Original Article

Radiological Patterns in Sickle Cell Disease Patients with Acute Chest Syndrome: Are There Age-Related Differences?

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Abstract

Background: Acute chest syndrome is a major cause of pulmonary disease and mortality in sickle cell disease patients. Its diagnosis can be delayed due to differing imaging patterns between children and adults.

Objective: The purpose of this study was to describe the pulmonary and extrapulmonary imaging findings in sickle cell disease patients with acute chest syndrome and determine differences in findings between adult and pediatric patients.

Patients and Methods: This retrospective study analyzed the data of all sickle cell disease patients who were admitted with a diagnosis of acute chest syndrome to King Fahd Hospital of the University, Al Khobar, Saudi Arabia, between January and June 2015 ($n = 150$). After grouping the patients into adults and pediatrics, the pulmonary and extrapulmonary characteristics were identified and the digital radiography, computed tomography and laboratory findings were compared.

Results: A total of 116 patients with 163 acute chest syndrome episodes met the inclusion criteria, of which 69 (60%) were adults. In both adult and pediatric patients, the most frequent pulmonary finding was consolidation of the lung parenchyma. The right lung was most frequently involved: the lower lobe in adult patients and the middle lobe in pediatric patients. In addition, pleural effusion was observed in both age groups. Extrapulmonary radiological findings, such as avascular necrosis and cardiomegaly, were significantly more common in adult patients than in pediatric patients ($P < 0.05$). Compared with adults, pediatric patients had significantly lower hemoglobin levels ($P = 0.001$) and oxygen tension fraction in arterial blood ($P = 0.007$).

Conclusions: Pediatric and adult sickle cell disease patients with acute chest syndrome typically exhibited similar pulmonary characteristics, whereas extrapulmonary findings were more prominent in adult patients. Furthermore, low levels of hemoglobin and oxygen tension fraction were dependent predictors of acute chest syndrome.

Keywords: Acute chest syndrome, chest radiography, extrapulmonary, pulmonary, sickle cell disease

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INTRODUCTION

Acute chest syndrome (ACS) is a major cause of pulmonary disease and early mortality in sickle cell disease (SCD) patients, occurring in 15%–43% of all cases.[1-4] In Saudi Arabia, the prevalence of ACS in SCD patients varies across regions.[5] Although ACS can occur at any age, children in general are most likely to be affected; worldwide, the annual incidence of ACS among children with SCD is 24.5 cases per 100 patients compared with an annual incidence of 8.8 cases per 100 adult SCD patients.[6,7] Notably, adults have a higher mortality rate than children (4.3% vs. 1.8%, respectively).[8-10]

ACS is characterized by chest pain, shortness of breath, tachypnea, cough, hypoxia and low-grade fever, and has distinctive radiological changes, defined as new pulmonary lobar or multilobar opacities.[1-4] The presence of new pulmonary airspace densities in chest X-rays is an essential criterion for the diagnosis of ACS. However, the diagnosis can be missed for several days because of the delayed appearance of some infiltrate(s) on chest X-rays.[3,11] In terms of radiographic findings in different age groups, a study showed that in children diagnosed with ACS, the upper lobe is most commonly affected, whereas in adults, the lower lobe is usually affected or multipolar infiltrations are commonly observed.[11,12] Importantly, although the radiological presentation of ACS is similar to that of bacterial pneumonia, ACS findings in SCD patients are more likely to exhibit multiple lobe involvement and recurrent manifestation of infiltrates. In addition, the length of clinical illness and radiologic infiltrate time to clearance are commonly prolonged to ≥10 days.[11,13]

Pulmonary complications are the most common cause of death in SCD patients. However, it should be noted that several extrapulmonary complications may occur in SCD patients, regardless of the presence of ACS such as neurological complications including infarction, atrophy and cognitive deterioration. In addition, the musculoskeletal system can exhibit persistent red marrow involvement, resulting in an increased susceptibility to osteomyelitis, bone marrow infarction and secondary septic arthritis. Kidney functions can also be disrupted, leading to hematuria, proteinuria, nephrotic syndrome and renal failure. The spleen is involved in most SCD cases; it typically exhibits enlargement, infarction, infection or abscess formation. Hepatic complications of SCD include fibrosis, cirrhosis, intrahepatic biliary duct stenosis resulting in cholestasis, and transfusion-associated (non-A, non-B) hepatitis secondary to repeated transfusions.[11,12]

