Late diagnosis of severe COVID-19 later complicated several life-threatening complications misdiagnosed solely for concomitant severe malaria initially: a case report

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Abstract: Severe forms of coronavirus disease 2019 (COVID-19) are the main causes of COVID-19-related deaths due to their life-threatening complications which often warrant intensive care management to improve patients' outcomes. We herein, present a case of severe COVID-19 with several critical complications in an Intensive Care Physician misdiagnosed initially for severe malaria and later adequately diagnosed and managed successfully at Douala General Hospital in Cameroon. We report a case of a 35-year-old obese African Anaesthesiologist and Intensive Care Physician with a recent history of exposure to COVID-19 patients who presented to the emergency department with signs, symptoms and laboratory test suggestive of severe malaria. He had no remission with parenteral anti-malarial drugs. Within some few days he developed pulmonary embolism, myocardial infarction, septic shock, acute kidney injury and mild hepatocellur lysis and had a positive reverse time-polymerase chain reaction (RT-PCR) to COVID-19. His outcome was uneventful within five days of intensive care management and close monitoring. The case pinpoints the common practice of misdiagnosing COVID-19 for severe malaria especially in patients without respiratory symptoms in our malaria endemic zone. This often leads to late diagnoses of COVID-19 with several potentially life-threatening complications which may lead to a fatal outcome of the patient if not managed appropriately. Hence, a high index of clinical suspicion of COVID-19 remains paramount especially for those with COVID-19 risk factors such recent exposure to COVID-19 patient and obesity.

Keywords: Coronavirus disease 2019 (COVID-19); critically ill; late diagnosis

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Introduction

The coronavirus disease 2019 (COVID-19) is a global health crisis caused by a pathogen called severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (1,2). COVID-19 is respiratory infection transmitted via respiratory droplets and aerosols from infected person and/or through contact with contaminated surfaces (3). At this writing on November 09, 2020, 50,740,556 persons have been globally infected by COVID-19, 35,796,914 have recovered and 1,262,168 have died, hence, a global case fatality rate of 25% (4).

Once the SARS-CoV-2 enters the body of a health

individual, it invades the alveoli and links to the angiotensin-converting enzyme 2 (ACE2) receptor of type 2 pneumocytes through their spike proteins from where if affects primarily the lungs and then other organs (5). Depending on the degree of affection, a patient can either have mild or severe COVID-19 reported at a prevalence of 75–80 or 15% to 20% respectively (3,5). Mild forms often present with benign systemic symptoms such as fever, fatigue, rhinorrhea, diarrhea, agnosia, joint pains, and headaches which are sometimes self-limiting and misdiagnosed for common cold or malaria fever (6). As such mild forms, even when diagnosed timely can be treated at home or may require a short length of hospital stay (7). Severe COVID-19 on the other hand typically manifests with life-threatening complications such pulmonary embolism, acute respiratory distress syndrome (ARDS), severe cardiac arrhythmias, acute coronary syndrome (AVS), heart failure, cardiogenic chock, acute kidney injury, and septic shock necessitating urgent intensive care management (6). Hence, COVID-19 has a clinical polymorphism of presentation affecting all body organs or systems due to an inflammatory cytokine-induced storm by especially by IL1, IL6, and TNF-alpha. This marked generalized inflammation has led to COVID-19 being described as a multi-systemic disease (7). Herein, we report the case of a health provider who initially presented with a mild form of COVID-19 which was misdiagnosed for simple malaria and later, severe malaria and managed ambulatory. Then, diagnosed with severe COVID-19 when he presented with the pulmonary embolism, AVS, acute kidney injury and septic shock. Despite the severity of his symptoms, his outcome was favourable. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/jxym-20-116).

Case presentation

We report the case of a 35-year-old an Camerooninan Anesthesiologist and Intensive Care Physician with an eventful past history of android obesity (body mass index =33 kg/m^2) and intermittent daily exposure for 23 days with COVID-19 patients including four with severe forms. His family and psychosocial histories were uneventful. He presented to the outpatient consultation unit of the emergency department of our tertiary care hospital with a four-day history of mild retrosternal pain associated with stage IV New York Heart Association (NYHA) dyspnea, generalized myalgia, stiffness of all his joints without irradiation of the pain nor hyperthermia. Three hours later, there was persistence of his presenting complaints with new onset of a temperature of 38.2 ℃. A laboratory panel run revealed a complete blood count (CBC) with lymphocytosis at 29.6% despite a normal white blood cell (WBC) count of 4,200/mm^3; a C-reactive protein (CRP) level at 7.43 mg/L; a procalcitonine (PCT) level <0.05 ug/L; a positive thick blood film for malaira (<0.1/fields). A working diagnosis of simple malaria was made and he was prescribed the following drugs to be taken in ambulation; artesunate and mefloquine (600 mg/750 mg): one oral tablet twice daily for three days and a single dose of paracetamol 1,000 mg per os by a general practitioner.

