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Imaging of Multifocal and Diffuse Sclerotic Bone Lesions

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This module meets the American Board of Radiology's (ABR's) criteria for self-assessment toward the purpose of fulfilling requirements in the ABR Maintenance of Certification (MOC) program. Please note that in addition to the SA-CME credits, subscribers completing the activity will receive the usual ACCME credits.

After participating in this activity, the diagnostic radiologist should be better able to identify and interpret the imaging findings of multifocal and diffuse sclerotic bone lesions on radiographs and cross-sectional imaging.

CME Category: General Radiology Subcategory: Musculoskeletal Modality: Radiography

Key words: Multifocal Sclerotic Bone Lesions, Diffuse Sclerotic Bone Lesions

Sclerotic bone lesions are encountered commonly in clinical practice. The differential diagnosis remains broad and includes traumatic, vascular, infectious, drug-induced, neoplastic, metabolic, myeloproliferative, developmental, and miscellaneous causes. This article seeks to discuss the various imaging findings in the most commonly encountered multifocal and diffuse sclerotic bone lesions with emphasis on differentiating features through imaging and clinical correlation.

Introduction

Sclerotic bone lesions are regions of increased density within the bone. The broad spectrum of etiologies includes benign and malignant tumors, infection, trauma, vascular, drug induced, metabolic, myeloproliferative, developmental, and miscellaneous causes. The imaging appearance of the sclerotic bone, clinical history, and patient age can be helpful in narrowing the differential diagnosis.

Sclerotic bone lesions may be categorized as focal, multifocal, or diffuse (Table 1). Focal sclerotic bone lesions are single discrete lesions within the skeleton that demonstrate increased density, and they were discussed in volume 38, number 5, 2014. Multifocal lesions manifest as multiple discrete regions of increased density within the involved bone, whereas diffuse sclerotic bone lesions demonstrate widespread increased density. Although many causes of skeletal sclerosis can be grouped in multiple categories (e.g., focal and multifocal or both multifocal and diffuse), the various causes of sclerotic bone lesions are discussed in this article in their most common category. For example, osteoblastic metastases can be focal, multifocal, or diffuse, but they most frequently are multifocal and, therefore, discussed under that heading.

Multifocal Sclerotic Bone Lesions

Neoplasm

Osteoblastic Metastases. Osteoblastic metastases represent sclerotic foci of tumor originating from a distant primary neoplasm, and they may be focal, multifocal, or diffuse. The primary tumors that most commonly cause sclerotic metastases in adults include carcinomas of the prostate, breast, lung, and bladder; and carcinoid and Hodgkin lymphoma. In children, the most frequent primary tumors causing sclerotic metastases are medulloblastoma, neuroblastoma, and Ewing sarcoma. The vertebrae,

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Table 1. Categories of Sclerotic Bone Lesions

Vascular Bone infarct Neoplasm Metastases (osteoblastic) Metabolic Paget disease Hyperparathyroidism/renal osteodystrophy **Developmental** Osteopoikilosis Miscellaneous Sarcoidosis **Tuberous sclerosis** Melorheostosis **Diffuse sclerotic bone lesions** Neoplasm Metastases (osteoblastic) Metabolic Hyperparathyroidism/renal osteodystrophy Myeloproliferative Mastocytosis **Myelofibrosis** Drugs Hypervitaminosis D Fluoride toxicity **Developmental** Pyknodysostosis Osteopetrosis

proximal femur, ribs, sternum, pelvis, skull, and shoulder girdle are involved most commonly, because these areas contain red marrow that persists into adulthood. Metastases are most often multiple, and patients commonly present with progressive axial pain that may be referred or radicular. Spinal compression fractures may occur, and there may be neurologic dysfunction in patients with spread of tumor from the spine to the epidural space.

Osteoblastic metastases most frequently involve the spine, often affecting both the vertebral body and posterior elements. Metastases can range from a few millimeters to involvement of the entire vertebral body, which produces diffuse sclerosis known as the "ivory vertebra." In other bones, radiography demonstrates multiple mottled areas of sclerosis within the

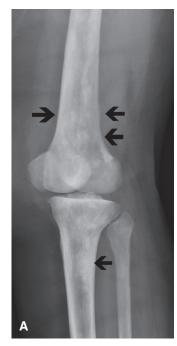
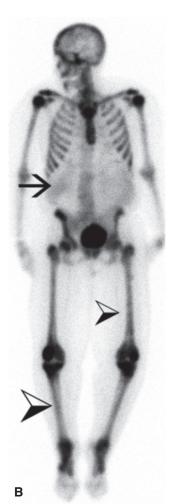


