory response to the virus through the release of IL-6 and a deficiency of B cell-derived IL-6, albeit in a mouse model, may abrogate spontaneous autoimmune germinal center formation and thus protect against a systemic autoimmune response [10]. B cells and IL-6 induce activity and proliferation of cytotoxic T lymphocytes, promote CRP production, and enhance antibody production by inducing proliferation and differentiation of B cells, suggesting that it is deeply involved in COVID-19 severity [11,12]. In this case, D-dimer and CRP during hospitalization were classified as moderate [13]; however, B-cell count (<1%) had decreased even before the onset of COVID-19, and no increase in inflammatory cytokines was associated with COVID-19 severity [14]. Furthermore, although a relationship between viral proliferation in the body and severe disease has been suggested [15], the duration of viral shedding and the amount of virus collected from two nasal sites in our case were comparable to those of immunocompetent COVID-19 patients. These results indicate that the risk of severe disease in this patient was low. Inflammatory cytokine levels have been proven to be involved in the severity of COVID-19, suggesting that this may be true for PAD patients as well. In a study of severe COVID-19 among PAD patients, a robust T cell function was observed despite the absence of detectable SARS-CoV-2 specific antibodies [16]. Although the inflammatory response is enhanced by cytokine production by T cells, the low involvement of T cells in this case, based on cytokine transition, may also have affected the mildness of the disease.

Antibody production requires differentiation from IgM naïve B cells through germinal center B cells to plasma cells [17]. Although IgG antibodies were not detected in this case, even hypogammaglobulinemia patients with a B cell ratio <1% before the onset of COVID-19 may have enough B cells that differentiate into plasma cells and produce IgM antibodies upon SARS-CoV-2 stimulation. It should be noted, however, that hypogammaglobulinemia patients are likely to not produce IgG antibodies and remain at risk for reinfection with SARS-CoV-2.

Immunocompromised patients have been reported to have longer periods of SARS-CoV-2 RNA viral shedding, generally from 3–46 days after symptom onset [18], but it is unclear why our patient did not experience prolonged viral shedding [19]. The viral load distribution in the nasal cavity of hypogammaglobulinemia patients was similar to that of healthy immune-status individuals, with a consistent trend toward a higher viral load in the nasopharyngeal region than in the anterior nasal region [20].

Limitations

Our case report has several limitations. First, the virus that infected the patient was a delta variant and not the omicron variant that is currently prevalent. Second, this is only a single case report. To overcome our limitations, different backgrounds and clinical course of many PAD patients affected by COVID-19 are necessary, and conducting a unified multicenter research protocol is important. Establishing the number and function of B cells, as well as the various inflammatory cytokines they induce, may provide a springboard for the development of new therapeutic approaches focused on B cells. This could then be applied to the treatment of a wide range of COVID-19 patients, not just those with PAD.

Conclusion

In conclusion, low B cell counts and released inflammatory cytokines levels in hypogammaglobulinemia patients may decrease COVID-19 severity.

Declarations

Ethics approval and consent to participate: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and its later amendments. Written informed consent was obtained from the patient's parent because of the patient's intellectual disability.

Consent for publication: Because this manuscript contains personal patient information, corresponding author, Dr. Daisuke Tamura, has obtained written consent from the patient's parent (because of the patient's intellectual disability) for the publication of patient information.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author, Dr. Daisuke Tamura upon reasonable request.

Competing interests: DT has a joint research grant from Sekisui Medical. All other authors report no potential conflicts of interest.

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Author contributions: All authors meet the ICMJE authorship criteria. DT, YM, KT, YK, HY, MS, TY, and HO contributed to the study conception and design. Material preparation, data collection, and analysis were performed by DT, YM, KT, and YK. The first draft of the manuscript was written by DT and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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