Multifocal Skeletal Uptake of Labeled Leukocytes: Infection Versus Tumor Metastasis

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DESCRIPTION OF CASE

A 31-yr-old white man presented at the Mayo Clinic with diffuse skeletal pains, a mild productive cough, an 18-kg weight loss, and diarrhea. The patient had been well until 3 mo prior to this visit, at which time he had been hospitalized for epididymitis; 1 mo later he had undergone rectal surgery for an anal fissure and had a postoperative abscess.

One week postoperatively, he was again seen as an outpatient for evaluation of severe pain in his left hip and lower back. Radiographs of his hips, pelvis, and spine were negative. The diagnoses of left trochanteric bursitis and musculoskeletal low back pain were made, and he was given a local injection of bupivacaine (Marcaine). Three weeks prior to the present visit, he had been seen by another physician for upper respiratory symptoms. A chest radiograph showed right lower lobe pneumonia. He was treated with erythromycin for 10 days and then with ciprofloxacin hydrochloride (Cipro). His medical history also included a splenectomy (1976), epididymitis (1979), and an abcessed tooth (February 1989). He had a 20-yr history of smoking one to two packs of cigarettes a day.

At the present admission, the patient was afebrile and ill-appearing; he moaned with every movement. Fine crackles were noted in the right midlung. Admission laboratory data included normal values for the complete blood cell count and chemistry group. Radiographs and computed tomography of his chest showed an infiltrate in the right lower lobe posteriorly, consistent with pneumonitis. The admission diagnosis was pneumonitis, diarrhea, and skeletal pains of uncertain cause, to be evaluated.

Bronchoscopy revealed scattered mucopurulent secretions, predominantly on the right side. No endobronchial changes were noted. The standard blood cultures, sputum cultures, urethral cultures, and fungal serologic tests were negative as were serologic tests for *Chlamydia* and *Legionella*, tuberculin tests (PPD), angiotensin-converting enzyme (ACE), and assay for antibody to human T-lymphotropic virus (anti-HTLV III). An echocardiogram was negative. Stool cultures and stool examinations for ova and parasites and for *Clostridium difficile* were negative. Colonoscopy, including random mucosal biopsies, was nondiagnostic. Small bowel biopsy and radiographs and 72-hr fat excretion were normal. The chest radiographs remained unchanged over a 3-wk period. A radiograph of the pelvis was negative.

A whole-body scan with indium-111-labeled leukocytes (^{111}In-WBC) was performed in search of an occult infectious process. The autologous leukocyte-enriched preparation was labeled by the oxine method. The injectate contained 321×10^6 leukocytes (75% polymorphonuclear cells, 2% bands, 7% lymphocytes, 16% monocytes), 221×10^6 erythrocytes, and 621×10^6 platelets. Labeling efficiency was 96%. The volume injected was 5.8 ml and contained 489 μCi of ^{111}In. At 24 hr postinjection, the most striking abnormality was irregular uptake in the axial skeleton with prominent foci of increased uptake in the spine, ribs, and pelvis. There was marked hepatomegaly and increased focal uptake in the left subdiaphragmatic region, consistent with known accessory spleens. The impression was widespread bone marrow and skeletal metastasis or, less likely, infection (Fig. 1).

A bone scan with technetium-99m-labeled hydroxymethylene diphosphonate (^{99m}Tc-HDP) (Fig. 1) revealed multiple foci of increased uptake in the calvarium and the upper sternum and degenerative changes in the cervical spine. A mild irregularity in uptake in several posterior and anterior ribs was noted. It was thought that, because of the focal abnormality in the skull, ribs and sternum, skeletal metastasis should be considered. A bone marrow aspirate showed the presence of foreign cells suggestive of metastasis. Bone marrow biopsy showed the marrow to be virtually replaced by metastatic tumor cells (Fig. 2) consistent

