

Bone Scintigraphy in the Detection of Chronic Recurrent Multifocal Osteomyelitis

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In this study, we describe the importance of the whole-body bone scan in diagnosing the multifocality of chronic recurrent multifocal osteomyelitis (CRMO) and in distinguishing it from unifocal acute hematogenous osteomyelitis. **Materials:** The medical records and two-phase, whole-body bone scans of 14 patients (mean age 10.5 yr) with the diagnosis of CRMO, were retrospectively reviewed. The diagnosis of CRMO was based on bone biopsy in 9 patients and clinical course/laboratory findings in 5. Bone scans were evaluated for geographic and anatomic locations of their lesions. Correlative radiographs of areas of abnormal uptake were performed to assess the radiographic appearance of the lesions. **Results:** The presentation of the disease was localized to one painful, tender and swollen periarticular site 86% of the time. The number of lesions detected by bone scan varied from 1–18 (mean 6). Most lesions were metaphyseal, proximal or distal tibial lesions. Purely sclerotic or mixed (sclerosis and lysis) lesions were found on radiographs. Bilateral lesions were seen in 64% of patients. Biopsies were negative for organisms in all patients and exhibited subacute or chronic histologic changes in most instances. Complications of chronic hyperemia included marked overgrowth (5), diffuse demineralization (1), angular deformity (1) and length discrepancy (1). **Conclusion:** The identification of the multifocal configuration of the disease process by two-phase (soft-tissue and delayed) whole-body bone scintigraphy results in appropriate diagnosis and therapy of CRMO. Additional sites for possible bone biopsy become apparent for exclusion of other diagnoses. Supportive (nonsteroidal, anti-inflammatory medication) instead of antimicrobial therapy can be initiated with significant cost savings.

Key Words: angular deformity; bone scan; cost savings; chronic recurrent multifocal osteomyelitis; pinhole; SPECT

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Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition occurring in children and adolescents. It was first described by Giedion et al. (1) in 1972 as a “subacute and chronic symmetrical process” with multiple symmetric lytic lesions in the metaphyses of tubular bones. The osseous features were typical of osteomyelitis, but no pathogens were isolated from the affected areas. Giedion suggested this was an autoimmune process with infection as a precipitating factor. Bjorksten et al., in 1980, proposed the term CRMO (2), because the disease showed a benign, self-limited clinical course with periodic exacerbations and remissions. The initial clinical complaints are usually unifocal and feature inflammatory symptoms. Fewer than 100 cases of this disorder have been described in the literature since 1972, but the condition is probably much more common than suspected. Whole-body bone scintigraphy, when properly performed and interpreted, permits the early recognition of multiple unsuspected osseous lesions, thus the proper diagnosis of CRMO and its appropriate therapy. The

elimination of unnecessary regimens of intravenous and oral antimicrobial regimens proves to be much more cost effective. This article details the characteristic bone scan findings, as well as the adjunct techniques, that enhance the ability to make the diagnosis of CRMO.

MATERIALS AND METHODS

The medical records and imaging studies of 14 patients (8 women, 6 men; age range 6–21 yr) treated at the DuPont Hospital for Children for CRMO between 1986 and 1996 were retrospectively analyzed. Diagnosis of CRMO was based on bone biopsy in 9 patients and clinical course/laboratory findings in 5. Cultures of specimens were processed for aerobic and anaerobic bacteria, fungi and mycobacterium species. Bone biopsies in 9 patients (64%) were performed to exclude other diagnoses. Biopsy specimens were fixed in 70% formalin, and the embedded blocks were cut in sections and stained with hematoxylin and eosin.

To be included in this study, a patient must have had at least one whole-body multiphase bone scan. Scans were two-phase studies (soft-tissue and delayed imaging) performed with ^{99m}Tc -methylene diphosphonate in a dose of 7.4 MBq/kg (200 $\mu\text{Ci/kg}$). The scans were performed using a small field-of-view gamma camera equipped with a high-resolution parallel-hole collimator. Specialized procedures included single-head SPECT in two patients and high-resolution pinhole collimation in another two patients. All patients had radiographic examinations of symptomatic sites. Additional correlative radiographs were obtained of most asymptomatic sites detected by scintigraphy. Radiographs were obtained in 76 of 85 osseous foci (90%).

