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Evaluation of Complicating Osteomyelitis with Tc-99m MDP, In-111 Granulocytes, and Ga-67 Citrate

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**Studies with gallium-67 and three-phase bone imaging (TPBS), though very sensitive, are not very specific in evaluating suspected osteomyelitis (OM) that is superimposed upon other diseases causing increased bone turnover. A total of 57 patients with suspected OM were studied; this included 48 with increased bone turnover. All of the patients were studied with granulocytes labeled with In-111 acetylacetone (In-111 GRAN), TPBS and 29 of these patients had Ga-67 studies as well. In-111 GRAN had a sensitivity of 100% in acute OM and 60% in chronic OM, with a specificity of 96%. Gallium-67 was excellent in ruling out OM when the study was normal, or in ruling in OM when the relative uptake of Ga-67 exceeded the uptake of Tc-99m MDP, or when the Ga-67 in bone had a different distribution from the TPBS. Unfortunately, these criteria were met in only 28% of our subjects. We conclude that when added to TPBS, the In-111 GRAN study plays an important role in detecting complicating OM.**

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The usefulness of both three-phase bone scintigrams (TPBS) and Ga-67 imaging in evaluating uncomplicated osteomyelitis (OM) has been well known (1,2). However, when OM is superimposed on an area of healing fracture, neurotropic osteopathy, postsurgical changes, etc., the specificity of TPBS falls markedly, since these conditions, as well as OM, cause increased bone turnover (IBT) and thus appear as increased uptake on TPBS (3,4). Likewise, Ga-67 shows increased activity in areas of IBT, making OM evaluation difficult when superimposed on such conditions (4,5).

Recently In-111-labeled white blood cells (In-111 WBC) have been proposed for the study of OM; they have been found very specific but less sensitive, especially in the chronic form of OM (6,7). The main drawbacks to the use of In-111 WBC are the more complex preparation, the high cost, and the relatively high radiation dose to the spleen.

It would be valuable if the high sensitivity of the Ga-67 and TPBS for OM could be combined with the high specificity seen with the In-111 WBC. Accordingly, 57 patients with suspected OM were studied, 28 patients with TPBS and In-111 granulocytes (In-111 GRAN), and 29 with TPBS, Ga-67, and In-111 GRAN.

MATERIALS AND METHODS

**Patient population.** In this study (approved by the Institutional Review Board), 57 consecutive patients with suspected OM and abnormal TPBS were evaluated after giving informed consent. There were 17 female and 40 male patients, with age range 17 to 80 yr (mean 48 yr). Forty-eight of the patients had suspected OM superimposed on conditions with IBT, and nine patients with suspected OM had no other conditions causing IBT.

**Three-phase bone imaging.** The TPBS procedure outlined by Park et al. was followed (8). Approximately 20 mCi of Tc-99m medronate was injected intravenously while serial 3-sec flow images were obtained (Phase 1).

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A 500,000-count blood-pool image was obtained at 5–10 min after injection (Phase 2) and 500,000-count bone images were obtained 2½ to 3 hr later (Phase 3).

**Granulocytes with labeled In-111 acetylacetone.** Autologous granulocytes were obtained by the method of discontinuous density gradients, slightly modified after English and Anderson (9). Following Volex-induced erythrocyte sedimentation, leukocyte-rich plasma was divided equally among 6–8 sterile 7-ml tubes. The plasma was underlaid first with 1 ml of a Ficoll-Hypaque solution with a sp g of 1.08, then 1 ml of Ficoll-Hypaque with sp g 1.13. After a 10-min centrifugation ( $g$ -max = 750), the granulocytes were harvested from the interface between the two Ficoll-Hypaque gradients and washed with ACD:saline (1:7 v/v). Labeling was carried out by resuspending the granulocyte pellet in 3 ml of In-111 acetylacetone labeling solution and incubating at room temperature for 10 min. The labeling solution was prepared immediately before use by a modification of Sinn's technique (10), adding 0.5–0.6 mCi of  $^{111}\text{InCl}_3$  to 3 ml of 22 mM acetylacetone in 22 mM HEPES buffered saline (pH 7.6). Labeling yield following a plasma wash typically exceeded 80%. The labeled granulocytes were resuspended in the patient's own plasma, examined microscopically to check for absence of aggregated cells, and reinjected within 1 hr of labeling. The cellular composition of the final injection was routinely greater than 95% granulocytes. Images were obtained at 2 to 4 hr, and about 24 hr after injection.