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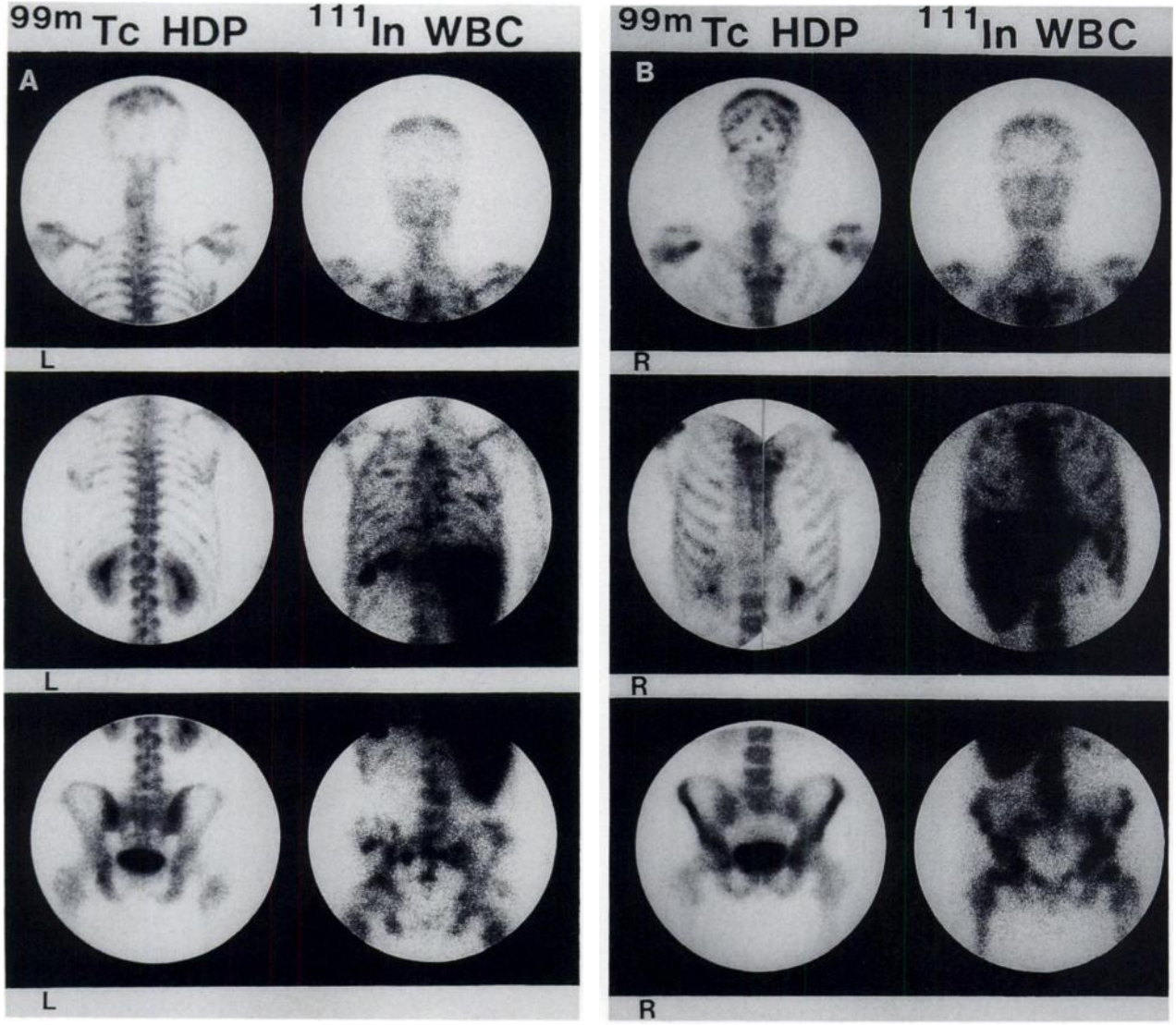

FIGURE 1
Multiview whole-body scintigrams showing posterior (A) and anterior (B) views of axial skeleton and proximal long bones. In each set, *right* is scintigram with ^{111}In-labeled leukocytes and *left* is corresponding ^{99m}Tc-HDP bone scintigram.

with small cell carcinoma of the lung. The diagnosis of metastatic small cell carcinoma of the lung was made. After a negative computed tomography scan and magnetic resonance imaging of the brain, chemotherapy was started.

DISCUSSION

During the initial work-up, this patient was thought to have an infectious process; however, final confirmation of this was not achieved. The ^{111}In-WBC scan was ordered to assist in the search for an occult infection. This scan showed multiple focal skeletal abnormalities which raised the question of a widespread infection, perhaps involving bone marrow and bone. However, this was not consistent with the clinical picture, and the question of skeletal and bone marrow metastasis was raised. This shifted the diagnostic effort away from infection.

The whole-body ^{99m}Tc-HDP bone scintigram showed only a few foci of abnormal uptake in bone, but their location in mostly trabecular bone of the skeleton supported the diagnosis of metastasis. This was finally proven by examination of the bone marrow. Bone marrow metastasis occurs early in small cell carcinoma of the lung and is found in 17%–23% of patients during pretreatment staging (*1–3*).

