Simultaneous Occurrence of Rib Infarction and Pulmonary Infiltrates in Sickle Cell Disease Patients with Acute Chest Syndrome

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In order to determine if a relationship exists between rib infarction and the acute chest syndrome (ACS) in sickle cell disease patients, bone scans were reviewed in 55 episodes in 38 patients with pain of suspected osseous origin. A bone scan was positive for thoracic bone infarction if abnormally increased or decreased uptake was present in ribs, sternum or thoracic spine. Radiographs were considered to be positive for ACS if there was pulmonary infiltrate or pleural effusion in the absence of laboratory or clinical evidence of bacterial pneumonia. ACS by chest x-ray was present in 22 episodes, 21 of which showed evidence of infarction of the bony thorax on bone scan. Thoracic bone infarction occurred in the absence of chest x-ray changes in only 11 episodes. This association between bone infarction and radiographic ACS was statistically significant ($p < 0.001$, Fisher's exact test). A strong association exists between ACS and infarction of the bony thorax. It is possible that bone infarction leads to pain, hypoventilation and the clinical picture of ACS.

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In sickle cell diseases, pulmonary infiltrate may occur in the absence of infection. The infiltrate may be accompanied by pleuritic chest pain, pleural effusion, fever and/or chest wall tenderness. This constellation of signs and symptoms, seen in both children and adults, has been termed the acute chest syndrome. In the absence of clear evidence of bacterial infection or pulmonary emboli, it has been attributed to nonembolic infarction of lung parenchyma (*1–6*).

In a preliminary report, we described the simultaneous occurrence of rib infarction and the acute chest syndrome, in a small, select group of children and adults with sickle cell syndrome (*7*). We now report the bone scan and chest x-ray findings in a much larger group of sickle cell patients.

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MATERIALS AND METHODS

We reviewed all bone scans performed in sickle cell patients between January, 1987 and December, 1990 at a large children's hospital and an adjacent adult academic hospital that have a combined sickle cell disease care program. Thirty-eight patients were included: seven under 12 yr of age; 20 between 12 and 18 yr; and 11 over 18 yr. Patients under 18 yr of age were studied at the pediatric hospital and those over 18 at the adult hospital with one 18-yr-old patient studied at both. A total of 86 bone scans were reviewed in this retrospective study.

Because of possible persistence of bone scan uptake from one study to another, bone scans performed within 90 days of each other were grouped and considered as a single episode. In order to take into account the expected duration of radiographic and scintigraphic findings, a chest radiograph was considered to be appropriately timed in relation to a bone scan for analytic purposes if it was performed no more than 90 days before the bone scan and no more than 5 days after the bone scan. When seven episodes without appropriate timed chest radiography were eliminated, there were 55 episodes with one or more bone scans that could be evaluated. In the results that follow, only one chest radiograph was performed more than three weeks prior to the corresponding bone scan, and no chest radiograph was performed more than three days after the corresponding bone scan. Seven of the 55 episodes were reported in an earlier publication (*7*).

A history of chest pain was recorded in 16 of the episodes in pediatric patients and in 13 episodes in patients over 18 yr of age. Clinical signs and symptoms and bacteriologic data did not suggest that bacterial or other infectious pneumonitis accompanied any of the 55 episodes. The primary complaints for which the bone scans were performed are listed in Table 1.

The bone scans and chest radiographs were reviewed separately, each by the author most skilled in the interpretation of that technique, without knowledge of the clinical history or the result of the other imaging study. The bone scan study was considered to be positive for infarction of the bony thorax if any bone scan within the 90-day grouping demonstrated abnormally increased or decreased uptake in the ribs, sternum or thoracic spine. Chest radiographs were considered to demonstrate evidence of acute chest syndrome if pulmonary infiltrate or pleural

TABLE 1
Presenting Skeletal Complaints and Bone Scan Findings in 55 Episodes Imaged by Bone Scan and Chest Radiograph

Presenting complaint	Thorax only	Uptake on bone scan: Thoracic and nonthoracic abnormalities*	Uptake on bone scan: Nonthoracic abnormalities only*	Normal
Chest pain only	2 (2)	7 (6)	2 (2)	0
Chest and nonthoracic skeletal pain	2 (2)	13 (4)	1 (0)	2 (0)
Nonthoracic skeletal pain	1 (1)	6 (5)	7 (5)	10 (7)
Pain site not stated		1 (1)		1 (1)
Total	5 (5)	27 (16)	10 (7)	13 (8)

*Symmetrically increased uptake in the metaphyses of long bones has been excluded.
Numbers in parentheses indicate episodes studied at the pediatric hospital.

effusion was present. Atelectasis alone was not considered adequate radiographic evidence of acute chest syndrome. If either modality met these criteria for abnormality, appropriately timed studies using the other modality were reviewed to determine if any were also abnormal.

