Heterotopic Bone Formation: Clinical, Laboratory, and Imaging Correlation

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The clinical findings, laboratory data, radiographs, and radionuclide studies of 50 patients referred for evaluation of possible heterotopic bone formation (HBF) were reviewed. HBF begins approximately 17 days following injury or neurologic insult, heralded by an acute rise in serum alkaline phosphatase (SAP), and increased vascularity on three-phase radionuclide bone imaging (RNBI). RNBI soft-tissue uptake is evident at 24 days and radiographic calcification is visible 1 wk later. Clinical signs and symptoms occur relatively late in the course of disease. HBF mimics thrombophlebitis and should be considered in all patients referred for venography if the clinical situation is appropriate. Serial SAP measurements and three-phase RNBI should allow early definitive diagnosis in virtually all cases.

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Heterotopic bone formation (HBF) or myositis ossificans is a disorder characterized by an initial inflammatory lesion of muscle and other soft tissues followed by heterotopic ossification (*1*,*2*). Although the etiology is uncertain, it is believed to result from transformation of primitive mesenchymal derived cells present in soft tissue, into bone forming cells in response to a variety of stimuli (*3*). It can occur as a rare progressive congenital form, but most commonly is seen after direct muscle trauma and as a complication of paralysis from spinal cord or brain insult (*4*,*5*). It complicates total hip arthroplasty in up to 53% of cases (*6*). Mature HBF consists of cortical and trabecular architecture and marrow elements (*7*).

HBF causes considerable morbidity due to swelling, pain, and loss of range of motion of the affected extremity with resultant delay in rehabilitation (*8*). HBF may result in ankylosis of affected joints, requiring surgical excision of heterotopic bone to restore range of motion (*9*). The early inflammatory phase of this illness causes additional morbidity by clinically mimicking tumor, infection, and thrombophlebitis (*10*).

Contrast arteriography shows intense hyperemia in acute (early) HBF which diminishes as maturation occurs (*11*). Radionuclide bone imaging (RNBI) has been utilized in the evaluation of HBF and three-phase imaging has been advocated for early diagnosis and serial monitoring of disease activity (*12*).

Surgical resection of heterotopic bone has been employed to free ankylosed joints and entrapped nerves, however, this approach is frequently plagued by recurrence of HBF, especially if surgery is not deferred until the metabolic activity has stabilized or decreased (*9*).

Medical treatment of HBF has included the use of forceful range of motion, steroids, aspiration, calcitonin, local irradiation, and oral diphosphonates (*13–16*). The oral diphosphonates appear to be the most promising therapeutic agents and have been effective when started early in the course of HBF or when used prophylactically to prevent recurrence of surgically excised heterotopic bone (*17*). The mechanism of action is not certain but available evidence suggests they prevent calcification of hydroxyapatite bone matrix (*18*).

Though RNBI has been widely utilized for evaluating HBF since the original report by Suzuki (*19*), no protocol for optimum evaluation of HBF exists. In addition, the relationship of RNBI to other diagnostic modalities such as serum alkaline phosphatase (SAP) and radiography is not well-defined. To explore these relationships and to optimize the effectiveness of RNBI for evaluating HBF, we conducted a review of the clinical history, radionuclide imaging studies, laboratory chemistries, radiographs, and therapeutic response of patients referred

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to our imaging department for diagnosis and evaluation of HBF during a 2-yr interval.

METHODS

Patient material

The medical records, pertinent laboratory chemistries, RNBI studies, and radiographs of all patients referred to our imaging department for the initial diagnosis or evaluation of HBF during a 2-yr interval were reviewed. The average clinical follow-up from initial RNBI to completion of the review was 22.5 mo. The date and nature of the precipitating insult, patient population characteristics, clinical course, laboratory data, and response to therapy were documented from the medical record.

RNBI technique

All studies were performed with an Anger LFOV 37 tube scintillation camera and high resolution parallel-hole collimator using a 15% energy window centered on the 140 keV ^{99m}Tc photopeak. The patient was positioned with the region of clinical suspicion under the camera and 25 mCi of [^{99m}Tc]hydroxymethylenediphosphonate were injected as a bolus into a large peripheral vein or central venous catheter. Serial 4 sec first-pass images were acquired for 1 min followed by immediate blood-pool and delayed static images (3–4 hr) of all areas of possible HBF.