Improvements in care have resulted in pediatric SCD patients reaching adulthood; however, managing disease in adult SCD patients, with or without ACS, remains a challenge because of the increased rates of mortality and complications. Further, adults experience more hospitalizations than pediatric patients as they would have undergone transfusions/chelation and exhibit classic chronic conditions.[3,13] However, there is a lack of studies comparing extrapulmonary complications between pediatric and adult SCD patients with ACS, both in Saudi Arabia and internationally. Therefore, the current study aimed to describe the pulmonary and extrapulmonary findings on digital radiography and chest computed tomography (CT) in SCD patients diagnosed with ACS and to determine differences in findings between adult and pediatric patients. The findings of this study would likely provide helpful information for clinicians, including intensivists, internists, pediatricians and diagnostic radiologists, with regard to clarifying the various discrepancies between pediatric and adult patients, and thus enable timely implementation of treatment and minimization of complications.

PATIENTS AND METHODS

This retrospective cohort study included all SCD patients who were admitted with a diagnosis of ACS to King Fahd Hospital of the University, Al Khobar, Saudi Arabia, between January and June 2015. All clinical data were reviewed to confirm the diagnosis of ACS according to the most accepted definition: finding a new density on chest radiograph accompanied by fever and/or new respiratory symptoms, such as chest pain, cough and shortness of breath or hypoxia.[14] Patients with incomplete records as well as those whose radiological images were not available for review were excluded from this study.

Results of blood tests, liver and renal function tests and assessments of arterial blood gases were reviewed. In addition, radiological images of the chest, including CT scans and digital radiographs, were reviewed and reported by three certified radiologists with an average of 8 years of experience. To assess reliability, internal consistency (Cronbach's alpha) was calculated and agreement on all results was 0.949 (94.9%), indicating adequate reliability.

Ethical approval for conducting this study was obtained from the Institutional Review Board of Imam Abdulrahman Bin Faisal University (IRB-2014-01-370) on December 21, 2014. All patients included in the present study had

provided written informed consent prior to their data being collected.

Imaging studies

Bedside digital radiographs were obtained using a Mobilett Plus X-ray unit (Siemens AG, Erlangen, Germany). All radiographs were obtained in supine or semi-recumbent position, with the following standardized parameters:

- Parameters for adult patients: 125 kV, 0.6 mA, 2.99 mGy/m^2, according to body mass index, focus–film distance 1 m
- Parameters for pediatric patients: 70 kV, 1.9 mA, 1.75 mGy/m^2, according to body mass index, focus–film distance 1 m.

All CT scan examinations were performed using a 64-row multidetector CT scanner (Lightspeed VCT, GE Healthcare, Waukesha, WI, USA) with the following parameters:

- Parameters for adult patients: 5-mm-thick slices; 120 kVp; 244 mA; pitch (gantry) rotation time, 100–200 ms; scan time, 4.69 s; rotation time, 0.65 s; dose–length product, 657.0 mGy; table feed, 3:1
- Parameters for pediatric patients: 5-mm-thick slices; 120 kVp; 195 mA; pitch (gantry) rotation time, 100–200 ms; scan time, 4.20 s; rotation time, 0.65 s; dose–length product, 509.0 mGy; table feed, 3:1.

In total, 30 and 253 digital radiographs of pediatric and adult patients, respectively, were analyzed. In addition, thoracic CT scans of three pediatric and four adult patients were analyzed.

Statistical analysis

Continuous variables are described as mean ± standard deviation and were analyzed using the independent *t*-test and Mann–Whitney U-test. Categorical variables were reported as frequencies with percentages and analyzed using chi-square and Fisher's exact tests. $P < 0.05$ was considered statistically significant.