The morning succeeding his emergency department consultation, was notable for exacerbation of his temperature from 38.2 to 39.3 ℃ associate with marked prostration; severe generalized headaches and several episodes of vomiting. This prompted a second emergency department admission in our hospital where a repeat thick blood and thin blood films showed 50,000 *Falciparium pallidium* trophozoites per/ mm3 in favour of severe malaria. He was hospitalized at the emergency department and placed on intravenous (IV) artesunate 250 mg (2.4 mg/kg) on admission, then at 12 and 24 hours following the dose administered on admission. Faced with the persistence of the clinical condition and the onset of NYHA stage II dyspnea, a thoracic CT-scan was performed for suspected COVID-19. Its results were normal. The next morning, he suddenly developed a mild retrosternal pain without irradiation associated with stage IV dyspnea of the NYHA, a respiratory rate of 39 cycles per minute, SPO_2 at 99% in ambient air, crackles at the right base of the thorax, orthopnea, blood pressure at 190 mmHg/110 mmHg, and tachycardia at 110 beats/min with no fever and no clinical sign of deep vein thrombosis. The rest of the physical examination was unremarkable. A repeat laboratory panel requested showed; a WBC of 3,400/mm^3 with 47% lymphocytosis and 42% neutrophils; hypokalaemia at 3.2 mmol/L; serum urea at 0.22 g/L; serum creatinine at 5 mg/L; normal CRP (5.67 mg/L) level; an ultra-sensitive troponin I (<1.50 ng/L). The ECG showed a sinus rhythm of 93/min, left ventricular hypertrophy with systolic overload. The thoracic CT-angiography showed a left posterobasal subsegmental endoluminal thrombus with parenchymal infarction opposite. He was transferred to internal medicine for non-massive pulmonary embolism treatment and hospitalization by cardiologists, pneumologists and internists. His treatment consisted of

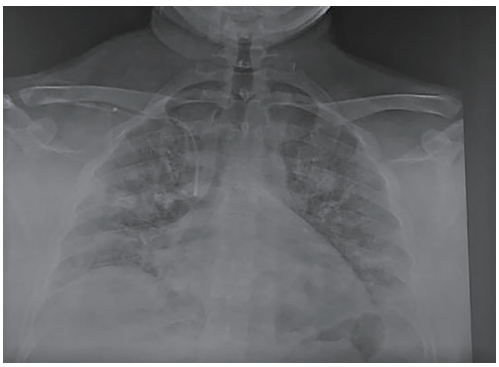

Figure 1 Chest X-ray of the patient showing bilateral interstitial opacity which when confronted with the clinical picture was suggestive of acute respiratory distress syndrome.

subcutaneous enoxaparin 100 mg/12 h (1 mg/kg/12 h), IV omeprazole 40 mg/24 h, dextrose 5% 500 mL/12 h and hydroxyzine 25 mg morning and evening per os. The outcome was marked on day 2 of hospitalization by a in temperature of 39 ℃, eight episodes of watery stools non-bloody stools and phlebitis in the right hand (site of several injections for of peripheral venous access). Nine hours later, his level of consciousness dropped to a Glasgow Coma Score (GCS) at 13/15, signs of respiratory distress (respiratory rate at 50cycles per breath, nasal flaring, intercostal recessions, SPO_2 at 60% in ambient air, PaO_2/FiO_2 =183 mmHg) his temperature spiked from 39 to 41 ℃, he had a quick SOFA score of 3/3 and hypotension with mean arterial blood pressure (MAP) at 51 mmHg, refractory to a fluid bolus. A chest-ray showed marked bilateral opacities (*Figure 1*) and repeat thoracic CT-scan showed bilateral ground opacities of both lungs consistent with the diagnosis of acute respiratory distress syndrome (ARDS). Laboratory investigations requested showed a positive COVI-19 PCR, leucocytosis at 19,700/mm^3 with thrombocytopenia at 103,000/mm^3, a PCT at 18.19 µg/L, hyperkalaemia at 5.26 mmol/L, uremia at 0.65 g/L, creatinemia at 35.2 mg/L, aspartate transferase (SGOT) at 125 IU/L and alanine transferase (SGPT) at 61.6 IU/L. The diagnosis of severe COVID-19 complicated by pulmonary embolism, ARDS, septic shock, acute kidney injury and mild hepatocellular lysis was made. He was transferred to intensive care unit (ICU) and put on noradrenaline (through an electric pump syringe), IV imipenem (1,000 mg/8 h), IV normal saline 0.9% (500 mL/6 h), hydroxychloroquine (200 mg/8 h) per os, azythromycin (500 mg/24 h) per os and zinc (20 mg/24 h) per os, in addition to the treatment instituted the previous day [enoxaparin 100 mg/12 h (1 mg/kg/12 h), IV omeprazole 40 mg/24 h, dextrose 5% 500 mL/12 h and hydroxyzine 25 mg morning and evening per os].

