CASE REPORT
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COVID-19 in Chronic Granulomatosis Disease: A Case Report

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ABSTRACT

A novel coronavirus disease known as Coronavirus Disease 2019 (COVID-19) has spread quickly throughout the world, and it was declared a pandemic in March 2022. Chronic granulomatous disease (CGD) is a diverse group of genetic disorders characterized by recurrent bacterial and fungal infections, resulting in granulomas due to the inability of phagocytes to destroy microbes. Even though it is thought that impaired neutrophil activity is a protective mechanism against severe COVID-19-induced cytokine storms and hyper-inflammatory responses, patients with CGD have normal immunity to most viruses. Here, we present two CGD patients who were hospitalized due to severe COVID-19 infections, which suggests that COVID-19 might have a different pathogenesis than other viruses.

Keywords: Chronic granulomatous disease; Coronavirus disease 2019

INTRODUCTION

The novel coronavirus disease, known as coronavirus disease 2019 (COVID-19), is an acute infectious respiratory disease that has spread quickly throughout the world, officially declared as a pandemic in March 2020.[1-3] COVID-19 patients most frequently show mild symptoms such as fever, dyspnea, and cough. However, a small proportion of patients develop life-threatening complications.[4]

Multisystem Inflammatory Syndrome in Children (MIS-C) is one of the late complications of COVID-19, which develops 4–6 weeks following SARS-CoV-2 infection, as a result of hyperinflammation. To diagnose this syndrome, the criteria suggested by the Center for Disease Control and Prevention of the United States is used, which is described as follows:

An individual aged <21 years with current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the four weeks before the onset of symptoms, which is presenting with fever ≥38.0°C for ≥24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement with no alternative diagnosis.[5]

T cell response plays the most important role in immunity against viruses, while B cells are less

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important. However, the lack of B cells and antibodies in COVID-19 patients may increase the risk of relapse.[6] Polymorphonuclear leukocytes (PMNs) are the first responders against invasive infections as the most potent cells of the innate immune system, especially in defense against bacterial agents.[7] Although PMNs are of vital importance in human immunity, an excess number of these cells can have detrimental effects on physical health, such as ARDS, due to cytokine storms caused by this family of cells.[8] Chronic granulomatous disease (CGD) is a disorder of PMNs that results from the defective intracellular killing potential directed against bacteria and intracellular pathogens by neutrophils and macrophages because of defects in the respiratory burst mechanisms in phagocytic leukocytes.[9] Since PMNs are essential for the response against bacterial pathogens, the patients with defects in neutrophil function usually present with skin abscesses, recurrent pneumonia, and gingivitis.[10] In COVID-19 patients, the neutrophil to lymphocyte ratio (NLR) has been proved to be of prognostic value in the context of inflammatory response against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[11]

It seems that COVID-19 has no serious complications in patients with CGD. One hypothesis even suggested that impairment of neutrophil activity could be a protective agent in CGD patients;[12] however, herein, we present two CGD patients who were hospitalized due to severe COVID-19.

CASE PRESENTATION

Case 1

A 22-month-old, full-term boy, known case of CGD, was referred to our hospital with the chief complaint of dyspnea, cough, and anorexia from 1 week before admission. He was diagnosed with CGD at the age of 3 months after episodes of recurrent pneumonia. Based on the patient's clinical signs, immunodeficiency was suspected; therefore, a dihydroergotamine (DHR) flow cytometry test of neutrophil oxidase activity (DHR assay) was performed for him, which revealed an MFI of 6 (Normal range: more than 60), and the diagnosis of CGD was confirmed. Genetic analysis of the patient confirmed autosomal recessive CGD (AR-CGD). The patient's previous medical history revealed treatment with Itraconazole 50 mg every 12 hours, and TMP-SMX 5 cc daily for prophylaxis. The patient had no history of any contact with COVID-19 patients. On physical examination, his heart rate was 141 beats/min, and the temperature was 36.8°C. He had a respiratory rate of 26 respirations per minute and his blood pressure was 107/81mmHg. The peripheral O2 saturation was 95% in room air. Bronchial breath sound was decreased and dullness was detected on percussion over the lower lobe of the right lung. No other abnormal signs were detected in the physical examination. Table 1 shows the laboratory data of the patient. A Nasopharyngeal COVID-19 PCR test was performed which turned out to be positive. Spiral HRCT of lungs showed patchy ground-glass and air space opacities in the left lower lobe and right middle and lower lobes, which were in favor of COVID-19 infection. Furthermore, collapse consolidation in the lower lobe of the right lung was reported with some area of inhomogeneity in the medial aspect of the lower lobe of the right lung (Figure 1). The patient had anemia, prolonged PT and PTT, decreased creatinine, increased serum calcium, and LDH. Renal and liver function tests were normal. He had a negative blood culture.

