CLINICAL SCIENCES

DIAGNOSTIC NUCLEAR MEDICINE

Evaluation of Bone-Marrow Scanning with Technetium-99m Sulfur Colloid in Pediatric Oncology


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Eighty-six technetium-99m sulfur colloid (Tc-SC) bone-marrow scans in 56 pediatric oncology patients were reviewed. The distribution of the sulfur colloid was similar to that in adult bone marrow in normal children older than 10 yr, and involved progressively more marrow of the extremities in normal children under 10 years of age. After irradiation or chemotherapy there was an extension of the Tc-SC to peripheral marrow sites. There was also diminished uptake of the tracer in sites corresponding to irradiated areas. In most patients there was recovery of these defects by 6 mo after completion of therapy. Tumor replacement of the marrow was reflected in the scans, and the extent of the scan defect paralleled the course of the disease. In four patients, despite normal bone scans and radiographs, marrow-scan abnormalities due to tumor replacement were present and confirmed by needle aspiration and/or biopsy. In two other patients, the marrow-scan abnormality preceded radiographic and histologic evidence of tumor metastasis. Two patients who responded clinically showed persistent defects; biopsy in one revealed fibrosis. Technetium-99m sulfur colloid bone-marrow scanning appears to be a sensitive monitor of marrow alteration caused by metastases, irradiation damage, or tissue fibrosis in children receiving treatment for cancer.


Bone-marrow aspiration and biopsy are the accepted methods to document marrow replacement by malignant tumors. Because of the focal nature of tumor involvement within the marrow, these procedures may miss the specific site of metastasis. This limitation may be avoided by whole-body bone-marrow imaging, which offers a convenient and sensitive method to view the whole-body distribution of marrow and to monitor its changing pattern with age, stress, and disease.

Technetium-99m sulfur colloid (Tc-SC) particles are widely used for reticuloendothelial system (RES) imaging, mainly liver and spleen. Although only about 5–10% of the injected material localizes in the bone marrow (1), this quantity is sufficient for adequate imaging with a gamma camera. The value of bone-marrow scanning in adults with var-

<table>
<thead>
<tr>
<th>TABLE 1. DIAGNOSIS AT REFERRAL</th>
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<tbody>
<tr>
<td>Neuroblastoma</td>
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<tr>
<td>Hodgkin's disease</td>
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<tr>
<td>Wilms' tumor</td>
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<tr>
<td>Non-Hodgkin diffuse lymphomas</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
</tr>
<tr>
<td>Anemia</td>
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<tr>
<td>Miscellaneous neoplasms</td>
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<td>Total</td>
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ious diseases, and in children with sickle cell disease, has been established (2,3), but the usefulness of Tc-SC for bone-marrow scanning in children with tumors has not been adequately studied. This study reports on the normal bone-marrow distribution in children and the changes resulting from tumor involvement, chemotherapy, and radiation.

MATERIALS AND METHODS

Eighty-six bone-marrow scans on 56 children were available for evaluation. Some children had serial scans during various phases of their disease. All had either known or suspected malignancies, and their established or presumptive diagnoses are listed in Table 1. The four patients with anemia were found to have underlying malignancies.

The dosage of Tc-SC was calculated according to an approximation of Webster’s formula (4) with the adult (older than 15 yr) dose being 10 mCi. All patients had a routine eight-view liver-spleen scan before bone-marrow imaging. On completion of the liver-spleen scan, the camera’s detector was centered over the pelvis anteriorly or posteriorly and the time required for 200,000–300,000 counts was noted. Subsequent images over lower back, thighs, legs, posterior (and occasionally anterior) chest, shoulders, and skull used the same time as the pelvis. Forearms were not imaged routinely. The scintillation camera was equipped with a low-energy all-purpose parallel-hole collimator.

For evaluation of the bone-marrow scan data, other diagnostic studies were performed, including radiographs, Tc-99m HEDP or -MDP, whole-body bone scans, gallium-67 citrate whole-body scans, and bone-marrow aspirations and biopsies. In some cases, excisional biopsy or tumor resection established the diagnosis. Correlative information was also obtained from surgery and/or autopsy.