Areas of abnormal soft-tissue diphosphonate uptake were imaged with computer data acquisition using a 128 by 128 matrix. Regions of interest were manually drawn over HBF lesions and a contralateral normal control region. The average number of counts per pixel in these matched regions was calculated and the ratio of HBF to control activity was determined for each HBF lesion. Computerized image acquisition was not obtained in all patients.

Review protocol

RNBI and radiographs were reviewed without knowledge of the original interpretation or the clinical course and any disagreement in interpretation was resolved by consensus of the authors. The RNBI studies, including first-pass, blood-pool, and delayed static images were evaluated for hyperemia and abnormal soft-tissue uptake, subjectively comparing symptomatic and contralateral normal regions. No attempt was made to grade the abnormal findings but qualitative comparisons were made on serial studies. RNBI was correlated with the onset of clinical signs and symptoms of disease, laboratory chemistries (SAP and serum calcium), and radiographic evidence of HBF. The effect of oral diphosphonate therapy was evaluated by clinical response, effect on RNBI, and radiographic evidence of calcification.

TABLE 1
Patient Characteristics and Precipitating Injury in 43 Cases of HBF

Characteristic	N (%)
Sex, average age	
Male- 29.6 yr	30 (70)
Female- 32.1 yr	13 (30)
Race	
White	35 (82)
Black	5 (12)
Hispanic	1 (2)
Native American	1 (2)
Asian	1 (2)
Nature of injury	
Spinal cord trauma	27 (63)
Paraplegics	17 (40)
Closed head injury	7 (16)
Periperal trauma	6 (14)
Cerebral vascular insult	2 (5)
Burn	1 (2)
Cause of injury	
Motor vehicle accident or fall	35 (81)
Gun-shot wound	5 (12)
Stroke	2 (5)
Gasoline burn	1 (2)

RESULTS

Patient population

Of 50 patients referred for evaluation, 43 were proven to have HBF. As shown in Table 1, HBF affected a wide variety of races and occurred over a wide age range (16–86 yr). The typical patient was a 29-yr-old white male paraplegic, injured in a fall or high speed motor vehicle accident. This series contained no elective hip arthroplasty patients due to the acute trauma and rehabilitation orientation of our institution. The large number of spinal cord injury patients in our series is consistent with the known incidence of HBF in this population (*20*).

Clinical findings

The relative frequency of the clinical signs and symptoms of HBF is shown in Table 2. The typical patient had multiple findings and pain was common when sensation was intact. Symptomatic disease occurred later than the earliest biochemical evidence of HBF disease activity. The inflammatory nature and resultant extremity swelling of early HBF frequently resulted in an incorrect initial clinical diagnosis of thrombophlebitis, cellulitis, or osteomyelitis. In 23 of 43 patients with HBF,

TABLE 2
Signs and Symptoms of Acute HBF

Sign/symptom	Patients (43) N (%)
Stiffness/loss ROM	21 (49)
Swelling/erythema/warmth	16 (37)
Pain	15 (35)
Other (fever, abnormal lab)	9 (21)

TABLE 3
Distribution of 81 HBF Lesions in 43 Patients

Region	Lesions (81) N (%)	Patients (43) N (%)
	N, (%)	N, (%)
Hip	45(55.5)	33(76.7)
Shoulder	11(13.6)	8(18.6)
Proximal thigh	10(12.3)	10(23.3)
Elbow	10(12.3)	8(18.6)
Distal thigh/knee	5(6.2)	3(7.0)
Leg	1(1.2)	1(2.3)

the original clinical diagnosis was deep venous thrombosis, resulting in a request for RNV as the initial diagnostic study.

RNBI investigation of HBF

Eighty-nine studies were performed in 50 patients. HBF was confirmed in 43 of these 50 patients and correctly excluded in the remaining seven. Although all patients with HBF had abnormal RNBI, in 15 of 43 patients the first-pass and blood-pool portions of the three-phase study were much more impressive than soft tissue uptake. In three of these 43 patients only the first-pass or blood-pool images were sufficiently abnormal to suspect HBF (Fig. 1). Soft-tissue uptake, diagnostic of HBF, was confirmed in these three patients within 1 wk by repeat RNBI. Failure to perform first-pass and blood-pool images would have resulted in three to 15 false-negative studies and a fall in sensitivity to between 65% and 93%. Two studies were performed when the SAP was within normal limits, though rising, and these studies were clearly abnormal.

