CASE REPORT

Diagnostic Challenge in a Sickle Cell Disease Patient with COVID-19

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Abstract

Acute chest syndrome is a life-threatening complication in sickle cell disease. Infections are frequently implied, and like other viruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be a trigger. In addition, due to their inflammatory status, they may present a higher risk for severe coronavirus disease 2019 (COVID-19). Pneumonia and acute chest syndrome share clinical, laboratory, and radiological features and may overlap, which makes their differential diagnosis especially challenging. We describe a case of an adolescent with homozygous sickle cell disease that developed acute chest syndrome in the context of COVID-19. With it, we intend to bring awareness to the potential role of imaging in the differential diagnosis and in establishing the best approach for the patient. Chest computed tomography findings were suggestive of an alternative diagnosis to COVID-19 pneumonia and red cell transfusion, fluid management, analgesics, and antibiotics were administered with favorable outcome.

Keywords: Acute Chest Syndrome/diagnosis; Acute Chest Syndrome/diagnostic imaging; Acute Chest Syndrome/therapy; Adolescent; Anemia, Sickle Cell/complications; COVID-19/complications; Diagnosis, Differential; SARS-CoV-2; Tomography, X-ray Computed

Introduction

Sickle cell disease is one of the most common blood disorders worldwide, particularly in developing countries.[1] Sickle cell disease encompasses a group of autosomal recessive hemoglobinopathies caused by a point mutation, resulting in a structurally abnormal hemoglobin molecule. This may cause a wide variety of acute and chronic complications, depending on the inherited genetic phenotype and other comorbidities.[2] The disease features a complex interaction between vaso-occlusion, tissue ischemia, and inflammation, all stemming from the propensity for erythrocytes to change into the abnormal sickle-shape.[1]

Acute respiratory illness is a major cause of morbidity and mortality in patients with sickle cell disease, who are at increased risk of life-threatening respiratory complications, such as acute chest syndrome.[3] Acute chest syndrome is loosely defined by fever and/or respiratory symptoms accompanied by the presence of a pulmonary infiltrate on chest radiography.[4] A high index of suspicion is required since clinical presentation may range from mild illness to acute respiratory distress syndrome.

In children with acute chest syndrome, infection must always be considered and the most frequently identified agents are bacteria (predominantly *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes,* and *Haemophilus influenzae)*, atypical bacteria (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae),* and viruses (more frequently in younger children).[5]

As the coronavirus disease 2019 (COVID-19) pandemic keeps evolving, questions remain on how this disease may affect sickle cell disease patients, particularly in the pediatric population.[2] Since infections are particularly common in children and a frequent causal agent of acute chest syndrome, the implications that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may trigger acute chest syndrome need to be discussed.[5] As with other outbreaks, such as H1N1,[6] it is also possible that complications and more severe forms can be more likely in sickle cell disease patients who become infected with SARS-CoV-2, particularly those with a previous history of pulmonary comorbidities. Indeed, complicated cases of COVID-19 in pediatric sickle cell disease patients have been reported.[2] Nevertheless, the published case series so far and international registries mostly describe a mild disease.[7-10]

An additional challenge in these patients may be the difficulty in distinguishing between acute chest syndrome and pneumonia, given the many similarities

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both diseases share. In many cases, they could coexist, as viral and bacterial pneumonia do as well, increasing the possibility of a worse outcome. On the topic, we share the peculiar case of a 15-year-old sickle cell disease patient who developed acute chest syndrome concurrently with COVID-19.

Case Report

A 15-year-old male of African descent presented to the emergency department with severe left thoracic pain for 12 hours. He also reported rhinorrhea and loss of taste and smell for the past three days. He has a diagnosis of homozygous sickle cell disease (HbSS), complicated by recurrent vaso-occlusive crisis, nephropathy, splenomegaly, and low basal hemoglobin (Hb) (8.5 g/dL), requiring frequent red cell exchange transfusions and hydroxyurea. He was fully immunized, including 23-strain pneumococcal and seasonal influenza vaccines. On admission, he denied fever, cough, or dyspnea. There was no recent history of trauma, travel, or other suspicious exposure. He exhibited paleness with dehydration, tachycardia (130 beats/minute), tachypnea (60 cycles/minute), and chest retractions, saturation of oxygen in the blood (SpO_2) 98% room air and moderate splenomegaly without hepatomegaly.

