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Case Report

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A case of granulomatosis of polyangiitis presenting with COVID-19 infection: False-positivity or co-existence?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was declared a global pandemic and a public health emergency worldwide in March 2020. COVID-19 presents with non-specific symptoms of the upper airway and pulmonary system, which can overlap with other diseases involving the respiratory system as granulomatosis with polyangiitis (GPA). Both diseases have high morbidity and mortality rates and it is important to promptly differentiate and treat them. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) is currently the recommended method for diagnosing COVID-19. Antibody-based tests are used to diagnose both pat and current COVID-19 infections.

We present a previously healthy thirteen-year-old girl who was admitted with upper airway symptoms and pulmonary involvement, and progressed to acute kidney failure. Laboratory findings showed leukocytosis, anemia, elevated kidney function tests and 2+ proteinuria. Computed tomography (CT) of the lungs showed multiple nodules, cavities, and ground-glass opacities (GGOs). We performed RT-PCR tests for COVID-19 for three times. Results were all negative, but the COVID-19 immunoglobulin (Ig)M test sent simultaneously was positive. Based on the cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) positivity, upper airway, pulmonary, and renal involvement, she was diagnosed as GPA.

This report highlights that COVID-19 antibody tests can be false-positive in patients with autoimmune diseases including GPA.

Keywords: COVID-19, Granulomatosis with polyangiitis, False-positive antibody test

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic and a public health emergency by the World Health Organization (WHO) on March 11, 2020 [1]. COVID-19 presents with nonspecific symptoms, including sore throat, rhinorrhea, low-to-high fever, non-productive cough, myalgia, dyspnea, and fatigue. Differential diagnosis with other life-threatening diseases involving respiratory system symptoms can be challenging. Granulomatosis with polyangiitis (GPA) (formerly known as Wegener granulomatosis) is a necrotizing, pauci-immune small-vessel vasculitis that primarily affects the upper and lower respiratory tract, lungs, and kidneys. Although, it is rare in childhood, most pediatric patients with GPA are adolescent girls and they experience a progressive clinical course. Collecting an upper respiratory nasopharyngeal (or oropharyngeal) swab and conducting an evaluation through real-time reverse transcriptase polymerase chain reaction (RT-PCR) is currently recommended for initial COVID-19 testing [2, 3]. Additionally, antibody-based tests may aid in diagnosing both previous and current SARS-CoV-2 infections. In this paper, we aim to present a case of false-positive antibody test results for COVID-19 in a patient with GPA.

2. CASE REPORT

A previously healthy thirteen-year-old girl was admitted to the emergency service with complaints of recurrent otitis media, headache, and rhinorrhea for one month. It was discovered that she had been treated with antibiotics several times during this period. There was no family history of chronic disease. Upon admission, she appeared pale, and her respiratory sounds were decreased. Her body temperature was 37.1°C, blood

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pressure was 115/65 mmHg, and peripheral oxygen saturation was 93%. Cardiac and abdominal examinations were normal. Laboratory findings showed leukocytosis (white blood cell count (WBC): 21.600/mm^3), anemia (hemoglobin (Hb): 4.7 g/dL), hypoalbuminemia (albumin: 2.7 g/dL), elevated kidney function tests (urea: 137 mg/dL, creatinine (Cr): 3.3 mg/dL), hyperuricemia (uric acid: 7.04 mg/dL), and 2+ proteinuria in urinalysis. Microscopic examination of the urine revealed 30-35 erythrocytes, most of which were dysmorphic. There was no evidence of hemolysis in her peripheral smear, and the haptoglobin level was within the normal range. Renal ultrasonography (US) revealed normally sized kidneys with increased parenchymal echogenicity. Computed tomography (CT) of the lungs showed multiple nodules, cavities, and ground-glass opacity (GGO) (Figure 1). The purified protein derivative (PPD) test was negative, and there was no growth of acid-fast bacilli in sputum smears. We collected nasopharyngeal swabs from the upper respiratory tract on two alternate days, and RT-PCR tests for SARS-CoV-2 were negative. Her kidney function tests deteriorated, and she experienced massive hemoptysis on the third day of hospitalization. She developed respiratory failure, which prevented the possibility of a kidney biopsy. Due to the rapid progression of kidney failure, respiratory symptoms, and radiological findings, we conducted an immunologic profile, which revealed a strong cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) positivity (3+). She was diagnosed with GPA, and methylprednisolone pulse therapy was initiated. Due to the progression of respiratory symptoms and a subfebrile status, we conducted two Ig tests for SARS-CoV-2, both of which showed positive IgM levels (1+), while the IgG level was initially negative and later returned as weakly positive in the second test. However, the RT-PCR test was repeated at the same day with antibody tests for the third time and the result was negative once again. Consequently, favipiravir treatment was initiated. She also received treatment with intravenous cyclophosphamide, intravenous immunoglobulin (IVIG), and plasmapheresis. As her clinical condition was critical, extracorporeal membrane oxygenation and continuous renal replacement therapy were initiated. Unfortunately, despite significant improvement in her respiratory symptoms, she succumbed to fungal septicemia.