Eighty-one HBF lesions were detected in the 43 patients with HBF. This represents 1.9 lesions per patient with a distribution and relative frequency as illustrated in Table 3. The hip region was the most common location of HBF. No lesions were detected above the level of spinal cord injury, on the contralateral normal side in hemiparesis, or remote from the site of direct soft-tissue trauma. This distribution is well described in the literature (*20*).

Eleven patients had radiographs at sufficiently frequent intervals to determine the temporal relationship

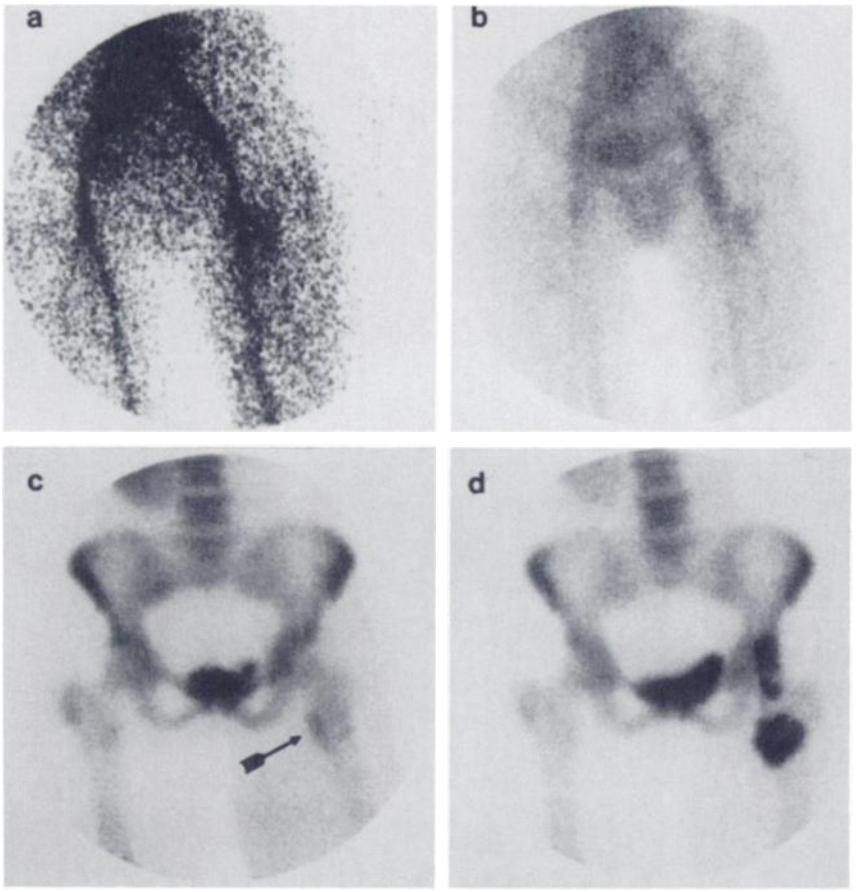


FIGURE 1
Initial three-phase RNBI (a–c) 16 days following acute cord injury with paraplegia demonstrates hyperemia but minimal soft-tissue uptake (arrow). Repeat study (delayed static image only) 1 wk later shows diagnostic soft-tissue uptake (d)