An ^{111}In-WBC scan performed after injection of an autologous leukocyte-enriched labeled blood cell preparation normally shows uniform uptake in the bones of the axial skeleton, in proximal long bones, and in the periarticular regions of the appendicular skeleton. This pattern is thought to represent uptake of labeled cells (platelets, erythrocytes, and leukocytes, probably in this

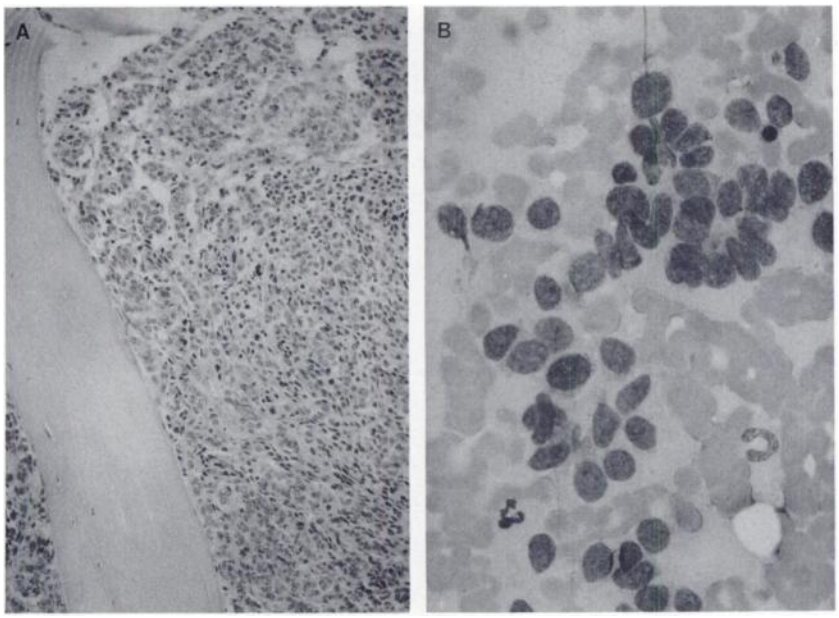

FIGURE 2
(*A*) Bone marrow biopsy, showing replacement of bone marrow by islands of tumor cells. (Wright's stain; ×160.) (*B*) Bone marrow aspirate, showing abundant malignant cells. (Hematoxylin and eosin; ×650.)

order of affinity) or of free ^{111}In in the erythrocyte precursors and reticuloendothelial cells in the bone marrow. Similar bone marrow uptake is seen when ^{111}In-labeled platelets, erythrocytes, or purified leukocytes are given alone or when $^{111}InCl_2$ is injected.

Focal abnormal uptake on an ^{111}In-WBC scintigram, as either a photopenic (cold) or an intense (hot) spot, in bone can result from bone marrow replacement by tumor metastasis. In the case of a photopenic lesion, tumor cells which do not show tracer uptake replace the bone marrow. In this case, the scintigram is interpreted like a bone marrow scan with ^{99m}Tc-sulfur colloid. If the standard ^{99m}Tc bone scintigram is abnormal at the same site, this suggests that there is bone involvement through the endosteum. In the case of a hot spot on the ^{111}In-WBC scintigram, one would suspect that there is tracer uptake by the tumor. Again, the ^{99m}Tc-HDP bone scintigram could be normal or could show a hot spot by the same mechanism as above.

In the case described here, there was a mixed pattern of focal increase and decrease in uptake on the ^{111}In-WBC scan with matched or mismatched focal uptake on the HDP bone scan, suggesting that there were definite foci of uptake of ^{111}In by the tumor. There was no evidence of metastasis in the predominately compact bone of the appendicular skeleton on either scan.

Although ^{111}In-granulocyte scintigraphy has become a well-established method for detection of occult infections and inflammatory processes, uptake by tumor is an occasional reason for confusion. Reports vary as to the sensitivity, specificity, and accuracy of ^{111}In-WBC scans for detection of infection; values of 88%, 90%, and 89%, respectively, have been achieved (*4*) and even high values (98%) when a three-phase bone scintigram also was used (*5*). Sporadic case descriptions (*5–16*) and, recently, several more systematic reviews (*17–20*) of ^{111}In-WBC localization in tumors have appeared in the literature.