RESULTS

The mean age at onset of symptoms was 10.5 yr. The most common presentation was a locally painful, tender and swollen periarticular site with progression in severity from days to weeks. Symptoms were present from 3 days to 2 yr before initial presentation (mean 5 mo) in 13 patients. One patient had known disease for 8 yr before presentation at our institution. The presentation was unifocal in 12 of 14 patients (86%). One patient exhibited weight loss, and no patients presented with pustulosis palmoplantaris. The blood counts were unremarkable except for a slight white blood cell count elevation in one patient and slight anemia in another. The Westergren sedimentation rate was performed in 13 patients with a mean of 49 mm/hr (range 11–116). The sedimentation rate was normal in 2 patients. Lyme tests (5 patients) and antinuclear antibodies (4 patients) were negative. The number of lesions in the skeleton detected by bone scan varied from 1 to 18 (mean 6 lesions). The geographic locations were metaphyseal (45 sites), metaphyseal-equivalent (19), diaphyseal (10), diaphyseal-metaphyseal (7), metaphyseal-epiphyseal (2) and unclassifiable (2). The radiographic findings included sclerosis (28 sites), mixed sclerosis and lysis (23), normal (22), not imaged (9) and lytic (3). The most common skeletal locations of these lesions were the lower extremities (42 sites), the upper extremities (13), the pelvis (11)

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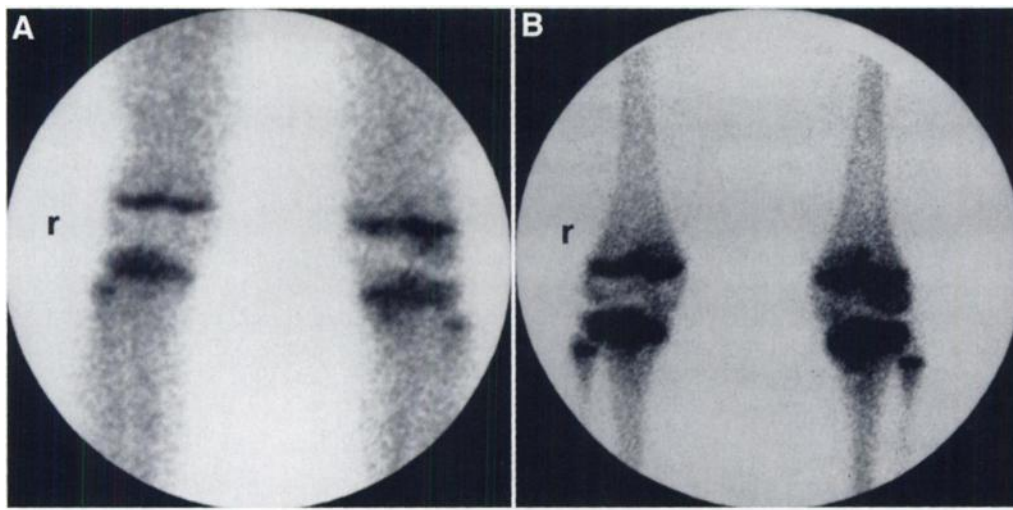


FIGURE 1. Symmetric epiphyseal disease. (A) Anterior soft-tissue images of knees with bilateral symmetric involvement of proximal tibial epiphyses. Left tibial metaphysis also involved as well as lateral portion of left distal femoral epiphysis. (B) Anterior delayed images of knees demonstrating involvement of proximal tibiae with some difficulty in separating physeal activity from epiphyseal and metaphyseal uptake. Definite increased uptake in left distal femoral epiphysis.

and the thoracic cage (11). The most common anatomic sites were the proximal and distal tibiae (23 sites), the metatarsals (9), the ribs (7) and femora (7). Bilateral symmetric scintigraphic patterns were seen in 9 of 14 patients (64%) at 14 sites [proximal tibiae 5 sites, distal tibiae 4, distal ulnae 2, distal

femora, proximal fibulae and clavicles (Fig. 1)]. Bilateral radiographic changes were confirmed in 11 of 14 locations. In 7 of 11 sites, the lesions were symmetric in extent (amount of osseous involvement) and phase (sclerosis, lysis) of the disease. The histopathology in 9 patients was classified as acute,

