Natural History and Distribution of Bone and Bone Marrow Infarction in Sickle Hemoglobinopathies

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Methods: Over a period of 11 y, 50 patients (22 males, 28 females; age range, 8 mo to 22 y) presenting with sickle cell-associated bone pain underwent 93 sequential examinations with 99mTc-sulfur colloid bone marrow scanning and 99mTc-diphosphonate bone scanning. Multiple examinations were performed on 21 patients. The number and distribution of total acute, healed, and nonhealed infarcts by location were recorded on a skeletal homunculus. Results: For this population, the total number of sites of bone and bone marrow infarction was 464. Of these, 175 were classified as acute by clinical and scintigraphic findings. There were a total of 61 nonhealed sites and 162 healed sites. Conclusion: Knowledge of the distribution and natural history of sites of bone and bone marrow infarction is of considerable clinical and diagnostic import in the ongoing evaluation and treatment of sickle hemoglobinopathies. Key Words: sickle cell disease; skeletal scintigraphy; infants and children


Sickle cell disease has numerous consequences; one of the most characteristic is injury to the skeletal system. Necrosis of bone marrow, bone infarction, osteomyelitis, and avascular necrosis are common complications in sickle cell patients (1, 2). Bone and bone marrow infarction is a common cause of acute morbidity in patients with sickle hemoglobinopathies (3) and may be a precursor to acute chest syndrome (4). Although the pathogenesis of the vascular occlusion leading to an infarct is not entirely clear, vasoocclusion of the marrow is considered to be one of the main culprits in sickle cell pain crises (3, 5, 6). These vasoocclusive crises are a significant source of pain and suffering in children with sickle cell disease (7).

The signs of acute infarction can include warmth, tenderness, erythema, and swelling over the site of vasoocclusion (8). However, these clinical signs are nonspecific and may also occur in acute osteomyelitis. Thus, recognition of bone marrow infarction often relies on the use of imaging modalities. MRI has not been found to have the specificity or sensitivity of radionuclide studies (9). Patients with sickle cell disease retain a significant amount of hematopoietic activity in their appendicular skeleton, allowing for bone marrow reticuloendothelial visualization using 99mTc-sulfur colloid (SC) (10). Bone scanning with 99mTc-phosphate complexes reveals increased tracer uptake in new bone that is repairing recent infarcts or decreased uptake when the vascular supply has been completely compromised (10). A combination of bone marrow scintigraphy and immediately sequential skeletal scintigraphy has been shown to accurately identify sites of osteomyelitis (11).

Although the identification of bone and bone marrow infarction in patients with sickle cell disease has often been discussed in the literature, little information has been published on the distribution, epidemiology, and repair (or lack thereof) of these infarcts. Keeley and Buchanan (8) described the distribution of infarcts in the appendicular skeleton of their population of patients, correlating those infarcts with clinical symptomatology, laboratory data, and scan findings. We undertook a retrospective review of 50 patients presenting over an 11-y period with symptoms of vasoocclusive pain crisis and analyzed companion bone marrow scans and bone scans to gain a more thorough understanding of the number, distribution, and healing patterns of bone marrow infarcts in sickle cell disease.

MATERIALS AND METHODS

Fifty patients (22 males, 28 females; age range, 8 mo to 22 y) with sickle cell disease underwent 93 sequential 99mTc-SC and 99mTc-methylene diphosphonate examinations (performed
within a 24-h period). Twenty-nine of the patients were evaluated only once, and 21 had multiple studies (between 2 and 5). SC radionuclide bone marrow imaging was performed after the intravenous administration of 10.36 MBq/kg $^{99m}$Tc-SC. The minimum dose for marrow scintigraphy was 74 MBq $^{99m}$Tc-SC, and the maximum was 666 MBq. Whole-body scintigraphy followed by static scintigrams of 300–500,000 counts were obtained. Triple-phase bone scanning was performed after the intravenous administration of 10.36 MBq/kg $^{99m}$Tc-methylene diphosphonate. The minimum dose for skeletal scintigraphy was 74 MBq $^{99m}$Tc-methylene diphosphonate, and the maximum was 666 MBq. Whole-body and selected 500,000- to 1,000,000-count views were then obtained.