RESULTS

Data from 150 cases were reviewed, of which 116 cases with 163 episodes of ACS were found to be eligible and included in this study. The mean age of the study participants was 21 (±13) years, and 68% ($n = 76$) were male. The pediatric age group (≤16 years) accounted for 40% ($n = 47$) of ACS patients and adults 60% ($n = 69$). During the study period, five patients who were reported as pediatric patients at the inception of the study became adult patients. Therefore, the 116 cases included a total of 111 individual patients. In our cohort, the incidence rate of ACS was higher among adult than pediatric patients ($P < 0.0005$), and 54% (88 of 163) of all episodes were in patients who experienced a single episode of ACS.

Radiological findings

Digital chest radiography was the most commonly used imaging modality in the early diagnosis of ACS (90%). On chest radiographs, lung consolidation was the predominant pulmonary opacity observed during ACS episodes; the right lung was more commonly involved ($n = 93$; 57%). Of these, the right lower lobe was most frequently affected in adults ($n = 32$; approximately 34%), followed by the left lower lobe ($n = 30$; approximately 32%). In contrast, the middle lobe was more commonly involved in pediatric patients ($n = 18$; approximately 38%) [Figure 1]. The most frequent pulmonary radiological signs found on digital radiography and CT scans of both age groups during the ACS episodes were consolidations of the lung parenchyma ($n = 91$; 56%) [Figures 2-4]. Cardiomegaly was observed in 73 episodes (45%) and pleural effusion was noted in both age groups ($n = 41$; 25%). Atelectasis was present in 1.4% ($n = 1$) of cases.

Chronic lung changes, caused by exposure to multiple ACS episodes, pulmonary hypertension and/or cor pulmonale, were found only in adults with recurrent ACS episodes ($n = 4$, 3.4% of 116 cases, 5.79% of 69 adults). In addition, rhizomelic avascular necrosis (affecting shoulder and/or hip joints) was observed more frequently in adults ($n = 33$, 28% of 116 cases, 47.8% of 69 adults) than in pediatric patients ($n = 11$, 9.48% of 116 cases, 23.4% of 47 children). Among the adult patients, splenic calcification and cholecystectomy were encountered in 1.4% ($n = 1$) and 7.2% ($n = 5$), respectively. No splenic calcification and only a single case of cholecystectomy were reported among the

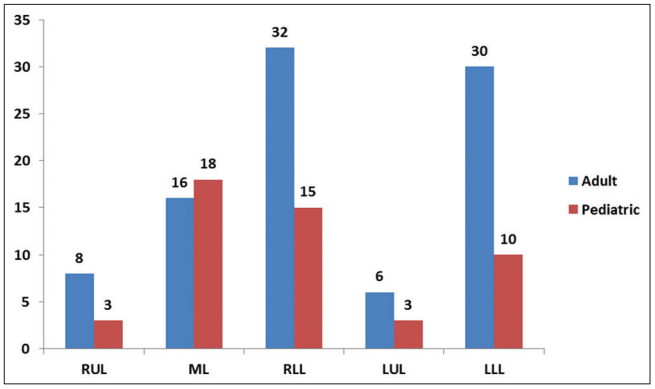

Figure 1: Distribution of lobar consolidations in adult and pediatric patients with acute chest syndrome. RUL – Right upper lobe; ML – Middle lobe; RLL – Right lower lobe; LUL – Left upper lobe; LLL – Left lower lobe

pediatric group. However, hepatomegaly was found in both age groups (n = 11; 15.9% of 69 adults and 23.4% of 47 children) [Figures 5 and 6].

Laboratory findings indicated that hemoglobin levels were considerably low in both adult and pediatric patients. The hemoglobin level was significantly lower in pediatric patients compared with that in adults (7.8 g/dL vs. 9 g/dL, respectively; $P < 0.001$). Moreover, the oxygen tension fraction level in arterial blood gas was significantly lower in pediatric patients than that in adult patients (56.7 mmHg vs. 82.6 mmHg; $P = 0.007$). Other laboratory investigations were comparable between the groups [Table 1].

