—Case Reports—

A Case of X-Linked Agammaglobulinemia and COVID-19 in a Japanese Infant

Junya Sugihara[1], Mami Kurihara[1], Hikaru Takeshita[1], Hanako Tajima[1], Jun Hayakawa[1], Hidehiko Narazaki[2], Makoto Migita[1] and Yasuhiko Itoh[2]

[1]Department of Pediatrics, Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan
[2]Department of Pediatrics, Nippon Medical School, Tokyo, Japan

An infant was diagnosed as having X-linked agammaglobulinemia (XLA) at age 3 months and was receiving immunoglobulin replacement therapy. He developed SARS-CoV-2 infection at age 7 months and was treated with intravenous immunoglobulin, remdesivir, and dexamethasone. His respiratory symptoms improved quickly, and the infection resolved. Viral disappearance was confirmed via PCR, and the result of a SARS-CoV-2 test was negative on day 67 of illness, as a result of antiviral therapy. Immunoglobulin administered to the patient did not contain anti-SARS-CoV-2 antibodies, and no seroconversion of anti-SARS-CoV-2 antibodies was observed after healing. These findings suggest that humoral immunity did not contribute to infection in our patient. Thus, the importance of cellular immunity against COVID-19 was confirmed. In the future, it is hoped that testing companies will be able to use the ELISPOT assay to check cellular immunity in order to confirm the effectiveness of vaccines and the history of infection. (J Nippon Med Sch 2024; 91: 574–578)

Key words: X-linked agammaglobulinemia, COVID-19, infant, primary immunodeficiency, treatment

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the early stages of the outbreak in Japan, there were few pediatric cases, and the proportion of subclinical cases was high[1]. After mutation to the Omicron subvariant, the proportion of symptomatic cases increased, even among children[2]. The risk of severe disease was lower in infants than in elderly adults but was higher in children younger than 1 year than in older children[3]. Although many antiviral and antibody drugs have been developed, evidence of effectiveness in children is limited for most, and the drugs are approved only for adults and children >12 years of age, which limits the drugs specific for SARS-CoV-2 that can be administered to infants. Therefore, vaccination of infants ≥6 months of age is recommended in many countries[4,5].

Immune response has been analyzed for various infectious diseases. IgG2 has an important role in *Streptococcus pneumoniae* and *Haemophilus influenzae*[6]; however, it is not clear whether humoral or cellular immunity is more important against COVID-19.

X-linked agammaglobulinemia (XLA) is a humoral immunodeficiency disorder that manifests as hypogammaglobulinemia or agammaglobulinemia owing to impaired differentiation of mature B-cells. There have been >1,000 cases of XLA worldwide and >250 cases in Japan[7]. Bruton-type tyrosine kinase (BTK), localized to the long arm of the X chromosome, is important for B-cell differentiation and proliferation. In cases of BTK-deficiency, pro-B-cell to pre-B-cell differentiation is impaired, which leads to hypogammaglobulinemia or agammaglobulinemia. XLA causes severe symptoms not only in infections by bacteria with capsular membranes but also in viral infections, where antibody deficiency can cause severe and prolonged symptoms. COVID-19 is also a concern because of this risk[7,8].

Herein, we report a case of XLA in an infant who received scheduled immunoglobulin replacement therapy and developed COVID-19 shortly thereafter.

Correspondence to Hidehiko Narazaki, MD, PhD, Department of Pediatrics, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: nara@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2024_91-606
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Case Description

Our patient was a boy born at 40 weeks and 3 days via normal delivery and weighing 3,258 g. He had an older brother who was diagnosed as having XLA at age 3 years. There was no specific family history on the mother's side, but the father's younger brother died of pneumonia at age 2 years. The father developed nephrotic syndrome at age 5 years, which relapsed at age 20 years. Our patient was admitted to hospital with bilateral cervical lymphadenitis at age 3 months and was found to have hypogammaglobulinemia. At age 5 months his B-cells were <0.3% in peripheral blood. Furthermore, BTK gene abnormality (BTK 1569 del, IGLL1 235 C>T) was identified via genetic testing, which led to a diagnosis of XLA. Periodic immunoglobulin replacement therapy was started at age 6 months. He also had a history of urinary tract infection at age 6 months. Vaccination records included three doses of Hib vaccine, three doses of PCV13, three doses of DPT-IPV, three doses of HB vaccine, and three doses of rotavirus vaccine. He did not receive BCG.