Fisher's exact tests were used for statistical comparisons between groups and corrected for multiple comparisons when appropriate.

RESULTS

Bone scans showed evidence of infarction of the bony thorax in 32 of 55 episodes. In many episodes, scintigraphic abnormalities typical of bone infarction were present elsewhere in the skeleton (Table 1). The presence or absence of infarction of the bony thorax was closely related to the presence or absence of radiographic findings of pulmonary infiltrates and pleural effusion. On radiographs, pulmonary infiltrate was present in 19 episodes, pleural effusion without infiltrate in one and both in two. In 21 of these 22 episodes with abnormal radiographic findings, there was scintigraphic evidence of infarction of the ribs, sternum or thoracic spine (Table 2). In 11 other episodes, there was bone scan evidence of infarction of the bony thorax in the absence of infiltrate and pleural effusion on chest radiographs. In the remaining 22 episodes, the chest radiograph was normal and the bone scan was also normal in the thorax. This association between the occurrence of thoracic skeletal abnormalities on bone scan and the presence or absence of radiographic evidence of the acute chest syndrome on the chest radiograph was highly significant ($p < 0.001$, Fisher's exact test). The data were then re-analyzed three times: (1) after elimination of four patients with nonpulmonary bacterial infection (three with Salmonella osteomyelitis and one with Staphyloccal osteomyelitis), (2) considering only the first episode in each patient and (3) considering only the first episode in each patient and eliminating the four with nonpulmonary infection. The occurrence of osseous infarction in the thorax and the acute chest syndrome were again closely related in the pediatric patients and in the mixed group of pediatric and adult patients (Tables 3 and 4).

TABLE 2
Comparison of Bone Scan and Chest Radiograph Findings in All 55 Episodes

		Rib infarction* by bone scan: +	–	
Acute chest syndrome by chest radiograph	+	21	1	22
	–	11	22	33
		32	23	55

*Includes thoracic spine and sternal infarction.
$p < 0.001$, Fisher's exact test.

The presence or absence of chest pain was also related to the presence or absence of bone scan changes in the bony thorax in the 53 episodes where adequate historical data were available ($p < 0.001$, Fisher's exact test). In addition, the presence or absence of chest pain was related to the presence or absence of the plain radiographic changes of the acute chest syndrome ($p = 0.004$, Fisher's exact test). Abnormal chest radiographs consistent with the acute chest syndrome were obtained in five of seven episodes where bone scan abnormalities were noted in the absence of chest pain. In contrast, in none of the five episodes where chest pain was noted in the absence of bone scan changes was there radiographic evidence of the acute chest syndrome. Examples of abnormal bone scans and radiographs are depicted in Figures 1 and 2.

DISCUSSION

Pulmonary complications in sickle cell disease patients include bacterial pneumonia, multiple thromboemboli and embolization of necrotic fat and marrow (*2,8,9*). However, there is seldom unequivocal evidence of these

TABLE 3
Results of Statistical Analysis (Fisher's Exact Test) for Various Subgroups

	Pediatric hospital	Adult hospital	All
All studies	$p < 0.001$ $n = 36$	$p = 0.04$ $n = 19$	$p < 0.001$ $n = 55$
Infection excluded	$p < 0.001$ $n = 33$	$p = 0.07$, ns $n = 18$	$p < 0.001$ $n = 51$
Multiple studies excluded	$p < 0.001$ $n = 27$	$p = 0.12$, ns $n = 11$	$p < 0.001$ $n = 38$
Infection and multiple studies excluded	$p < 0.001$ $n = 24$	$p = 0.12$, ns $n = 11$	$p < 0.001$ $n = 35$

complications and more often a diagnosis of the acute chest syndrome is made. Although radiographs may be consistent with either bacterial pneumonia or the acute chest syndrome, clinical and laboratory evidence of bacterial infection is seldom present (*2,3,6,8*). Acute chest syndrome is occasionally fatal, accounting for up to 25% of hospital mortality in sickle cell patients (*10,11*). In this study, we have limited the scope of our investigation to the imaging findings, i.e., radiographic and scintigraphic evidence of involvement of the bony thorax, pleura and pulmonary parenchyma.

On bone scintigraphy, bone infarcts may be seen as areas of decreased uptake, decreased uptake surrounded by increased uptake or increased uptake depending on the size and age of the infarct. Although these findings are not specific for bone infarction, sterile bone infarction is much more common than osteomyelitis as the cause of the bone scan abnormalities (*12,13*).

