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CASE REPORT

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Leptospirosis during the COVID-19 pandemic: a case report

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ABSTRACT

Since SARS-CoV-2 disease (COVID-19) has been labeled as a pandemic, it took the spotlight in the differential diagnosis for patients presenting with acute respiratory and systemic symptoms. Leptospirosis is one of the most common zoonoses in the world, yet it is mainly a disease of differential diagnosis for places that do not have it as an endemic. Due to the high burden of COVID-19 on the healthcare field, patients suffering from other infections may have been inadvertently neglected. COVID-19 infection can mimic other infectious diseases and can confuse physicians in their search for a confirmatory diagnosis. Nonetheless, it is very crucial to broaden the differential diagnosis and keep diseases like leptospirosis within the differential diagnosis despite its rarity, especially in patients presenting with unexplained systemic infectious symptoms. This is a unique case of a patient who presented with dyspnea, jaundice and change in urine color who was suspected to be COVID-19 positive. After a detailed investigation, the patient was diagnosed with leptospirosis instead of COVID-19 and was treated with plasmapheresis and antibiotics accordingly.

KEYWORDS: Leptospirosis. COVID-19. Plasmapheresis. ARDS. Hyperbilirubinemia.

INTRODUCTION

Leptospirosis is caused by a spirochete *Leptospira* and is one of the most common zoonoses in the world. It is a potentially fatal zoonosis that is endemic in many tropical regions and is known to cause large epidemics after heavy rainfall and flooding. Potential forms of exposure include direct contact with an infected animal or through indirect contact with soil or water contaminated with excretions of infected animals, such as rodents, dogs, and livestock[1,2]. The symptoms of leptospirosis can mimic other unrelated infections such as influenza, meningitis, hepatitis, dengue, or other viral hemorrhagic fevers. Thus, a significant amount of leptospirosis patients may go undetected or be misdiagnosed[3,4]. The symptoms of leptospirosis are broad and can range from a subclinical infection to a severe syndrome of multiple organ failure with devastatingly high mortality, also known as Weil's disease[5].

Due to the high burden of SARS-CoV-2 (COVID-19) on the healthcare field, patients suffering from other infections may have been inadvertently neglected. This is especially true for patients who were labelled as COVID-19 suspects and placed in isolation[6]. During the COVID-19 pandemic, many patients have presented with severe acute respiratory distress syndrome (ARDS) which has mainly been attributed to SARS-CoV-2 infection. Nonetheless, it is very crucial to broaden the differential diagnosis for ARDS before making a conclusion on the cause.

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We are reporting a unique case of a patient who presented dyspnea, jaundice and change in urine color, who was suspected to be COVID-19 positive. After a detailed investigation, the patient was diagnosed with leptospirosis instead of COVID-19 and was treated with plasmapheresis and antibiotics accordingly.

CASE REPORT

A 52-year-old caucasian male living in the western Black Sea region of Turkey, with no known past medical history, presented with four days of jaundice, darkening of urine color, fatigue, and dyspnea. During his emergency room visit, the patient underwent computed tomography (CT) of the chest and was tested for COVID-19 with a polymerase chain reaction (PCR) to rule out COVID-19 infection. The PCR test came back negative, but the chest CT was consistent with COVID-19 pneumonia, according to the COVID-19 Reporting and Data System (CO-RADS).

The patient's vital signs included tachycardia, with a heart rate up to 150 beats per minute, normal blood pressure, a respiratory rate of 50 breaths per minute, and oxygen saturation as low as 80% with 15 L of O_2 support from a non-rebreather mask. The patient was quickly admitted to the medical intensive care unit (ICU), with the admission laboratory results that are shown in the table below (Table 1). The patient underwent a diagnostic workup which included toxoplasma, rubella, HSV, EBV, CMV, HIV, hantavirus, and *Leptospira* serologies along with ANA, ANCA, anti-dsDNA, haptoglobin, IGG, IGM, IGA, IGE, direct and indirect coombs, complements C3 and C4. Moreover, the peripheral blood smear demonstrated no schistocytes and the abdominal ultrasonography revealed a mild hepatomegaly.

