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Chest computed tomographic findings in patients with sickle cell disease–related acute chest syndrome: A retrospective study

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ABSTRACT

Background: Sickle cell disease (SCD) is a hematological condition with significant pulmonary involvement, especially in episodes of acute chest syndrome (ACS). Defining radiographic pulmonary features during an ACS episode can expand our understanding of this complication. *Aim:* We aimed to describe the radiological pulmonary features of SCD patients with ACS to better understand this condition from a radiographic perspective. *Method:* This retrospective study was conducted on adult patients with ACS admitted to King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia during the period from January 2016 to June 2020. Data collection included clinical and demographic information and radiological descriptions of inflammatory and fibrotic features from computed tomography (CT) of the chest. *Results:* We reviewed chest CTs for 44 patients, including 30 males (68.2%) and 14 females (31.8%). Hemoglobin SS (HbSS) was the dominant HB genotype in 34 patients (77.3%). The most frequent findings on the chest CTs were consolidation, mainly in the lower zones, which was noted in 32 patients (72.7%), and cardiomegaly in 23 patients (52.3%). Fibrosis was noted in 14 patients (31.8%), assessed by the presence of parenchymal scarring, subpleural reticulation, architectural distortion, traction bronchiectasis, or volume loss. The distribution of abnormalities was predominantly in the lower lung zones. *Conclusion:* Inflammatory changes in lung parenchyma were common in ACS, mainly in the lower lung zones. In the SCD patients, cardiomegaly was a common cardiac radiographic abnormality. Pulmonary fibrosis was noted in one-third of the patients, dominated by scattered parenchymal scarring that lacked a specific fibrotic pattern.

Keywords: Sickle cell disease, interstitial lung disease, pulmonary embolism, chest computed tomography

1. INTRODUCTION

Sickle cell disease (SCD) is one of the inherited hematological disorders identified by the presence of hemoglobin S (HbS). HbS makes red blood cells more vulnerable to sequestration in small vessels and thus, hemolysis leading to vaso-occlusion crises in different organs that manifest as pain and tissue ischemia (Vichinsky, 1991). Acute chest syndrome (ACS), one of the pulmonary complications of SCD, is characterized clinically by fever, chest pain, tachypnea, wheezing, crepitation, or cough, and development of a new infiltrate involving at least one lung segment. It requires prompt management to prevent a serious morbidity and mortality (Charache et al., 1979; Vichinsky et al., 2000). Previous studies have reported various chest imaging findings in SCD, particularly during ACS at variable frequencies including both inflammatory and fibrotic sequelae, such as consolidation, mosaic attenuation, ground-glass opacities (GGO), prominent central vessels, irregular linear opacities, loss of lung volume, traction bronchiectasis, and interlobular septal thickening (Dessap et al., 2014; Alves et al., 2016).

In Saudi Arabia, the prevalence of SCD is highest in the eastern and southern regions (Al-Qurashi et al., 2008). The radiographic characteristics of ACS in Saudi population have been reported in prior research focusing on the eastern region of Saudi Arabia which was consistent with prior findings (Al-Sharydah et al., 2019). Our study aims to characterize the radiographic features of ACS in the patient population at King Abdulaziz University Hospital.

2. MATERIALS AND METHODS

Case Identification

In this retrospective study, we aimed to describe the radiographic characteristics of ACS in patients presenting with SCD. We included SCD cases who had an admission for ACS during the period from January 2016 to June 2020. Data collection was started January 2022 and finalized mid-April 2022. The patients were screened according to the inclusion criteria, which included the following: SCD diagnosis, age ≥ 18 years, and at least one episode of acute chest syndrome diagnosed by a hematologist and defined as a clinical syndrome consisting of fever, chest pain, tachypnea, wheezing, crepitation, or cough, and a new infiltrate involving at least one lung segment. We excluded patients who were <18 years old and those with no prior CT chest image available in the electronic patient record system. Of the 500 patients with SCD, 44 had at least one ACS episode and one available CT chest for analysis.

Data collection

The following data were collected from the health information system for the patients who fulfilled the inclusion criteria: age, gender, type of SCD hemoglobinopathy, and hemoglobin level at the time of ACS.