DISCUSSION

ACS is a common occurrence in SCD patients, typically encountered in pediatric patients;[1,2,7,8] however, mortality rates are higher in adult patients.[9,10] Notably, the diagnosis of ACS can be delayed due to differing imaging patterns between the two age groups.[11] Previously, several studies have focused on determining mortality rates in SCD patients diagnosed with ACS. Nonetheless, these studies used differing diagnostic criteria, mainly based on pulmonary characteristics and provided differing results; the major distinguishing factor was delineation of the affected lung.[7]

Recently, several diagnostic studies have investigated predicting susceptibility to ACS in SCD patients, such as using immunohistochemistry to evaluate platelet activation of plasma marker CD40 ligand together with thrombospondin, or using cytogenetics to study certain glycoprotein polymorphisms of vasculogenesis in embryological bases, which typify a raw and promising potential marker to evaluate susceptibility to ACS in sickle cell anemia patients.[15,16] However, to the best of the authors' knowledge, few studies have extrapolated the associated extrapulmonary radiological characteristics for improving bedside imaging diagnosis of ACS.[17,18] Improving the imaging diagnosis of ACS will enable timely implementation of treatment to minimize complications. Thus, it is important to identify imaging pattern discrepancies between pediatric and adult patients,

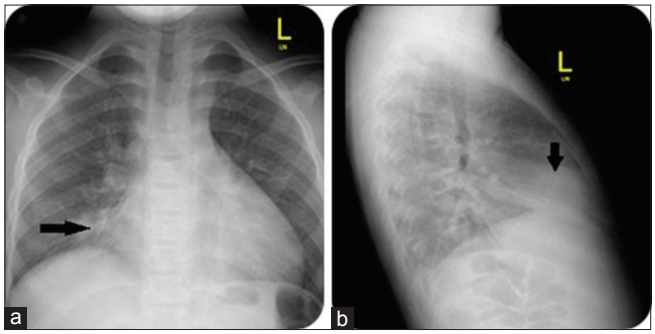

Figure 2: Radiographs of a 7-year-old female patient with sickle cell disease: (a) Frontal chest radiograph showing ill-defined patchy opacity, with air bronchogram in the right lower lung zone silhouetting the right cardiac border (arrow); (b) Lateral chest radiograph showing wedge-shaped consolidation overlying the cardiac border, representing middle lung lobe consolidation (arrow)

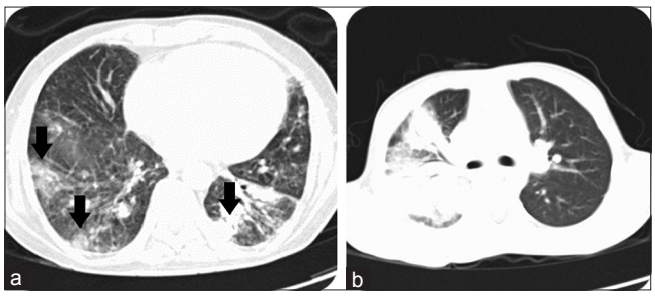

Figure 4: (a) Chest computed tomography scan of an adult patient showing multiple bilateral basal wedge-shaped consolidations, representing pulmonary infarction (arrows); (b) Chest computed tomography scan of a pediatric patient showing right middle/lower lobe consolidation and air bronchogram

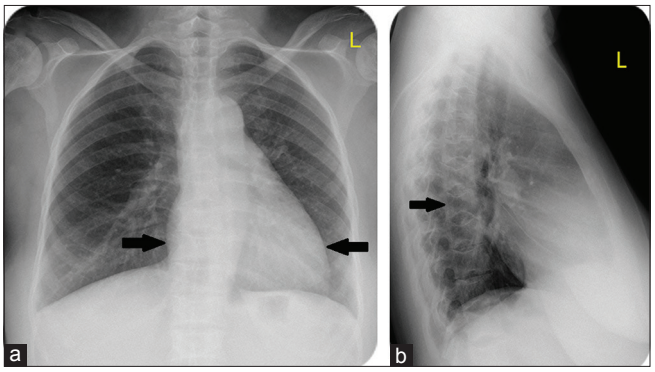

Figure 3: Radiographs of a 32-year-old female patient with sickle cell disease: (a) Frontal chest radiograph showing increased cardiothoracic ratio (arrows) and avascular necrosis of both humeral heads; (b) Lateral chest radiograph revealing H-shaped thoracic vertebrae (avascular necrosis of the vertebral body) (arrow)

