Radionuclide Diagnosis of Vertebral Osteomyelitis: Indium-111-Leukocyte and Technetium-99m-Methylene Diphosphonate Bone Scintigraphy

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Seventy-six ^{111}In-labeled leukocyte images performed on 71 patients with possible vertebral osteomyelitis were reviewed. Twenty-eight cases of vertebral osteomyelitis were diagnosed. Vertebral labeled leukocyte activity was normal in 2, increased in 11, and decreased in 15 cases of osteomyelitis. The median duration of symptoms was significantly longer in patients with osteomyelitis and decreased vertebral activity than in patients with osteomyelitis and increased activity (3 mo versus 2 wk; $p = 0.019$). No significant relationship between the duration of antibiotic therapy and the appearance of vertebral osteomyelitis on leukocyte images was identified ($p = 0.62$). Increased vertebral activity was highly specific (98%) for osteomyelitis but relatively insensitive (39%). Decreased activity was neither sensitive (54%) nor specific (52%). Seven patients with clinically resolved infection underwent follow-up imaging. Of four patients who initially presented with increased activity, one had normal and three had decreased vertebral activity on follow up studies. All three patients with decreased activity initially had decreased activity on follow-up. Using increased or decreased activity as criteria for infection, the accuracy of leukocyte imaging for diagnosing vertebral osteomyelitis was 66%, similar to that of ^{99m}Tc bone imaging (63%) in our population. Leukocyte imaging did however provide important information about extraosseous infection in 12 of the patients studied.

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Indium-111-labeled leukocyte scintigraphy is a useful procedure for diagnosing osteomyelitis (*1–5*). Although typically manifest as an area of increased accumulation of labeled white cells relative to some reference point, osteomyelitis presenting as a zone of photopenia, especially in the spine, has been described (*4–11*). We retrospectively reviewed leukocyte images performed on 71 patients with possible vertebral osteomyelitis in order to more precisely characterize the appearance of this entity on leukocyte imaging, as well as to assess the utility of this modality for the diagnosis of osteomyelitis of the spine.

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MATERIALS AND METHODS

Patient Population

Seventy-one patients, 42 males and 29 females, with a mean age of 59 yr (range: 2–90 yr) who underwent a total of 83 leukocyte studies, were included in this review. Seventy-six studies were performed as part of an initial diagnostic evaluation in the seventy-one patients. Seven patients with vertebral osteomyelitis were restudied between 2 and 18 mo after initial imaging. In addition to labeled leukocyte imaging, 57 ^{99m}Tc-methylene diphosphonate (MDP) bone scans (including 31 two-phase studies) were performed as part of the initial diagnostic evaluation. The seventy-six spinal regions of concern included *9* cervical, *19*, thoracic, *47* lumbar, and *1* sacral. Final diagnoses were based on laboratory studies including microbiologic and histologic data, radiographic findings, and clinical course.

Scintigraphy

Leukocyte imaging was performed 24 hr after injection of approximately 18.5 MBq (500 μCi) of mixed autologous leukocytes labeled with ^{111}In according to the method of Thakur et al. (*12*). Imaging was performed on a large field of view gamma camera equipped with a medium-energy parallel-hole collimator using 20% windows centered over the 174 keV and 247 keV photopeaks of ^{111}In. Six-minute anterior and posterior static images of the region of interest were obtained in all cases. Whole-body imaging was performed when clinically indicated.