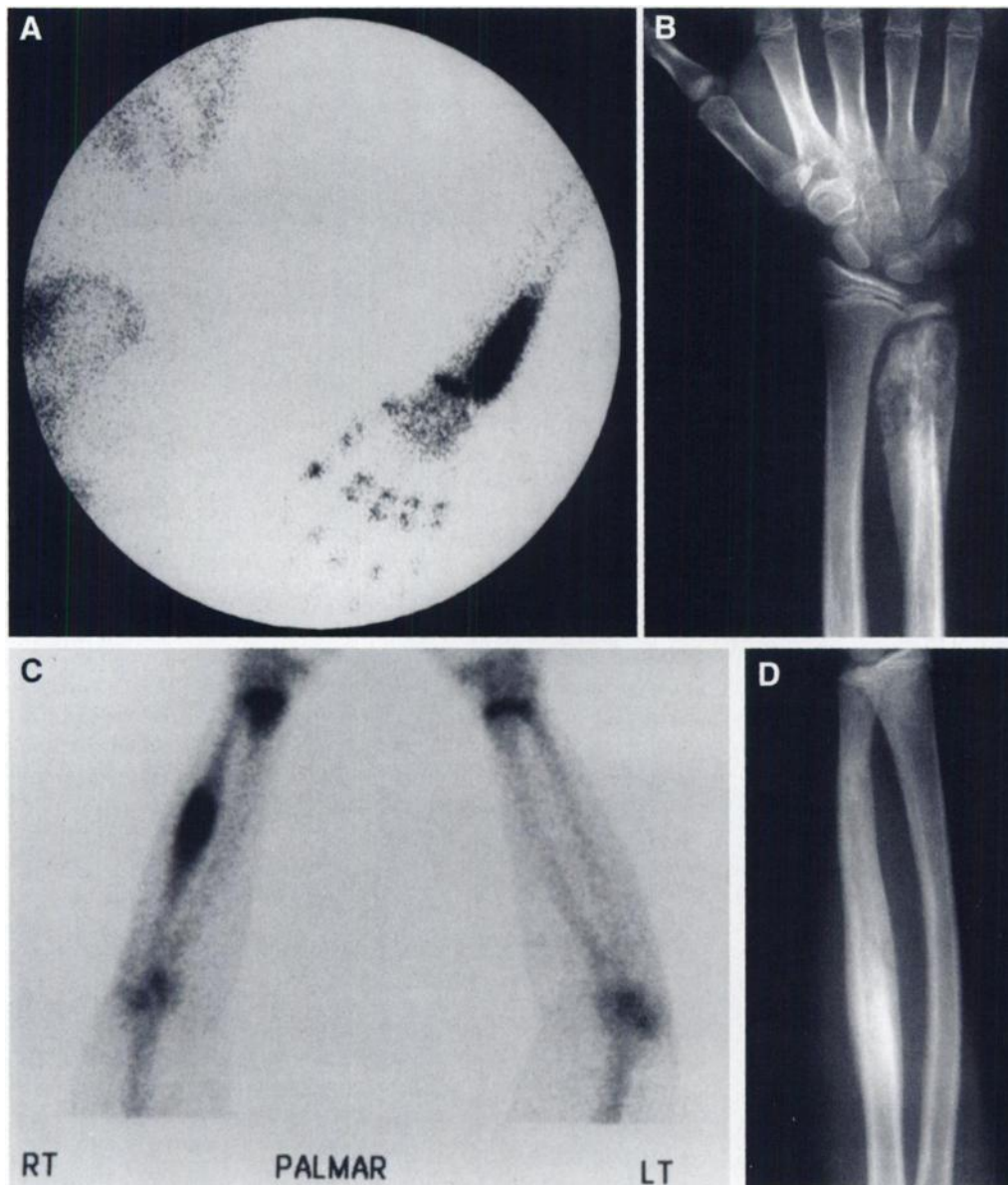


FIGURE 2. Migrating lesion. (A) Metaphyseal-diaphyseal location of intense activity in distal ulna on delayed posterior image of right wrist. (B) Posterior-anterior radiograph demonstrating an expanded area of both sclerosis and lysis in metaphyseal-diaphyseal region of right distal ulna. (C) Three years later, anterior delayed scan exhibiting activity in right mid-ulnar diaphysis and distal radial metaphysis. (D) Anterior-posterior view of right forearm showing mainly sclerotic expanded diaphysis and subtle sclerosis in distal right radial metaphysis.

subacute and/or chronic depending on the presence and prevalence of plasma cells, lymphocytes, neutrophils, macrophages, necrosis and fibrosis. Most of the lesions exhibited a combination of mainly subacute and chronic features of infection microscopically and a mixture of sclerosis and lysis radiographically. The radiographic pattern of two lesions was predominantly lytic, one with acute and the other chronic, histopathology. No organisms were cultured from any of the specimens except for aspergillus, felt to be a contaminant in a patient with evidence of sterile disease for at least 8 yr. Complications of the chronic hyperemic process included marked overgrowth (5 patients) (Fig. 2), angulation (1 patient), diffuse demineralization (1 patient) and length discrepancy (1 patient). Biopsies were not obtained in those patients with clinical findings (mildly-elevated sedimentation rate, lack of systemic findings), geographic locations (hands, feet, clavicles, metaphyses of distal ulnae, radii and fibulae) and radiographic appearances (combination of lytic, sclerotic and mixed patterns in the same individual) not typical for neoplasia in pediatric patients (6–21 yr). These patients were followed closely with periodic clinical and radiographic evaluations.

