COVID-19 in an adolescent with aplastic anemia undergoing immunosuppressive therapy: a case report and details of antibody testing for SARS-CoV-2

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Abstract

The clinical course of COVID-19 in pediatric patients with aplastic anemia (AA) have not been thoroughly investigated. We report a case of COVID-19 in a 15-year-old male with AA treated via immunosuppressive therapy. The patient initially presented with a fever and mild sore throat. He continued cyclosporine treatment, and his symptoms improved with a single dose of hydrocortisone. Antibody testing showed increased anti-S1 and anti-RBD IgA levels, followed by elevation of anti-S1 and anti-N IgM/IgG levels. Our results suggest that AA is not necessarily associated with a higher risk of severe COVID-19.

INTRODUCTION

The increase in the cumulative incidence of COVID-19 cases was accompanied by a gradual increase in reported pediatric cases.[1] However, the clinical course of COVID-19 in pediatric patients with aplastic anemia (AA) has not been thoroughly investigated. As of May 2021, only one pediatric and eight adult cases of COVID-19 in patients with AA have been reported. Some patients exhibited mild and transient symptoms, while others suffered from severe manifestations with fatal outcomes.[2-6] Data on the ability of these patients to produce antibodies against the virus under insufficient immune function are also limited.

We report our experience with COVID-19 in a patient with AA receiving immunosuppressive therapy (IST) and the dynamic results of the serological assay. We analyzed the change in immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) titers against three different proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): S1 subunit of spike protein (S1); receptor-binding domain (RBD) within the S1 subunit, which is a major target of anti-SARS-CoV-2 neutralizing antibodies[7-9]; and nucleocapsid protein (N).

CASE DESCRIPTION

A 15-year-old male receiving cyclosporine for AA was admitted to the University of Tokyo Hospital due to fever. He was diagnosed with severe AA four months ago. Since a human leukocyte antigen-matched sibling donor was unavailable, he received IST with corticosteroids, rabbit antithymocyte globulin, and cyclosporine combined with eltrombopag. He was discharged and barely achieved a partial response two months after IST initiation (Fig. 1). At the time of his hospitalization, he presented with a fever (39.2@C) and mild sore throat that was noted one day previously. His white blood cell count was 1.0×10^9/L, with absolute neutrophil and lymphocyte counts of 0.67×10^9/L and 0.18×10^9/L, respectively. The hemoglobin level was 9.8 g/dL, and the platelet count was 45×10^9/L without transfusion for more than two months. The serum IgG level was low at 503 mg/dL (reference value, 861–1747 mg/dL). Other blood examinations were unremarkable. The chest radiograph did not show any evidence of pneumonia.

On day 2 (the onset of COVID-19 was considered day 0), the patient tested positive on nasopharyngeal swab polymerase chain reaction testing for SARS-CoV-2. As a part of IST, cyclosporine was continued with trough concentrations of 150–250 ng/mL. After receiving intravenous immunoglobulin and a single dose of hydrocortisone, he became afebrile on day 2. Although the complete blood count fluctuated slightly, he did not require transfusion or granulocyte-colony stimulating factor. He was discharged on day 10 without sequelae attributed to COVID-19 for four months.

IMMUNOLOGICAL ASSAY

To investigate antibody kinetics to SARS-CoV-2, we performed serial SARS-CoV-2 serological tests by chemiluminescent immunoassay using iFlash 3000 and iFlash-SARS-CoV-2 IgG/IgM/IgA kits (Shenzhen YHLO Biotech Co., Ltd., Shenzhen, China). The serum IgG, IgM, and IgA antibodies against S1, RBD, and N were quantified. The patient's blood samples collected on days -8 (during a regular checkup), 1, 2, 4, 6, 9, 32, 59, 79, 100, and 136 were examined. The cutoff values used were based on the results of 249 samples collected from the University of Tokyo Hospital (137 samples from SARS-CoV-2 RNA-positive patients and 112 samples from SARS-CoV-2 RNA-negative patients).