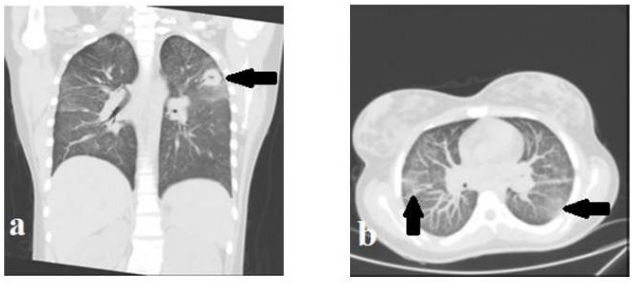

Figure 1. *Thorax tomography images of the patient.*
a. 24x19 mm cavitation in the upper lobe of the left lung
b. Ground-glass opacities in the middle and lower lobe of the right lung and in the upper zone of the left lung

3. DISCUSSION

COVID-19 was declared a pandemic by the WHO on March 11 2020. As of February 3, a total of 103362039 confirmed cases of COVID-19, including 2244713 deaths, have been reported to the WHO. COVID-19 presents with a range of clinical symptoms, including dyspnea, cough, and constitutional symptoms. Lung involvement is the primary cause of intensive care unit admissions and deaths [3, 4].

Granulomatosis with polyangiitis is an uncommon ANCA-associated vasculitis (AAV) that presents with at least three of the following six criteria: granulomatous inflammation, upper airway involvement, pulmonary involvement, kidney involvement, laryngo-tracheo-bronchial obstruction, and positive c-ANCA [5]. Our case met four of the six criteria (upper airway involvement, pulmonary involvement, renal system involvement, and positive c-ANCA) and was diagnosed with GPA. Pulmonary system involvement is the major prognostic factor, and respiratory complications are the most common cause of death in childhood GPA. Therefore, early diagnosis and treatment are crucial. Common radiologic manifestations in GPA include poorly or well-defined nodules of varying sizes, GGOs, consolidations, masses, and cavities, as observed in our patient [6, 7].