Acetaminophen, ketorolac, and morphine were started for pain management and blood tests, including blood cultures, were performed. Laboratory findings showed a moderate elevation of inflammatory markers as well as anemia with evidence of hemolysis (Hb 6.8 g/dL, 14.6% reticulocyte index, total bilirubin 1.69 mg/dL, 3% of Hb F) (Table 1). Polymerase chain reaction done in nasopharyngeal and respiratory secretions samples was positive for SARS-CoV-2 and negative for other respiratory viruses and atypical bacteria. Nasal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) was positive.

Chest radiography showed bilateral interstitial infiltrates and cardiomegaly (Fig. 1). Because of the suspicion of acute chest syndrome, he received a simple red cell transfusion (on day two), intravenous fluid, acetaminophen, and was started on cefotaxime and clindamycin. Given the possibility of COVID-19 pneumonia and according to COVID-19 treatment guidance at the time, he was treated with hydroxychloroquine and enoxaparin in a prophylactic dose. He was not enrolled in any clinical trial. Control electrocardiograms were carried out every 48 hours after the first dose of hydroxychloroquine. Due to concern for prolonged corrected QT interval, which was detected on day two, treatment was interrupted for 24 hours to wait for the normalization of the electrocardiogram, and then restarted for a total of five days of treatment.

Due to the onset of fever and the need for oxygen therapy to a maximum of 2 L/min on day three, a chest computed tomography (CT) scan was ordered. Findings included bilateral infiltrates in the lower lobes with atelectasis, bilateral pleural effusion, and pericardial effusion, with sparce areas of ground-glass opacities (Fig. 2). These findings were classified as indeterminate for COVID-19 according to the British Society of Thoracic Imaging guidelines.

Table 1. Laboratory findings

	Admission days					
	0	**2**	**3**	**6**	**8**	**14**
Hb (g/dL)	7.3	6.8	7.6	8.1	7.7	6.7
Hematocrit (%)	-	20.3	22.3	23.4	23	20
WBC (cells/µL)	16,670	8,310	6,330	5,480	5,680	7,560
Neutrophils (cells/µL)	11,330	5,470	3,260	2,620	3,360	4,750
Lymphocytes (cells/µL)	4,000	2,000	2,370	2,270	1,790	2,030
Monocytes (cells/µL)	420	560	330	370	400	560
Platelets (cells/µL)	126,000	141,000	126,000	129,000	141,000	190,000
Fibrinogen (g/L)	-	3.6	4.9	3.3	3.6	2.1
D-dimers (µg/L)	-	927	807	734	1032	309
LDH (IU/L)	835	678	526	459	499	474
CRP (mg/dL)	7.7	9.79	14.0	5.22	2.58	0.79
PCT (ng/mL)	-	0.59	0.18	-	0.06	0.29
Ferritin (ng/mL)	-	-	731	818	-	-
ESR (mm/h)	-	-	69	89	75	52

CRP - C-reactive protein; ERS - erythrocyte sedimentation rate; Hb - hemoglobin; LDH - lactate dehydrogenase; PCT - procalcitonin; WBC - white blood count.

During hospitalization, his clinical status and bloodwork progressively improved, which allowed analgesic tapering. He completed 14 days of intravenous antibiotics and was discharged after 15 days with favorable evolution.

Discussion

The clinical presentation of COVID-19 is widely variable, particularly in children.[11] Symptoms are usually milder than in adults and they are not useful to differentiate these cases from other viral respiratory infection.[11] However, severe COVID-19 can lead to multiorgan failure and acute respiratory distress syndrome.[11] Differential diagnosis of severe cases of COVID-19 comprises many etiologies, including acute chest syndrome. The wide phenotypic variability in acute chest syndrome and COVID-19 means it is virtually impossible to perform a clear diagnosis of either entity in a sickle cell disease patient presenting with acute thoracic pain and hypoxemia.[4,11]

Imaging may play a significant role in overcoming this doubt.[12] Contrary to adults, where chest CT may be considered as a screening tool given that COVID-19 pneumonia has a quite characteristic presentation, in the pediatric population, pulmonary involvement is often less extensive and a chest CT is not considered a reliable method for diagnosis.[7,13,14] However, imaging may guide individual patient management decisions, especially if looking for complications or an alternative diagnosis.[15] In our patient, the clinical presentation and laboratory abnormalities could be present both in viral pneumonia and acute thoracic syndrome, requiring further imaging studies to clarify our diagnosis. Although there is not a specific pattern for COVID-19, particularly suggestive chest CT findings include bilateral, multifocal, halo consolidations, and ground-glass opacities, especially if located in the peripheral, posterior, or lower parts of the lung.[14] Multifocal lobar consolidations, atelectasis, bilateral pleural effusion, and pericardial effusion are considered atypical findings that suggest an alternative diagnosis. These features were helpful to discriminate the diagnosis of acute chest syndrome and guide our approach to the patient.[15]