In 43 of the 55 episodes in this study (78%), the bone scan of the thorax and chest radiographs were either both positive or both negative. In 11 of the 12 remaining episodes, the bone scan was positive but the chest x-ray was normal. Statistical analysis confirmed that thoracic bone infarction, demonstrated on bone scan, was closely associated with the presence of pulmonary infiltrate and/or pleural effusion. When all 55 episodes were considered, this association was statistically significant for episodes in the pediatric population (Table 2), the adult population and the combined adult and pediatric population. Reanalysis of the data after exclusion of scans performed in the presence of nonpulmonary infection and again after exclusion of all episodes except the first in each patient yielded similar results. The results continued to be highly significant for episodes studied in the combined populations and in the pediatric population (Tables 3 and 4). However, when the data were reanalyzed with a smaller sample size, the results of the adult population were no longer statistically significant (Table 3). Statistically significant associations were also noted between chest pain and bone scan abnormalities in the thorax and between chest pain and the radiographic changes of the acute chest syndrome.

TABLE 4
Comparison of Bone Scan and Chest Radiograph Results in 35 Episodes (After Elimination of Multiple Studies and Patients with Infection)

		Rib infarction* by bone scan		
Acute chest syndrome by chest radiograph		+	−	
	+	13	1	14
	−	5	16	21
		18	17	35

*Includes thoracic spine and sternal infarction.
$p < 0.001$, Fisher's exact test.

An abnormal bone scan finding may persist for months. For that reason, we considered all bone scans performed within a 90 day period as a single data point. In actuality, 98% of the bone scans were performed no more than three days before or three weeks after the comparison chest radiograph. It is unlikely that either a significant pulmonary infiltrate will disappear in three days or that a significant focus of abnormal bone physiology will disappear in three weeks. Eleven of 33 patients who had normal chest radiographs had abnormal bone scans of the bony thorax. It is possible that some of these abnormal bone scan findings are the residue of bone infarcts that occurred at some time in the past, reflecting prior events unrelated to the acute clinical and chest radiographic findings. It is also possible that a few of the positive bone scans associated with positive chest x-rays may also have been caused by prior bone infarcts. However, the strong statistical significance of the data suggests that this is not an important confounding variable.

In 27 of the 32 episodes with bone scan abnormalities in the thorax, additional bone scan abnormalities were present elsewhere in the skeleton. Of 22 episodes of acute chest syndrome by chest x-ray, not only were 21 associated with bone scan abnormalities in the thorax, but 17 had abnormal uptake at other skeletal sites. Thus, patients with the acute chest syndrome usually have multifocal bone involvement. All bones are prone to damage by sickling because of the low shear rates engendered by

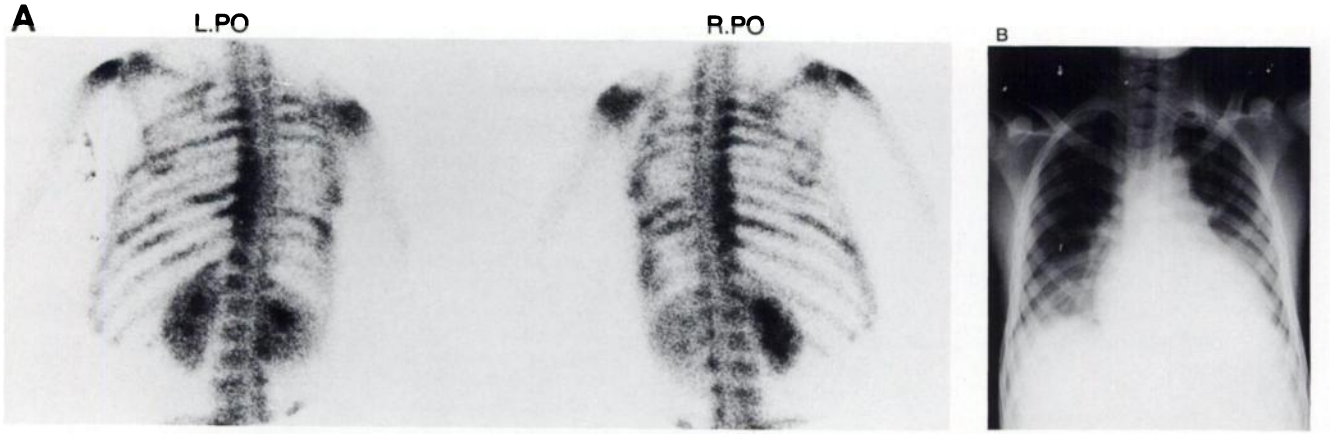

FIGURE 1. (A) A 14-yr-old male with sickle cell disease (Hgb SS). On the bone scan there are multiple areas of increased and decreased uptake in the ribs and multiple thoracic vertebra with increased uptake. (B) Chest radiograph demonstrates bilateral lower lobe infiltrates.

the sinusoidal blood flow through bone that favors adhesion of sickled cells either to vascular endothelium or to other sickled cells (*14–16*).