Chest CT data collection

Three radiologists (A. A., A. E, and F. J., with 13, 18, and 4 years' experience, respectively) blinded to the clinical data read the chest CT images. The descriptions of chest CT findings during the ACS episode were based on Fleischner Society guideline definitions (Hansell et al., 2008). The presence of the following features was identified and reported: GGO, interlobular septal thickening, mosaic attenuation, parenchymal nodules, consolidation, thickened bronchovascular bundle, cavities, cysts, mediastinal/hilar lymphadenopathy, bronchiectasis, emphysema, pleural thickening, pleural effusion, pulmonary embolism (PE), and pneumothorax. An enlarged pulmonary artery trunk was defined as a pulmonary artery to aorta ratio (PA: A) >1 or pulmonary artery diameter > 28 mm and cardiomegaly. Lung fibrosis was considered present if any of the following fibrotic features were identified: honeycombing changes, subpleural reticulation, traction bronchiectasis or bronchiolectasis, architectural distortion, volume loss, or parenchymal scarring.

The extent of radiological abnormalities was defined as limited if two lobes or less were involved and as diffuse if more than two lobes were involved. The distribution of the abnormalities was recorded as well, based on upper- vs. lower-lobe predominance and central vs. peripheral distribution. Upper lung zone predominance was considered when most of the abnormalities were visualized above the level of the tracheal carina, and lower zone predominance when most of the abnormalities were visualized below the level of the tracheal carina. Peripheral distribution was present when the abnormality was ≤ 3 cm from the pleural line, and centrally distributed abnormalities were present when the abnormality was > 3 cm from the pleural line. Dependent atelectasis was also noted and reported if present.

Statistical analysis

Categorical variables were described as percentages and frequencies, and continuous variables were presented as means and standard deviations. Comparison between categorical variables was conducted using Fisher's exact and Pearson's chi-square tests. A P value of <0.05 was counted as significant. We used IBM SPSS Statistics software (version 26) to run the statistical analysis.

3. RESULTS

Patients' clinical characteristics

A total of 44 adult patients were included in this study. The mean age was 27.48 ± 7.987 years, and 30 were male (68.2%). The mean hemoglobin level was 7.539 ± 1.3037 g/dl. The HbSS genotype was reported in 34 patients (77.3%) (Table 1).

Table 1 Patients' clinical characteristics

Variable		Frequency (N = 44)	Mean ± Std. Deviation
Age		44	27.48 ± 7.987 years
Hemoglobin		44	7.539 ± 1.3037 g/dl
			Percentage
Gender	Male	30	68.2%
	Female	14	31.8%
SCA Genotype	HbSS	34	77.3%
	HbSC	9	20.4%
	HbSB	1	2.3%

Abbreviation SCA: Sickle cell anemia, HbSS: Hemoglobin SS, HbSC: Hemoglobin SC, HbSB: Hemoglobin S beta thalassemia

Chest computed tomography (CT) findings

Consolidation was reported in 32 patients (72.7%), followed by cardiomegaly in 23 patients (52.3%) and GGO in 22 patients (50%). Airway involvement was not dominant; bronchiectasis was not reported in any patients. The distribution of abnormalities was lower lobe–predominant and limited to one or two lobes (Table 2). Fibrosis was reported in 14 patients (31.8%), as assessed by the presence of parenchymal scarring, subpleural reticulation, architecture distortion, traction bronchiectasis, volume loss, or honeycombing (Figure 1 and 2).

Table 2 Frequency of chest computed tomography (CT) findings

CT pattern	Frequency (n = 44)	Percentage
Ground glass opacities	22	50%
Interlobular septal thickening	11	25%
Mosaic attenuation	5	11.4%
Nodules	3	6.8%
Consolidation	32	72.7%
Thickened bronchovascular bundle	10	22.7%
Cavities	1	2.3%
Mediastinal/hilar lymphadenopathy	8	18.2%
Bronchiectasis	0	0%
Cysts	1	2.3%
Emphysema	1	2.3%
Pleural thickening	3	6.8%
Pleural effusion	16	36.4%
Pulmonary embolism	3	6.8%
Pneumothorax	1	2.3%
Fibrosis	14	31.8%