Figure 1. Neoplastic cause of multifocal sclerotic bone lesions. Osteoblastic metastases. *A*: Frontal radiograph of lower leg in a 70-year-old woman with breast cancer reveals multiple ill-defined, sclerotic lesions within the femur and the tibia (*arrows*). Breast cancer metastases can be both sclerotic and lytic. *B*: Anterior planar image from a Tc 99m methylene diphosphonate bone scan dem-



onstrates the "superscan" appearance. There is relatively little radiotracer uptake within the kidneys (*arrow*) and soft tissues, with relatively increased uptake within bone (*arrowheads*).

involved bone (Figure 1A). CT may detect a paravertebral or epidural soft-tissue mass adjacent to a metastatic focus in the spine. On MR imaging, osteoblastic metastases have low signal on T1-weighted images, variable signal on T2-weighted images, and variable enhancement. MRI is superior to CT for demonstrating a paravertebral or epidural soft-tissue mass associated with a metastatic focus in the spine. Sclerotic metastases typically show increased tracer uptake on bone scintigraphy. This may produce the so-called "superscan," with diffusely increased skeletal uptake and relatively decreased radionuclide in the soft tissues and kidneys (Figure 1B).

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Figure 2. Developmental cause of multifocal sclerotic bone lesions. Osteopoikilosis. Frontal radiograph of the pelvis in a 41-year-old man shows numerous punctate oval sclerotic foci within the pelvis and the femurs bilaterally (*arrows*). Note epiphyseal involvement, which helps differentiate osteopoikilosis from osteoblastic metastases.

Osteoblastic metastases most frequently involve the spine, often affecting both the vertebral body and posterior elements.

In addition to osteoblastic metastases, the differential diagnosis for an ivory vertebra includes Paget disease of bone and lymphoma. Paget disease of bone typically demonstrates concomitant expansion of the involved bone with thickened trabeculae. The clinical history and the presence of extensive lymphadenopathy can suggest lymphoma as the underlying cause for an ivory vertebra, although at times it may be impossible to differentiate lymphoma from osteoblastic metastasis.

The treatment of osteoblastic metastases depends on the primary tumor but commonly includes radiation therapy and possible chemotherapy.

Developmental

Osteopoikilosis. Osteopoikilosis is an autosomal dominant, sclerosing bone dysplasia that represents multiple enostoses. These multiple bone islands develop in childhood and never regress into adulthood.¹ They are asymptomatic and typically cluster around joints and are aligned parallel to surrounding trabeculae (Figure 2). The pathognomonic appearance on radiographs is sufficient for the diagnosis. However, it is essential that osteopoikilosis not be mistaken for a pathologic condition, such as osteoblastic metastases, which have a more random distribution, irregular margins, and typically spare the epiphyses. Osteopoikilosis requires no treatment.

The multiple bone islands of osteopoikilosis develop in childhood and never regress in adults; typically cluster around joints and spare the epiphyses.

Miscellaneous

Sarcoidosis. Sarcoidosis is an inflammatory disorder resulting in noncaseating granulomas in virtually any tissue in the body. It most commonly occurs in the third or fourth decade, especially in African-American women. Sarcoidosis involves the musculoskeletal system in about 5% to 10% of affected patients, about 90% of whom also have characteristic radiographic findings on chest radiographs.² Musculoskeletal sarcoidosis is rarely symptomatic, but it can cause pain and arthralgias. It usually produces lacy lytic bone lesions in the hands and feet. The rarely multifocal sclerotic bone lesions produced by sarcoidosis may occur anywhere in the skeleton (Figure 3A), particularly in the vertebral bodies. A definitive diagnosis usually requires biopsy. Sarcoidosis usually responds well to corticosteroid therapy.

Although the bone lesions of sarcoidosis usually are lytic in the hands and feet, rarely they are multifocal and sclerotic anywhere in the skeleton.

Tuberous Sclerosis. Tuberous sclerosis is a rare autosomal dominant neurocutaneous syndrome that can cause multifocal sclerotic bone lesions. Children with tuberous sclerosis typically present with seizures, mental deficiency, and adenoma sebaceum. Although the tuberous sclerosis complex is associated more commonly with renal and intracranial hamartomas, skeletal manifestations are quite common and occur in 40% to 65% of patients.³ Children with this syndrome can have multifocal dense sclerotic foci (Figure 3B), which most often affect the bones of the cranial vault and the posterior portions of the vertebral bodies.³ Hypertrophic osteoarthropathy may develop in the hands and feet. Treatment varies and is targeted toward individual symptoms.