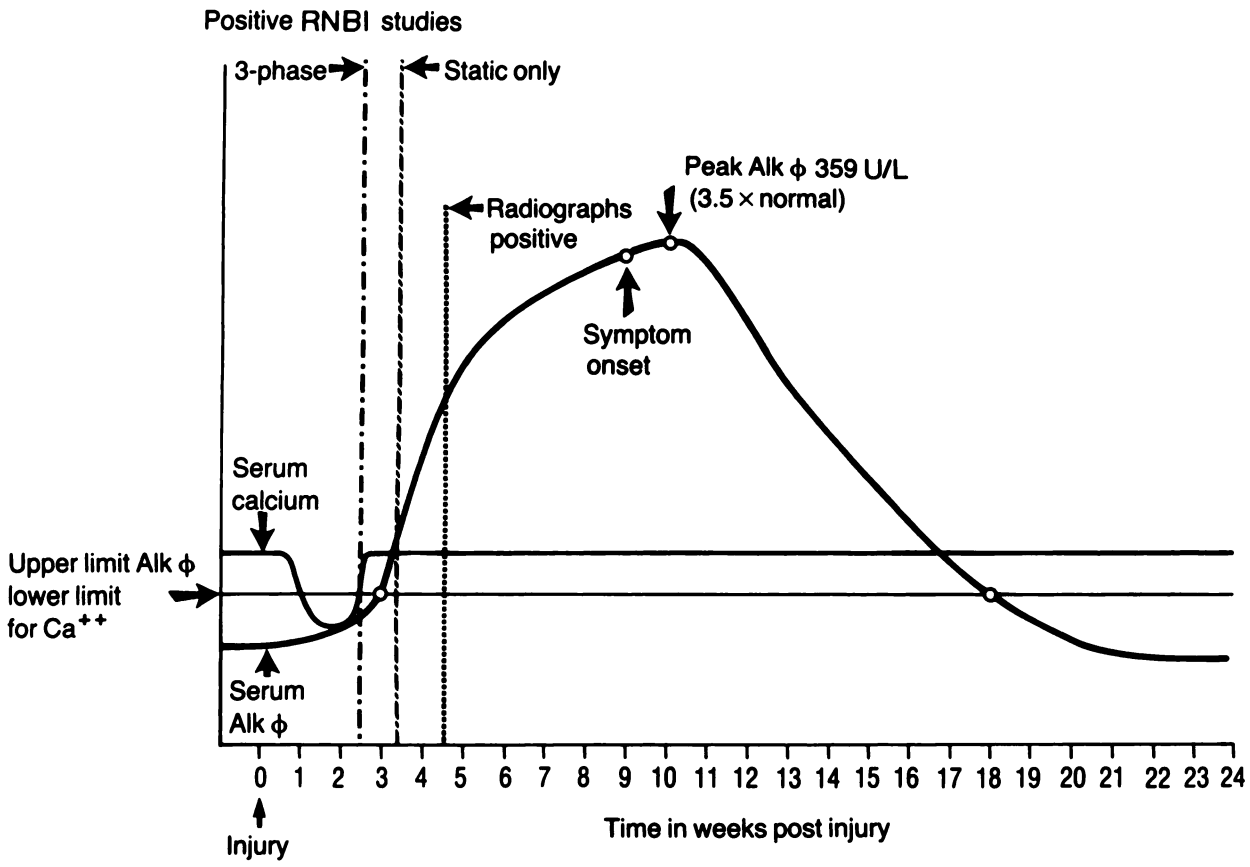


FIGURE 2
SAP and calcium behavior in acute HBF and relationship to RNBI and radiographic studies

between abnormal RNBI and radiographic soft tissue calcification. Radiographic documentation followed RNBI by an average of 15 days (range 6–21 days). No lesion seen radiographically was missed by RNBI and the true extent of HBF was consistently underestimated radiographically in the acute stage.

Six patients were followed serially with an average of four RNBI studies (including computer acquired images) at intervals of 5 to 6 mo. HBF/normal bone activity ratios were followed serially as suggested by Tanaka et al. (*21*). Maturation of heterotopic bone and response to oral diphosphonate therapy resulted in decreasing ratios which generally correlated with subjective image interpretation of disease activity.