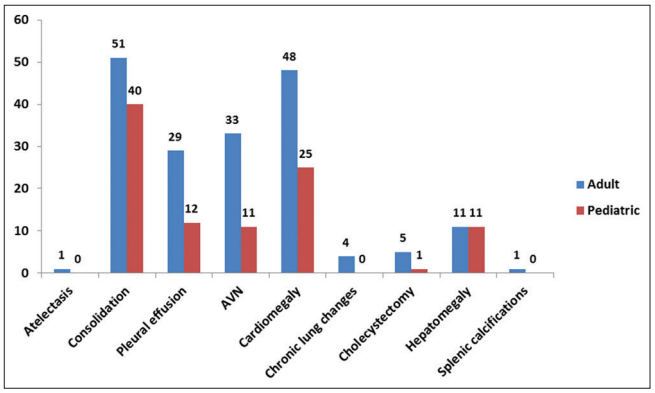

Figure 5: Frequency distribution of pulmonary and extrapulmonary findings during acute chest syndrome episodes in adult and pediatric patients with sickle cell disease. AVN – Avascular necrosis

Table 1: Laboratory results of sickle cell disease patients with acute chest syndrome on presentation

Variables	Adult (*n* = 69)	Pediatric (*n* = 47)	*P**
Median age (range)	27 (19-69)	9 (1-18)	<0.0001*
Median hemoglobin level (range), g/dL	9 (3.8-12.7)	7.8 (2.4-11.9)	<0.001*
Reticulocyte count (range)	8.8 (1.7-63)	7.8 (0.2-18.5)	0.088
Median leukocyte count (range), 10^9 cells/L	16.9 (2.7-47.8)	17.4 (4.1-181.4)	0.104
Median platelet count (range), 10^9 cells/L	288.5 (44.3-747)	374.5 (32.4-1100)	0.115
Median bilirubin level (range), mg/dL	3.3 (1.0-267)	2.75 (0.4-35.8)	0.082
Median AST level (range), U/L	55.0 (1.0-660)	61.0 (9.4-150)	0.754
Median ALT level (range), U/L	44.0 (12.0-2331)	37.0 (4.2-537.0)	0.099
Prothrombin time (range)	14.3 (10.9-33.0)	14.8 (12.1-19.0)	0.399
INR (range)	1.29 (0.89-2.01)	1.21 (0.30-9.00)	0.339
Median lactate level (range), mmol/L	1.0 (0.4-26.3)	1.7 (0.8-2.5)	0.578
pO_2 (range), mmHg	82.6 (5.7-377)	56.7 (24.8-190.4)	0.007*
HCO_3 (range), mEq/L	24.0 (4.2-28.4)	22.65 (10.1-29.0)	0.083
PH (range)	7.4 (6.8-7.5)	7.4 (7.13-7.49)	0.329
pCO_2 (range), mmHg	36.15 (15.4-83.9)	36.4 (22-47.8)	0.866

*Statistical significance ($P \leq 0.05$). AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; INR – International normalized ratio