In the ICU, the patient was placed on a high-flow nasal cannula due to acute hypoxemic respiratory failure. The patient was started on empirical treatment with meropenem and doxycycline while the blood culture results were pending. At the same time, a femoral central venous catheter was inserted and plasmapheresis was initiated due to severe hyperbilirubinemia, defined as total serum bilirubin more than 13 mg/dL[7]. A total of 60 units of fresh frozen plasma was used during five sessions of plasmapheresis.

By the end of day, after the five sessions of plasmapheresis, the total bilirubin level had dropped down to 19.6 mg/dL. On day four of admission, the *Leptospira* test using real-time PCR came back positive, confirming the suspected diagnosis of leptospirosis. Medical treatment was continued with both meropenem and doxycycline, as the patient showed significant clinical improvement.

The patient stayed for a total of eight days in the medical ICU. He was weaned off of oxygen and his laboratory values and chest X-ray greatly improved (Figure 1). He was later transferred to the infectious diseases ward and then was discharged from the hospital shortly afterwards. The patient had an uneventful recovery and no further complications.

Table 1 - Laboratory findings.

PARAMETER	ADMISSION	RANGE
Glucose	168	70-100 mg/dL
Urea	67	17-43 mg/dL
Creatinine	1.08	0.67 – 1.17 mg/dL
ALT	208	0 – 50 U/L
AST	314	0 – 50 U/L
Bilirubin (Total)	29.8	0.3 – 1.2 mg/dL
Bilirubin (Direct)	15.11	0 – 0.2 mg/dL
Bilirubin (Indirect)	14.69	0.11 – 1.01 mg/dL
Na	124	136-146 mmol/L
K	3.2	3.5 – 5.1 mmol/L
LDH	767	0 – 248 U/L
CK	3,754	0 – 171 U/L
Ferritin	468	21.8 – 274.6 ug/L
hsTn I	112.4	0 – 34.2 ng/L
Myoglobulin	>1,200	0 – 154.9 ug/L
BNP	681.3	0 – 100 ng/L
PT	12.3	7 – 12.9 sec
aPTT	31.9	21.3 – 36.3 sec
INR	1.17	0.8 – 1.3
Fibrinogen	835	200 – 400 mg/dL
D-dimer	727	0 – 500 ugFEU/L
Anti – HIV	Negative	-
Anti – HCV	Negative	-
HBsAg	Negative	-
Anti-HBs	Positive	-
Procalcitonin	1.81	< 0.5 ng/mL
IL-6	486.9	0 – 7 pg/mL
CRP	254	0 – 5 mg/L
WBC	16.66	4 – 10 k/uL
HGB	8.5	11 – 16 g/dL
HCT	26.3	37 – 54%
PLT	59	100 – 400 K/uL

DISCUSSION

The outbreak of COVID-19 started in December 2019 in China and spread globally, causing a pandemic. Diagnosis of COVID-19 is performed with PCR testing and can be confirmed via chest CT imaging. Leptospirosis and other

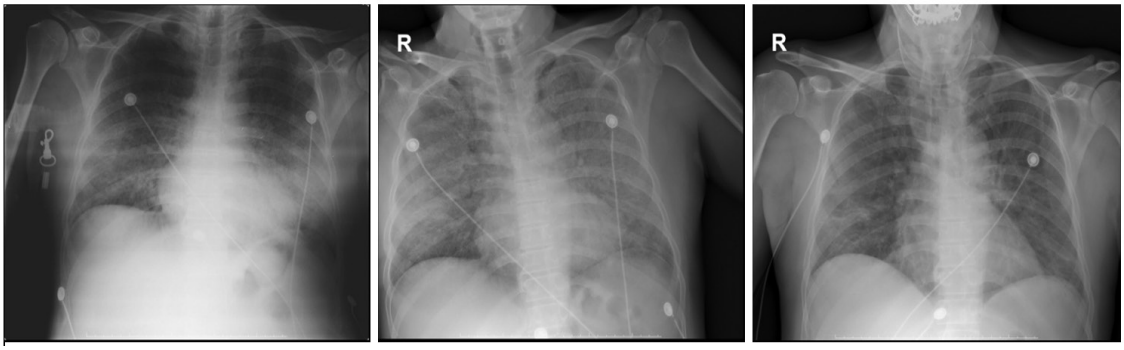

Figure 1 - Chest radiographs of the patient from left to right; on admission, three days after admission, six days after admission.