Enlarged pulmonary artery	11	25%
Cardiomegaly	23	52.3%
Atelectasis	16	36.4%
Distribution of abnormalities:		
Limited	23	52.3%
Diffuse	15	34.1%
Upper zone	4	9.1%
Lower zone	29	65.9%
Peripheral distribution	17	38.6%
Central distribution	4	9.1%

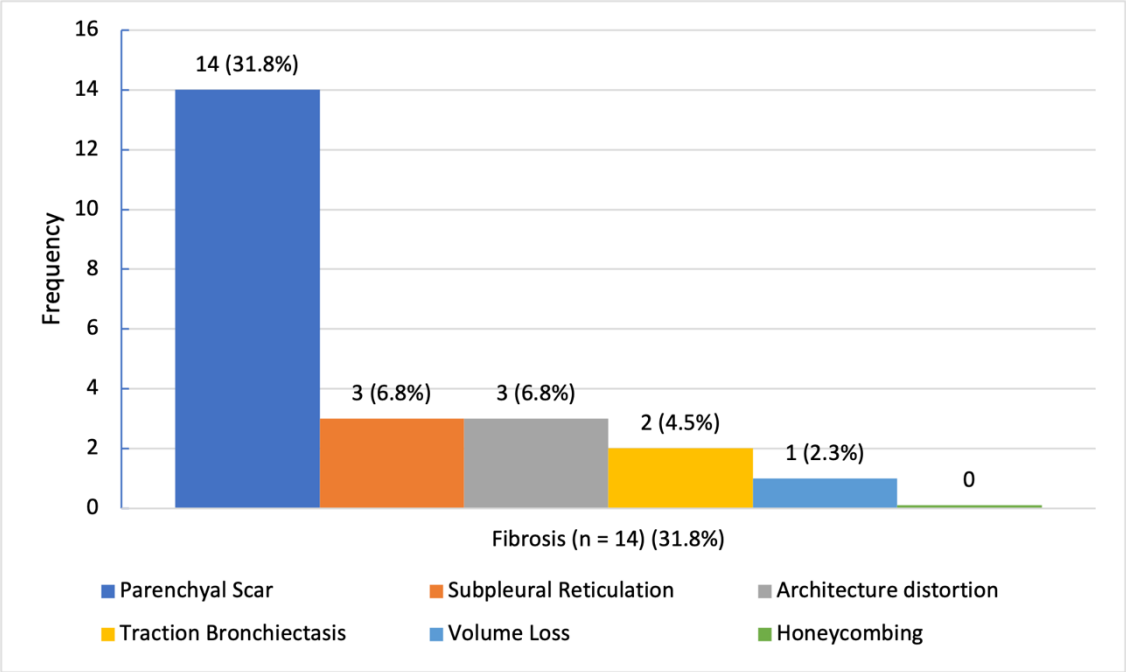

Figure 1 Frequency of fibrosis features.