Treatment plans that cover COVID-19 and acute chest syndrome might also prove challenging. If there is a high suspicion of bacterial co-infection in COVID-19, such as moderate to severe disease with leukocytosis with neutrophilia, elevated C-reactive protein, and/or procalcitonin, antibiotic therapy should be started, adjusted to the clinical features, age, patient characteristics, and local epidemiology.[16]

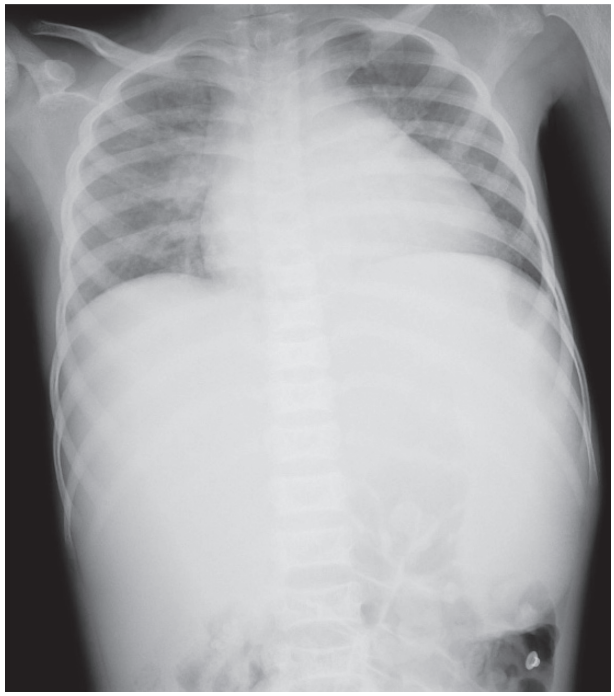

Figure 1. Lung with hyperinflation, bilateral interstitial infiltrates, and cardiomegaly.

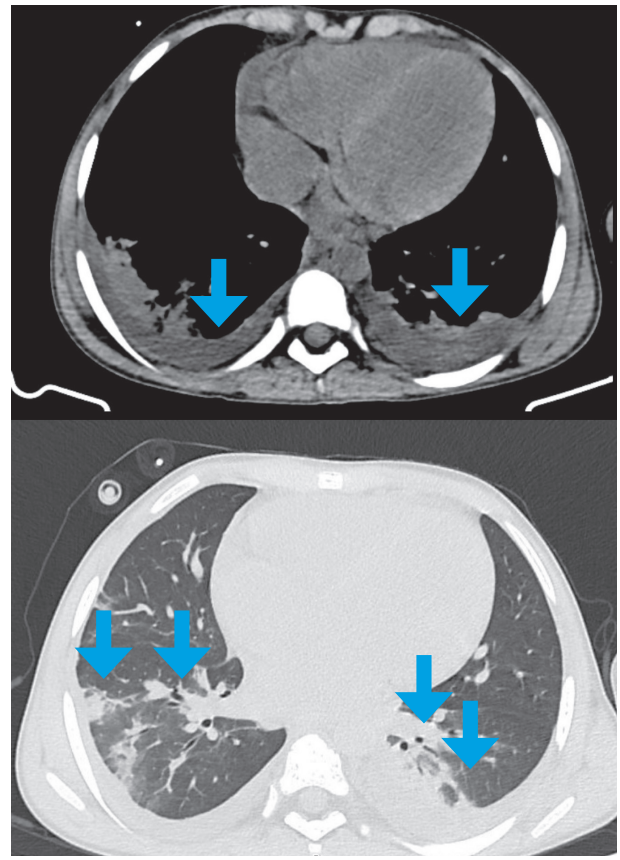

Figure 2. Patient chest computed tomography shows bilateral pleural effusion and pericardial effusion (A), bilateral pulmonary parenchymal ground-glass, and consolidative pulmonary opacities with atelectasis and air bronchogram with peripheral lung distribution on both lower lobes (B).