tropical infections can have similar clinical presentations and can be difficult to distinguish from one another[8]. For a group of patients who are suspected to have COVID-19, the epidemiological data should be accounted for, as it may provide a diagnostic clue for leptospirosis. It is possible that the cases associated with water consumption and environmental disasters, such as floods, may cause outbreaks of leptospirosis[9]. There were many reported catastrophic floods in the west of the Black Sea region of Turkey just two weeks prior to our patient's initial symptoms. Even though leptospirosis is a rare disease within this region, it is possible that these recent floods may have led to the infection of this patient. The incubation period of leptospirosis ranges from 1 to 30 days (average 7-14 days), which coincides with our patient's time of diagnosis[10]. The vast clinical spectrum of leptospirosis ranges from mild anicteric presentation to severe disease with multiple organ dysfunction, hemorrhagic features and sepsis or shock. Severe hyperbilirubinemia and acute renal failure have been associated with high mortality[11]. The patient described in this case report showed many of the cardinal features of severe leptospirosis, including non-oliguric renal failure, marked hyperbilirubinemia (a bilirubin level up to 30-40 mg/dL), elevated aminotransferase levels, and thrombocytopenia. Given the severity of the disease process, plasmapheresis was performed.

Traditional treatment options for leptospirosis include antibiotics and supportive therapies. There is a lack of evidence regarding optimal antimicrobials for leptospirosis. According to guidelines provided by World Health Organization (WHO), doxycycline can be used for prophylaxis and the mild disease, and ampicillin or penicillin G for the severe disease. Ceftriaxone is a suitable alternative for the treatment of the severe disease and in patients with a penicillin allergy[12]. There are notable reports of severe leptospirosis being treated successfully with plasma exchange. Taylor and Karamadoukis[13], Tse *et al.*[14] and Cerdas-Quesada[15] described cases of patients with multiple organ failure from severe leptospirosis who improved significantly after plasma exchange. According to a case series of 114 patients with leptospirosis complicated by pulmonary hemorrhage, the survival rate of patients treated with two plasma exchanges and cyclophosphamide was 61%. In comparison, only 17% of patients who received supportive treatment managed to survive[16].

Severe hyperbilirubinemia has been reported to exert multiple cellular toxic effects, disrupting cellular respiration, membrane integrity, and transport functions. Excessive buildup of bilirubin is associated with worsening of renal tubular damage which contributes to the persistence of renal failure. Removal of serum bilirubin by plasmapheresis after liver transplantation complicated by severe hyperbilirubinemia is known to produce favorable clinical outcomes. As a result, treatment of the hyperbilirubinemia can be beneficial when it comes to reducing toxic insults to kidney and liver cells. Plasma exchange may provide other advantages, including the removal of circulating endotoxins, catabolic products, and inflammatory mediators in patients suffering from severe hyperbilirubinemia. This information is relevant to our case report due to the fact that after plasma exchange, the bilirubin levels of our patient declined significantly and were consistent with favorable clinical outcomes, marking plasmapheresis as the turning point in the patient's clinical course[14,15].

CONCLUSION

It is true that COVID-19 infection can mimic the signs and symptoms of other infectious diseases and confuse physicians in their search for a confirmatory diagnosis. In this report, we described a case that can encourage healthcare professionals to broaden their differential diagnoses, especially in the current era of the COVID-19 pandemic. It is crucial to keep diseases like leptospirosis within the differential diagnosis despite its rarity, especially in patients with unexplained systemic infectious symptoms. Additionally, a unique approach with plasmapheresis was

performed on our patient with severe hyperbilirubinemia. Although plasmapheresis can be an effective measure in reducing plasma bilirubin levels, it is still an aggressive treatment and should be reserved for severely ill patients. In our case, we believe that plasmapheresis played a vital role in the patient's rapid recovery. Much of what is known about the use of plasmapheresis in cases of severe leptospirosis has been gathered from case reports and small case series; therefore, more research is needed in this evolving field.

AUTHORS' CONTRIBUTIONS

MEA: participated in data collection, data analysis, and writing of the manuscript; MY: participated in collecting references and writing of the manuscript; DC, KI and ACG: participated in editing of the manuscript and patient care; SY: participated in editing of the manuscript, patient care and medical decision-making.

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