INTRODUCTION

Sickle cell disease (SCD) patients with coronavirus disease 2019 (COVID-19) may not necessarily have a worse prognosis than patients without SCD. COVID-19 may, however, trigger sickle cell crises even in the absence of severe COVID-19 related respiratory symptoms and therefore this patient population should be closely monitored and appropriately managed.

COVID-19 has swept across the globe over the past 11 months, stretching health facilities to the limit. COVID-19 primarily affects the lungs and typically presents with symptoms such as fever, cough, breathlessness, myalgia.1 Headache, rhinorrhea, blocked nose, rigors,
SCD is a serious, hematological, inherited condition that affects millions of people globally. The homozygous genotype (HbSS) has very grave manifestations and results from substitution of glutamic acid by valine in position 6 of the Beta chain. HbSC, one of the heterozygous genotypes, has a comparably less severe manifestation and is due to substitution of glutamic acid by lysine on the Beta chain.

In Ghana, an estimated 2% of newborns have SCD. SCD patients are prone to developing vaso-occlusive crises (VOC), acute chest syndrome (ACS) and thromboembolic conditions with sometimes fatal consequences.

SCD patients are prone to a prothrombotic state affecting both the arterial and venous systems. The pronounced inflammation in COVID-19 patients also predisposes them to a hypercoagulable state (COVID-19–associated coagulopathy) with high mortality rates. This state encompasses the various elements of Virchow's triad: damage to the endothelium, stasis due to decreased mobility especially in critically ill patients; and hypercoagulability from increased thrombogenic agents in the circulation such as factor V11, von Willebrand factor, D-dimer and fibrinogen abnormalities. Hypercoagulability may affect both the venous (deep vein thrombosis/pulmonary embolism) and arterial systems (ischemic stroke, acute occlusion of the arteries of the limbs, mesenteric ischemia).

In the absence of an effective, approved, drug therapy and vaccine against the virus, there is concern about the potential negative impact of the pandemic in SCD patients. Literature from France, the United Kingdom and America have described the presentation and outcomes of COVID-19 in SCD patients. There is, however, a scarcity of data on the impact of COVID-19 on patients in Africa where an estimated 75% of people affected by SCD reside. We discuss the clinical evolution and outcomes of 3 patients with SCD and COVID-19 pneumonia admitted at the Highly Infectious Isolation Unit (HIIU) of the Komfo Anokye Teaching Hospital (KATH) in Ghana. The patients were referred from peripheral facilities and had tested positive for COVID-19 by real-time reverse transcriptase polymerase chain reaction of the nasopharyngeal swabs, prior to admission to HIIU.

## CASE 1

A postnatal, 30-year-old female with SCD (genotype HbSC) was admitted to the HIIU with a 2-day history of dry cough, fever, vomiting and dark-colored urine.

She had delivered in another facility 2 weeks before presentation and had a history of multiple transfusions during pregnancy.

At presentation, her temperature was 37.7°C but rose to 40°C on day 2 of admission. There was jaundice, pallor, pulse rate of 94 b/m and oxygen saturation (SpO2) of 96% in room air.

Chest X-ray showed bilateral, peripheral, ground-glass opacities in the middle and lower lobes suggestive of COVID-19 pneumonia. ECG was normal with a QT interval (QTc) of 0.471 second.

Laboratory investigations revealed severe anemia, thrombocytopenia, deranged transaminases, elevated urea and creatinine (See Table 1) with elevated urea:creatinine of 11.6 and elevated serum bilirubin (29.0 micromol/l).

Urine dipstick showed trace leukocytes and proteinuria (2+).

She was given intravenous meropenem 1 g 8 hourly, prophylactic dose of subcutaneous enoxaparin – 40 mg daily, oral hydroxychloroquine 200 mg 8 hourly × 10 days, oral azithromycin 500 mg stat, then 250 mg daily × 4 (in accordance with National Guidelines), oral zinc 40 mg daily, oral folic acid 5 mg daily and oral multivitamins one 12 hourly. She never required supplemental oxygen. She was also rehydrated adequately and hemotransfused with a total of 9 units of packed cells due to ongoing hemolysis (evidenced by jaundice and passage of dark-colored urine) and recurrent fall in hemoglobin. After receiving the 7th unit of packed cells, oral prednisolone was prescribed on day 6 for a possible hyperhemolysis syndrome (HS). Hemolysis stopped after she received prednisolone and her hemoglobin rose to 6.2 g/dL on day 11 of admission.