He was admitted to our hospital as scheduled at age 7 months to receive immunoglobulin replacement. His vital signs were temperature 36.7°C, blood pressure 102/56 mmHg, heart rate 169 beats/min, respiratory rate 27 breaths/min, and SpO_2 98% (room air). Physical examination revealed no pallor, no ocular conjunctival hyperemia, no eye discharge, no cervical lymphadenopathy, no labored breathing, normal breath sounds, no heart murmur, a flat and soft abdomen, and no hepatosplenomegaly. Eczema and dryness around the lips were noted. SARS-CoV-2 PCR testing on admission was negative, and immunoglobulin product (not including anti-SARS-CoV-2 antibody) was received on the first day of admission. His IgG level on admission was 305 mg/dL (**Table 1**). On the second day of admission he developed cough, and on the third day a fever of 37.6°C. He was diagnosed with COVID-19 on the basis of a positive result on the SARS-CoV-2 PCR test. Two days before admission, his older brother developed a fever and had a positive SARS-CoV-2 PCR test result. Although his blood examination showed no elevation of inflammatory markers, there were no significant findings on a chest X-ray and no oxygen requirement. The patient was classified as high risk for severe COVID-19 because of his background of immunodeficiency and worsening cough symptoms. He was treated with remdesivir (5 mg/kg/day on the first day and 2.5 mg/kg/day on the second and third days) and dexamethasone (DEX) (0.3 mg/kg/day for the first 5 days and 0.15 mg/kg/day for the next 5 days). On the 4th day of hospitalization, his fever decreased to 36.6°C and his cough improved. On the 13th day of hospitalization, he was discharged owing to good progress (**Fig. 1**). Chest X-rays showed no significant abnormal findings from admission to discharge.

The patient's guardians provided oral permission for the submission and publication of this case report (including the clinical data and images).

Discussion

We treated an infant diagnosed with XLA at age 3 months who developed COVID-19 at age 7 months. The mortality rate for infants with primary immunodeficiency who develop COVID-19 is 23%, which is much higher than the rate for healthy infants (0.18%). Moreover, prolonged symptoms have been reported in agammaglobulinemia, combined immune deficiency (CID), common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS), and XLA[9]. At that time, few people in Japan had a history of COVID-19; hence, it is likely that the immunoglobulin product from the blood donation did not contain anti-SARS-CoV-2 antibodies, which could have caused severe symptoms. Our patient had no respiratory symptoms on admission, and we carefully considered administering DEX because some reports suggest that it might harm patients without respiratory problems[10]. A report was published on an adult with XLA who had persistent pneumonia due to COVID-19 who was treated with remdesivir and had COVID-19-specific CD8 T cells present[11].

Ultimately, we determined that DEX and remdesivir would contribute to improvement, as this patient had XLA. The number of children with respiratory symptoms is increasing since the outbreak of the Omicron subvariant. Furthermore, our patient's cough symptoms tended to worsen. Subsequently, we confirmed that the immunoglobulin preparation administered to the patient did not contain antibodies against SARS-CoV-2. Although it has been reported that the duration of COVID-19 symptoms is prolonged in patients with XLA[9], symptoms completely disappeared on the 13th day of admission in our patient and he was discharged. However, the virus was still detected via PCR on the 30th day after onset, and its disappearance was not confirmed until the 67th day of illness. Anti-SARS-CoV-2 spike (S) protein antibodies were not detected 1-2 months later, suggesting that cellular immunity and antiviral agents successfully eradicated the virus, without humoral immunity.

Table 1 Results of laboratory testing during hospitalization

Day after admission	Day 1	Day 3	Day 9
Hematology			
WBC (/L)	15.34×10^9	3.36×10^9	6.58×10^9
STAB (%)	0.0	38.7	1.0
SEG (%)	9.0		17.5
LYMP (%)	84.0	40.8	75.0
MONO (%)	2.5	19.3	4.0
RBC (/L)	5.30×10^{12}	4.41×10^{12}	5.47×10^{12}
Hb (g/L)	128	108	133
PLT (/L)	694×10^9	414×10^9	617×10^9
Biochemistry			
AST (IU/L)	49	34	35
ALT (IU/L)	41	26	25
Sodium (mmol/L)	139	136	140
Potassium (mmol/L)	4.7	4.0	4.6
Chloride (mmol/L)	105	104	104
TP (g/dL)	6.7	6.2	6.8
ALB (g/dL)	4.7	3.8	4.0
BUN (mg/dL)	4.9	5.2	9.5
Creatinine (mg/dL)	0.16	0.22	0.20
CRP (mg/dL)	≤0.03	0.07	≤0.03
IgG (mg/dL)	305	N.A.	995
IgA (mg/dL)	≤10	N.A.	≤10
IgM (mg/dL)	≤5	N.A.	≤5
Coagulation			
APTT (sec)	N.A.	16.6	25.5
PT-INR	N.A.	1.28	0.90
FIB (mg/dL)	N.A.	161.9	191.2
FDP (μg/mL)	N.A.	2.8	≤2.5
D-dimer (μg/mL)	N.A.	1.10	0.62

WBC: white blood cells, STAB: stab cells, SEG: segmented cells, LYMP: lymphocytes, MONO: monocytes, RBC: red blood cells, Hb: hemoglobin, PLT: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TP: total protein, BUN: blood urea nitrogen, CRP: C-reactive protein, APTT: activated partial thromboplastin time, PT-INR: prothrombin time international normalized ratio, FIB: fibrinogen, FDP: fibrin and fibrinogen degradation products, N.A.: not applicable.