The diagnosis of COVID-19 is established based on clinical features, exposure history, RT-PCR testing, and CT findings. The predominant radiologic findings are multifocal bilateral GGOs with a peripheral and posterior distribution, and later, superimposition of consolidations. As reported by Eslambolchi et al., rheumatologic diseases with pulmonary involvement can sometimes obscure, mask, or mimic the features of COVID-19 [7]. The diagnosis of COVID-19 is established based on clinical features, exposure history, RT-PCR testing, and CT findings. The predominant radiologic findings are multifocal bilateral GGOs with a peripheral and posterior distribution, and later, superimposition of consolidations. The diagnosis of COVID-19 also includes antibody-based tests. The sensitivity of antibody tests depends on the time interval between the onset of symptoms and the date the test is performed. Deeks et al., reported that studies have shown the ability of antibody tests to detect SARS-CoV-2 infection is very low in the first week (average sensitivity 30.1%, 95% Confidence Interval (CI) 21.4 to 40.7) and only moderate in the second week post-symptom onset (average sensitivity 72.2%, 95% CI 63.5 to 79.5) [8]. The average sensitivity for IgG/IgM tests across all included studies was estimated to be 91.4% (95% CI 87.0 to 94.4) between 15 and 21 days and 96.0% (95% CI 90.6 to 98.3) between 22 and 35 days [8]. The rate of false-positivity was determined to be 2% in individuals without COVID-19. According to the literature, conditions such as nasopharyngeal carcinoma, colon cancer, duodenal carcinoma, diabetes, diffuse bronchitis, viral infections, and rheumatologic diseases have been reported as potential causes of false-positive test results [9-12]. In our patient, it was challenging to distinguish whether the observed result was due to cross-reactivity or a true infection, as the IgG status changed from negative to weakly positive. In 2004, Wang et al., reported the presence of SARS-CoV antibodies in

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individuals without SARS, which included 114 healthy controls and 104 patients with autoimmune diseases [13]. Among the 114 healthy controls, 4 (3.6%) tested positive for SARS-CoV-IgG antibodies, while all 114 (100%) tested negative for SARS-CoV-IgM antibodies. In contrast, out of the 104 patients with autoimmune diseases, 26 (25%) tested positive for IgG, 5 (4.8%) tested positive for IgM, and 13 (12.5%) tested positive for both IgM and IgG. However, among all samples with positive SARS-CoV-IgG and – IgM antibodies in both autoimmune disease patients and healthy controls, SARS-CoV RNA, and, as in our case, antibodies were all negative by RT-PCR. They suggested that the high levels of autoantibodies to cell antigens in their serum led to a response to antigens in the Vero E6 cell lysates, resulting in false-positivity for SARS-CoV antibodies [13]. Recently, Tzouvelekis et al., also reported a case of GPA with a false-positive COVID-19 antibody test [14].

Based on upper airway, pulmonary, and renal system involvement, radiological findings, positive c-ANCA, and negative RT-PCR results for COVID-19, we diagnosed our patient with GPA and believe that IgM and IgG showed false-positivity for COVID-19.

Patients with chronic diseases are at a higher risk of severe illness and admission to the intensive care unit in the presence of a COVID-19 infection [15, 16]. The co-occurrence of chronic diseases and COVID-19 has been reported previously. Hussein et al. and Uppal et al., reported cases of c-ANCA-associated vasculitis in COVID-19 patients [17, 18]. The first case presented with pulmonary hemorrhage, and the second case presented with pneumonia and acute kidney injury. COVID-19 infection can develop in patients with chronic diseases, and sometimes chronic diseases can be misdiagnosed as COVID-19 infection. It is crucial to promptly differentiate between COVID-19 infection and chronic diseases, especially in cases presenting with respiratory symptoms, as delayed treatment can be life-threatening, particularly in autoimmune diseases like GPA. Our patient was admitted to our hospital with persistent upper airway and pulmonary symptoms that had been ongoing for approximately one month. There are several reasons for the delay in diagnosing these patients. The similarity of the initial symptoms of AAVs and COVID-19, as well as patients' concerns about hospital admission due to the COVID-19 pandemic, can be listed as the most significant reasons. Additionally, false-positive antibody tests contribute to the delay, as they can lead to the misdiagnosis of these patients as having COVID-19. Clinicians must be aware of false-positive antibody tests in rheumatological diseases, especially in atypical cases of COVID-19.

Compliance with Ethical Standards

This work was conducted ethically by following Helsinki World Medical Association Declaration.

Patient Consent: The parents gave their consent for images and other clinical information related to this patient to be reported in a medical publication.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Authors Contributions: MK: Collected the data, conceived, designed and wrote the paper, IG:Contributed data, conceived and designed the paper, SG and SP: Contributed data, HA: Supervised the paper. All authors read and approved the final version of this manuscript.

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