DISCUSSION

CRMO has appeared in the literature under many different names including subacute symmetric osteomyelitis (1), chronic symmetric osteomyelitis (3), chronic multifocal symmetric osteomyelitis (4), chronic multifocal cleidometaphyseal osteomyelitis (5) and tumorous osteomyelitis (6,7). Osteitis of the anterior chest wall is the most common component of a new disease complex, known as SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis), that has been described recently in adults by rheumatologists. Symmetry, multifocality, metaphyseal location and destruction of bone are not always necessary findings to make the diagnosis of CRMO. Symmetric occurrence of osseous lesions is not uniformly characteristic of CRMO (64% of the patients in our series). Symmetric disease refers to bilateral lesions, but these bilateral foci are only sometimes (64% in our series) in the same phase of the disease process. In the literature, the most frequent anatomic sites (two-thirds of patients) of bilateral changes were the distal femora or proximal tibiae (8). In our study population, the proximal and distal tibiae were the most frequent [69% of symmetric disease sites (Fig. 1)]. Typical clavicular lesions probably represent a unifocal manifestation of CRMO as shown in Figure 3. One of our patients had a single bone, typical clavicular presentation (9). In the literature, the tibia (27%) and the clavicle (13%) are most commonly involved bones (2). In our series, the tibia (26%) was also among the most commonly affected bones. The clavicle contributed only 5% of the osseous lesions. The metaphysis (53% in our series) is the most common location of CRMO, similar to typical hematogenous osteomyelitis. The lesions also can be diaphyseal, epiphyseal, metaphyseal-equivalent, metaphyseal-epiphyseal and metaphyseal-diaphyseal (8). The proximal and distal juxtaphyseal regions of the tibiae are involved most commonly in the literature [26% in our series (Figs. 1 and 4)]. The radiographic appearance varies from lysis or sclerosis to a mixture of both lysis and sclerosis.

Women are affected more commonly than men (8:6 in our study population). Children and adolescents comprise most of the population of patients with CRMO. The disease occurs in the latter half of the first decade and the first half of the second decade of life (mean age 10.5 yr). A few adults have been reported with CRMO. In our population of patients, there was a 21-yr-old with an 8-yr history of recurrent disease before his presentation at our institution. Patients with CRMO may expe-

rience symptoms for up to 15 yr, with the average being 2 yr (10). The clinical spectrum is nonspecific with an insidious onset of localized warmth, tenderness, pain and swelling at one site. Other asymptomatic foci can be present at the time of presentation (Fig. 5). New sites of involvement can occur as old sites resolve or are in various phases of healing, thus the name, chronic recurrent multifocal osteomyelitis. An association of CRMO with palmoplantar pustulosis (a rare chronic relapsing condition causing red patches and pustules on the soles of the feet and palms of the hands) has been emphasized in the literature. In fact, it is not common in children with CRMO. None of our patients exhibited this cutaneous manifestation. In a study by Cyniak and Pais (11) in 1986, 9 of 33 cases of CRMO in children were reported to exhibit palmoplantar pustulosis. This manifestation appears rarely in the U.S. with only one of the above-reported 9 patients living in the U.S. Systemic manifestations of CRMO may include pain with weight bearing, a low-grade fever and general malaise. Weight loss also may occur. Laboratory investigations demonstrate elevation of antistreptolysin titers in 25% of patients (12), and there may be a history of previous throat infection. The erythrocyte sedimentation rate is frequently mildly elevated. The white blood cell count is usually normal or slightly elevated. Indolent bacteria, slow-growing organisms and viral agents have been implicated as causative agents. Most blood and bone cultures have been negative (13).

The lesions of CRMO are almost always multiple, but the initial symptoms manifest only in one location (86% of the time in our series). The ability to recognize multifocality of this disease rests in the use of the bone scan. The bone scan is able, with one injection of radiotracer, to detect many asymptomatic, radiographically obscure foci of the disease. These areas of increased uptake can be correlated with radiographs and may prove to be more surgically accessible to biopsy. Unnecessary blood tests and recurrent regimens of antimicrobial therapy can be prevented by initially recognizing the disease process as CRMO. Many of the lesions are not recognizable on plain radiography before localization by bone scintigraphy. Bilateral juxtaphyseal processes can be difficult to resolve on routine delayed planar images. The soft-tissue phase images help to localize the small lesions adjacent to the active physis (metaphysis, epiphysis or epiphysis-metaphysis) and subtle bilateral symmetric metaphyseal involvement (Fig. 1). Specialized techniques of magnification and tomography can be added to the imaging regimen to refine the diagnosis of CRMO. Pinhole high-resolution magnification images also are able to differentiate the complex intense activity of the juxtaphyseal lesions (Fig. 4). SPECT enables the detection of subtle activity differences in complex osseous environments (metaphyseal-equivalent lesions of the pelvis, ribs of the thorax, end-plates of the vertebrae), discrimination of vertebral regions (pars interarticularis, spinous processes, pedicles of vertebrae) (Fig. 5) and separation of contiguous small bones of the hands and feet. Bone scans can assess the metabolic activity of chronic lesions. Radiographic sclerosis may at times be inactive and display a normal bone scan image (Fig. 6).