It has been reported that humoral immunodeficiency, such as XLA, and B-cell deficiency diseases often do not have a severe course. This could be attributed to the absence of IgG overproduction, which is thought to contribute to the severity of COVID-19[9]. However, the pathogenesis of COVID-19 includes direct viral cell injury, renin-angiotensin-aldosterone system (RAAS) dysregulation from downregulation of ACE2, decreased cleavage of angiotensin I and angiotensin II, endothelial cell damage and thrombosis, virus-induced interferon signaling inhibition, T-cell depletion, and dysregulation of immune response and hyperinflammation via production of inflammatory cytokines, especially IL-6 and TNFα[12]. Thrombocytopathy and endotheliopathy with COVID-19[13], as a result of these factors, are conditions that can occur even in patients with XLA who do not overproduce immunoglobulin, as immunoglobulin is not substantially involved in pathogenesis.

Although efficient antibody production after vaccination is unlikely in patients with XLA[14], induction of RBD-specific CD8+ and CD4+ T cells has been observed, as have appropriate cytokine responses after antigen stimulation[15]. Passive humoral immunity was absent in our patient, and the virus was still detectable on day 30, when the antiviral drug had been completely metabolized by the body. However, PCR testing on day 67 confirmed that the virus had disappeared, which suggests that effective cellular immunity was acquired in our patient

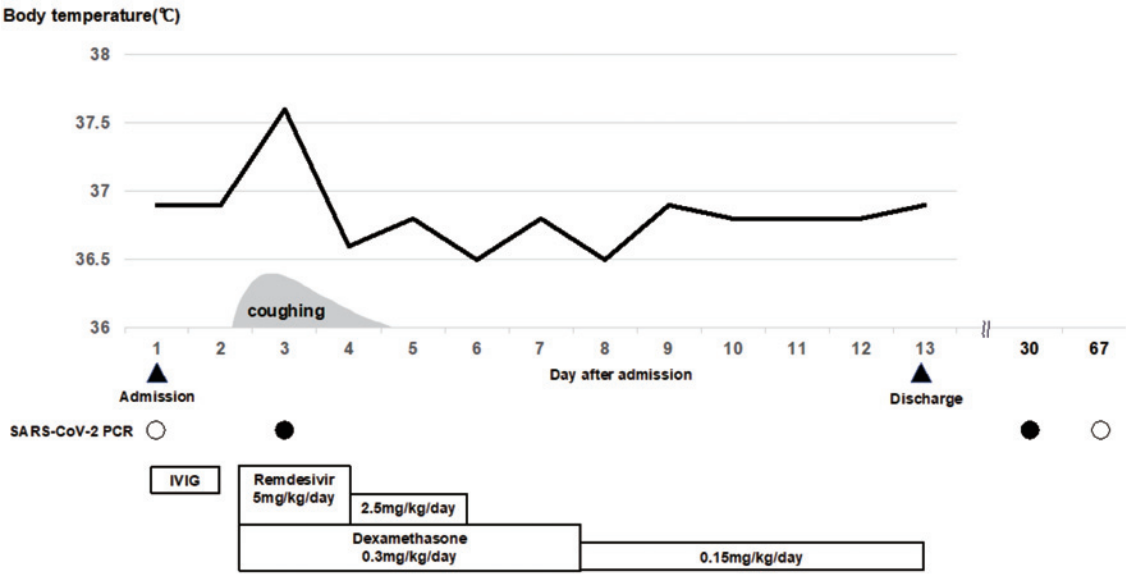

Fig. 1 The clinical course of the patient
Open circles indicate negative results and closed circles indicate positive results on SARS-CoV-2 PCR testing.

and that it contributed to the elimination of the virus. No studies have examined life-threatening adverse events in patients with XLA. Vaccination is recommended for infants with XLA, and standard techniques to confirm the efficacy of vaccine-induced cellular immunity should include methods such as ELISPOT assay confirmation of INF-gamma production of SARS-CoV-2 specific CD8+ T cells[16].

Authors' Contributions: All authors meet the ICMJE authorship criteria. JS and HN wrote the manuscript. JS, MK, HT, HT, JH, and MM collected and interpreted the clinical data. HN, MM, and YI supervised the conduct of this study. All authors reviewed the manuscript critically.

Acknowledgments: The authors would like to thank Enago (https://www.enago.jp/) for English language editing.

Conflict of Interest: JS, MK, HT, HT, JH, HN, MM, and YI declare no conflicts of interest.

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(Received, June 9, 2023)
(Accepted, August 9, 2023)

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