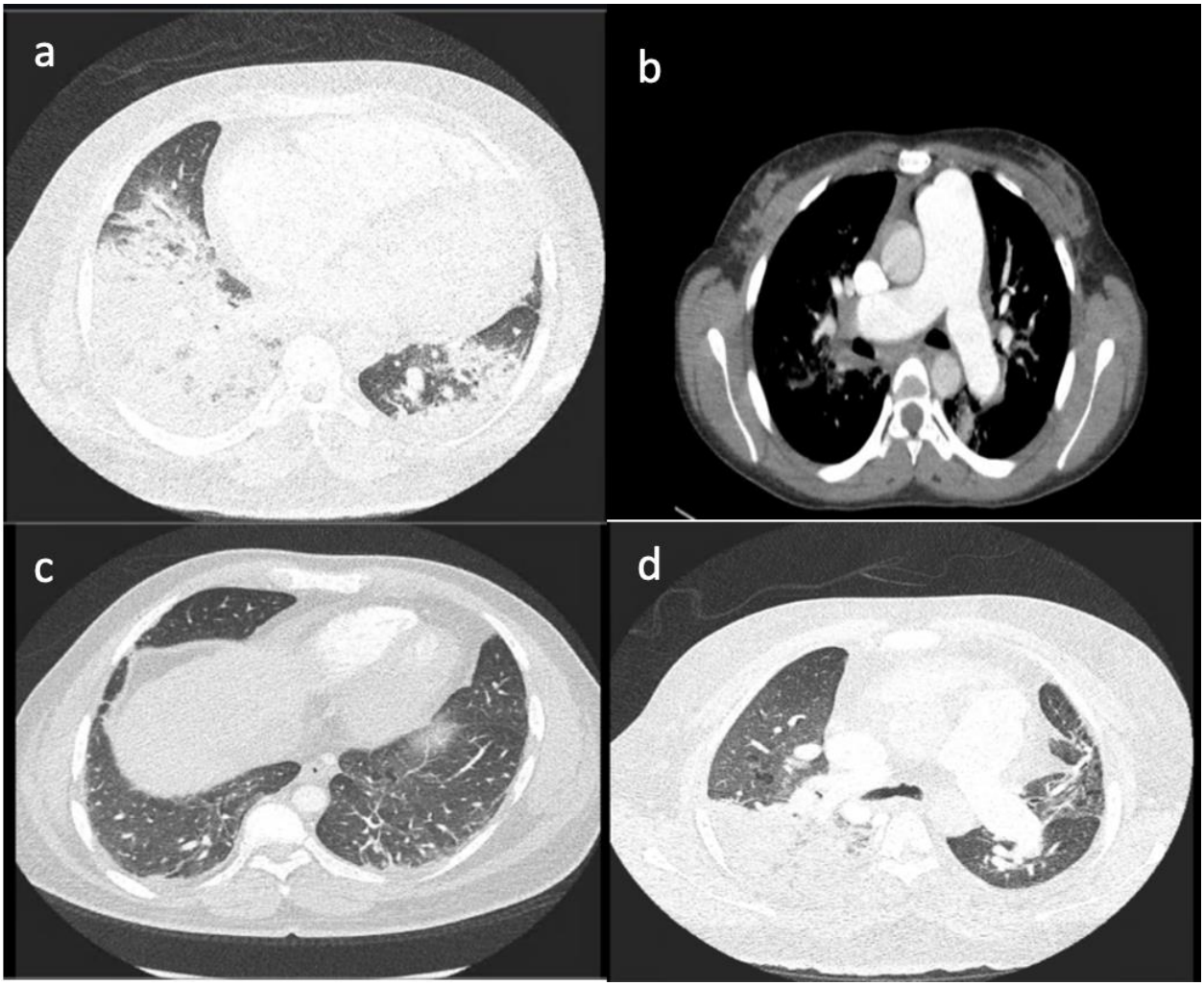

Figure 2 a) Lower lobe consolidation is noted bilaterally. b) Enlarged pulmonary artery as measured by pulmonary artery to aorta ratio (PA: A) > 1. c) Fibrosis features demonstrated by scattered parenchymal scarring bands. d) Fibrosis features demonstrated by volume loss and architectural distortion of the lingula, also right lower lobe consolidation is noted.

The relationship between gender and CT features was significant for consolidation and PE. In the CTs, 25 males (83.3%) and 7 females (50%) had consolidation (OR: 0.20, 95% CI: 0.048–0.828, P value = 0.032). PE was not present in the male group and was found in 3 female patients (21.4%) (P value = 0.027) (Table 3). The relationship between SCA genotypes and CT features was not statistically significant (Table 4).

Table 3 Relationships between gender and CT features

Variable (N = 44)		Gender				
		Male (n = 30)	Female (n = 14)	OR	95% CI	P value
Consolidation	Yes	25 (83.3%)	7 (50%)	0.200	0.048–0.828	0.032
	No	5 (16.7%)	7 (50%)			
Pulmonary embolism	Yes	0	3 (21.4%)	-	-	0.027
	No	30 (100%)	11 (78.6%)			
Fibrosis	Yes	9 (30%)	5 (35.7%)	1.296	0.338–4.968	0.738
	No	21 (70%)	9 (64.3%)			
Ground glass opacities	Yes	13 (43.3%)	9 (64.3%)	2.354	0.635–8.725	0.195
	No	17 (56.7%)	5 (35.7%)			
Mosaic attenuation	Yes	4 (13.3%)	1 (7.1%)	0.500	0.051–4.939	1.000