The patient had on and off abdominal pain. Consequently, due to the chance of obstruction in CGD patients, the patient underwent abdominopelvic sonography, in which no abnormalities were found. Due to the positive COVID-19 test, transthoracic echocardiography was done for the patient, which revealed normal systolic function with an Ejection Fraction of 80%. He underwent rigid bronchoscopy due to his continuous reduction of lung sounds on physical examination, rising fever, respiratory distress, and peripheral O2 saturation levels below 90%. It only revealed mild secretion for which therapeutic suction was done and cytology was negative. The culture of aspiration was also negative. He received supplemental oxygen with a reservoir mask and high flow rates. Besides supportive care, the patient received empirical antibiotic therapy with vancomycin 150 mg every six hours, Piperacillin/Tazobactam 1g every six hours, and Voriconazole 50mg every 12 hours during his course of hospitalization due to his poor condition and susceptibility of these patients to infection. The patient’s signs and symptoms got better gradually and he was discharged after 25 days. The patient was recommended to use Ciprofloxacin 250 mg daily and clindamycin 100 mg every six hours at home. The patient was followed monthly for 2 months in the clinic and was in good condition.

Table 1. The results of the laboratory tests of our two patients

Lab data	Normal range	Case 1	Case 2
WBC (/mm3)	4000-11000	8100	21700
Neutrophil (%)	40-60%	40%	78%
Lymphocyte (%)	18-45%	53%	12%
Monocyte (%)	1-10%	6%	7%
Hb (gm/dL)	13-17	9.2	9.5
Platelet (/mm3)	150-250	272	667
PT (sec)	11-13.5	15.2	15.6
INR (index)	0.9-1	1.13	1.16
PTT (sec)	25-35	36.1	33
Fibrinogen (mg/dL)	200-400	302	662
LDH (U/L)	60-100	530	397
CRP (mg/L)	<10	9	139
Ferritin (ng/mL)	15-200	115.3	269.7
Serum Ca (mg/dL)	8.5-10	10.4	9.6

WBC, white blood cell; Hb, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; LDH, lactate dehydrogenase; CRP, c-reactive protein.

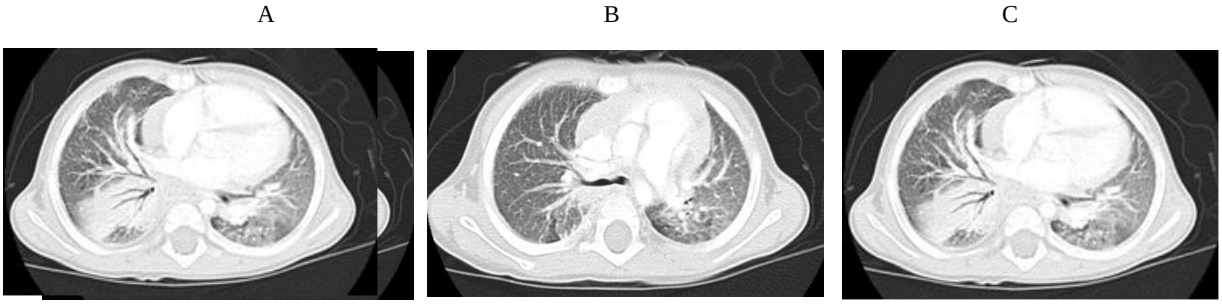

Figure 1. A 22-month-old, full-term boy known case of CGD, presenting with dyspnea, cough, and anorexia. (A and B), Axial computed tomographic (CT) scan in parenchymal window shows patchy ground-glass opacities and some area of inhomogeneity in superior segments of both lower lobes , (C) Axial CT image shows consolidation with air bronchogram at right lower lobe. A few patchy ground glass opacities are also seen in right middle lobe.