Two-phase bone scintigraphy was performed after injection of approximately 740 MBq (20 mCi) of ^{99m}Tc-MDP. (Although three-phase bone scintigraphy was usually performed when evaluating the cervical or lumbosacral spines, dynamic imaging of the thoracic spine was unsatisfactory due to activity in the heart and great vessels; therefore for the purposes of this study only blood-pool and delayed images were evaluated.) Imaging was performed on a large field of view gamma camera equipped with a low-energy high-resolution parallel-hole collimator using a 20% window centered over the 140 keV photopeak of ^{99m}Tc. Five

hundred thousand count anterior and posterior blood-pool images of the region of interest were obtained. Delayed bone images performed 2–3 hr after injection were acquired using this same technique. When bone scintigraphy was performed first (n = 26), at least 48 hr elapsed before leukocyte imaging was performed. When leukocyte imaging was performed first (n = 31), bone scintigraphy was generally performed immediately afterwards. Regardless of the order in which they were performed, however, both studies were always performed within five days of each other.

Image Interpretation

Radiotracer uptake on both leukocyte and bone images was compared to adjacent and presumably normal, vertebral activity, and classified as normal (equal to), increased, or decreased. For purposes of analysis, three different criteria for a positive leukocyte image were evaluated: (1) increased activity only, (2) decreased activity only, and (3) increased or decreased activity. Two-phase bone images were considered positive for infection when discrete hyperemia in the region of interest was present on blood-pool images, and diffusely increased activity in the vertebra(e) in question was present on delayed bone images. Diffusely increased activity in the vertebra(e) in question was considered positive for infection when delayed images only were interpreted.

RESULTS

Twenty-eight cases of vertebral osteomyelitis were identified. Twenty-four cases were confirmed by biopsy and four cases were classified as osteomyelitis by positive blood cultures plus radiographic changes consistent with osteomyelitis plus clinical improvement following appropriate antibiotic therapy. Final diagnoses in the remaining 48 cases were: metastasis (8), Paget's disease (5), arthritis (5), disc herniation (5), compression fracture (4), meningitis (2), neuritis (2), radiculopathy (1), and extraosseous infection (16). (Four patients with vertebral osteomyelitis also had extraosseous sites of infection.)

Normal vertebral activity was present on 26 leukocyte images, including two cases of osteomyelitis. Increased vertebral activity was present on 12 of 76 leukocyte images, including 11 cases of osteomyelitis. One patient with acute pyelonephritis also demonstrated increased uptake in the 3rd lumbar vertebra; however there was no other evidence to support the diagnosis of vertebral osteomyelitis and the study was classified as false-positive. Decreased vertebral activity was present on 38 leukocyte images including 15 cases of osteomyelitis (Table 1, Fig. 1). Noninfectious conditions associated with decreased vertebral activity are listed in Table 2. The duration of symptoms was longer than 2 mo in only 2 of 11 patients with osteomyelitis and increased activity on leukocyte images, as compared to 10 of 15 patients with osteomyelitis and decreased activity on leukocyte images. The median duration of symptoms in patients with osteomyelitis and increased activity was 2 wk, while the median duration of symptoms in patients with osteomyelitis and decreased activity was 3 mo. The median test was performed using the grand median duration (=2 mo) in all 26 cases as the cutoff value. The difference between the two median durations (2 wk versus 3 mo) was statistically significant ($p = 0.019$ by the median test with the Fischer exact test). Sixteen patients were