She gradually improved clinically. Her COVID-19 test was repeated after completion of hydroxychloroquine and was negative. ECG was normal with QTc of 0.431 second.
She was discharged after 14 days to continue follow up at the SCD clinic.

3 | CASE 2

A 34-year-old female with SCD (HbSC genotype) presented to the HIIU with a 2-week history of fever and cough and a 2-day history of breathlessness and severe left thoracic pain. She had a history of a yearly occurrence of a VOC.

At presentation, her temperature was 37.0°C. She was pale, jaundiced and tachypnoeic (44 cycles per minute). SpO₂ was 95% in room air. Chest X-ray showed bilateral infiltrates involving peripheral zones as well as findings suggestive of lung infarction from an ACS (Figure 1).

Her QTc was 0.447 second.

Laboratory investigations revealed microcytic, hypochromic anemia (See Table 1), hypoalbuminemia of 30.2 g/L and hyperbilirubinemia of 30.2 micromol/L.

Urine dipstick showed trace leukocytes and protein.

She was given intranasal oxygen at 5 liters/minute for a day, intravenous ceftriazone 2 g 12 hourly, oral hydroxychloroquine 200 mg 8 hourly, oral folic acid 5 mg daily, oral paracetamol, prophylactic subcutaneous enoxaparin, oral multivitamins one 12 hourly and adequately hydrated with intravenous and oral fluids.

She was also hemotransfused with one unit of packed cells.

On day 2 of admission, her respiratory rate declined to 29 cycles/min. It further declined to 18 cycles/min on day 3 with complete resolution of the chest pain.

She improved after 4 days at HIIU, so was transferred to a lower level hospital for further care from where she was subsequently discharged after a negative COVID-19 test.
4 | CASE 3

A 20-year-old female, with SCD (genotype HbSS) presented at HIIU with a week’s history of breathlessness, following a cesarean section.

She had a history of hemotransfusion 4 years ago.

On examination, she was afebrile (36.5°C) and pale. Respiratory rate was 24 cycles per minute. She was hypoxic with SpO₂ of 51% in room air and 98% on a nonrebreather mask at 15 liters/minute.

Her chest X-ray showed massive cardiomegaly (probably from sickle cell cardiomyopathy) and bilateral, patchy, peripheral, ground-glass opacities in the lower zones suggestive of COVID-19 pneumonia.

ECG showed sinus rhythm and normal QTc (0.417 second).

Laboratory investigations revealed anemia (Table 1), hypoproteinemia of 26 g/L and hyperbilirubinemia of 27.1 micromol/L. Urine dipstick revealed protein (2+).

She was given intravenous dexamethasone 12 mg stat, 8 mg daily × 5, prophylactic dose of subcutaneous enoxaparin, oral hydroxychloroquine, oral furosemide 40 mg daily, oral multivitamins, oral folic acid and oral azithromycin. She was also adequately hydrated and transfused with 3 units of packed cells.

On day 3, her oxygen requirement improved and her saturation was 98% on intranasal prongs. On day 4, her temperature rose to 41°C. Samples were taken for blood and urine cultures and antipyretics and intravenous cefuroxime were administered. No organism was isolated from the cultures.

The fever resolved on day 6 and she was weaned off oxygen on day 9. She continued to improve clinically and was discharged on day 11 for review at the hematology clinic.

5 | DISCUSSION

Fever, cough, fatigue, vomiting and breathlessness were among the admission symptoms reported by our patients. This is in agreement with what has been observed by other authors. 20,21

It is hypothesized that SCD patients coinfected with COVID-19 would be at a higher risk of a more severe disease presentation and course since they usually have pre-existing pulmonary compromise and are also at high risk of infections due to immune dysfunction and compromise. 22,23 In our case series, only patient 3 had a presentation indicative of severe COVID-19 infection although admission to the intensive care unit and ventilation were not needed. Patients with the homozygous sickle cell gene tend to have severe immune dysfunction from autopsplenectomy, impaired B and T cell function, abnormal chemotaxis and opsonization so making them vulnerable to developing severe viral and bacterial infections and this could explain the severe presentation in this patient. 24