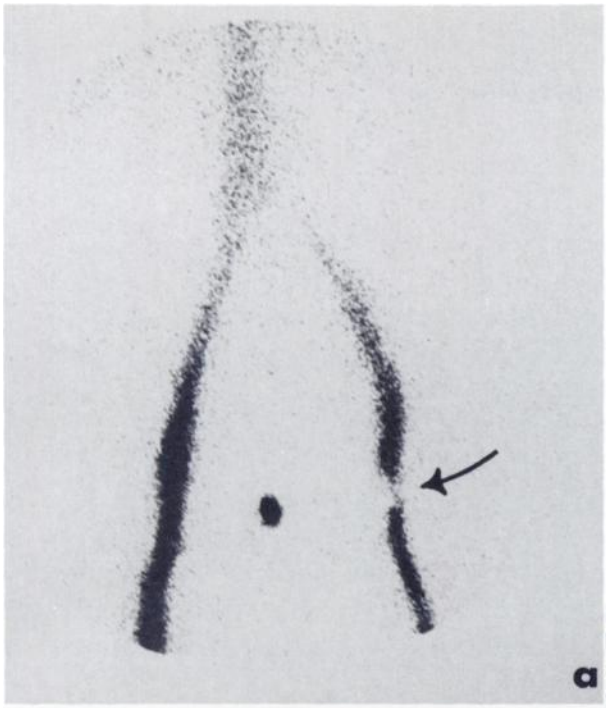
Serum alkaline phosphatase

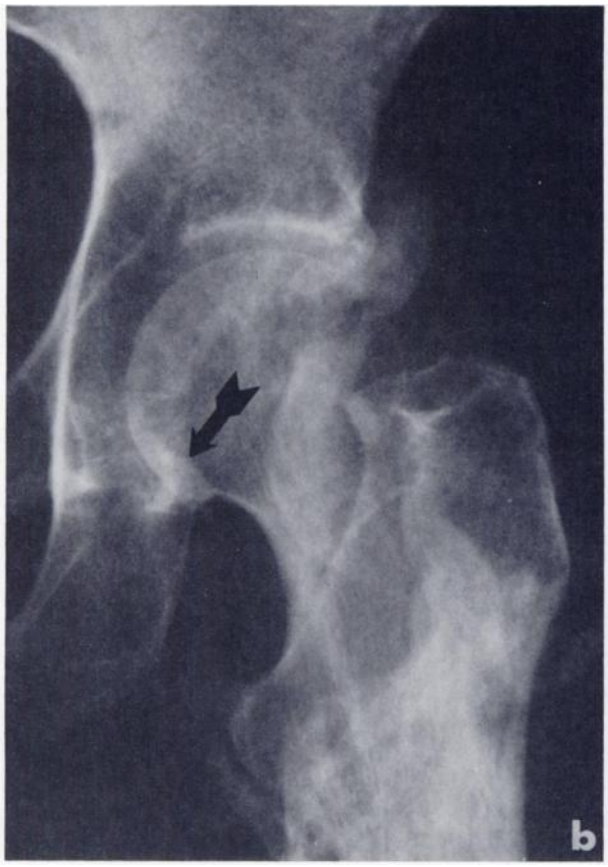
Sufficient data were available in 35 of 43 patients with HBF to comment on the SAP in acute HBF and its temporal relationship to clinical signs and symptoms and results of RNBI and radiography. SAP levels (353 exams) are summarized in Fig. 2.

SAP was abnormal in all patients, rising briskly an average of 7 wk before signs and symptoms led to clinical suspicion of HBF. The average peak SAP was 355 U/l (3.5 times normal) with a range of 1.3 to 13.4 times normal. In two cases the SAP was rising but still within the normal range when RNBI documented early HBF and in five of 43 patients the SAP had returned to normal when the diphosphonate study showed persistently increased HBF metabolic activity. Peak values of SAP did not correlate well with the number or extent of HBF lesions; however, a persistently high value generally indicated extensive and active disease.

Serum calcium

In 24 of 43 patients with HBF 149 paired determinations of total serum calcium and albumin were available. Ionized calcium was estimated from total calcium and albumin values (*22*). Serum calcium was transiently depressed an average of 0.7 mg/dl below the lower limit of normal (range 0.2 to 2.2 mg/dl) in 23 of 24 patients. This occurred an average of 5.3 days following injury and persisted an average of 9.9 days. Serum calcium returned to normal before any rise in SAP. Tetany, electrocardiographic changes, or other complications of hypocalcemia, were not sought or documented. Serum calcium was normal in all seven patients without HBF.