TABLE 1
Leukocyte Imaging in 28 Patients with Vertebral Osteomyelitis

Pt.*	Sex	Age	Location	Duration	Image	Organism
1	M	41	Lumbar	2 days	I	B. hemolytic strep
2	M	70	Thoracic	3 days	I	*S. aureus*
3	M	81	Lumbar	3 days	I	*S. fecalis*
4	M	72	Thoracic	3 days	I	*S. aureus*†
5	M	77	Thoracic	1 wk	I	*S. aureus*†
6	F	73	Lumbar	2 wk	I	*S. aureus*
7	F	57	Lumbar	3 wk	D	Purulence
8	M	4	Lumbar	3 wk	D	Purulence
9	F	59	Lumbar	4 wk	I	*S. aureus*
10	M	72	Cervical	4 wk	I	*S. aureus*†
11	M	50	Lumbar	4 wk	D	*S. aureus*
12	F	85	Lumbar	4 wk	D	Purulence
13	M	20	Cervical	4 wk	N	*S. viridans*
14	M	72	Cervical	6 wk	N	*S. epidermidis*
15	M	67	Lumbar	2 mo	I	*Enterobacter cloacae*
16	F	56	Thoracic	2 mo	D	B. hemolytic strep†
17	M	66	Lumbar	3 mo	D	*S. aureus*
18	M	58	Lumbar	3 mo	D	Purulence
19	F	52	Sacrum	3 mo	D	Purulence
20	M	52	Thoracic	5 mo	I	*S. aureus*
21	M	42	Lumbar	5 mo	D	*S. aureus*
22	M	70	Lumbar	6 mo	I	*S. aureus*
23	M	60	Thoracic	6 mo	D	Purulence
24	M	57	Thoracic	6 mo	D	Purulence
25	F	87	Thoracic	8 mo	D	Purulence
26	F	31	Thoracic	12 mo	D	M. tuberculosis
27	M	83	Thoracic	12 mo	D	*S. aureus; P. mirabilis*
28	F	62	Cervical	18 mo	D	M. tuberculosis

I = increased, D = decreased, and N = normal.
* Patients are listed in order of increasing duration of symptoms.
† Positive blood culture, no tissue specimen obtained.

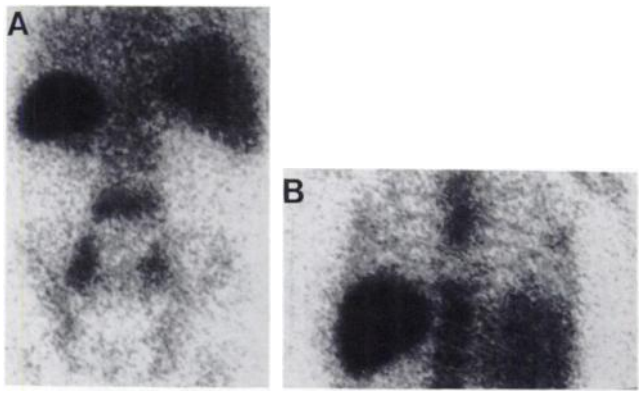

FIGURE 1. (A) Intensely increased leukocyte activity is present in L5 in an 81-yr-old male with vertebral osteomyelitis. The causative organism was *S. fecalis*. (B) A well-defined photopenic defect involving approximately T8 and T9 is present in a 31-yr-old female who had been symptomatic for 12 mo. The causative organism was M. tuberculosis.

TABLE 2
Noninfectious Conditions Associated with Decreased Vertebral Activity on Leukocyte Images

Condition	n
Metastasis	8
Paget's disease	5
Degenerative arthritis	5
Compression fracture	3
Idiopathic	2
Total	23

receiving antibiotic therapy at the time of leukocyte imaging. There was no significant difference in duration of antibiotic therapy between six patients with increased uptake (median duration = 10 days) and ten patients with decreased uptake (median duration = 8 days) ($p = 0.62$ by the median test with the Fisher exact test).

Twelve of 31 two-phase bone studies were interpreted as positive for infection, including eight cases of osteomyelitis. Thirty-seven of 57 (delayed) bone scans were interpreted as positive for infection, including 19 cases of osteomyelitis. Among the criteria evaluated, increased uptake on leukocyte imaging had the highest positive predictive value (92%), while a normal leukocyte image yielded the highest negative predictive value (92%). Table 3 compares sensitivity, specificity, accuracy and predictive values of leukocyte and bone imaging.

Seven patients with vertebral osteomyelitis underwent follow-up leukocyte imaging between two and 18 months after the initial study. All seven were clinically judged to have been adequately treated. Four initially presented with increased activity and three initially presented with decreased activity. One patient, who initially presented with increased uptake, demonstrated normal vertebral activity on a follow-up study performed 3 mo later. The remaining six patients, including three who initially presented with increased uptake, all demonstrated decreased uptake on follow-up studies (Table 4).