On day 3 hospitalization in the ICU, he regained full consciousness (GCS =15/15) with persistence of a plateau fever at 40.5 ℃, persistence of hemodynamic instability and dyspnea on slightest exertion, a decrease in the frequency of stools (4 stools/24 h). There was a new onset of total hematuria. The requested CBC will show leukocytosis at 17,800/mm^3 and thrombocytopenia at 87,000/mm^3. The CRP was 167 mg/L and the PCT 151 µg/L. His renal function test mildly improved as evident by a decrease in serum creatinine (26.7 mg/L) and uremia (0.5 g/L). All ongoing treatment was continued except enoxaparin which was switched to rivaroxaban (15 mg/12 h) and IV levofloxacin 500 mg/24 h was added.

On day 4 hospitalization in the ICU, there was complete regression of diarrhea but persistence of fever and dyspnea. In addition, the patient suddenly felt a burning retrosternal pain of a high intensity which lasted about 30 minutes. The latter was associated with unsupported monomorphic ventricular tachycardia seen on the electrocardioscope. The requested investigations showed a persistent undershift of the ST-segment in the infero-lateral and signs of necrosis on ECG suggestive of myocardial infarction. There was, thus, an AVS without a shift in the ST-segment (non-ST + ACS) with a differential, acute myocarditis due to COVID-19. Biologically, there was an increase in troponin I (1,572 ng/L), D-dimers (8,581 ng/L), CPKs [739]. The LDH ws 2,391 IU/L. It was not possible to perform diagnostic coronary angiography by default of the technical platform. Thus, a medical treatment for non-ST + ACS was instituted, namely: clopidogrel 300 mg as a loading dose then 75 mg/24 h per os, aspirin 300 mg as a loading dose then 75 mg/24 h both orally and atorvastatin 80 mg/24 h per os. He was also put on Amiodarone at a dosage of 1,200 mg/24 h per os in order to prevent possible recurrence of ventricular tachycardia. We did not introduce beta blockers or ACE inhibitors due to hemodynamic instability. Given the potential pro-arrhythmogenic effects of hydroxychloroquine, despite the non-prolonged QTc of the patient, we stopped hydroxychloroquine and replaced it by lopinavir/ritonavir (200 mg/50 mg) per os.

On day 5 hospitalization in the ICU, we noted the decrease in fever to 38.5 ℃, improvement in breathing with NYHA stage III dyspnea, a respiratory rate at 26 cycles per minute and tachycardia at 119 beats per minute. The

requested assessments will show a decrease in troponin I (403.2) and transaminases (SGOT =68.6 UL/L and SGPT =32.1 UL/L).

On day 16 of ICU hospitalization, improvement in breathing was noted with stage II dyspnea of NYHA, respiratory rate of 21 breaths/minute and apyrexia. The control test showed CRP at 26.7 mg/L, PCT at 12.85 µg/L, normal renal and hepatic function. The patient was discharged from the ICU and transferred to a COVID-19 specialized treatment center for COVID-19 patients with minor symptoms. The patient was discharged on imipenem (stopped on day 10 of treatment with imipenem), levofloxacin, zinc, lopinavir/ritonavir, vitamin C, rivaroxaban at the starting doses.

On day 7 following ICU discharge, the patient was in good general condition and asymptomatic. Stop all medications except Rivaroxaban which will continue until day 30 and then changed to 20 mg/24 h until 3 months.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

This case demonstrates the diagnostic challenge of mild COVID-19 in resource-limited setting but also re-iterates COVID-19, especially its severe form as a potentially fatal multi-systemic disease to always be considered in its case management.