**Ga-67.** Five mCi of Ga-67 citrate were injected intravenously and 400,000-count images using 3 Ga-67 photopeaks were obtained at 24 hr, and as indicated.

**Timing of the procedures.** The TPBS was always the first procedure performed; it was followed by the In-111 GRAN study. When feasible, a delay of at least 1 day was used between these studies to prevent any possible interference by Tc-99m remaining from the TPBS. When no delay was possible, a 10% window at 173 keV and a 20% window at 247 keV were used to exclude the 140-keV gamma from the residual Tc-99m (11). The Ga-67 was injected at the completion of the In-111 GRAN study. The minuscule residual In-111 activity gave no significant contribution to the Ga-67 images.

If started on a Monday, all three studies could be completed in 1 wk, but more often they extended into a second week. Twenty-eight patients required immediate surgery or other therapy, in which case only TPBS and In-111 GRAN studies were obtained. The other 29 patients had all three studies.

**Final diagnosis.** The final diagnosis in 33 patients (58% of the cases) was established by needle biopsy and culture, or by open surgery. In 24 patients who did not go to surgery (most frequently those diagnosed as not having OM), the final diagnosis was established on clinical grounds and confirmed, when possible, by outpatient follow-up.

**Interpretation.** Imaging procedures were interpreted individually as completed, and later correlated with other studies. Three nuclear medicine staff physicians reread all studies without clinical or pathological information. On rare occasions when the readings differed, the final result was by consensus.

## RESULTS

Table 1 lists the results of the studies obtained in all 57 patients, with the method of establishing the final diagnosis. There were 32 patients with OM; 24 of them were proven histologically, and the other eight had clinical follow-up confirming the diagnosis. Twenty-five patients had no OM; nine of them were confirmed histologically and 16 clinically.

Table 2 summarizes the results of the In-111 GRAN study in all patients. In-111 GRAN had an overall sensitivity of 75% and a specificity of 96%. If only pathologically proven (PP) diagnoses are considered, the sensitivity is 79% and the specificity is 89%.

Since all of the In-111 GRAN "false negatives" occurred in cases of chronic OM, acute OM had a sensitivity of 100%. If only the patients with chronic OM are considered, In-111 GRAN had a sensitivity of 60% (PP = 55%). We encountered one patient with a "false positive" In-111 GRAN due to a metastatic breast carcinoma that took up the In-111 GRAN; this is similar to the results reported by Sfakianakis (12) and by Georgi (13).

Table 3 compares In-111 GRAN and Ga-67 in those patients who had both studies. Gallium-67 had an overall sensitivity of 100% and a specificity of 25% (PP = 50%). Gallium-67 was abnormal in all but one patient, regardless of superimposed OM; this made the usefulness of Ga-67 in our patient population very doubtful.

Some investigators suggest that a Ga-67 image strongly suggests an acute inflammatory process if it disagrees with the bone images in either intensity or distribution of uptake (3,14). We found increased intensity relative to TPBS, gave a sensitivity of only 14%, but a specificity of 100% (Table 4). Disparate distribution gave a sensitivity of 24% and a specificity of 100%. One patient had both increased Ga-67 intensity and disparate distribution; another patient had a normal Ga-67 distribution, thus ruling out OM.