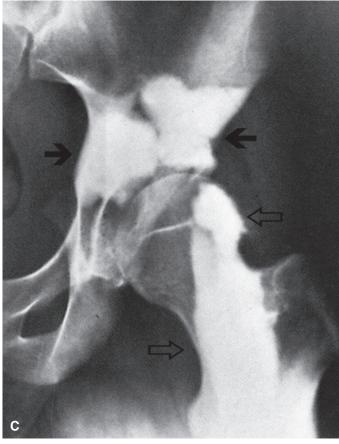
Melorheostosis. Melorheostosis is a rare, nonhereditary disease that also results in multifocal sclerotic lesions within bone as a result of failure of intramembranous bone formation. Although melorheostosis usually is asymptomatic, presenting in teenagers and young adults, it may occasionally cause pain, stiffness, or joint contractures. Melorheostosis usually involves one bone or multiple bones of a single extremity, along a sclerotomal distribution.⁴ A lower extremity is most commonly affected, and there is never involvement of the face or skull. Radiographs demonstrate irregular sclerotic thickening of the cortex that begins at the proximal end of bone and extends distally, resembling wax flowing down a burning candle (Figure 3C). Cortical thickening is primarily periosteal but may be endosteal with intramedullary extension. Treatment is supportive and aimed at reducing pain. Sympathectomy may be required in severe cases.

Melorheostosis most commonly affects the lower extremities but never involves the bones of the face or skull.

Diffuse Sclerotic Bone Lesions Metabolic

Hyperparathyroidism/Renal Osteodystrophy. Hyperparathyroidism results from excessive levels of parathyroid hormone and may be primary, secondary, or tertiary. Primary hyperparathyroidism typically occurs in a middle-aged adult with a parathyroid adenoma. Secondary hyperparathyroidism is generally a complication of chronic renal disease in a patient





older than 40 years. Tertiary hyperparathyroidism occurs from a hyperplastic autonomously functioning parathyroid gland that is unresponsive to serum calcium levels. Most patients with hyperparathyroidism are asymptomatic, although they

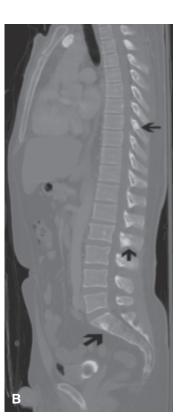


Figure 3. Miscellaneous causes of multifocal sclerotic bone lesions. A: Sarcoidosis. Frontal radiograph of the hand of a 31-year-old woman reveals soft-tissue swelling and erosive change around the third proximal interphalangeal joint with lytic lace-like lesion in the third middle phalanx (arrow). There are also multifocal sclerotic lesions in the third proximal phalanx (arrowhead) and distal ulna (open arrow) that are much less common in sarcoidosis. B: Tuberous sclerosis. Sagittal reformatted CT image of the spine demonstrates multiple sclerotic lesions within various parts of the spine (arrows). C: Melorheostosis. Frontal radiograph of the pelvis in a 29-year-old woman shows cortical undulating hyperostosis ("candle wax") that extends into the intramedullary cavity of the left iliac bone (closed arrows) and proximal femur (open arrows).

may present with nephrolithiasis, nonspecific bone pain, nausea, vomiting, and anorexia.

The most characteristic radiographic appearance of secondary hyperparathyroidism in chronic renal failure is the "rugger jersey" spine. This radiographic feature manifests as sclerotic bands with irregular endosteal margins at the superior and inferior margins of multiple contiguous vertebral bodies.⁵ There often is a "smudgy" transition between the normal and dense bone. In the skull, a typical radiographic finding is the "salt and pepper" skull, in which patchy sclerosis is superimposed on generalized bone resorption. Other common areas of diffuse osteosclerosis in hyperparathyroidism are the pelvis and the metaphyses of long bones (Figure 4).

Neither CT nor MRI plays a significant role in identifying the primary cause of the bone disease in patients with hyperparathyroidism. Parathyroid sestamibi scintigraphy is the primary imaging modality for localizing a parathyroid adenoma in primary hyperparathyroidism. Bone scintigraphy can demonstrate the "superscan" appearance of intense skeletal uptake in the setting of secondary hyperparathyroidism.

Primary hyperparathyroidism usually is treated with surgical resection of the parathyroid adenoma. The treatment of secondary hyperparathyroidism includes phosphate binders, vitamin D replacement, and ultimately renal transplantation.

