The etiology of most cases of acute chest syndrome (ACS) in sickle cell disease (SCD) is unknown. Although pulmonary fat embolism (PFE) is frequently found on autopsy, it is rarely considered in the differential diagnosis in pediatric patients. We conducted a study to determine if we could identify PFE in SCD patients with ACS, define the clinical and laboratory course of PFE, and determine if bronchoalveolar lavage is safe and useful in diagnosis of PFE. Twenty-seven SCD patients with ACS were evaluated and compared with 43 control patients. Serial tests (complete blood count, platelet count, nucleated red blood cells [NRBCs], chest x-ray, and oxygen saturations) were compared with steady-state results. Diagnosis of PFE was made by quantitative evaluation of pulmonary macrophages for intracellular fat. No serious complications from bronchoscopy were observed. In the study, the clinical course of the two groups was quite different. All PFE+ patients experienced bone pain and 11 of 12 had chest pain. In contrast, only 6 of 15 PFE− patients had bone or chest pain. Neurologic symptoms developed in 6 of 12 of the PFE+ group and in none of the PFE− group. Mean hospital days for PFE+ was 13 compared with 7 for PFE−. Laboratory studies in PFE+ showed a significant decrease in hemoglobin (−2 g, P < .05), platelet count (−293,000, P < .001), and an increase in NRBCs/100 white blood cells (+8.3, P < .001) compared with PFE−. These results indicate that when PFE is associated with ACS, it is characterized by a distinct clinical course, and that bronchial lavage is a safe and useful test in diagnosing PFE in patients with ACS.

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Study Populations

Sickle cell patients with ACS. Of the 90 children with SCD who were admitted to Children's Hospital Oakland for ACS between September 1991 and September 1993, 27 participated in the study. Entry criteria included the following: (1) physical findings consistent with acute pulmonary inflammation, (2) initial chest x-ray findings consistent with acute pulmonary disease involving at least one complete lung segment, (3) ability to obtain pulmonary macrophages for lipid analysis, and (4) the patient's willingness to participate. The mean age of these patients was 10 years (range 2 to 23 years). Ten children with SCD who were at least 2 months past an acute event were studied and represented the SCD control group. The mean age of these patients was 9 years (range 2 to 19).

Nonsickle cell patients. Eight children (mean age 4 years, range 1 month to 16 years) with a history of gastroesophageal reflux, esophagitis, and recurrent aspiration pneumonia were considered as positive, nonsickle cell, controls. Negative, nonsickle cell, control patients consisted of 25 children (mean age 2 years, range 1 month to 12 years) who underwent bronchoscopy as part of an evaluation for chronic pulmonary disease. The diagnosis in these patients included 4 patients with bronchial pulmonary dysplasia, 6 with acquired immune deficiency, 2 with respiratory syncytial virus pneumonia, 2 with cystic fibrosis, 2 with leukemia, 2 with idiopathic acute respiratory distress syndrome, and 7 with chronic infiltrates who had no evidence of gastroesophageal aspiration.

ACS Treatment Protocol

The treatment protocol for patients with ACS included hydration, at a maximum of 1 times maintenance, parenteral cefuroxime, and oral erythromycin. Clinical severity was assessed daily by physical examination, chest x-ray, blood oxygen saturation measured while patients were breathing room air, and a complete blood count (CBC), and platelet count. A clinical respiratory scoring system, as described by Emery et al., was used to quantitate clinical severity. Briefly, 0 = no respiratory distress, 1 = age adjusted tachypnea, 2 = tachypnea and retractions. A decision to transfuse was made by the attending physician based on an assessment of the patient's clinical course and laboratory parameters.

Laboratory Assessment

The laboratory findings during ACS were compared with the average results obtained during the patient's steady state. The CBC and indices, as well as the platelet counts, were determined on a Coulter Model STKS (Coulter Electronics, Hialeah, FL). Confirmatory manual platelet counts were determined by the Unopette method of Becton Dickinson (Mountain View, CA). Nucleated red blood cells (NRBCs) were determined by a manual technique (no. NRBCs/100 white blood cells [WBCs]). Arterial blood gas measurements were determined using an AVL 995 (AVL Scientific Corp, Roswell, GA). Oxygen saturations were determined using an N1000 Nelcor (Nelcor, Hayward, CA).