TABLE 3
Comparison of Leukocyte and Bone Scintigraphy for Diagnosis of Vertebral Osteomyelitis

Criterion	Sen	Spc	Acc	+PV	−PV
Leukocyte (I) (n = 76)	39%	98%	76%	92%	73%
Leukocyte (D) (n = 76)	54%	52%	53%	39%	66%
Leukocyte (I or D) (n = 76)	93%	50%	66%	52%	92%
Two-Phase bone (n = 31)	47%	71%	58%	67%	53%
Delayed bone (n = 57)	86%	49%	63%	51%	85%

Sen = sensitivity; Spc = specificity; Acc = accuracy; +PV = positive predictive value; −PV = negative predictive value; I = increased; and D = decreased.

TABLE 4
Follow-up Leukocyte Imaging in Seven Patients with Vertebral Osteomyelitis

Pt. no.	Location	Initial image	Follow-up image	Interval*
1	Lumbar	I	D	6 mo
4	Thoracic	I	N	3 mo
6	Lumbar	I	D	3 mo
12	Lumbar	D	D	3 mo
18	Lumbar	D	D	3 mo
20	Thoracic	I	D	2 mo
21	Lumbar	D	D	18 mo

* Time interval between initial leukocyte imaging and follow-up imaging.

DISCUSSION

While leukocyte images are usually interpreted as positive for infection when the area of interest demonstrates increased activity relative to some reference point, osteomyelitis presenting as an area of photopenia, especially in the spine, has been described (*4–11*). It has been postulated that this photopenia results from occlusion of the microcirculation of the involved bone resulting in acute inflammation and necrosis (*6*). Infection-induced death of reticuloendothelial cells that normally accumulate labeled leukocytes may also play a role (*4*). While recent work by Whalen et al. (*11*) suggests that the photopenic appearance of vertebral osteomyelitis may be related to previous antibiotic therapy, we found no significant relation between the duration of antibiotic therapy and the appearance of this entity on leukocyte imaging. We did, however, find that the median duration of symptoms was significantly longer in individuals presenting with photopenia than in individuals presenting with increased activity on leukocyte images (3 mo versus 2 wk, $p = 0.019$), and we speculate that the appearance of vertebral osteomyelitis on leukocyte imaging may be dependent, at least in part, on the pathophysiology of the disease itself as well as the predominant cellular immune response at the time of imaging.

Vertebral osteomyelitis presumably originates as a septic embolism that lodges in the metaphyseal artery, an end-arteriole in the vertebral body metaphysis. This embolus propagates retrograde into the metaphyseal anastomosis, and circumferentially around the vertebral body sequentially occluding other metaphyseal arteries. The regions of the vertebral metaphysis supplied by each of these metaphyseal arteries undergo sequential septic infarction producing osteomyelitis (*13*).

Acutely, an infection is characterized by a neutrophilic response. This response subsides over time and is replaced by a monocyte/macrophage response. Because we label a mixed population of leukocytes, approximately 60%–80% of the cells reinjected are neutrophils, while only 2%–8% are monocytes, probably too few to be successfully imaged. Consequently increased activity on leukocyte images will