The diagnosis of CRMO remains a challenge with its diagnosis being one of exclusion. The differential diagnosis includes multifocal bacterial osteomyelitis, multifocal trauma, pauciarticular rheumatoid arthritis, histiocytosis, leukemia/lymphoma, multifocal primary neoplasms (Ewing's sarcoma or osteosarcoma) and metastatic secondary malignancies (i.e., sarcoma, neuroblastoma). If attention is focused on a single symptomatic lesion, such as a diaphyseal sclerotic lesion with periosteal reaction (Figs. 2,3), the neoplasm becomes more of a

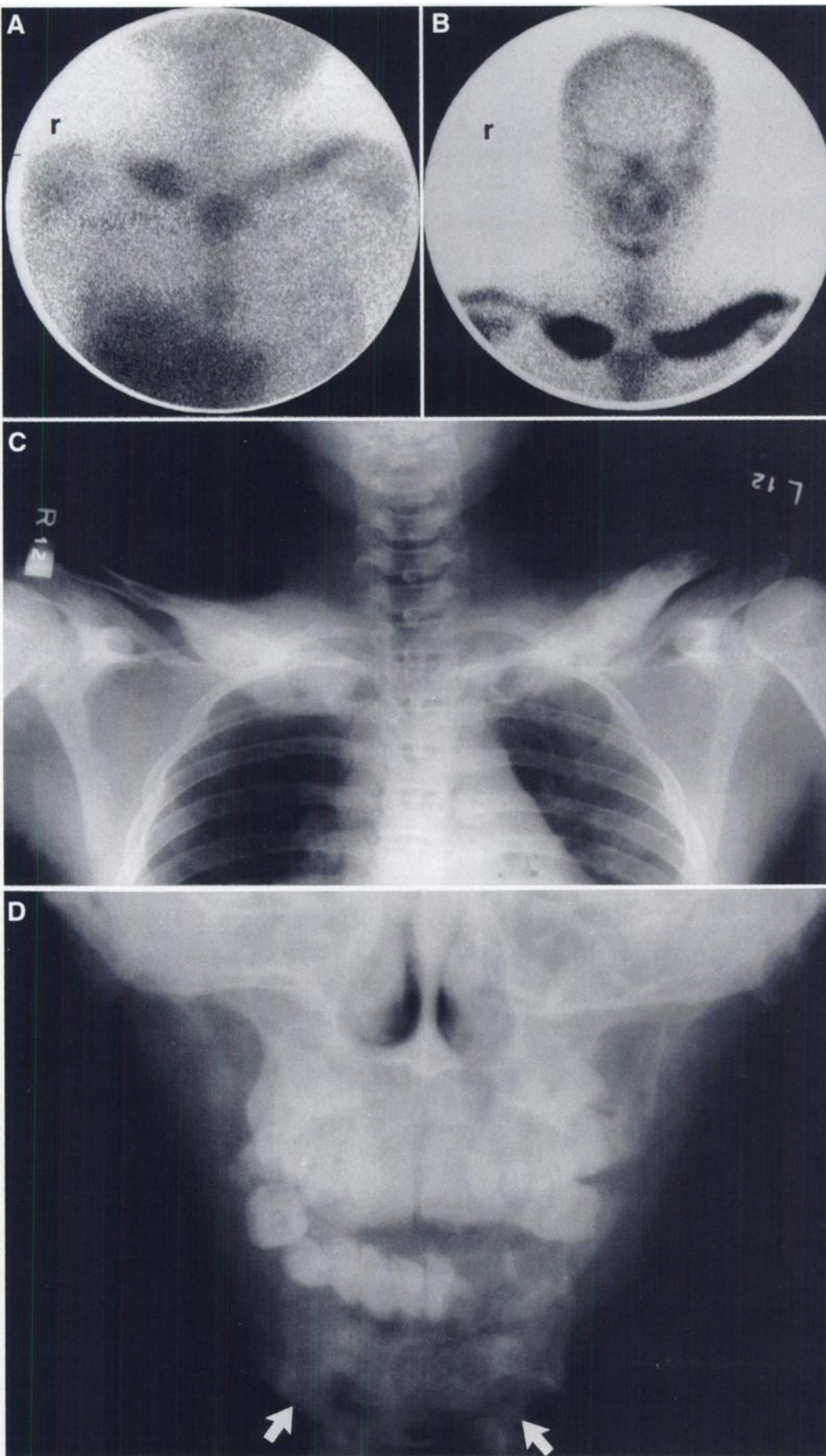


FIGURE 3. Tumorous clavicles and vanishing mandible in 21-yr-old man with 8 yr of symptoms. (A) Anterior soft-tissue phase of thorax demonstrating bilateral hyperemia of clavicles, left more extensive than right. (B) Anterior delayed images of thorax maintaining bilateral, but asymmetric, involvement of clavicles and minimal central uptake of activity in mandible. (C) Anterior radiographs with mainly sclerotic tumorous involvement of proximal two-thirds of right clavicle and entire left clavicle. (D) Some residual mineralization in mental portion of mandible (arrows) and lack of any mineralization in mandibular rami. Some floating teeth on right side.