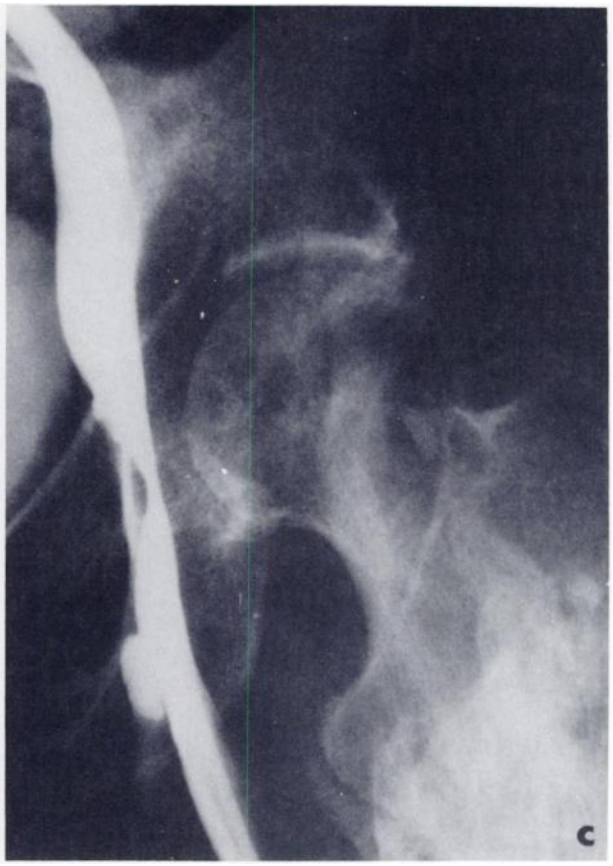


FIGURE 3
RNV (a) demonstrates focal narrowing (arrow) at site of HBF shown in radiograph (b). Retrograde femoral contrast venogram (c) documents extrinsic venous compression

OTHER RADIONUCLIDE STUDIES

Radionuclide venography

Of the 50 patients referred for evaluation of possible HBF 28 (56%) had radionuclide venography (RNV) on one or more occasions for suspicion of deep venous thrombosis. All 28 of these patients had antecedent or subsequent proof of active HBF and 12 of these 28 patients (42.9%) had abnormal RNV suggesting deep venous disease. On review, it was apparent that seven of the 12 abnormal studies were probably due to extrinsic compression by active HBF, though this was confirmed

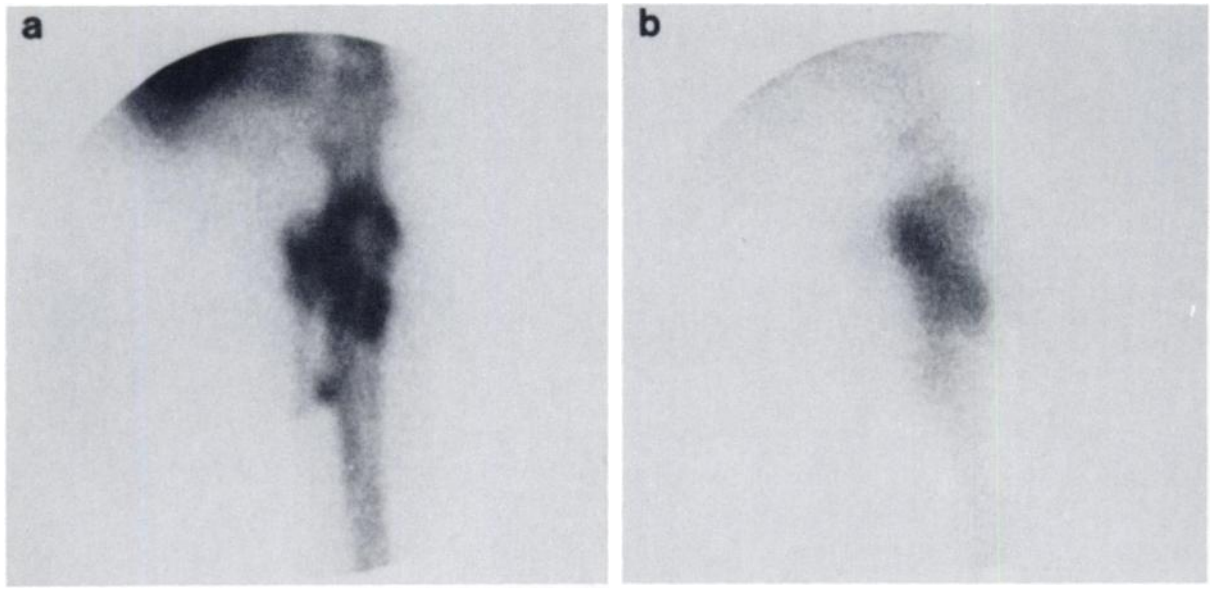


FIGURE 4
Paraplegic 4 wk following injury. HBF lesion of thigh shows diagnostic RNBI soft-tissue uptake (a) and avid gallium citrate accretion (b)

with contrast venography in only two patients (Fig. 3).