<p>| TABLE 2. BONE-MARROW DISTRIBUTION (83 STUDIES*) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>PF</th>
<th>MF</th>
<th>EF</th>
<th>EF + PT</th>
<th>EF + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 2 (N - 10)</td>
<td>—</td>
<td>—</td>
<td>2(1C)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2 - 5 (N - 17)</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>1(1CR)</td>
<td>7(2C,1R,2CR)</td>
</tr>
<tr>
<td>5 - 10 (N - 22)</td>
<td>—</td>
<td>5</td>
<td>10(1C,1CR)</td>
<td>6(1C,4R,1CR)</td>
<td>1(1R)</td>
</tr>
<tr>
<td>10 - 15 (N - 19)</td>
<td>5(1C)</td>
<td>6(1C)</td>
<td>2(1C,1R)</td>
<td>3(1C,2R)</td>
<td>3(1C,2R)</td>
</tr>
<tr>
<td>15 - 20 (N - 15)</td>
<td>4(1C)</td>
<td>3</td>
<td>1</td>
<td>4(4C)</td>
<td>3(2C,1R)</td>
</tr>
</tbody>
</table>

PF = proximal femurs only (less than ½)
MF = mid-femurs only
EF = entire femurs
EF + PT = entire femurs and proximal tibiae only
EF + ET = entire femurs and entire tibiae
C = on chemotherapy, or off for less than 3 months
R = radiation therapy
CR = chemotherapy and radiation
* Three patients with no discernible bone-marrow activity have been excluded from this table.

RESULTS

Normal distribution. The distribution of the bone marrow in lower extremities in 83 studies is detailed in Table 2. Three studies are excluded from the table because they did not show marrow activity. When the findings from Table 2 are summarized, the normal distribution of bone marrow in various age groups appears as follows. In children under 2 yr, bone-marrow activity is present throughout the femurs and tibiae (Fig. 1). Between ages 2 and 5, marrow activity is evident in entire femurs but only proximally in tibiae (Fig. 2). Marrow activity is seen in most of the femurs in children between ages 5 and 10 years. After age 10, the distribution is similar to that in adults, being confined to the proximal third or less of the femur (Fig. 3). There was always

FIG. 1. Normal TcSc bone-marrow scan in a 1-year-old, showing marrow activity throughout lower extremities. There is slightly more activity at ends of long bones, probably because of increased vascularity of epiphyseal plates.
activity. The visualization of marrow in the femoral head was variable, but normally it would be the same—whether present or absent—on both sides. There was always some lung uptake of Tc-SC, but the pattern was inconsistent. The intensity of lung uptake could not be correlated with liver function tests, tumor type, degree of marrow involvement, the patient’s immune status, form of therapy, chest radiographs, or the scanning technique.

Effect of chemotherapy and radiation. It is evident from Table 2 that chemotherapy and radiation had a definite effect on the distribution of Tc-SC in the bone marrow. Invariably, patients on chemotherapy showed peripheral extension of the tracer into the marrow of the long bones.

In 14 of 86 studies, defects in the bone marrow were observed, and these corresponded to known radiation ports. Figures 4 and 5 show bone-marrow scans on a 7-year-old patient with Hodgkin's disease before and after radiation therapy. The study performed after mantle radiation shows decreased activity in the thoracic vertebrae as well as peripheral extension of the Tc-SC into the tibiae. Of four patients who had radiation therapy and followup bone-marrow scans, two showed functional recovery of the bone marrow by 6 mo (Fig. 6). In one patient after radiation therapy to left hemipelvis, the marrow scan showed absent activity in the region of radiation port, but 2 days later a Tc-99m MDP bone scan was completely normal (Fig. 7).

Tumor replacement. Tumor replacement was di-

FIG. 2. Normal bone-marrow scan in a 3-year-old. Activity is confined to femurs and proximal tibiae.

FIG. 3. Normal bone-marrow scan in a 13-year-old, showing adult distribution with marrow activity mainly in proximal femurs. There is symmetrical uptake in femoral heads.

FIG. 4. Normal bone-marrow scan in a 7-year-old with Hodgkin's disease, before initiation of any therapy. Bone marrow is confined to femurs.
chemotherapy, followup marrow and bone scans (Figs. 9C and 9D) are normal except for some peripheral marrow extension. In most patients, this was the usual pattern—the remission of the disease was accompanied by improvement in the bone-marrow picture. On the other hand, patients with pro-

FIG. 5. Follow-up bone-marrow scan in patient of Fig. 4. After mantle radiation and chemotherapy, there is absent marrow activity in thoracic vertebrae, with peripheral extension all the way to distal tibiae. This was typical of patients treated with radiation and/or chemotherapy.