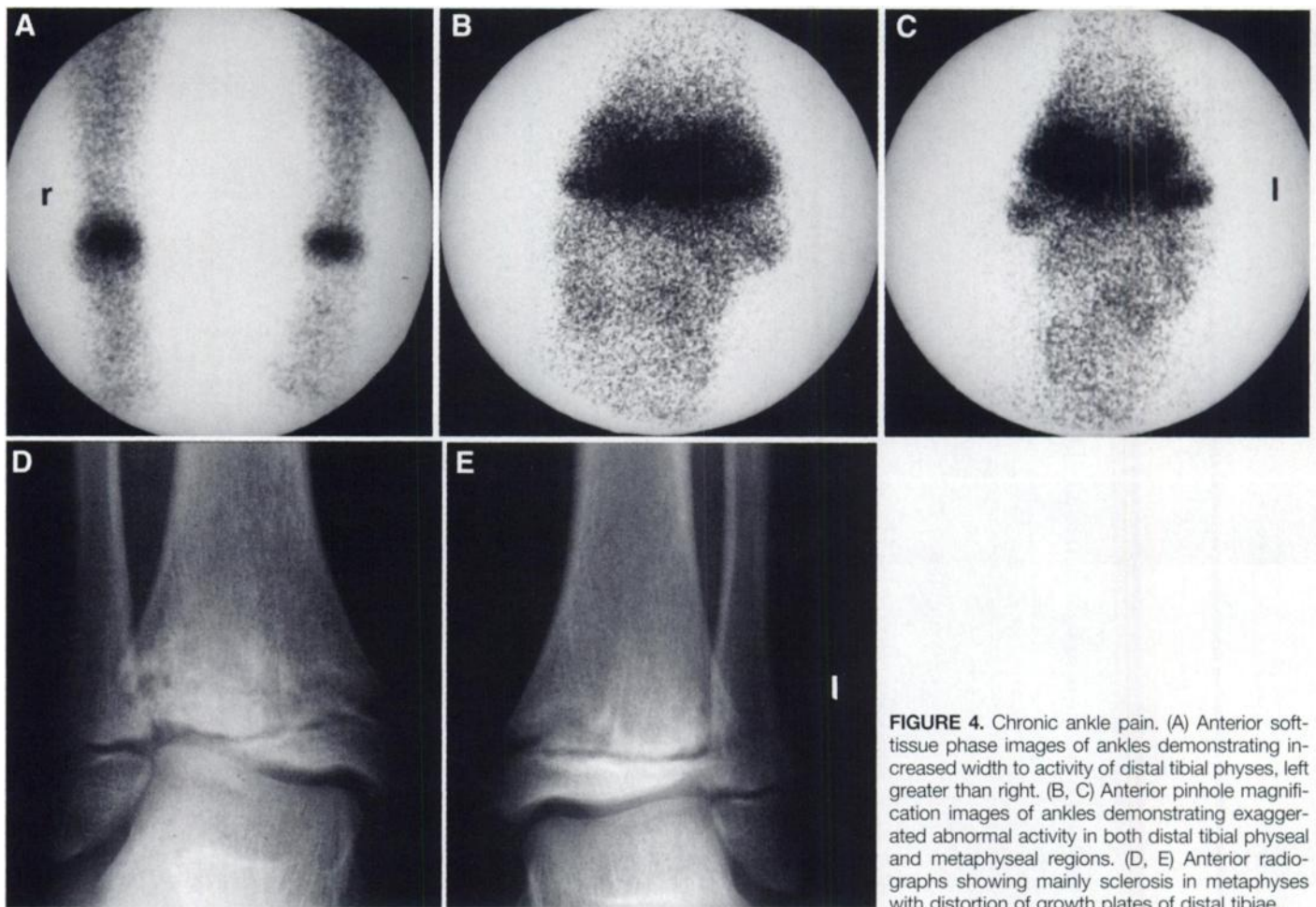


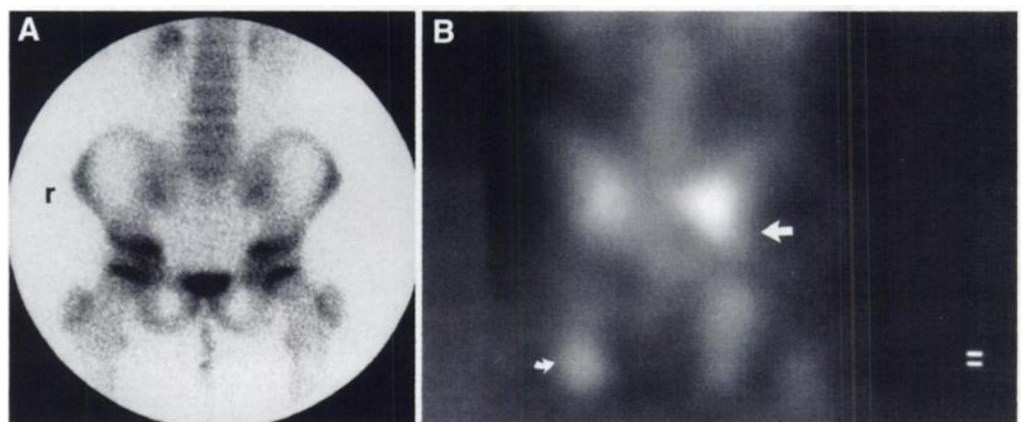
FIGURE 4. Chronic ankle pain. (A) Anterior soft-tissue phase images of ankles demonstrating increased width to activity of distal tibial physes, left greater than right. (B, C) Anterior pinhole magnification images of ankles demonstrating exaggerated abnormal activity in both distal tibial physal and metaphyseal regions. (D, E) Anterior radiographs showing mainly sclerosis in metaphyses with distortion of growth plates of distal tibiae.

consideration than the infection. The bone scan may reveal other more characteristic metaphyseal lesions to incriminate infection. Metaphyseal lesions in the forearms, the small bones of the hands and feet and the more typical clavicular lesions mitigate against neoplasm (Figs. 2, 3 and 6). However, bone biopsy is mandatory for a definite diagnosis. Biopsies usually consist of extensive fibrosis with focal infiltration of plasma cells, often with variable numbers of neutrophils, lymphocytes and histiocytes. Cultures of biopsy specimens usually remain negative. In addition, necrotic bone and granulomas can be seen. The granulomas can be tuberculoid, particularly around necrotic bone. Caseation and acid-fast bacilli are not typically seen. The greater the degree of suppuration with polymorphonuclear infiltration, the more acute the process. The most

common lesions in our series, as well as the literature, are in the subacute and chronic phases of inflammation.

Antibiotics have been shown to have no impact on the course of the disease. Systemic steroid therapy may have some beneficial effect. Symptomatic relief is achieved with nonsteroidal anti-inflammatory medications, analgesics and other supportive measures. The disease process usually resolves spontaneously with time. The potential for permanent deformity with paraphyseal involvement has not been emphasized. Premature physal fusion with shortening or angular deformity results from the chronic hyperemia of this disease process (Fig. 6). Coxa magna, limitation of subtalar motion, valgus of the ankle (12) and progressive kyphosis (14) ultimately requiring spinal fusion have been reported. Complications of bone short-

FIGURE 5. Asymptomatic subtle lesions. (A) Anterior image of pelvis demonstrating either normal or slightly more intense uptake in left sacroiliac joint and right ischium. (B) Representative coronal slice of SPECT showing more uptake in left sacroiliac region (arrow) and inferior aspect of right ischium (curved arrow), which was confirmed with additional transaxial and sagittal projections.



