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The quandary over Antiviral Therapy for a COVID-19 Patient with Glucose-6-Phosphate Dehydrogenase Deficiency, Hypertension, and Resolved Hepatitis B Infection: A Case Report

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Case Report

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ABSTRACT

Coronavirus disease (COVID-19) pandemic has affected worldwide health care. Given the possibility for coronavirus to prompt oxidative stress, masked glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency in the presence of the COVID-19 viral infection may instigate hemolytic crisis and dangerous consequences in affected individuals. G6PD deficiency is an X-linked recessive disorder that affects some 400 million people worldwide, with a higher prevalence in Africa, the Mediterranean Region, and Asia. A dearth of studies and literature on available antivirals for managing COVID-19 patients with G6PD deficiency brings the healthcare workers to a conundrum. Here, we report an interesting symptomatic case of COVID-19 patient with G6PD deficiency, hypertension, and resolved hepatitis B. Antiviral therapy for COVID-19 positive patients with G6PD deficiency should be individualized by considering the risk and benefit of treatment involved, recommending a multidisciplinary team approach.

CASE REPORT

A 51-year-old male patient attended our hospital with dry coughs, weakness, a history of fever for five days (afebrile on presentation), and a recent history of contact with a coronavirus disease (COVID-19) patient. Interviewing the patient revealed he was treated for hepatitis B virus infection 13 years ago. Eleven years back, he had experienced an episode of hemolytic anemia with jaundice after receiving the anti-malarial drug chloroquine. On examination, the patient showed to be glucose-6-phosphate dehydrogenase (G6PD) deficient. The patient revealed no significant history of blood transfusion, recurrent anemia, or spontaneous jaundice. He had systemic hypertension for the last ten years, controlled by antihypertensive medications, i.e., atenolol. General examination showed he was afebrile, and vitals were within normal limits; his oxygen saturation (S_PO2) on room air was 99%, with equal and clear air entry in the chest. There was no respiratory distress or use of accessory muscles for breathing. The polymerase chain reaction (PCR) test for COVID-19 was positive. Investigations are depicted in Table (Table 1).

A multidisciplinary team, including a general medicine physician, pulmonologist, anesthesiologist, hematologist, and pharmacologist, reviewed the case in detail and planned the treatment. The patient was initiated on vitamin-c, zinc, dexamethasone, and levocetirizine in recommended doses. Due to normal lab parameters and mild clinical symptoms, a decision was taken not to start any aggressive antiviral (Primum non-nocere) therapy. During his stay, the vitals and lab parameters showed no significant abnormality in trends (Table 1), and he was eventually discharged after seven days with the recommendation of 10 days isolation at home. Phone follow-up revealed no relapse of symptoms, and he was in overall good general condition.

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Table 1. Investigations and lab parameters on the day of admission versus on the day of discharge.

Parameters	Admission day	Discharge day (after 7 days)
White Blood Cell Count (10*3/uL)	5.06	5.31
Differential Count (N/L/M/E/B) %	46.2/40/10/3.6/0.2	48/39/9.4/3.4/0.2
Random Blood Sugar (mg/dl)	114	109
Haemoglobin (g/dL)	14.5	14.1
Platelet Count (10*3/uL)	200	212
Red Cell Distribution Width - Coefficient of Variation (RDW-CV) %	12.9	12.3
Red Cell Distribution Width - Standard Deviation (RDW-SD) fL	50.2	51
Peripheral Smear	Normocytic Normochromic, Mild Anisocytosis, With Adequate Platelets and Absent Malarial Parasite	Normocytic Normochromic, With Adequate Platelets and Absent Malarial Parasite
C-Reactive Protein (Q) [mg/L]	1.29	2.4
Lactate Dehydrogenase (U/L)	184	192
Ferritin [ng/ml]	208	250
Blood Urea [mg/dl]	19.3	20.1
Creatinine [mg/dl]	0.81	0.85
Sodium [mmol/L]	141	143
Potassium [mmol/L]	3.7	4
Total Bilirubin [mg/dL]	0.64	0.71
Direct Bilirubin [mg/dL]	0.25	0.3
ALT (U/L)	19.4	16
AST (U/L)	18.9	21.1
Tot Protein [gm/dl]	7.17	7
Albumin [gm/dl]	4.60	4.2
CXR- Chest X-Ray- PA View	Prominent Broncho Vascular Markings Seen in Bilateral Upper Zone, Rest Appear Normal	No Radiological Deterioration, From Previous CXR, Broncho Vascular Markings in Bilateral Upper Zone, Rest Appear Normal
ECG - Electrocardiogram	Normal Sinus Rhythm	Normal Sinus Rhythm
HBsAg. – Hep. B Antigen	Non-Reactive	Non-Reactive

DISCUSSION

Confirmed symptomatic COVID-19 cases devoid of shortness of breath or hypoxia befall under the mild category of a clinical management protocol for COVID-19 by the Ministry of Health and Family Welfare, Government of India. These patients receive symptomatic treatment augmented by immunomodulatory /antiviral in the form of ivermectin or hydroxychloroquine in recommended dose alongside supportive treatments [1]. In the present case, only supportive management was provided because, alongside COVID-19 mild symptoms, the patient was also G6PD deficient and had hypertension with resolved hepatitis B.

Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is a widespread global medical condition; in India, the prevalence varies from 1-27% [2]. This deficiency renders the red cell extremely vulnerable to any oxidative stress. The major clinical manifestations of this disorder are drug-induced hemolytic anemia and/or neonatal jaundice [3]. A small proportion of G6PD deficient individuals have chronic non-spherocytic hemolytic anemia. Drugs such as primaquine, sulphonamides, nitrofurantoin, and several anti-inflammatory agents possess oxidant properties and are most frequently associated with hemolysis [4].