Myeloproliferative

Mastocytosis. Mastocytosis is a rare heterogeneous neoplastic process that results from mast cell proliferation, predominantly in the gastrointestinal tract, skin, and skeleton. Most patients are adults, who present with abdominal pain, diarrhea, urticaria pigmentosa, and bone pain from pathologic fractures in the spine.

The diagnosis of mastocytosis is made by bone biopsy. Nevertheless, diffuse osteosclerosis is a characteristic radiographic pattern in the skeleton (Figure 5A). On MR imaging,

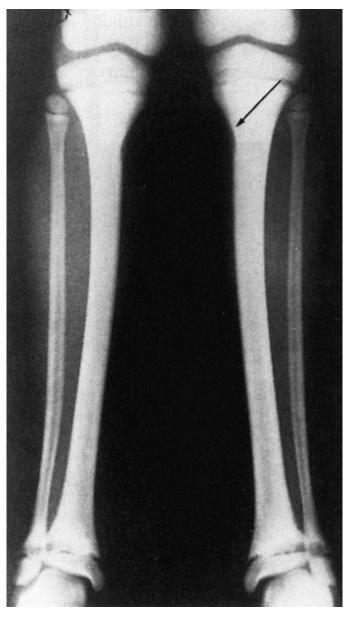


Figure 4. Metabolic causes of diffuse sclerotic bone lesions. Secondary hyperparathyroidism. Bilateral frontal radiographs of the lower legs of an 11-year-old boy with chronic glomerulonephritis, renal rickets, and secondary hyperparathyroidism shows diffuse increased skeletal density. Note widened zone of provisional calcification at the physes of the ankles and subperiosteal resorption along the medial margin of the upper tibial shaft (*arrow*).

the involved bone has low signal on T1-weighted images and is hyperintense on T2-weighted images. However, if the lesion is densely sclerotic, it also will have low signal intensity on T2-weighted images. Cytoreductive therapy is employed only if the patient is symptomatic.

Myelofibrosis. Myelofibrosis is a chronic hematologic disorder in which the bone marrow is gradually replaced by fibrosis. This process occurs most commonly after the age of 60 years and is rare in children. It may be idiopathic or may be a result of such malignant or nonmalignant processes as leukemia and collagen vascular disease. Patients with myelofibrosis typically present with fever, fatigue, weight loss, night sweats, anemia, and hepatosplenomegaly.

In nearly 50% of patients with myelofibrosis, radiographs demonstrate widespread diffuse osteosclerosis that primarily involves the spine, ribs, and pelvis but also can involve the

long bones and skull. A characteristic radiographic finding is uniform obliteration of the fine trabecular margins of ribs, which results in sclerosis simulating "jail bars" crossing the thorax (Figure 5B). MRI demonstrates low signal intensity of the involved bones on all pulse sequences, indicating replacement of fatty marrow by fibrosis.

The bones involved with myelofibrosis demonstrate low signal intensity on all MR sequences and do not enhance on postcontrast sequences.

Myelofibrosis must be differentiated from diffuse osteoblastic metastases in patients with long-standing disease. Radiographically, myelofibrosis tends to have more diffuse and homogeneous bone involvement. On MR imaging, osteoblastic metastases usually demonstrate some enhancement in areas of viable tumor, whereas myelofibrosis does not enhance on postcontrast sequences.

The definitive treatment of myelofibrosis is allogenic bone marrow transplant.

Drugs

Vitamin D. Hypervitaminosis D can occur in both children and adults and can be a cause of diffuse osteosclerosis. In children, it is associated with treatment for rickets or the accidental ingestion of large quantities of vitamin D. Typical symptoms of hypervitaminosis D include irritability, nausea, constipation, fatigue, and muscle weakness. In children, the characteristic radiographic finding is dense metaphyseal bands combined with widening of the zone of provisional cartilage in tubular bones.⁶ In adults, calcification typically occurs in the periarticular soft tissues, joint capsules, and synovial bursae. Treatment remains supportive, decreasing the elevated vitamin D levels by avoiding intake of vitamin D supplements.⁶

Fluoride. Chronic fluorine intoxication results in skeletal abnormalities in patients of all ages, as 99% of fluoride retained in the body is deposited in bone.⁶ Fluorosis can result from industrial exposure (manufacturing of aluminum) or medical therapy with fluoride-containing drugs. Fluorosis occurs endemically in South Africa and Asia, where there is a high natural fluoride content in drinking water. Symptoms of fluoride toxicity include nausea, joint pain, and joint immobility. With a predilection for involving the spine and pelvis, the main radiographic finding of fluorosis is generalized osteosclerosis (Figure 6), typically with a granular pattern and thickened trabeculae, enthesopathy (particularly at the iliac crests and ischial tuberosities), and ligamentous calcification. Increased fragility of the osteo-sclerotic bone predisposes patients to pathologic fracture.⁶

With a predilection to involve the spine and pelvis, fluorosis produces generalized osteosclerosis on radiographs.