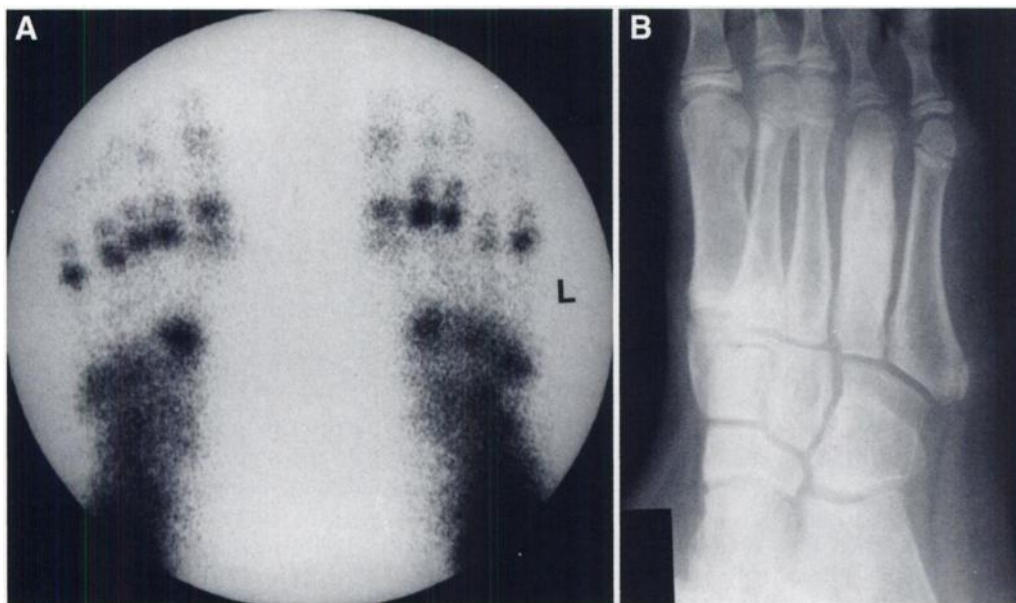


FIGURE 6. Premature physal fusion secondary to chronic hyperemia. (A) Anterior delayed image of feet demonstrating shortening and reduction in activity of physis of fourth left metatarsal, relative increased uptake in physes of left second and third metatarsals (just beginning physiologic closure). (B) Anterior view of left foot with sclerotic and broadened fourth metatarsal (not active on bone scan) with prematurely fused physis from several years of chronic hyperemia preceding current bone scan. Physes of second and third metatarsals are beginning to fuse.

ening of a metatarsal and valgus angulation of the ankle occurred in two of our patients. Diaphyseal overgrowth occurred in four instances (Figs. 2, 3 and 6). Diffuse demineralization of the mandible with loosening and loss of teeth occurred in another patient.

CONCLUSION

The scintigraphic patterns we reviewed in our series of 14 patients with CRMO emphasized the importance of performing whole-body scans of children from 5–15 yr of age who present with unifocal complaints suspicious for the presence of osseous infection. The adjuncts of soft-tissue imaging of the extremities, pinhole projections, as well as SPECT, can add to the refinement of the diagnosis. With the maximum number disease foci determined, the most accessible lesion can be biopsied. The knowledge of the existence of CRMO at presentation, rather than an osteomyelitis presumably of staphylococcal origin, can prevent needless intravenous and oral antimicrobial therapy and result in significant cost savings. Most therapy for CRMO is supportive, and relief is obtained with nonsteroidal anti-inflammatory medications. Even though most cases of CRMO resolve eventually with an uneventful outcome, patients should be closely followed with the awareness of the possible complications of the presence of a chronic hyperemic bone disease.

REFERENCES

- Giedion A, Holthusen W, Masel LF, et al. Subacute and chronic "symmetrical" osteomyelitis. *Ann Radiol* 1972;15:329–342.
- Bjorksten B, Boquist L. Histopathological aspects of chronic recurrent multifocal osteomyelitis. *J Bone Joint Surg Br* 1980;62:376–380.
- Gustavson KH, Wilbrand HF. Chronic symmetric osteomyelitis: report of a case. *Acta Radiol* 1973;15:551–557.
- Speer DP. Chronic multifocal symmetric osteomyelitis [Editorial]. *Am J Dis Child* 1984;138:340.
- Probst FP. Chronic multifocal cleido-metaphyseal osteomyelitis: report of a case. *Acta Radiol* 1976;17:531–537.
- Starinsky R. Multifocal chronic osteomyelitis with exuberant periosteal formation. *Pediatr Radiol* 1991;21:455–456.
- Kozlowski K, Anderson RJ, Hochberger O, et al. Tumorous osteomyelitis. *Pediatr Radiol* 1984;14:404–406.
- Manson D, Wilmot DM, King S, et al. Physal involvement in chronic recurrent multifocal osteomyelitis. *Pediatr Radiol* 1989;20:76–79.
- Jurik AG, Moller BN. Inflammatory hyperostosis and sclerosis of the clavicle. *Skeletal Radiol* 1986;15:284–290.
- Tan BS, Nayanar V, Mansberg R, et al. Two cases of chronic recurrent multifocal osteomyelitis: radiological and scintigraphic findings. *Australas Radiol* 1996;40:437–441.
- Cyriak D, Pais MJ. Chronic recurrent multifocal osteomyelitis. *Skeletal Radiol* 1986;15:32–39.
- Brown T, Wilkinson RH. Chronic recurrent multifocal osteomyelitis. *Radiology* 1988;166:493–496.
- Hummell DS, Anderson SJ, Wright PE, et al. Chronic recurrent multifocal osteomyelitis: are the mycoplasma involved? [Letter] *N Engl J Med* 1987;317:510–511.
- Carr AJ, Cole WG, Roberston DM, et al. Chronic multifocal osteomyelitis. *J Bone Joint Surg Br* 1993;75:582–591.