Antibiotic therapy should cover the main causal agents of complicated community-acquired pneumonia like *Streptococcus pneumoniae*, *Staphylococcus aureus, Streptococcus pyogenes,* and atypical bacteria.[16] Infection and acute chest syndrome in sickle cell disease patients also require broad-spectrum antibiotics usually a third-generation cephalosporin in association with a macrolide to cover for atypical bacteria.[4,5,17] The option for clindamycin in this case was justified by the MRSA colonization.

At the moment, there is no specific antiviral treatment for COVID-19. At the time of hospitalization in April 2020, international and national guidelines considered the use of hydroxychloroquine in high-risk patients with mild or moderate disease, followed by remdesivir in case of severe disease.[18,19] In the authors' opinion, the patient's multiple comorbidities, evidence of laboratory and imaging abnormalities, and the risk of complications justified starting treatment, even though the medical team was aware of the risks regarding the use of antimalarial agents in this situation. Current knowledge tells us that hydroxychloroquine probably had a residual effect.[18]

Both illnesses may require normohydration, oxygen therapy, analgesics and antimicrobial therapy.[4,16,17] Red cell and exchange transfusions also play an important role in managing children with sickle cell disease.[3] Sickle cell disease patients are also at major risk from thromboembolic events such as venous thromboembolism and pulmonary embolism.[3] In addition, coagulopathy and thrombosis were also found to be common complications of COVID-19, contributing to higher morbidity and mortality.[20] The current cumulative evidence suggests that sickle cell disease patients presenting with COVID-19, especially with clinically significant disease, inability to walk, and/or suggestive family or past history, may benefit from prophylactic anticoagulants.[19,20]

In agreement with the published literature so far, our case had a benign course, which further corroborates that COVID-19 in children with comorbidities may present with a good outcome. We believe that our initial approach may have made an impact on the clinical course, with early, aggressive transfusion, anti-inflammatory agents, anticoagulants, and antibiotic therapy.[4,5] Further studies are required for a better understanding of the optimal management and clinical consequences of COVID-19 in children, particularly in the sickle cell disease population. Still, clinicians need to be aware that SARS-CoV-2 may be a precipitating factor to acute chest syndrome, and the diagnosis and emergent treatment of this entity needs to be considered in SARS-CoV-2 infected sickle cell disease patients.

WHAT THIS CASE REPORT ADDS

- Like other viruses, SARS-CoV-2 can trigger an episode of acute chest syndrome.
- Acute chest syndrome and pneumonia may overlap, which may be a confusing factor in SARS-CoV-2 infected patients.
- Computed tomography imaging in COVID-19 may be helpful to decision-making, especially if there is an atypical course of disease, suspicion of complications, or of an alternative diagnosis.
- Early diagnosis and management of acute chest syndrome is key to a favorable outcome in SARS-CoV-2 infected patients.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Desafio Diagnóstico num Doente com Anemia Falciforme e COVID-19

Resumo

A síndrome torácica aguda é uma complicação potencialmente fatal na doença de células falciformes. As infeções estão frequentemente implicadas e, como outros vírus, o coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2) pode provocar a síndrome torácica aguda. Adicionalmente, devido ao estado hiperinflamatório, estes pacientes apresentam maior risco de doença do coronavírus 2019 (COVID-19) grave. A pneumonia e a síndrome torácica aguda partilham semelhanças a nível clínico, laboratorial e imagiológico e podem sobrepor-se, complicando o seu diagnóstico diferencial. Os autores descrevem o caso de um adolescente com doença de células falciformes em homozigotia S, que desenvolveu síndrome torácica aguda em contexto de COVID-19. Através deste caso, procuramos alertar para o potencial papel da imagem no diagnóstico diferencial destas entidades e orientação terapêutica destes doentes. Neste caso, os achados na tomografia computorizada torácica foram sugestivos de um diagnóstico alternativo à pneumonia COVID-19 e a intervenção terapêutica com transfusão eritrocitária, normohidratação, analgesia e antibióticos conduziu à evolução favorável do caso.

Palavras-Chave: Adolescente; Anemia Falciforme/complicações; COVID-19/complicações; Diagnóstico Diferencial; SARS-CoV-2; Síndrome Torácica Aguda/diagnóstico; Síndrome Torácica Aguda/diagnóstico por imagem; Síndrome Torácica Aguda/tratamento; Tomografia Computorizada