Respiratory Secretions

Bronchoscopy was performed in 49 patients using a flexible fiberoptic pediatric bronchoscope. All patients were monitored with a pulse oximeter and cardiac monitor during the procedure. The procedure was performed in the Pulmonary Function Treatment Room or in the Pediatric Intensive Care Unit, depending on the patient's clinical condition. All patients received supplemental blow-by oxygen. Patients were administered meperidine hydrochloride (1 to 2 mg/kg) and midazolam (.05 to .1 mg/kg) in preparation for bronchoscopy. Topical anesthesia with 2% lidocaine hydrochloride was applied to the nose and larynx. Bronchial lavage was performed with a 5-ml aliquot of sterile normal saline. The amount of final sterile solution instilled depended on the patient's size, and sample fluid recovery ranged from approximately 5 mL to 60 mL. The bronchoscope was inserted transnasally, advanced into the trachea, and wedged into a subsegmental bronchus of the involved lobe. After wedging, the sterile saline was infused and subsequently aspirated through a mucus specimen trap.

In 21 patients, sputum was collected after either inhalation of aerosolized saline or tracheal aspiration. When tracheal aspiration was performed, a nasopharyngeal polyethylene tube, which was attached to a 5-cc sterilized plastic bottle connected to a suction ball, was introduced into the trachea without anesthesia. Respiratory secretions were only evaluated if they contained columnar ciliated respiratory epithelial cells and pulmonary macrophages.

Quantitation of Intracellular Lipid

Secretions were suspended on a slide, fixed with formalin vapor, and stained with oil-red-O followed by hematoxylin. Intracellular lipid was evaluated according to a modification of the index proposed by Corwin and Irwin. Only samples containing pulmonary macrophage cells were evaluated. The amount of lipids per macrophage cell was graded from 0 to 4. The grades from 100 cells counted were summed and an index was obtained with a potential maximum of 400. The reported index represented the average of two computations performed by a single investigator on two separate occasions. Samples were coded so that the patient's diagnosis was not known. An index greater than 100 was considered positive.

RESULTS

Corwin Index of Lipid-Laden Macrophages

We stratified patients with sickle cell anemia and ACS into two groups based on their Corwin index. The PFE− group had a mean index of 130, range 100 to 208, and the PFE+ group had a mean index of 15, range 0 to 65. Nine of 15 of the PFE+ groups had 0 fat indexes. A 0 index was confirmed in all of the sickle cell patients studied in steady state. The control, nonsickle cell anemia patients, who had aspiration pneumonia had a mean index of 70, range 34 to 102. All but five of the 25 chronic nonaspiration pneumonia control patients had 0 for their Corwin index (mean index 3, range 0 to 22) (Fig 1).

Clinical and Laboratory Course

Although patients with ACS associated with PFE were similar in age and hemoglobin (Hb) phenotype to ACS patients without PFE, the degree of pulmonary decompensation, frequency of painful events before onset of ACS, changes in specific laboratory parameters, and the presence of neurologic dysfunction differed in each group (Table 1). The mean age of both groups was 11 years. Thirteen of 15 PFE− and 10 of 12 PFE+ cases had a diagnosis of homozygous sickle cell anemia. The remainder of the ACS patients had a diagnosis of sickle cell-hemoglobin C disease. A concomitant vasoocclusive crisis and chest pain appeared to be the characteristic presentation for the PFE+ group. A painful event localized to an extremity preceded or occurred simultaneously with every case of ACS associated with PFE. Chest pain occurred in 11 of 12 cases (92%) and severe respiratory
distress in 6 of 12 (50%). In contrast, the patients with ACS who were PFE− were less likely to present with a vasoocclusive crisis (6 of 15, 40% \( P < .01 \)) or chest pain (6 of 15, 40%, \( P < .05 \)), and only 2 of 12 (17%) patients experienced severe respiratory distress.

Central nervous system (CNS) symptoms were noted in 50% of the PFE+ patients. Four patients experienced lethargy and confusion that could not be attributed to narcotic utilization for pain. One patient, who experienced severe frontal headaches and confusion, had a negative computed axial tomography scan. A 17-year-old patient with sickle cell-hemoglobin C disease developed generalized tonic clonic seizures followed by opundation and confusion. A magnetic resonance image (MRI) of the brain showed four small vessel lesions. A 10-year-old boy experienced a sudden episode of weakness in the left leg that resolved spontaneously. His MRI was normal. In contrast, no patients in the PFE+ group experienced CNS symptoms.