The anti-S1 and anti-RBD IgA levels exceeded the cutoff levels on day 9 and rapidly decreased thereafter. The anti-N IgM level was elevated on day 32. The anti-S1 IgG and IgM and the anti-N IgG levels also increased, but their titers did not exceed the cutoff values. Meanwhile, the anti-RBD IgG and IgM levels hardly changed (Fig. 2).

DISCUSSION

Our patient exhibited no severe symptoms and fully recovered from COVID-19 despite his immunosuppressed status. The clinical course of COVID-19 was reportedly less severe in the pediatric population than adults.[1] His young age was possibly a contributing factor for the mild clinical course. Other known risk factors for severe COVID-19 include underlying diseases such as hypertension, diabetes, obesity, and lung diseases. However, the relationship between immunocompromised states due to the underlying disease or immunosuppressive treatment and COVID-19 severity remains controversial. Some studies reported that immunocompromised patients had favorable outcomes compared to the general population.[10,11]Hyperactivation of immune response and excessive inflammatory reaction were associated with the pathogenesis of severe COVID-19.[12] Among the previously reported nine cases of COVID-19 in patients with AA, there was one patient who developed COVID-19 during cyclosporine treatment and the patient fully recovered.[3] Therefore, immunosuppression from AA and IST, including continued cyclosporine use, possibly contributed to the uncomplicated course in our patient, despite an increased risk of viral invasion and delayed viral elimination.

To evaluate the immune response to SARS-CoV-2 in this patient, a serological assay was conducted. The anti-S1 and anti-RBD IgA levels significantly increased before the changes in IgG and IgM levels. This observation was consistent with the findings of a previous study, which conducted a serological assay in a non-AA cohort.[13]Since spike proteins are integral to viral entry into cells,[14,15] IgA might play an important role for effective control of the infection. The anti-S1 and anti-N IgG levels subsequently increased, but they peaked at levels below the cutoff values. The anti-RBD-specific IgG level was almost unchanged in our patient. These differed from what was observed in other patients with COVID-19 (mostly immunocompetent) in the University of Tokyo Hospital, whose anti-SARS-CoV-2 IgG level increased significantly in all cases.[16] In addition, in a previous case series on COVID-19 with AA, all four patients (with one on IST) had an elevated anti-spike protein IgG level after COVID-19.[3] However, the effect of AA and IST on decreased IgG production and a favorable outcome warrants additional investigation.

In summary, we reported a case of COVID-19 in a patient with AA undergoing IST. Together with previous reports, our findings suggest that AA patients do not necessarily have a higher risk of severe COVID-19 compared with the general population. Future investigations are needed to determine the optimal management for these patients and the ability of patients with AA to produce sufficient protective antibodies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study protocol was approved by the ethics board of the University of Tokyo (approval number: 2019300NI-3), and informed consent was obtained from the legal guardians of the patient.

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LEGENDS

FIGURE 1 Clinical course of the patient

Clinical course including treatment, absolute neutrophil and lymphocyte counts, and SARS-CoV-2 serostatus are illustrated. Each bar and point represent the period and timing in which drugs or blood transfusion were administered.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CS, corticosteroids; CyA, cyclosporine; EPAG, eltrombopag; rATG, rabbit antithymocyte globulin; RBC, red blood cell transfusion; Plt, platelet transfusion; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

FIGURE 2 Titers of anti-SARS-CoV-2 antibodies

Each chart illustrates the transitions of IgG, IgM, and IgA antibodies against each of S1, RBD, and N. The dashed lines depict the cutoff values for each antibody determined as mentioned in the method section.

IgA, immunoglobulin A; IgG, immunoglobulin G, IgM immunoglobulin M, N, nucleocapsid protein; RBD, receptor-binding domain; S1, S1 subunit of spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2