Fever is the most common symptom in COVID-19 (5). As an airborne disease, COVID-19 respiratory symptoms usually are the most common symptoms after fever and include cough, sputum production, and shortness of breath (5). A systematic review of the clinical aspects of COVID-19 reported the prevalence of the following respiratory signs cough (63.9%), sputum production (28.9%), and shortness of breath (19.7%). The most severe clinical manifestations were respiratory distress and respiratory failure in 14% and 5%, respectively (8). The severity of the disease is related to massive alveolar damage that results to ARDS (1,5,9). Pulmonary embolism is also common in sepsis-induced ARDS and contributes to aggravating the on-going respiratory failure (10). The indexed patient's initial presentation was quite misleading, considering the presence of dyspnea, generalized myalgia, generalized joint stiffness, fever, a positive malaria test, a normal thoracic CT-scan with no respiratory symptoms. Hence, the diagnosis of malaria was first made considering our endemic malaria zone. Also, this illustrates the low sensitivity of thoracic CT-scans in perhaps making the diagnosis of COVID-19 at the early stage of the disease. A COVID-19 rapid diagnostic test or a PCR COVID-19 test would have perhaps helped in making the diagnosis at the patient's initial presentation. However, COVID-19 rapid diagnostic tests and RT-PCR COVID-19 test are often rare in our resource-limited setting (6).

After the respiratory system, the second most affected body system known by COVID-19 is the cardiovascular system (11) especially in patients with obesity, age >60 years, diabetes mellitus and hypertension (5,11) and many patients have died of cardiovascular-pulmonary complications such as pulmonary embolism, ARDS or myocardial infarction mediated by the established predisposition of COVID-19 patients to develop atherosclerosis and ischemic heart disease (12). These explain the pathogenesis of severe COVID-19 in our obese patient. Our patient's later RT-PCR confirmed COVID-19 diagnosis with complications of pulmonary embolism, ARDS and myocardial infarction. COVID-19 patients with thromboembolism events have increase odds for morality (13). This was not the case of our patient, though diagnosed late but had an aggressive intensive care management which contributed to his survival.

Obesity plays a major role in the pathophysiology and severity of COVID-19. Hyper-expression of ACE2 receptor of type 2 pneumocytes (the receptors through which the SARS-CoV-2 binds to infect patients) has been found in obese persons leading to increased vulnerability to the infection (7). Also, obese patients have an increased fold for respiratory distress and major risk of systemic inflammation (14). Other cardiovascular diseases associated with COVID-19 include ventricular tachycardia probably due to the iatrogenic effects of hydroxychloroquine (15). This explains the predisposition of our obese patient to COVID-19 but also highlights the cause of his ventricular tachycardia to be probably induced by hydroxychloroquine.

SARSCoV-2 has a high renal tropism where it replicates in kidneys leading to acute kidney injury (16) as seen in our patient with sudden deteriorating renal function tests before its normalization.

Also, hematological manifestations are common in COVID-19 (17). Hematological abnormalities include anemia, leucocytosis, neutrophilia, increase in neutrophils/lymphocytes ratio, and low eosinophil, monocytes,

lymphocytes (T CD4/CD8), and platelet counts (18). Leucocytosis is secondary to bacterial infections (18) as seen in our patient with marker of sepsis such as an elevated procalcitonin (151 µg/L) who develop a state of septic shock warranting vaso-active amines (noradrenaline) for hemodynamic stability. Thrombocytopenia is due to an excess platelet consumption in peripheral sites of microthrombosis (18). An inflammatory syndrome is very characteristic of COVID-19 (18). It is induced by the cytokine storm and causes increased CRP as seen in our patient.

About 20% of COVID-19 patients have gastrointestinal symptoms in the following order of decreasing frequency: diarrhea, vomiting, and abdominal pain often occurring with signs of hepatocellular lysis as seen in the patient presented (19). This was the case of our patient with several episodes of vomiting diarrhea resolved on treatment.

Several authors have reported COVID-19 to be associated with neurological manifestations such as dizziness, headaches, impaired consciousness and cerebrovascular accidents (20). A transient impairment of consciousness as evident by a GCS of 13/15 was the sole neurological sign in our patient.

Conclusions

The above case presents COVID-19 as a multi-systemic disease that warrants early multidisciplinary management geared at lessening the burden of the disease. Through this case report, the authors also wish to pinpoint the common practice of misdiagnosing COVID-19 for severe malaria especially in patients without respiratory symptoms in our malaria endemic zone which may lead to late diagnoses of COVID-19 with several life-threatening complications. Hence, a high index of clinical suspicion of COVID-19 remains paramount especially for those with COVID-19 risk factors such recent exposure to COVID-19 patient and obesity.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/jxym-20-116

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym-20-116). The authors have no conflicts of interest to declare.

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