The mean duration of hospitalization for the PFE+ patients with ACS (13 days, range 7 to 43) was significantly longer than for the PFE− patients (7 days, range 3 to 14, \( P < .05 \)). One patient who initially developed respiratory failure requiring prolonged mechanical ventilation later developed chronic lung disease, necessitating nocturnal oxygen supplementation. The laboratory data for all SCD patients with ACS is summarized in Table 2. The nadir values noted during ACS are compared with steady-state results. Changes in laboratory values in the PFE+ group were more extensive than in the PFE− group. Despite administration of oxygen in five patients during the time of blood sampling, the oxygen saturation decreased from a steady state of 98% to 91%. The PFE− group’s mean oxygen saturation on room air decreased less. The change in Hb, platelet count, and NRBC counts was significantly greater in the PFE+ group than in the PFE− group. The Hb decreased 2 versus 1 g/dL (\( P < .05 \)), platelets decreased by 293,000 versus 130,000/mm\(^3\) (\( P < .001 \)), and the NRBC count increased to 8 versus 0/100 WBCs (\( P < .001 \)).

The chest x-rays were more likely to show multilobe infiltrates with pleural effusions in the PFE+ group. Bilateral infiltrates occurred predominantly in the lower lobes in both groups. Diffuse acute respiratory distress syndrome-like pictures were noted in two of the PFE+ group.

After bronchoscopy, none of the 49 patients experienced severe complications or required postbronchoscopy-assisted ventilation. However, eight patients experienced transient problems. These included two episodes of transient laryngeal spasm that corrected with temporary use of a bronchodilator, and six transient episodes of oxygen desaturation corrected by supplementary oxygen. All but one of these was mild. One patient, while on mechanical ventilation, decreased his arterial saturation to 75%. Removal of the bronchoscope

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**Table 1. Comparison of the Clinical Characteristics of PFE+ and PFE− ACS Patients**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>PFE+ Patients (n = 12)</th>
<th>PFE− Patients (n = 15)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>3-23</td>
<td>3-19</td>
<td></td>
</tr>
<tr>
<td>Associated symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain crisis</td>
<td>12 (100%)</td>
<td>6 (40%)</td>
<td>( P &lt; .01 )</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11 (92%)</td>
<td>6 (40%)</td>
<td>( P &lt; .05 )</td>
</tr>
<tr>
<td>Neuro symptoms</td>
<td>6 (50%)</td>
<td>0 (0%)</td>
<td>( P &lt; .01 )</td>
</tr>
<tr>
<td>Respiratory distress score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.5</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>1-2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Transfusion therapy patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital days</td>
<td>10 (83%)</td>
<td>8 (53%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

* See text: 0, mild; 1, moderate; 2, severe.

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**Fig 1.** The amount of lipid found in pulmonary macrophages recovered from sickle cell patients with ACS and their controls. The lipid index is a semi-quantitative score of the amount of intracellular lipid found in pulmonary macrophages. The amount of lipid per cell was graded 0 to 4 with 100 consecutive pulmonary macrophages scored. The grades were summed resulting in an index. An index greater than 100 is considered positive. PFE+, SCD patients with ACS and fat embolism (12 patients). Aspiration Pneumonia, non-SCD patients with documented aspiration pneumonia (8 patients). PFE−, SCD patients with ACS without evidence of fat embolism (15 patients). Chronic Pneumonia, non-SCD patients with severe pneumonia without evidence of aspiration (25 patients). SS Steady State, SCD patients who were at least 2 months past an acute event (10 patients). (-1 Mean. Values in parentheses indicate index range.)
corrected the hypoxia. The bronchoscope was reintroduced with temporary use of 100% oxygen in this patient and the remainder of the procedure was uneventful.

**DISCUSSION**

The clinical and laboratory course of PFE has been well characterized in patients who have had severe trauma. Overt clinical manifestation consistent with PFE has been reported in 10% to 50% of cases. Typically, patients develop respiratory distress and fever 1 to 3 days after injury. Nonfocal neurologic findings such as acute onset of confusion, delirium, and changing consciousness subsequently occur in 60% of cases. Anemia and or thrombocytopenia have been reported in 50% of cases. This classic presentation most likely represents one end of the spectrum of this disease because prospective studies have shown subclinical PFE in up to 50% of patients who have major fractures.