Occasionally Ga-67 uptake in soft-tissue inflammation adjacent to bone made the evaluation of disparate uptake between Ga-67 and TPBS difficult. Overall, the different intensity and/or distribution of uptake compared with TPBS or normal Ga-67 were diagnostic in 28% of our subjects.

Of 41 patients with soft-tissue infections, clinically only 11 showed soft-tissue uptake on the In-111 GRAN images. Five of the 29 patients who also had Ga-67 images showed abnormal soft-tissue uptake.

**TABLE 1. RESULTS OF ALL STUDIES IN 57 PATIENTS WITH SUSPECTED OSTEOMYELITIS (OM)**

Preexisting osseous condition	In-111	Ga-67	Pathologically Proven		Clinically Proven	
			OM	NO OM	OM	NO OM
No other bone abnormalities (nine patients)	Positive (5)	Positive	3			
		Negative				
	Negative (4)	Not performed	2			
		Positive	1		1	
Bone surgery or amputation (19 patients)	Positive (9)	Negative				
		Not performed	3			
	Negative (10)	Positive	1		2	1
		Negative			1	
Prosthesis (eight patients)	Positive (3)	Not performed	1			
		Positive	1	1		
	Negative (5)	Negative				1
		Not performed			2	1
Fracture (seven patients)	Positive (3)	Positive	1			
		Negative				
	Negative (4)	Not performed	2			
		Positive				1
Neuropathic osteopathy (ten patients)	Positive (3)	Negative				
		Not performed	2		1	
	Negative (7)	Positive			1	2
		Negative			1	
Arthritis (four patients)	Positive (2)	Not performed				
		Positive			1	
	Negative (2)	Negative			1	
		Not performed				1
<b>Totals</b>			<b>24</b>	<b>9</b>	<b>8</b>	<b>16</b>

**DISCUSSION**

As noted in the Results section, the sensitivity of the In-111 GRAN study is 100% in acute OM and only 60%

(PP = 55%) in chronic OM, while the specificity is 96% (PP = 89%). Histologically, during acute OM there is predominately neutrophilic infiltration with edema,

**TABLE 2. SUMMARY OF In-111 GRANULOCYTES IMAGING IN 57 PATIENTS WITH SUSPECTED OSTEOMYELITIS (OM)**

Pre-existing osseous condition	Number of patients	Final diagnosis					
		Acute OM		Chronic OM		No OM	
		TP	FN	TP	FN	TN	FP
No other bone abnormality	9	3	0	2	3	1	0
Bone surgery or amputation	19	4	0	5	4	6	0
Prosthesis	8	2	0	0	1	4	1*
Fracture	7	0	0	3	0	4	0
Neuropathic osteopathy	10	1	0	2	0	7	0
Arthritis	4	2	0	0	0	2	0
<b>Total</b>	<b>57</b>	<b>12</b>	<b>0</b>	<b>12</b>	<b>8</b>	<b>24</b>	<b>1</b>

\* Metastatic breast carcinoma.  
 TP = True positive.  
 FN = False negative.  
 TN = True negative.  
 FP = False positive.

vascular congestion, thrombosis, and bone destruction (15). In chronic OM, however, the inflammatory product contains mostly lymphocytes, plasma cells, and macrophages, with relatively fewer granulocytes (16). It is not surprising that the In-111 GRAN are not as well

**TABLE 4. Ga-67 UPTAKE RATIO\* COMPARED WITH Tc-99m MDP UPTAKE RATIO\***

Final diagnosis	Number of patients	MDP < Ga MDP = Ga MDP > Ga		
		MDP < Ga	MDP = Ga	MDP > Ga
Acute OM†	8	1	2	5
Chronic OM	13	2	3	8
No OM	8	—	2	6†

\* Uptake ratio is uptake in the lesion relative to uptake in the adjacent normal bone.  
 † In 1 case the Ga-67 image was normal.  
 ‡ Osteomyelitis.

concentrated in chronic OM as in acute.