Patients 1 and 2 presented with a hemolytic crises and ACS respectively probably triggered by COVID-19. This illustrates that SCD patients may present with crises without evidence of severe COVID-19 respiratory symptoms. Nur et al reported on 2 SCD patients who presented with VOC and ACS in the absence of typical COVID-19 pulmonary symptoms. 12 Beekens et al also documented VOC, ACS and hemolytic crises as part of the clinical features of a patient they reported on. 25

As a result of the prothrombotic state that SCD and COVID-19 predispose patients to, some experts currently recommend treatment of asymptomatic SCD patients with mild COVID-19 with prophylactic doses of low molecular weight heparin (such as enoxaparin 40 mg daily) while symptomatic patients with severe or critical COVID-19 should be treated with therapeutic doses of 1 mg/kg 12 hourly barring any contraindications. 13,26 Evidence of the thrombogenic nature of COVID-19 had not emerged at the time these patients were treated at HIIU and therefore patient 3 received only prophylactic doses of enoxaparin.

Patient 1 had been hemotransfused multiple times during her pregnancy. Despite transfusion of 7 units of packed cells at HIIU, her hemoglobin level failed to rise leading to suspicion of HS; a potentially fatal phenomenon seen in SCD patients with a past history of numerous transfusions (including use of compatible blood) as in this case. 27 The exact mechanism for this syndrome is unknown but it is postulated to be primarily due to bystander hemolysis where there is destruction of both the recipient’s red blood cells (RBCs) and the transfused RBCs by the recipient’s antibodies (alloantibodies) in the absence of expression of red blood cell antigens against which the antibodies are targeted. 27,28 HS is a diagnosis of exclusion although laboratory tests can aid in the diagnosis including the direct antiglobulin test (usually negative in the acute stage), lactate dehydrogenase (elevated) and reticulocyte count (usually reticulocytopenia). 27,28 These tests could not be done for our patient due to resource constraints. Treatment is with steroids and, if severe, immunoglobulins as well. Additional transfusions should be avoided if possible. 28 Our patient responded favorably to oral steroids but it was needful to give 2 more units of blood due to the presence of severe, symptomatic anemia.

Studies by Hussain et al and others mostly from outside Africa have shown good outcomes in SCD patients with COVID-19. 17,18,23 Similarly, none of our patients had an adverse disease outcome. SCD patients have a chronic inflammatory state at healthy, baseline state due to high levels of circulating IL-1, IL-6 and TNF alpha. 29 These cytokines, notably IL-6, have been implicated in the pathogenesis of the cytokine storm which has been shown to be responsible for lung damage and the multi-organ failure seen in severe COVID-19 pneumonia. It is possible that the usual baseline inflammatory state in SCD patients may have been protective against the cytokine storm since such patients are used to being in a persistent state of inflammation. 23,29 Nevertheless
SCD patients with COVID-19 coinfection should be monitored closely for features such as worsening hypoxia (which may be due to thromboembolic events, acute respiratory distress syndrome or acute chest syndrome), evidence of multi-organ damage and for vaso-occlusive or hemolytic crises and if these develop, aggressive management should be instituted.

6 | CONCLUSION

In conclusion, the patient with SS genotype had a severe presentation of COVID-19 respiratory features. The two other patients (SC) had hemolytic crises, VOC and ACS at presentation. All the patients, however, had a favorable clinical outcome and were successfully discharged home. This implies that COVID-19 may not result in dire outcomes in SCD patients. However, it may trigger crises in these patients even in the absence of severe COVID-19 related lung disease. This patient population should be closely monitored for sickle cell crises and if these develop they should be aggressively treated. This is, however, a small case series and in-depth studies with a larger population size are needed to enhance knowledge into the impact of COVID-19 in SCD patients, especially those with the HbSS gene.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors were involved in the clinical management of the patients. YH and YA: designed the study, collected the needed data, and wrote the case series. DAYA, AOA, KHM, JAD, SAK, KAD, POB, and COA: critically reviewed the study and provided important input. All the authors have approved of the final version.

ETHICAL APPROVAL

Ethical approval (reference no. KATH-IRB/AP/067/20) was obtained from the Institutional Review Board of the Komfo Anokye Teaching Hospital.

DATA AVAILABILITY STATEMENT

All data used for this case series are included in this published article.

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