For decades, hydroxychloroquine sulfate (HCQ) has been prescribed for malaria and autoimmune disorders. HCQ increases the phagolysosome pH and, thereby, interrupt virus fusion [5]. It also prevents the binding of the virus to cell surface receptors. The immunomodulatory effects of HCQ may also play a role in managing the cytokine storm associated with advanced COVID-19 disease. Concerns about the heart rhythm problems caused by HCQ for the treatment of COVID-19 have been reported by the Food and Drug Administration (FDA) [6]. COVID-19 infection may trigger severe acute hemolytic crisis in G6PD-deficient patients, and hydroxychloroquine can worsen this condition [7]. HCQ still has its place in the treatment protocol of the Indian Government, despite the results of the solidarity trial established by the WHO and the recovery trial [8,9]. Another drug, Favipiravir, a pyrazine carboxamide derivative, is a broad-spectrum antiviral drug. Human hypoxanthine-guanine phosphor-ribosyl-transferase (HPRT) is believed to play a vital role in favipiravir activation. Rosenstraus *et al.* (1975) and Pai *et al.* (1980) found that the genes responsible for glucose-6-phosphate dehydrogenase (G6PD) and HPRT activity were linked [10, 11]. G6PD deficiency occurs by a mutation in the *g6pd* gene and is inherited in an x-linked recessive pattern. The effectiveness of favipiravir in patients with a *hprt1* gene mutation or HPRT enzyme deficiency, especially in those who have G6PD deficiency, is a paramount concern [12].

Ivermectin and doxycycline are prescribed for patients with mild illness due to their antiviral properties, especially in those with cardiac QT interval prolongation

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and liver and renal abnormalities [1]. Ivermectin is probably a host-specific antiviral drug and acts as a specific inhibitor of importin α/β-mediated nuclear import inhibiting replication of several viruses and might inhibit SARS-CoV-2 using the same mechanism. In addition, several reports have revealed that ivermectin acts as an anti-inflammatory and immunomodulatory agent and can curb over-reacting innate and cellular immune responses; this explains how ivermectin could alleviate symptoms of COVID-19 patients at the viral replication phase, i.e., the first 7-10 days of infection and the later hyperinflammatory phase [13]. On the other hand, doxycycline is a broad-spectrum antibiotic with reported antiviral activities on several viruses, including SARS-CoV-2. The mechanism of the antiviral effects of tetracycline derivatives might be due to transcriptional upregulation of intracellular zinc-finger antiviral protein, which encodes genes in host cells [14]. Moreover, doxycycline has an immune dampening effect making it worthwhile to ease over-reacting immune systems [15]. Bhowmick *et al.* (2021), in their scoping review, found that there was not enough evidence to either promote or refute the efficacy of ivermectin, doxycycline, or their combination in COVID-19 management [16].

Our patient had a history of resolved hepatitis-B virus infection. Some patients with moderate to severe COVID-19 disease may develop severe respiratory symptoms due to an excessive immune response. Treatment of this condition may include immunosuppressive therapies, such as IL-6 receptor antagonists and corticosteroids, which pose a risk for patients with active or past hepatitis B virus (HBV) infection. Aldhaleei *et al.* (2020) reported a case where HBV reactivation was induced by COVID-19 in a young patient presenting with altered mental status and elevated liver enzyme levels [17]. Although the risk of HBV reactivation is low in patients with severe COVID-19 and resolved HBV infection undergoing immune modulator treatment, the follow-up of such patients is still advised as presentation of acute hepatitis warrants isolation and testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA and to detect an early abnormal rise in liver functions [18].

Remdesivir (initially named GS-5734) is an adenosine analog with a broad-spectrum antiviral activity. It is a prodrug and inhibits viral RNA polymerases when intracellularly metabolized to an ATP analog. *In vitro* inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV) suggested a promising therapeutic candidate for COVID-19 [19]. Frequent side effects include hepatotoxicity, gastrointestinal symptoms, and nephrotoxicity. Contrary to the solidarity trials, Beigel *et al.* (2020) found that remdesivir was superior to placebo in shortening the recovery time in COVID-19 hospitalized adult patients with lower respiratory tract infection [20]. Remdesivir, currently the only FDA-approved drug to treat COVID-19, is prescribed for hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefits at the advanced stage of the disease [21]. In its clinical guidelines [1], the Government of India keeps remdesivir under emergency use only for patients on supplemental oxygen and within ten days of onset of symptoms. These guidelines have increased inclination to use immunomodulators/anti-inflammatory therapy, anticoagulants, oxygen therapy, and optimum monitoring.

To date, even though there have been many case reports and trials, there is still no firm evidence regarding the safety of the antiviral medications used in COVID-19 management of symptomatic patients for population deficient of G6PD. Hence, the risk and benefit of a planned treatment should be evaluated very cautiously and continuously. In the present case, the symptoms were mild, and the inflammatory and hematological markers were within the normal range. So, we held the antiviral therapy and continued with supportive treatment. Had it been a moderately severe case requiring oxygen supplementation where the benefits of antiviral therapy outweigh the risks, then according to the available evidence, antiviral drug like remdesivir or a combination of ivermectin-doxycycline could have been tried along with strict and regular monitoring of any hemolysis with hemoglobin level, peripheral smear, reticulocyte count, lactate dehydrogenase levels, and bilirubin level. Hence, the antiviral therapy for COVID-19 patients with G6PD deficiency should be individualized by considering the risk and benefit of treatment, recommending a multidisciplinary team approach.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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