Gallium citrate imaging

Gallium citrate scintigraphy was performed in five patients for evaluation of possible cellulitis, soft-tissue abscess, or osteomyelitis at sites subsequently shown to be active HBF. Gallium soft-tissue uptake was demonstrated in HBF lesions in all five patients (Fig. 4). The absence of an infectious process was documented in all patients by one or more of the following: percutaneous needle or open biopsy and culture, the clinical course without antibiotic treatment, serial radiographs, or establishment of an alternative diagnosis.

Results of therapy

Oral diphosphonate therapy (etidronate disodium) was instituted in 17 patients with HBF. Dosage and treatment interval were those reported by Stover (*16*). Adequate follow-up data were available in 14 patients, all of whom developed HBF after spinal cord injury. No significant side effects were recorded and the treatment regimen was completed in all patients. Therapy was instituted 1 to 2 days prior to RNBI in three patients but did not interfere with RNBI diagnosis of HBF.

A good response to therapy was documented in seven of 14 patients (50%) with resolution of all signs and symptoms of HBF and resolution or improvement in RNBI. These patients were started on therapy before soft tissue calcification was seen radiographically and in no instance was soft-tissue calcification subsequently demonstrated.

A partial response to therapy was seen in three of 14 (21.4%) with resolution or improvement in symptoms and signs and stabilization or improvement in RNBI. These patients were started on therapy after minimal soft-tissue calcification was seen.

No significant response to therapy was demonstrated by RNBI and serial radiographs in four of 14 (28.6%) patients started on therapy after extensive soft-tissue calcification was documented radiographically.

DISCUSSION

SAP was originally reported to be normal in HBF (*23*). Later studies showed that it was invariably abnormal, rising at the time of radiographic appearance of soft-tissue calcification (*24*,*25*). Our data show that SAP is a sensitive indicator of early HBF, rising well in advance of symptoms and radiographic soft-tissue calcification. Unfortunately, abnormal SAP activity alone did not lead to clinical suspicion of HBF. SAP elevation was typically attributed to healing fractures, occult biliary disease, or normal bone growth in younger patients. SAP was frequently ignored, even when grossly elevated, possibly because it was not specifically requested but was measured incidentally along with more urgent laboratory tests. Our data suggest SAP is a reliable screening study for HBF, and we recommend following the SAP during the period of increased risk, reserving RNBI for confirmation when the SAP becomes abnormal. This would allow early diagnosis and provide a baseline study on which to assess response to therapy.

Serum calcium has been reported to be normal or even elevated in patients with HBF. Our observation of an