	No	26 (86.7%)	13 (92.9%)			
Pleural thickening	Yes	2 (6.7%)	1 (7.1%)	1.077	0.089–12.975	1.000
	No	28 (93.3%)	13 (92.9%)			
Mediastinal/hilar lymphadenopathy	Yes	5 (16.7%)	3 (21.4%)	1.364	0.276–6.737	0.695
	No	25 (83.3%)	11 (78.6%)			
Enlarged pulmonary artery	Yes	5 (16.7%)	6 (42.9%)	3.750	0.898–15.656	0.132
	No	25 (83.3%)	8 (57.1%)			
Cardiomegaly	Yes	14 (46.7%)	9 (64.3%)	2.057	0.556–7.605	0.276
	No	16 (53.3%)	5 (35.7%)			

Table 4 Relationships between SCA genotypes and CT features

Variable (N = 44)		SCA Genotype				
		HbSS (n = 34)	Non- HbSS (n = 10)	OR	95% CI	P value
Consolidation	Yes	24 (70.5%)	8 (80%)	1.667	0.300–9.272	0.702
	No	10 (29.5%)	2 (20%)			
Pulmonary embolism	Yes	3 (8.8%)	0	-	-	1.000
	No	31 (91.2%)	10 (100%)			
Fibrosis	Yes	10 (29.5%)	4 (40%)	1.600	0.370–6.921	0.701
	No	24 (70.5%)	6 (60%)			
Ground glass opacities	Yes	19 (55.9%)	3 (30%)	0.338	0.075–1.535	0.150
	No	15 (44.1%)	7 (70%)			
Mosaic attenuation	Yes	4 (11.8%)	1 (10%)	0.833	0.082–8.433	1.000
	No	30 (88.2%)	9 (90%)			
Pleural thickening	Yes	2 (5.9%)	1 (10%)	1.778	0.144–21.915	0.548
	No	32 (94.1)	9 (90%)			
Mediastinal/hilar lymphadenopathy	Yes	6 (17.6%)	2 (20%)	1.167	0.196–6.938	1.000
	No	28 (82.4%)	8 (80%)			
Enlarged pulmonary artery	Yes	9 (26.5%)	2 (20%)	0.694	0.124–3.904	1.000
	No	25 (73.5%)	8 (80%)			
Cardiomegaly	Yes	17 (50%)	6 (60%)	1.500	0.358–6.285	0.724
	No	17 (50%)	4 (40%)			

The relationship between the presence of fibrosis and consolidation was significant. Of the 14 patients with fibrosis, 7 (50%) had consolidation in their CT results, and of the 30 patients who did not have fibrosis, 25 (83.3%) had consolidation in their CTs (OR: 0.200, 95% CI: 0.048–0.828, P value = 0.032) (Table 5).

Table 5 Relationships between the presence of fibrosis and other CT features

Variable (N = 44)		Fibrosis				
		Present (n = 14)	No (n = 30)	OR	95% CI	P value
Consolidation	Yes	7 (50%)	25 (83.3%)	0.200	0.048–0.828	0.032
	No	7 (50%)	5 (16.7%)			
Pulmonary embolism	Yes	0	3 (10%)	-	-	0.540
	No	14 (100%)	27 (90%)			
Ground glass opacities	Yes	9 (64.3%)	13 (43.3%)	2.354	0.635–8.725	0.195
	No	5 (35.7%)	17 (56.7%)			
Mosaic attenuation	Yes	2 (14.3%)	3 (10%)	1.500	0.221–10.171	0.647
	No	12 (85.7%)	27 (90%)			

Pleural thickening	Yes	1 (7.1%)	2 (6.7%)	1.077	0.089–12.975	1.000
	No	13 (92.9%)	28 (93.3%)			
Mediastinal/hilar lymphadenopathy	Yes	1 (7.1%)	7 (23.3%)	0.253	0.028–2.288	0.402
	No	13 (92.9%)	23 (76.7%)			
Enlarged pulmonary artery	Yes	5 (35.7%)	6 (20%)	2.222	0.541–9.126	0.287
	No	9 (64.3%)	24 (80%)			
Cardiomegaly	Yes	8 (57.1%)	15 (50%)	1.333	0.372–4.785	0.659
	No	6 (42.9%)	15 (50%)			