FIG. 6. (A) bone-marrow scan after radiation therapy, showing reduced activity in thoracic vertebrae. (B) repeat scan 6 mo later demonstrates some return of function.

gnosed by focal or diffusely decreased or absent activity in the bone marrow. Tumor involvement of the marrow was evident in 20 of 86 studies. In 17 of these cases, presence of tumor in the marrow was confirmed by aspiration and/or biopsy. In the remaining three, indirect evidence was obtained from radiographs and other nuclear medicine procedures. Figure 8 is a bone-marrow scan on a 3-year-old with non-Hodgkin lymphoma, showing focal areas of decreased uptake in femurs and tibiae. Figure 9A is a scan from a patient with neuroblastoma, consistent with diffuse bone-marrow involvement with very little uptake. Marrow aspiration confirmed the presence of neuroblastoma cells. As noted earlier, there is more activity at the ends of long bones in the region of the epiphyseal plates. The bone scan on this patient was also grossly abnormal (Figure 9B). After intensive radiation therapy, bone scan (C) is normal but marrow scan (D) clearly shows marrow defects in region of radiation port.

FIG. 7. (A) preoperative Tc-99m MDP bone scan, and (B) Tc-99m sulfur colloid marrow scan. Bone scan shows obstruction at ureter-vesical junction from pelvic rhabdomyosarcoma. After radiation therapy, bone scan (C) is normal but marrow scan (D) clearly shows marrow defects in region of radiation port.

FIG. 8. Tc-SC marrow scan of femurs and tibiae showing focal areas of decreased activity in 3-year-old patient being worked up for anemia and suspected malignancy. Marrow aspiration before scan was negative. After the scan, repeat biopsy was consistent with histiocytic lymphoma.
FIG. 9. (A) Diffusely decreased bone marrow in a patient, age 2, with stage IV neuroblastoma, suggesting generalized bone-marrow involvement. Most prominent marrow activity is in region of epiphyseal plate. (B) Tc-99m MDP bone scan in the same patient, showing extensive bony metastases. (C) Repeat marrow scan is normal after intensive chemotherapy. (D) Bone scan is also normal after therapy.
gressive disease showed marrow defects either unchanged or worsened. Four patients with neuroblastoma had abnormal marrow scans but normal bone scans and radiographs.

In two patients in our series, the bone-marrow scan abnormalities persisted even though the patient was in remission clinically. Figure 10A and B shows bone-marrow scans from a 12-year-old girl with Hodgkin’s disease. The defects in femur and tibia were persistent over 6 mo. Gallium scans of the lower extremities (Figure 10C and D) showed somewhat decreased uptake in the areas of marrow abnormalities. A marrow aspiration was consistent with fibrosis without evidence of Hodgkin’s disease. Clinically, she has been in remission for the past 18 mo.

Among the 56 patients, the bone-marrow scan was the first study to locate disease in two patients. The one whose scan is shown in Fig. 8 was being evaluated for anemia and possible malignancy. Initial bone-marrow biopsy was negative, but after the marrow scan showed focal defects, the biopsy was repeated and was consistent with histiocytic lymphoma.

**DISCUSSION**

Since Engstedt et al (5) first described the feasibility of using radiolabeled colloidal particles for reticuloendothelial (RE) bone-marrow imaging, there have been several reports in the literature on the value of this examination for various hematologic and other conditions (6–10). It has been shown that in normals and in most pathologic conditions (excepting certain types of depressed erythropoiesis) the distribution of the RE marrow parallels that of erythropoietic marrow (11–14). The RES imaging agent, Tc-99m sulfur colloid, is the most practical radiopharmaceutical for the qualitative evaluation of bone marrow in pediatric patients with oncologic problems because of its ready availability, low radiation dose, and ability to image liver and spleen simultaneously. The particle size does not appear to be of much consequence. As discussed by McIntyre (14), the percentage of administered dose localizing in bone marrow is the same for gold-198 colloid (particle size 3–5 μm) and Tc-SC (300–2000 μm). The findings of Coupal et al. (15) were similar when they compared distributions of Tc-SC (particle size < 800 μm) and Tc-99m stannous chloride (particle size > 800 μm) in patients with liver disease. We have used commercial kits, and have seen no evidence of free pertechnetate in our studies (no urinary bladder activity in pelvic views).

The normal distribution of bone marrow in children has been described by Price and Reis (16). Our findings are in agreement with theirs and indicate that children over the age of 10 yr have adult bone-marrow distribution, i.e. activity localized in proximal femurs only. In addition, we have defined the bone-marrow distribution of sulfur colloid in various age groups under the age of 10 (Table 3). In all age groups, the normal marrow scans showed symmetrical activity in the femoral heads. Asymmetric uptake in the femoral heads signified disease on the side with decreased activity, consistent with a previous report in adults (17).