Case 2

A thirteen-year-old girl, known case of CGD, was admitted with fever and cough from one week before admission. She was diagnosed with CGD at five months of age, with persistent fever and cough. The patient had an MFI of 1.9 (Normal range: more than 60) in her DHR test. Moreover, a genetic analysis was done for her, which confirmed AR-CGD. The patient was receiving prophylactic Cotrimoxazole 80 mg/ 400 mg tablet and Itraconazole 100 mg tablet, once daily before admission. On admission, the patient's heart rate was 120 beats/min, and her respiratory rate was 25 respirations per minute. Her blood pressure was 100/80 mmHg, and her temperature was 38.5°C. The peripheral O2 saturation was 98% in room air. Other physical examinations were normal. Table 1 shows the laboratory data of the patient. The Nasopharyngeal COVID-19 PCR test was positive. The patient had a fever >38.0°C lasting more than 24 hours. The patient's laboratory data revealed leukocytosis, anemia, thrombocytosis,

prolonged PT, increased fibrinogen, CRP, LDH, and ferritin with negative blood culture. Renal and liver function tests were normal. Besides, she had pulmonary and hematologic involvement (anemia) without any alternative diagnosis; therefore, a diagnosis of MIS-C was suggested for her. There was apparent lung involvement in the chest X-ray (Figure 2). She underwent rigid bronchoscopy due to her severe cough, rising fever, and peripheral O2 saturation levels under 90%. There was mild secretion for which suction was performed, and the cytology of the secretion was negative. The culture of aspiration came back negative as well. She received supplemental oxygen with a reservoir mask and high flow rates. Other than supportive care, the patient received vancomycin 500 mg every six hours, Piperacillin/Tazobactam 3 g every six hours, Voriconazole 300 mg every twelve hours, and Meropenem 340 mg every eight hours during her course of hospitalization, due to her ill appearance and continuous fever despite the previous culture being negative. Due to her MIS-C diagnosis, the patient received IVIG and corticosteroid. The patient was discharged after 30 days with Ciprofloxacin 300 mg every twelve hours, Clindamycin 300 mg every six hours, and Voriconazole 200 mg every eight hours.

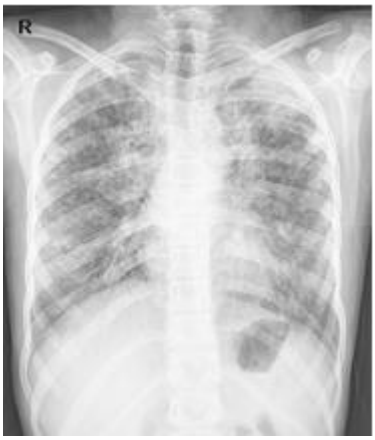

Figure 2. Chest X-ray of the second case showed diffuse patchy areas of ground-glass infiltration and consolidations

DISCUSSION

During every viral infection, both innate and adaptive immune cells are necessary for the anti-viral response of the body. They act by producing various pro-inflammatory cytokines and the activation of CD4+ and CD8+ T cells.[13] When a person gets infected by SARS-CoV-2, the virus enters the host cells by binding to angiotensin-converting enzyme 2 (ACE-2).[14] The innate immune system is the first line of defense against viruses such as SARS-CoV-2. Neutrophils are the most abundant circulating phagocytes and crucial components of the innate immune system; they have a vital role in the first-line defense against bacterial agents.[7] COVID-19 patients develop detectable serum antibodies against the receptor-binding domain of the viral spike protein with associated neutralizing activity.[15] Studies have also identified SARS-CoV-2-specific CD4+ and CD8+ T cell lines in patients who had recovered from COVID-19, which showed that T-cells are central players in the immune response against coronavirus.[16] As noted, increased neutrophil and leukocyte numbers have been observed in patients with severe COVID-19. Also, lymphopenia has been seen in most COVID-19 patients, indicating an impairment of the immune system.[17]