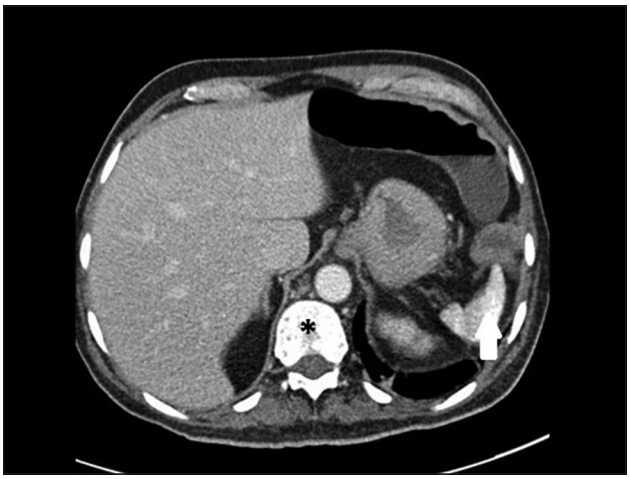

Figure 6: Abdomen computed tomography scan of an adult patient with acute chest syndrome showing hepatomegaly and a small calcification in spleen (arrow); marrow changes of the vertebral body are visible, which may be secondary to extramedullary erythropoiesis or indicative of chronic ischemia (*)

as pediatric SCD patients with ACS exhibit high morbidity while adults have high mortality rates.

This study found that in digital radiography, lung consolidation with prominent air bronchograms was the most common finding. Further, follow-up CT scans found that patients with parenchymal consolidative changes exhibited microvascular occlusion and areas of ground-glass attenuation [Figure 4]. It is critical to forestall tissue perfusion to prevent irreversible organ damage and chronic pulmonary arterial hypertension in SCD patients;[3,19] this highlights the important role of high-resolution CT scans in the initial evaluation and timely selection of a suitable course of treatment. Lung consolidations in ACS are due to the presence of fluids, proteinaceous exudates, or other products of disease that replace alveolar airspace; these cause the lung to become solid.[19,20]

In terms of differences in radiological patterns between pediatric and adult patients, the present study found that the right lower, left lower and middle lobes were most frequently affected in adults, whereas the middle lobe was most frequently affected in pediatric patients [Figure 1]. In both age groups, the most frequent pulmonary radiological signs found were consolidations and pleural effusion [Figure 5]. Compared with findings reported in the literature,[21] the predominance of consolidation in the lower lobes is in contrast to that observed during severe bacterial pneumonia, where typically there is no zonal predilection.[21] Moreover, despite its rarity, atelectasis was found in one patient in the current study using the conservative definition. This result is similar to previous findings, where atelectasis was reported and found to occur because of reduced inflation of a portion of the lung.[19,22]

In terms of extrapulmonary findings, this study found that cardiomegaly, rhizomelic avascular necrosis and hepatomegaly were present in both age groups. Therefore, these extrapulmonary findings are likely to aid in the diagnosis of ACS in all SCD patients. To the best of the authors' knowledge, no previous study has explored the extrapulmonary associations of ACS as complications of SCD.

A recent study showed associations between the levels of hemoglobin and peripheral oxygen saturation in patients with SCD.[23] Consistent with the finding of that study, the current study showed an association between reduced hemoglobin levels and oxygen saturation, which suggests the potential for novel therapeutic interventions by increasing the levels of HbF or hemoglobin–oxygen affinity.[24] The current study results may be clinically beneficial in the treatment of SCD hypoxic complications and additional studies should be conducted to validate the results of this study.

Limitations

A notable limitation of this study was that it was retrospective in nature. In addition, a low number of CT scans were available for analysis and, thus, further radiological findings may have been missed in digital radiographs. Importantly, the study and analysis were limited to a single CT scan during each ACS episode and the authors were unable to assess its progression over time. Therefore, to validate the findings of this study, the authors advocate that future studies be conducted with a larger patient pool cohort over a longer follow-up period. Prospective or retrospective multicenter analysis may further strengthen the findings of the present study. Moreover, as ACS is a disease with a high relapse rate, the authors included all ACS episodes during the study period, an approach that is commonly performed in the relevant literature.

CONCLUSION

The study found that lung consolidation is the most common pulmonary finding, frequently affecting the lower lobe (right more often than left) in adult SCD patients and the middle lobe in pediatric patients. In addition, pleural effusion was equally common in both age groups. Although pediatric and adult SCD patients with ACS had similar pulmonary findings, long-term complications are likely to differ. Extrapulmonary findings were more common in adult patients, most frequently comprising avascular necrosis, splenic sequestration and hepatomegaly, whereas cardiomegaly was commonly observed in both age groups.

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Conflicts of interest

There are no conflicts of interest.

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