4. DISCUSSION

Our study characterized the radiographic features of patients with ACS from the chest CT perspective. We found that the most common lung abnormality was consolidation, which is consistent with prior results (Dessap et al., 2014; Al-Sharydah et al., 2019). The mechanism of ACS is multifactorial, including a process of infection and infarction secondary to microthrombosis and fat embolism, both of which can present radiographically as airspace disease and are clinically difficult to distinguish (Vichinsky et al., 2000). In line with a prior report (Dessap et al., 2014; Al-Sharydah et al., 2019), we found that the dominant distribution of the consolidative patch was in the lower lung zones, a finding that perhaps relates to the perfusion gradient in normal lung anatomy (West et al., 1964). It is difficult to draw conclusions regarding the significant result of consolidation and the male gender. After performing a logistic regression analysis to adjust for confounders, we did not find a statistically significant association between consolidation and other variables. Conducting a larger study to examine this relationship is necessary for drawing conclusions about this finding.

The second most frequent imaging finding in our study was cardiomegaly, which was found in 52% of the cases. Hyperdynamic circulation in hemolytic anemia exerts a volume overload that results in high output status and leads to diastolic and systolic ventricular dysfunction with chronic heart failure (Wood et al., 2020). This event manifests radiographically as cardiomegaly, which is a frequent finding in these patients (Ramirez et al., 2014). In addition, pulmonary artery enlargement was noted in a quarter of our cases, and this finding probably indicates an increase in pulmonary artery pressure, which is not an uncommon complication in SCD (Gladwin et al., 2004). In SCD, pulmonary hypertension's pathophysiology (PH) is not completely understood, and it could be related to multiple mechanisms (group 5 PH). In addition, mechanisms contributing to PH development in SCD include pulmonary arterial hypertension (group 1 PH), PH due to left heart disease (group 2 PH), PH secondary to underlying lung diseases and/or hypoxia (group 3 PH), and PH due to pulmonary artery obstructions (chronic thromboembolic pulmonary hypertension; group 4) (Gordeuk et al., 2016). PH can be suggested by the gradual worsening of the respiratory status in SCD patients, along with signs of PH on physical examination and enlarged PA diameter on chest CT (Shen et al., 2014). Further evaluation of PH development in patients who show signs of PA diameter enlargement on CT images might have clinical significance (Klings et al., 2014). This evaluation can be performed by obtaining an echocardiogram; if it is suggestive of PH, right heart catheterization could confirm elevated PA pressure, and guiding treatment timely and properly would be crucial, as this morbidity can alter patients' clinical outcomes by increasing the risk of mortality (Savale et al., 2019).

Repeated lung parenchyma and microvascular injury can lead to a pathological trigger of a local fibrotic cascade (Weil et al., 1993). We found that a third of the patients had elements of pulmonary fibrotic changes on CT driven mainly by scattered parenchymal scars. Other features of pulmonary fibrosis—namely subpleural reticulation, traction bronchiectasis, architectural distortion, and volume loss—were noted in less than 7% of our cohort, which is lower than previous reports in SCD patients (Alves et al., 2016; Aquino et al., 1994; Lunt et al., 2014; Sylvester et al., 2006).

We reviewed the patients' first images during the study period, and we did not include follow-up images. It is possible that this process led to an underestimation of fibrosis that developed in subsequent images. The full picture of pulmonary fibrosis dominated by the presence of honeycombing, which pathologically represents the characteristic histology of usual interstitial pneumonia, was not seen in our cohort, and its prevalence in previous studies was low (Aquino et al., 1994; Ramirez et al., 2014; Wang et al., 2018; Lonergan et al., 2001). Fibrotic lung diseases in general include a wide variety of radiographic and pathologic features that are well characterized in the literature (Travis et al., 2013). Given the heterogeneity of SCD, fibrosis related to this condition is not expected to mimic other fibrotic interstitial lung diseases (ILD) from a radiologic or even pathologic perspective. Therefore, well-established pulmonary fibrosis might not be classically seen in SCD images, in particular the hallmark honeycombing changes of pulmonary fibrosis.