In four reports that specifically examined the use of ^{111}In-WBC in patients with tumors (*17–20*), the findings varied widely. In one report (*18*), only 1 of 117 cancer patients had a positive scan; in another study (*20*) 6 (12%) of 51 patients with known tumor had a positive scan. Schmidt et al. (*19*) observed tumor uptake of ^{111}In-WBC in 10 (40%) of 25 patients with malignant neoplasms. Lamki et al. (*17*) reported that, of 61 cancer patients studied for fever of unknown origin, 21 (34%) had abnormal localization of ^{111}In-WBC in neoplasms without clinical evidence of infection. Table 1 summarizes the reported cases in which ^{111}In-WBC localized in tumors. The mechanism underlying the uptake of leukocytes by tumor has been speculated on but is not completely understood. The following factors have been considered:

1. High blood-pool activity in the tumor and slow tracer disappearance from the blood, especially with highly vascular neoplasms, may contribute to tumor-associated activity. However, Fortner et al. (*20*) did not find significantly increased cardiac blood-pool activity or femoral vessel activity in cases with tumor uptake.
2. Some tumor uptake may be related to free indium in the plasma. When released from the cell, ionic indium binds immediately to transferrin. The ^{111}In-transferrin complex was proposed as a possible tumor imaging agent by Goodwin et al. (*21*). However, only a small fraction of the indium is in the plasma (*22,23*).
3. Indium-111-WBC localization in tumors and lym-

TABLE 1
Summary of Reported Cases in Which ^{111}In-WBC Localized in Tumors

Reference	No. of patients	Fever*	Primary site*	Localization			
				Tumor	Lymph nodes	Bones	Elsewhere
(6)	1	?	Thigh	+	−	−	−
(11)	1	?	Lung	−	−	Foot	−
(8)	4	?	?	−	−	−	Liver
	1	?	?	−	−	−	Liver
	1	?	Gallbladder	+	−	−	+
(7)	1	+	Prostate	−	−	+	−
	1		Hodgkin's	−	−	+	−
(9)	1	?	Sigmoid	+	−	−	−
(10)	1	?	Prostate	−	−	+	−
(12)	1	?	Astrocytoma (necrotic)	+	−	−	−
(13)	1	−	Cecum	+	−	−	−
(14)	2	?	Colon	+	−	−	−
			Colon, hepatic flex.	−	−	−	−
(5)	1	?	Sigmoid	+	−	−	−
(16)	1	?	Lung	−	−	Photopenic area, R acetabulum	−
(15)	1	+	?	−	−	−	Brain
	1	?	Lung	−	−	−	Brain
(19)	2	−	Non-Hodgkin's	+	+	−	−
	1	−	Colon	+	−	−	−
	1	?	Ovary	+	−	−	−
	3	−	Cerebrum	+	−	−	−
	3	−	?	−	−	−	Liver
(18)	1	?	Breast	−	−	+	−
(20)	1	+	Subhepatic space	+	−	−	−
	1	+	Liver	−	−	+	−
	1	+	Hodgkin's	−	+	−	−
	1	?	Stomach	+	−	−	−
	1	?	Cecum	+	−	−	−
	1	?	Breast	−	?	−	−
(17)	3	+	Lymphoma	+	+	−	−
	1	+	Leukemia	−	+	−	−
	2	+	Bladder	−	+	−	−
	1	+	Colon	−	+	−	−
	1	+	Seminoma	−	+	−	−
	1	+	Bone	−	+	−	−
	1	+	Malignant fibrous histiocytoma	+	−	−	−
	1	+	Lymphoma	+	−	−	−
	1	+	Epithelioid sarcoma	+	−	−	−
	1	+	Cholangiocarcinoma	+	−	−	−
	1	+	Bile duct	+	−	−	−
	1	+	Pancreas	+	−	−	−
	1	+	Prostate	−	−	+	−
	1	+	Bladder	−	−	+	−
	1	+	Angiosarcoma	−	−	+	−
	1	+	Larynx	−	−	+	−
	2	+	Myeloma	−	−	+	−

* ? = not mentioned in report; + (present) and − (absent).

phocytes may be related to some immunologic activity caused by fever and associated stress (*17*).

4. When mixed leukocyte preparations are used, the labeled cells always include lymphocytes and monocytes. It is possible that these labeled mononuclear cells localize in tumors and lymph nodes. They may be present in unusually large proportions in some cell preparations. A differential count of the injectate should be performed as a part of the ^{111}In-WBC scintigraphy to exclude this. Visualization of normal lymph nodes would be expected if lymphocytes formed a substantial part of the injected leukocyte preparation (this was not observed in the case described here).
5. Schmidt et al. (*19*) emphasized that tumor granulocyte infiltration was the single most important factor for accumulation of ^{111}In-WBC in malignant tumors. Microscopic studies after specific granulocyte staining revealed the greatest extent of granulocyte infiltration in tumors that took up ^{111}In activity. Kwai and Kaplan (*24*) found that, when they used mixed cell preparations irradiated with 4,500 cGy, the incidence of tumor localization was low (2.2%).

The patient died 7 mo after the diagnosis of small cell cancer was made. An autopsy was not performed.

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