Three explanations can be given for the high degree of association between thoracic bone infarction and radiographic abnormalities in the acute chest syndrome: (1) the two pathologic processes are causally related; (2) the two pathologic processes occur in the same population simultaneously but do not represent cause and effect; and (3) the findings are the result of selection bias. In the latter case, we are unaware of any factors in patient selection that would confound the results.

The acute chest syndrome has long been thought to be due to in situ red cell sickling in the lung vasculature, possibly as a consequence of hypoventilation with subsequent infarction of lung parenchyma (*1–3,5*). As a pos-

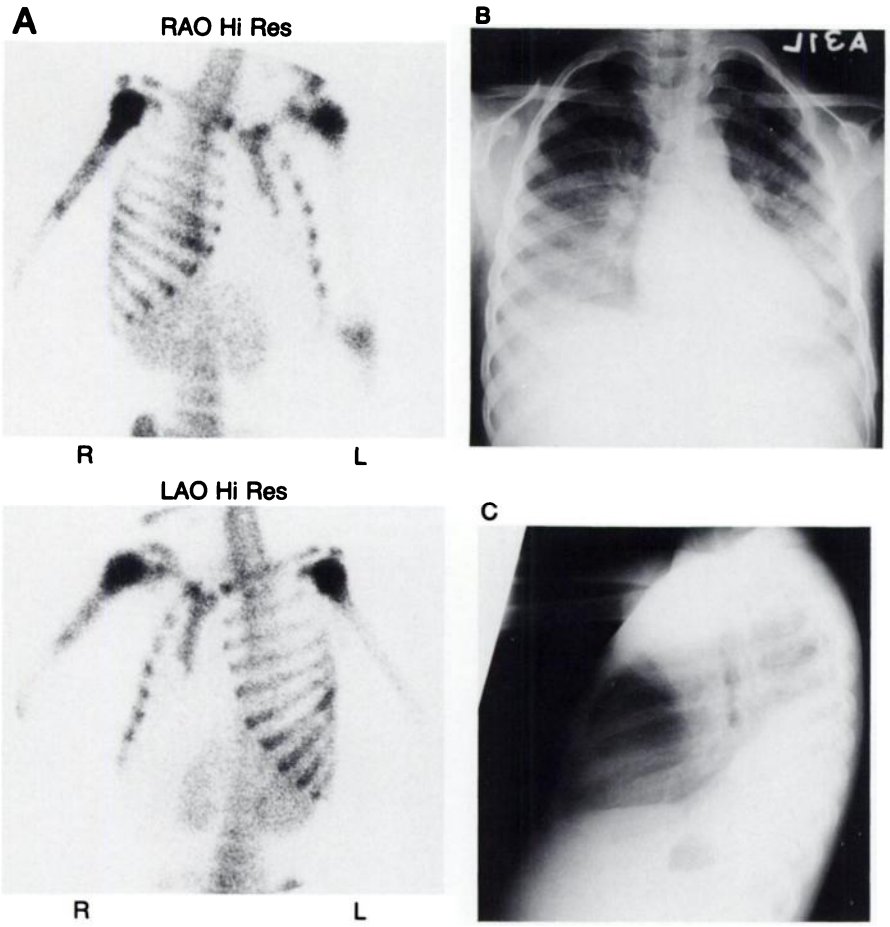

FIGURE 2. (A) An 11-yr-old male with sickle cell disease (Hgb SS). Short segments of two ribs on the right and one on the left have increased uptake. (B) There is also an extended area of increased uptake in the right proximal humerus. (B, C) Posterior-anterior and lateral chest radiographs demonstrate extensive lower lobe infiltrates.

sible causal relationship, one may hypothesize an extension of this chain of events: bone infarction (usually in the ribs) is followed by chest pain and, in some cases, by inflammation of the overlying pleura. These events in turn may lead to hypoventilation and pulmonary infiltrate by mechanisms that are yet to be elucidated. The effusions may be a direct result of pleural inflammation or pulmonary injury. If this hypothesized chain of events is correct, prevention of hypoventilation in sickle cell patients with chest pain becomes an important therapeutic goal. A prospective study that evaluates this approach is currently in progress.

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