Gallium-67 proved to be very accurate when the study was negative, when the Ga-67 uptake exceeded that of the TPBS, or when the distribution of the Ga-67 differed from that of the Tc-99m on the TPBS. Unfortunately, in this study 72% of the patients did not fulfill any of these stringent criteria. Thus, in 72% of these complex cases Ga-67 added no useful information beyond that obtained with TPBS alone.

Gallium-67 has several possible mechanisms of concentration in a lesion: granulocyte uptake (17); direct bacterial uptake (17); lactoferrin binding at the site of infection (17); or uptake in reactive bone (5). Because of the last mechanism, we question the usefulness of

**TABLE 3. COMPARISON OF In-111 GRAN AND Ga-67 IN ALL PATIENTS WITH BOTH STUDIES**

Underlying osseous condition	Number of patients		Final Diagnosis					
			Acute OM*		Chronic OM		No OM	
			TP	FN	TP	FN	TN	FP
No other bone abnormality	5	In-111 Gran	2	0	1	2	0	0
		Ga-67	2	0	3	0	0	0
Bone surgery or amputation	11	In-111 Gran	2	0	4	3	2	0
		Ga-67	2	0	7	0	1	1
Prosthesis	3	In-111 Gran	1	0	0	1	1	0
		Ga-67	1	0	1	0	1	0
Fracture	2	In-111 Gran	1	0	0	0	1	0
		Ga-67	1	0	0	0	0	1
Neuropathic osteopathy	6	In-111 Gran	1	0	2	0	3	0
		Ga-67	1	0	2	0	0	3
Arthritis	2	In-111 Gran	1	0	0	0	1	0
		Ga-67	1	0	0	0	0	1
<b>Total</b>	<b>29</b>	<b>In-111 Gran</b>	<b>8</b>	<b>0</b>	<b>7</b>	<b>6</b>	<b>8</b>	<b>0</b>
		<b>Ga-67</b>	<b>8</b>	<b>0</b>	<b>13</b>	<b>0</b>	<b>2</b>	<b>6</b>

\* OM = osteomyelitis.

Ga-67 in complicating OM.

Only 11 of 41 (27%) of the patients with clinically evident soft-tissue inflammation had identifiable soft-tissue uptake with In-111 GRAN; with Ga-67 the number was nine of 23 (39%). Like OM, soft-tissue inflammations appear to have active and chronic histologic phases (18). The active form has a large inflow of neutrophils, whereas the chronic lesion is composed of large numbers of mononuclear leukocytes, lymphocytes, fibroblasts, and necrotic debris, with fibrous connective tissue attempting to re-epithelialize the crater; there is little inflow or outflow of granulocytes. Many of our cellulitis patients were diabetics with foot ulcers of long duration, or paraplegics with chronic decubiti, thus these soft-tissue inflammations were not identified with greater frequency.

At times the differentiation of OM from cellulitis can be difficult, especially if the cellulitis is active and adjacent to the bone. Uptake in soft tissue can be differentiated from that in bone by obtaining perpendicular images standing and by comparing the tracer distribution with that seen on the third phase of the TPBS. When the In-111 GRAN study is started the day after the TPBS, the patient should be imaged using a 247-keV window and, without being moved, reimaged using the Tc-99m window. Repeating this procedure in the perpendicular projection allows the optimum anatomic evaluation and thus aids in the differentiation of cellulitis from OM.

In conclusion, there is no easy and accurate single test to evaluate complicating OM. We feel that the first study should continue to be TPBS, and it should be followed by In-111 GRAN. Although In-111 GRAN does not detect all of the chronic cases, it certainly increases the sensitivity and specificity in those cases where OM is superimposed on other lesions that cause IBT. In our hands Ga-67 imaging has added very little to the information obtained with TPBS, and did add cost and radiation burden to the patient. In known complicated cases we would not recommend the use of In-111 GRAN alone, since the TPBS provides valuable anatomic information that can be helpful in differentiating OM from adjacent overlying cellulitis.

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