It is well known that in children there is increased localization of the bone-seeking tracers in the region of the epiphyseal plates. This is due to the increased hydration and vascularity of the growing bone (18–19). We have seen similar findings in the bone-marrow scans, although not consistently. Most of the time increased activity was around the knee, which is consistent with previous observa-

![FIG. 10. Bone-marrow scans (A, B) showing defects in left femur and tibia in patient (age 12) with Hodgkin's disease. Although patient was in remission clinically, these defects were unchanged over six months. Gallium scan over these areas (C, D) was normal—in fact, there seemed to be less gallium uptake in left tibia than in right. Marrow biopsy showed evidence of fibrosis.](image-url)
tions (20). Increased vascularity as a cause is further confirmed by the observation that there is increased marrow activity at the sites of recent fractures in adults (21).

In our series there was some extension of bone marrow peripherally in patients receiving chemotherapy. This could be secondary to compromised hematopoiesis caused by the chemotherapeutic drugs (8). Although most of our patients did not consistently show evidence of granulocytopenia, some degree of anemia was usually present. Henry et al. (8) have indicated that in adults on chemotherapy, the peripheral extension of bone marrow was an early sign of toxicity, and after this extension the patient's tolerance of chemotherapy was poor. In our pediatric patients, this was not found to be the case, and the reason for the discrepancy is not clear.

Although Sykes et al. (22) have shown that permanent aplasia of the sternal marrow can be produced by total radiation doses of 3000 rads or more, the exact dose required to produce permanent marrow hypo- or acellularity remains unknown (23,24). The radiation dose in our patients who showed radiation-port defects varied from 2000 to 4000 rads. The two patients who showed recovery of marrow function after radioablation had received less than 3000 rads. This is consistent with the findings of other investigators (20,25); however, they do not mention the time course. In our patients the recovery was seen by 6 mo, which is earlier than reported in patients after total nodal irradiation (26), and perhaps this indicates better regenerating capabilities in the marrow of children.

Bone scanning has been reported to be a sensitive method of diagnosing changes in a radiation port (27). In one of our patients, however, who received 2500 rads to pelvis, the radiation changes were obvious on the marrow scan, although the bone scan was normal. The cytoidal dose for mature bone and cartilage is probably in the range of 5000 rads or more (28), which is higher than that required to render bone marrow acellular. This may explain the findings in our case, but bone-scan abnormalities have been noted in regions receiving radiation doses much lower than 5000 rads (27). Another explanation may be that since the bone is a much more dynamic organ in growing children than in adults (18,19), the changes produced by small radiation doses may not become apparent because of a rapid and pronounced reparative process. In any case, it appears that a bone-marrow scan may be a more sensitive indicator of local radiation changes, but more studies are needed to establish this fully.

Neoplasms metastatic to bone marrow appear as areas of focal or diffuse defects because of replacement of the normal functioning marrow with tumor cells (6,29). Occasionally, the marrow scans are positive even with normal bone scans and radiographs (30). We had four such patients, all of whom had neuroblastoma in the bone marrow confirmed by aspiration and/or biopsy. This finding probably indicates the specificity of the marrow scanning, not the insensitivity of bone scan and radiography, when the tumor is confined to marrow space. However, we did have two patients in whom the marrow scan was the first study to locate the diseased organ.

Although the bone-marrow scans parallel the course of the underlying disease processes, there were two patients in our series who were in remission clinically but showed persistent focal defects in the marrow. After chemotherapy, when the neoplastic killing is complete, usually the remaining normal hematopoietic precursor cells proliferate rapidly, and the marrow becomes normal as documented by marrow scans and aspirations. Marrow defects may persist, however, because of necrosis, infarct, fibrosis, recurrence of tumor, etc. In one of our patients, the biopsy showed fibrosis.

The limitations of Tc-SC bone-marrow scans include their inability to evaluate lower thoracic and upper lumbar vertebrae because of interfering liver or spleen activity, or through poor uptake in skull, ribs, and forearms. A diffusely abnormal marrow scan is not specific, since this can be seen in myelofibrosis as well as in generalized tumor involvement (7,29). The difficulty of measuring blood supply to the marrow militates against the use of Tc-SC to quantify bone-marrow function.

Despite these limitations, Tc-SC is currently the best tracer available for evaluation of bone-marrow function in children with malignancies.

ACKNOWLEDGMENT

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REFERENCES


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