Primary immunodeficiency (PID) is a heterogeneous group of diseases including disorders of humoral immunity, cellular immunity, combined B- and T-cell defects, phagocytic disorders, and complement deficiencies, not all of which affect the protection against coronavirus.

A meta-analysis by Ya Gao et al, revealed that primary immunodeficiencies are associated with an increased risk of severe COVID-19; however, these differences were not statistically significant.[1] Interestingly, another study involving 1,590 patients in China showed no correlation between immunodeficiency and the risk of mortality among

COVID-19 patients.[19] A cohort study in Iran among PID patients reported that COVID-19 affected the patients with combined immunodeficiencies and humoral immunodeficiencies more than the other types of PID.[20]

A study by Isabelle Meyts and colleagues conducted on 94 patients with PID and COVID-19 demonstrated that more than 30% of patients with PID had mild COVID-19 and risk factors for progression to severe COVID-19 among patients with PID were similar to the general population.[21] It seems that patients with a lack of B cells, as a sort of PID, are less likely to experience a severe course of this disease due to their immune system defect.[22] Quinti et al, reported that patients with agammaglobulinemia showed milder courses of COVID-19 compared to patients with common variable immunodeficiency (CVID). It could denote the effects of B cells in the pathogenesis of this disease.[23]

Although the patients with a lack of B cells seem to experience milder courses of COVID-19, the investigations revealed that T cell depletion is a possible risk factor for severe COVID-19. For example, Hoffmann et al. reported that a CD4+ T cell count of < 350/µL (odds ratio 2.85, p=0.01) is a risk factor associated with severe COVID-19.[24]

CGD is a diverse group of genetic disorders characterized by recurrent bacterial and fungal infections. The disease is caused by defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. This defect leads to the phagocytes' inability to destroy certain microbes and further granuloma formation.[25] The most common sites of infection in these patients are lungs, skin, liver, and lymph nodes. The common infections include pneumonia, skin abscesses, osteomyelitis, and superficial skin infections (cellulitis/impetigo). Although there are few investigations about CGD and COVID-19 in the literature, one hypothesis indicates that impaired neutrophil activity in CGD may be a protective factor against the cytokine storm and hyper-inflammatory response, which is observed in severe COVID-19.[12,26,27] As COVID-19 is a viral infection, it is expected that patients with T-cell mediated immunodeficiency would be at higher risk for severe COVID-19; however, based on an international study by Meyts et al, the patients with phagocytic cell disorders, such as CGD did not appear to have a higher risk of affliction with severe COVID-19. Six cases with phagocytosis defects are reported, 4 of them with CGD, one of them had X-linked and the other three had autosomal recessive forms, only one of the patients with CGD had died.[21] Usually, CGD patients do not have growth disorders unless recurrent infections lead to this complication. The growth disorder in our two patients was questionable for us. Gastrointestinal and endocrine workup was done for them, all of which were normal, and there was no justification for impairment of growth in these two patients. Also, brain imaging and neurological exams were normal. Herein, we present two CGD patients who had moderate to severe forms of COVID-19 who needed a long-term admission. Furtherly, the patients needed to undergo diagnostic and therapeutic bronchoscopy, which is not routine in COVID-19 patients.

It is hypothesized that diseases with impairment of phagocytes such as CGD would not prone the patients to viral infections such as COVID-19. However, in our study, these two CGD patients had severe COVID-19 and needed to be hospitalized. It can suggest that COVID-19 might have different pathogenesis compared to other viruses; however, more studies are needed to be conducted on this matter.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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