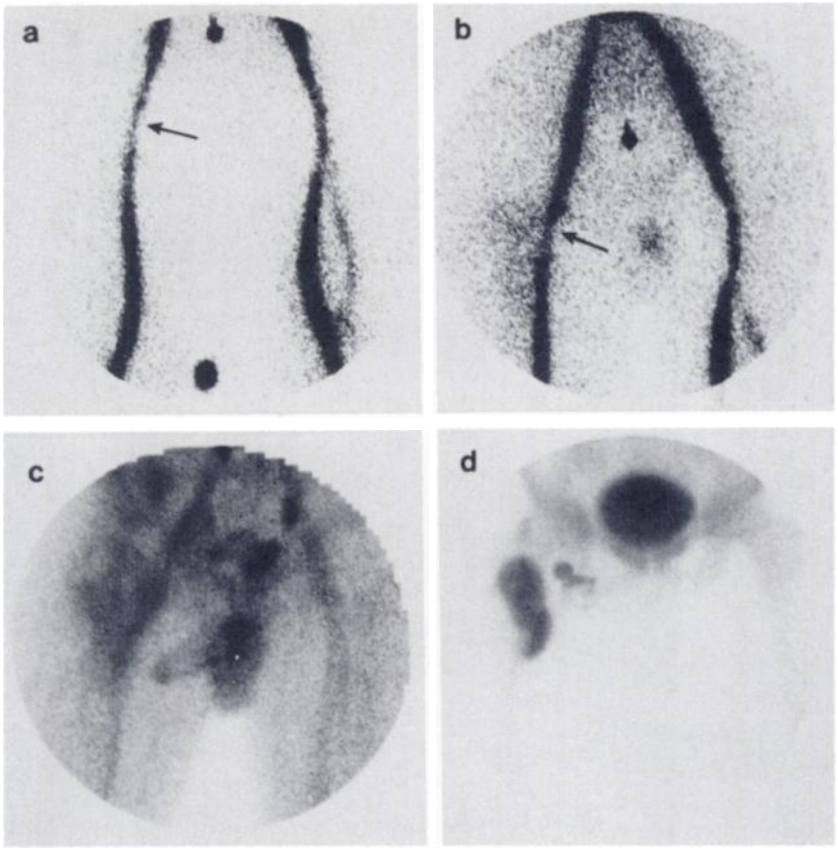


FIGURE 5
Quadraplegic 5 wk following injury. RNV performed with [^{99m}Tc]diphosphonate (a,b) demonstrates mild irregularity and narrowing of femoral vein (arrows). Immediate blood-pool (c) and delayed static images (d) are diagnostic of HBF, accounting for venous abnormality

acute depression in serum calcium has not been previously reported. Although the average depression in serum calcium observed in acute HBF was not great, this finding was so consistent that we speculate it may be the earliest biochemical indicator of HBF and might play a causative role in the pathogenesis of HBF. Depression of total and ionized calcium of a similar magnitude was demonstrated by Clowes and Simcone in surgical and traumatized patients (*26*), suggesting the alternative explanation that hypocalcemia may be a nonspecific result of trauma, unrelated to the development of HBF. A prospective study of ionized calcium in patients at risk for HBF is needed to resolve this issue.

Our previous demonstration that extrinsic venous compression from HBF can affect the RNV (*27*), suggests caution should be used in interpreting RNV in patients at risk for both HBF and thrombophlebitis. Abnormal RNV might require contrast venography for definitive diagnosis of thrombosis; conversely, a normal RNV should immediately suggest the possibility of HBF. One practical approach in such patients would be to inject a bone imaging agent through the dorsal veins of the feet to obtain an RNV (Fig. 5). This can be followed by immediate blood-pool and delayed static images of all possible areas of HBF. If RNV abnormalities cannot be attributed to extrinsic compression by HBF, the diagnosis of venous thrombosis is more secure. This approach sacrifices the first-pass information and the diagnostic efficacy of this combined study has not been established.

The clinical presentation of acute HBF frequently suggested a variety of infectious processes resulting in requests for gallium citrate imaging. While gallium localization in HBF has not been described, it is not surprising that gallium accretion occurs in the inflammatory lesion of early HBF and in the bone and marrow elements of mature HBF.

Diphosphonates are potent in vivo and in vitro inhibitors of calcification and our data, though from a small series, are in good agreement with the literature on the clinical effectiveness of these agents in the medical treatment of HBF (*17*). If treatment is to be effective it should ideally be instituted before there is radiographic evidence of heterotopic ossification.

HBF is a relatively common disease in the setting of neurologic insult, soft-tissue trauma, and joint arthroplasty. On the basis of this review, we can make certain suggestions to optimize the diagnosis and management of HBF.

1. Three-phase RNBI should be done in all patients suspected of HBF, even if an abnormal or normal but rising SAP is the only evidence of disease activity.

2. The first-pass study should examine the area of clinical suspicion and immediate blood-pool images should examine this and all other areas of possible disease distribution.

3. Delayed static images of all areas susceptible to HBF are indicated. If static images are negative, in the presence of hyperemia, repeat RNBI should be performed in 1 wk.

4. Radiographs may be obtained to demonstrate evidence of soft-tissue calcification but should not be relied on for early diagnosis.

5. If oral diphosphonate therapy is to be used, it should be started at the first symptom of disease or the earliest observed rise in SAP, pending imaging confirmation.

6. HBF should be considered in the differential of all patients referred for venography for suspected thrombophlebitis if the clinical setting is appropriate.

Finally, prospective studies are needed to define the relationship of serum calcium changes to the onset of HBF and to evaluate the clinical utility of serial RNBI studies (quantitative and qualitative) in monitoring disease activity.

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