The frequency of PFE in patients with SCD is not known. It is likely that tissue infarction, which can occur in the intramedullary cavity of a bone during a vaso-occlusive event, could generate an equivalent source of fat to that which accompanies a major fracture. When attempts to identify evidence of PFE during postmortem studies of patients with SCD have been made, the incidence of PFE has varied from 13% to 75%.

### Table 2. Comparison of the Clinical Characteristics of PFE+ and PFE− ACS Patients

<table>
<thead>
<tr>
<th></th>
<th>PFE+ patients (n = 12)</th>
<th>PFE patients (n = 15)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-Ray*</td>
<td>Multilobe = 11</td>
<td>Multilobe = 8</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>O2 Saturation % Acute/Baseline</td>
<td>(Δ - 7)</td>
<td>(Δ - 4)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb g/dL Acute/Baseline</td>
<td>6.6/8.6</td>
<td>7.4/8.4</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Platelets Acute/Baseline</td>
<td>200/493</td>
<td>326/456</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>NRBCs per 100 WBCs Acute/Baseline</td>
<td>84/1</td>
<td>2/2</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

* 7/12 PFE+ patients had effusion; 2/15 PFE− patients had effusion.

in SCD. However, it is quite likely that PFE is a common cause of ACS because almost half of the patients studied had findings consistent with PFE.

Several investigators have suggested a relationship between recurrent PFE and chronic lung disease in patients with SCD. Weil et al commented that in addition to vascular obstruction, the release of free fatty acids from the fat emboli could damage cell membranes and lead to injury within the pulmonary microvasculature. Infusions of free fatty acids into the pulmonary circulation has been associated with hypoxemia, bronchoconstriction, and increased pulmonary artery pressure. These physiologic changes may be mediated in part by conversion of fatty acids to vasoactive substances and by their oxidation and subsequent generation of free radicals. We hypothesize that one cause of chronic restrictive lung disease in patients with SCD may be secondary to vascular damage resulting from free fatty acids released from fat emboli.

Bronchocle alveolar lavage (BAL) appears to be a rapid, specific method for identification of PFE. Chastre et al evaluated the usefulness of bronchocle lavage to diagnose PFE in patients who had suffered severe trauma. Large amounts of intracellular fat in pulmonary macrophages were found in cases of fat embolism and in suspected cases, later confirmed by autopsy. None of the patients in the control group were positive for bronchocle alveolar fat. Vedrinne et al suggested that bronchocle lavage is not specific for fat embolism and may result in false-positive results, especially during sepsis, lipid infusions, and hypertriglyceridemia. However, Corwin and Irwin found the specificity of lipid-laden alveolar macrophages increases when fat content within the cells obtained by bronchocle lavage is quantitated. Our method was based on Corwin's and resulted in similar findings as those of Chastre et al.

Although BAL appears to be a specific test for PFE in SCD, there is no alternative method except for tissue biopsy for confirmation. Elevated urine fat and serum lipase are found in over 50% of all cases studied and are too sensitive to be of use. The diagnostic usefulness of fat in the blood has not been critically evaluated. The clear separation noted between PFE+ patients and controls supports the specificity of BAL.

Fiberoptic bronchoscopy appears to be a safe technique and few complications have been reported. In a survey of 24,000 fiberoptic bronchoscopy procedures, Credle et al found that, except for laryngospasm caused by inadequate
anesthetic, risks were slight. Recent application of fiberoptic bronchoscopy to seriously ill immunocompromised patients confirms the safety and low morbidity of this procedure.\footnote{25,26,55} Our results suggest that fiberoptic bronchoscopy is a safe procedure in patients with SCD who have ACS and that it is an effective method to obtain pulmonary microphages for analysis of intracellular lipid.

Optimal treatment for ACS in SCD will likely be based on establishing a specific diagnosis. The investigation for PFE including bronchoscopy may be indicated in a subset of patients with characteristic clinical and laboratory findings. In PFE\textsuperscript{+} cases, the efficacy of interventions such as steroids, simple or exchange transfusion, plasma infusions, or heparin should be evaluated.\footnote{27,28,29,30} Because infectious agents may precipitate both pain crises and PFE, we use antibiotics in all patients with ACS.

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REFERENCES

41. Chmeh B, Bertles JF: Hemoglobin S/C disease in a pregnant
Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia

E Vichinsky, R Williams, M Das, AN Earles, N Lewis, A Adler and J McQuitty