Although lung parenchymal changes in SCD might represents clinically significant findings (Klings et al., 2006; Sylvester et al., 2006). We did not correlate the CT findings with physiological lung dysfunction. Evaluating this correlation would be better assessed in prospective studies, and it would be of interest to examine the correlation between these fibrosis features and histological assessments to better understand the pathophysiology behind them. However, this approach may not be feasible in SCD patients. When making a clinical decision about obtaining a surgical lung biopsy in SCD patients with ILD, pulmonologists should weigh the risks and benefits of the procedure. Exposing patients to this intervention might pose an unjustified increased risk of cardiac and respiratory morbidities in the perioperative period to obtain a tissue sample for pathology assessment that might not lead to a change in the treatment plan. If other causes of ILD are highly suspected, it is most important to evaluate the patients' condition using clinical, laboratory, and radiographic data and if needed, bronchoscopy for cell count differential and cytology to assess for the alternatively suspected ILD diagnosis beyond SCD–related changes. We noted less fibrosis frequency in patients with consolidation, and this finding might be related to the active acute pathological process obscuring the visualization of fibrotic features. Follow-up images in non-ACS episodes would help to accurately examine the potential presence of underlying fibrosis.

SCD patients are at risk of PE because of their hypercoagulable state (Naik et al., 2013), and both fat and thrombotic events can increase mortality risk in SCD (Vichinsky et al., 2000). We observed PE in 3 patients (6.8%), which is lower than in previous reports (Dessap et al., 2014; Stein et al., 2006). The development of PE does not preclude the diagnosis of ACS, and indeed, pathological consideration of PE involvement in the pathogenesis of ACS is suggested (Weil et al., 1993). Given that not all the studies' images followed the pulmonary angiography protocol (33 cases; 75% with CTPA), underlying PE might have been missed, which could have led to the difference in PE frequency between male and female groups.

In addition, potential confounders in the female gender that might increase the risk of PE, such as pregnancy and the use of oral contraceptives, were not addressed. Using a contrast study protocol for every episode of ACS to check for PE would increase the risk of contrast-induced organ toxicity and pose a higher radiation dose than high-resolution CT chest, which is ideal for evaluating parenchymal process but does not offer clear visualization of the pulmonary circulation (Huda, 2007). Thus, using clinical judgment to decide which chest image modality to use can lead to an improper estimation of the prevalence of PE in SCD patients. The development of a clinical tool to help diagnose PE tailored to SCD patients is needed (Dessap et al., 2011).

Limitations

Our study described the radiographic appearance of lung changes during ACS, the findings that can contribute to the understanding of this condition. However, this study has important limitations: it was a retrospective study with a small sample size, and the significance of the findings might not be generalizable. In addition, our cohort was composed mainly of Saudi patients, and ethnic background may have affected the findings and their frequency. We did not examine the association between CT finding severity and physiological lung indices or cardiac assessments, so we were unable to examine this relationship. A prospective study would be more appropriate for evaluating such correlations on a long-term basis.

5. CONCLUSION

Acute inflammatory changes were the dominant finding in SCD patients presenting with ACS. Pulmonary fibrotic changes were observed in only one-third of the patients and were composed mainly of parenchymal scars denoting that the fibrotic process in SCD does not radiographically follow any of the well-characterized fibrotic lung diseases patterns. Cardiac involvement was evident in images by the presence of cardiomegaly and enlarged pulmonary artery diameter, which are common complications in patients with SCD.

Author contribution

R. Alsilmi (study supervision, conceptualization, methodology, data collection and processing, data analysis, manuscript original draft writing, editing and reviewing the final version)

Saeed. Alghamdi (methodology, data collection and processing, data analysis, manuscript original draft writing)

Salim. Alghamdi, R. Alshahrani, A. Alyoubi, O. Almassari, M. Alshaikhi (methodology, data collection and processing, manuscript original draft writing)

A. Barefah (conceptualization, methodology, editing and reviewing the final manuscript)

A. Ajlan, A. Eskander, F. Jabali (methodology, data collection, editing and reviewing the final manuscript)

M. Mustafa (methodology, editing and reviewing the final manuscript)

The final version of the manuscript version was read and approved by all the authors.

Ethical approval

The research ethics committee at the King Abdulaziz University Faculty of Medicine's Unit of Biomedical Ethics approved this study (Reference No. 619-20).

Informed consent

Obtaining an informed consent was waived by the ethical committee due to the retrospective nature of the study.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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