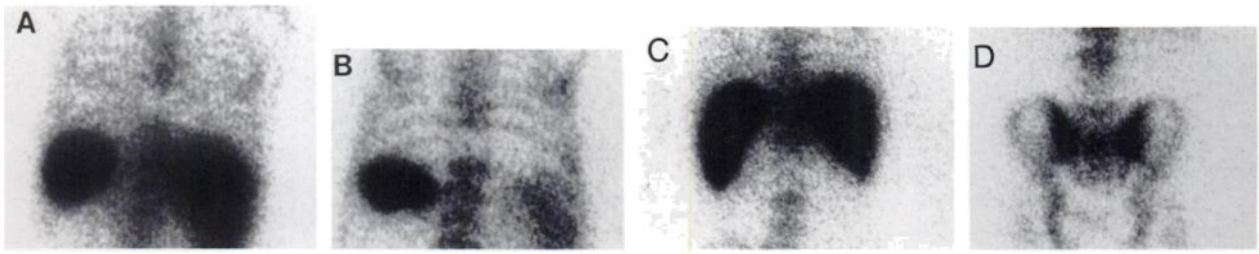

FIGURE 2. The principal limitation to labeled leukocyte imaging in vertebral osteomyelitis is the nonspecificity of skeletal photopenia, present in 54% of the cases of osteomyelitis in our series. We were unable to distinguish the skeletal photopenia seen in infection from other causes of skeletal photopenia. (A) Thoracic vertebral osteomyelitis in a 57-yr-old male symptomatic for 6 mo (purulence only was present in biopsy specimen—no organisms were cultured). (B) Prostate carcinoma metastases to the lower thoracic spine in a 73-yr-old male (photopenia involving a right lower posterior rib is also evident). (C) Lumbar spine compression fractures in a 66-yr-old female. (D) Paget's disease involving L5 in a 61-yr-old male.

be present only as long as a sufficiently intense neutrophilic response exists. As the neutrophilic response (and hence labeled cell activity) subsides, the only evidence that a pathologic process exists will be the photopenic defect produced by the initial insult.

Two patients with vertebral osteomyelitis presented with normal leukocyte images. One individual had been symptomatic for 4 wk, the other for 6 wk. It is possible that these "normal" images represented a transitional, isointense phase of an entity whose presentation varies with time, from increased to decreased activity.

Leukocyte images are typically interpreted as positive for infection when uptake in the region of interest exceeds uptake in some reference point. In the absence of infection, leukocytes are generally not incorporated into areas of increased bone mineral turnover, and therefore leukocyte imaging is highly specific for diagnosing osteomyelitis (*1–3*). This test is especially useful in the setting of underlying osseous pathology such as trauma, tumor, and other conditions that limit the usefulness of routine bone scintigraphy (*1–5*, *14–17*). This point is well illustrated in our patient population where the specificity of leukocyte imaging, when only increased activity was considered positive for infection, was 98% versus 71% for two-phase bone and 49% for delayed bone imaging. The sensitivity of this criterion, however, was only 39%. More than half (54%) of the cases of vertebral osteomyelitis in our population presented as photopenia. Skeletal photopenia on leukocyte images is nonspecific and has also been observed in tumor, previous radiation therapy, fracture, avascular necrosis, myelofibrosis, Paget's disease, and fibrous dysplasia. Therefore it is nondiagnostic for osteomyelitis (*5–10*, *18–22*). When we included decreased activity as a criterion for a positive study, the specificity was only 50%.

Using increased or decreased activity as criteria for infection, the overall accuracy of leukocyte imaging for diagnosing vertebral osteomyelitis was 66%, similar to the 63% accuracy of bone imaging. Unfortunately, the same conditions that adversely affect the specificity of bone scintigraphy such as tumor, trauma, and Paget's disease also had an adverse effect on the specificity of leukocyte imaging in our patients (Fig. 2).

In summary, the presentation of vertebral osteomyelitis on leukocyte imaging is variable, with more than half (54%) of the patients in our series presenting with skeletal photopenia. Although increased vertebral activity was highly specific for infection (98% specificity, 92% positive predictive value), decreased activity was associated with several other conditions and was nondiagnostic for osteomyelitis (52% specificity, 39% positive predictive value). The nonspecificity of decreased activity also limited the usefulness of the study for monitoring patient response to therapy. While the overall accuracy of leukocyte imaging (when decreased activity was included as a criterion for infection) was 66%, only slightly higher than that of bone imaging (63%) in our population, this procedure did provide important information about extraosseous infection in 12 patients.

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