These 2 examinations were performed diagnostically when patients with sickle cell disease presented with symptoms suggesting the presence of osteomyelitis. An acute infarct was diagnosed if decreased uptake was seen on the bone marrow scan and abnormal uptake associated with increased activity was seen in a clinically symptomatic area on the flow- and tissue-phase images of the bone scan (Fig. 1). An old or healing infarct was diagnosed if decreased uptake was seen in a non-symptomatic area on the bone marrow scan (Fig. 1D). A healed infarct was diagnosed if an infarct was no longer evident on a later bone marrow scan of a patient who had multiple studies. A nonhealed infarct was diagnosed if an infarct was present on more than 1 scan and remained present on the last scan obtained for the patient. No patients with a diagnosis of osteomyelitis were included in the study.

**RESULTS**

Infarcts were found in nearly every bone in the body. For this population, the total number of sites of bone or bone marrow infarction was 464. Of these, 175 were

**FIGURE 1.** Evaluation of 12-y-old boy with acute onset of right upper arm pain and swelling. (A) Early anterior skeletal-tissue-phase scintigram of upper torso immediately after administration of $^{99m}$Tc-methylene diphosphonate reveals increased soft-tissue activity in right arm. (B) Delayed anterior skeletal scintigram of upper torso reveals increased radionuclide uptake in right humerus. (C) Anterior bone marrow scintigram reveals corresponding absence of bone marrow tracer activity in right humerus. (D and E) Anterior whole-body bone marrow (D) and anterior whole-body bone (E) scintigrams indicate acute infarct of right humerus. Healing infarcts in proximal and distal right tibia and healed bone marrow infarct in left radius are also seen.
FIGURE 2. Total number of infarcts.

FIGURE 3. Number of acute infarcts.

FIGURE 4. Number of healed infarcts.

FIGURE 5. Number of nonhealed infarcts.
classified as acute by clinical and scintigraphic findings. There were 61 nonhealed sites and 162 healed sites. Figure 2 shows the total number of bone marrow infarcts by location; Figure 3, the number of acute infarcts; Figure 4, the number of healed infarcts; and Figure 5, the number of nonhealed infarcts. The number of acute and total infarcts in patients with the sickle cell phenotype is shown in Figure 6.

We found that the interval between scans was not truly representative of the time for infarct healing. The scan interval was determined by patient symptomatology.

DISCUSSION

These figures show that, similar to the findings of Keeley and Buchanan (8), the humerus, tibia, and femur were by far the most common sites of infarction, although there were also many infarcts in the pelvic bones. It is possible that the increased length of the nutrient arteries supplying the marrow in the long bones makes them more susceptible to occlusion. Acute symptomatic infarcts were nearly twice as common in the femur and tibia, suggesting that humeral infarcts may occur with less apparent clinical symptomatology.

We also found infarcts to heal at a surprisingly high frequency. One hundred sixty-two of the 464 total infarcts (34.9%) eventually healed for patients who had multiple studies. There were several sites at which infarcts formed again after healing, but we could not determine whether sites of previous infarction were more susceptible to infarction than sites that had never experienced infarction.

O’Conner et al. (12) reported that because of high fetal hemoglobin levels, neonates do not often experience bone marrow infarction. Our findings were consistent with that report; the youngest child in our study was 8 mo old. Acute dactylitis, sometimes one of the first manifestations of bone marrow infarction in children, was found only once in our population, although evidence of nonsymptomatic antecedent infarction of the metacarpals has been found numerous times (I).

Because bone marrow and skeletal scanning was performed only during episodes of symptomatology, the time between studies (for patients who had multiple studies) varied considerably (months to years). We had hoped to be able to present data concerning a time course for healing infarcts; however, the data were too variable to allow meaningful analysis.

We initially considered performing only bone marrow scintigraphy but were concerned that the short tissue phase of $^{99m}$Tc-SC would not allow identification of soft-tissue or joint abnormalities, and the inherent lack of anatomic resolution precluded the use of $^{99m}$Tc-SC by itself. Because red marrow in our patients was preserved in the appendicular skeleton long after the normally anticipated centripetal recession of red marrow in healthy individuals, the $^{99m}$Tc-SC dose that allowed adequate evaluation of the appendicular skeleton was equal to the amount of tracer administered for skeletal scintigraphy. Most of these patients had various degrees of hepatomegaly and variable splenic function and tracer uptake in the kidneys, presumably because of extramedullary hematopoiesis.

Patients with osteomyelitis presented with a different set of scintigraphic findings (persistent uptake on the bone marrow scintigram and increased uptake on the skeletal scintigram) but were excluded from this study.

CONCLUSION

Knowledge of the location and distribution, as well as the healing patterns, of bone marrow infarcts as revealed on bone marrow and skeletal scintigrams of patients with sickle cell disease may be valuable in its treatment and management.

REFERENCES


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