There is no definitive treatment of fluorosis. Fluorosis may be reversible with cessation or avoidance of fluoride ingestion.

Developmental

Pyknodysostosis. Pyknodysostosis is a rare autosomal recessive, lysosomal storage bone dysplasia characterized by

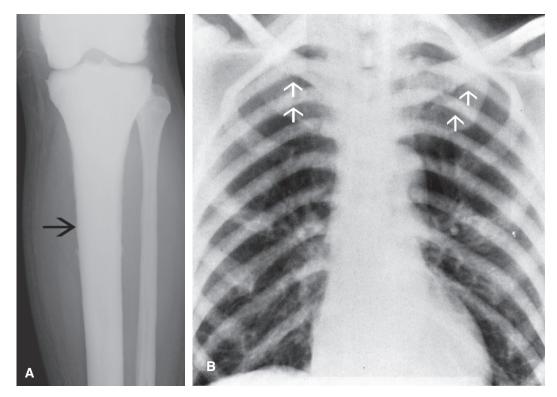


Figure 5. Myeloproliferative causes of diffuse sclerotic bone lesions. *A*: Mastocytosis. Frontal radiograph of the lower leg in a 41-year-old man reveals wide-spread osteosclerosis (*arrow*) in the tibia. *B*: Myelofibrosis. Frontal radiograph of the chest in a 57-year-old man demonstrates uniform obliteration of fine trabecular margins of ribs (*arrows*), which results in bone sclerosis simulating jail bars crossing the thorax.

diffuse osteosclerosis and short stature in children. Other findings of pyknodysostosis include short and broad hands, large head, abnormal dentition, hypoplastic nails, midface hypoplasia, and pathologic fracture with minimal trauma.⁷ Among the wide range of radiographic findings are characteristic osteosclerosis (Figure 7A) with pathologic fractures of long bones. Other findings include hypoplasia and acroosteolysis of the terminal phalanges, delayed bone age, wormian bones, frontoparietal bossing, calvarial thickening, vertebral segmentation anomalies, and hypoplastic clavicles. CT and MRI have no role except to assess healing of pathologic fractures, if radiographs are equivocal. The treatment of pyknodysostosis consists of supportive therapy for complications, especially pathologic fractures.

Osteopetrosis. Osteopetrosis is a diffuse, systemic hereditary disease characterized by reduced bone resorption from osteoclast failure. Children may have the infantile autosomal recessive form of osteopetrosis, which is fatal within the first few years of life.³ They present with failure to thrive, growth retardation, and cranial nerve deficits Adults with the autosomal dominant subtype have a normal life expectancy. They may present incidentally or have bone pain, pathologic fractures, or various orthopedic problems. Patients with both types of osteopetrosis typically have short stature, abnormal dentition, and frontal bossing.

Radiographically, osteopetrosis produces the pathognomonic appearance of uniformly dense bones without cortical or trabecular structure (Figure 7B), broadened metaphyses, and a sandwich appearance of vertebral bodies (horizontal layers of increased bone density along the endplates with a sharp margin between sclerotic and less sclerotic bone). The sandwich appearance must be distinguished from the "smudgy" border between the sclerotic endplates and more normal bone in the "rugger jersey" spine of secondary hyperparathyroidism.

Additional radiographic findings of osteopetrosis include undertubulation of the metaphyses of long bones and sclerosis and thickening of the cranial vault. CT and MRI have a limited role in establishing the diagnosis of osteopetrosis. However, MRI may be used to assess the degree of bone marrow involvement or such cranial complications as hydrocephalus and optic nerve atrophy.

The treatment of osteopetrosis is directed toward preventing and treating fractures and other complications of the disease. Patients with the infantile variety may undergo bone marrow transplant, as this can cure bone marrow failure from the intrinsic osteoclast defect.

Conclusion

Sclerotic bone lesions are encountered commonly in musculoskeletal imaging. This CME activity emphasizes that meticulous attention to the clinical history, location, distribution, and character of the bone sclerosis, and associated findings on radiographs and cross-sectional imaging, may permit the radiologist to arrive at the precise diagnosis or a limited differential diagnosis.

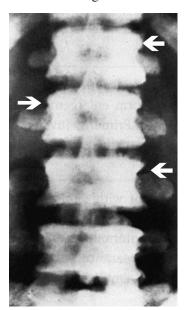


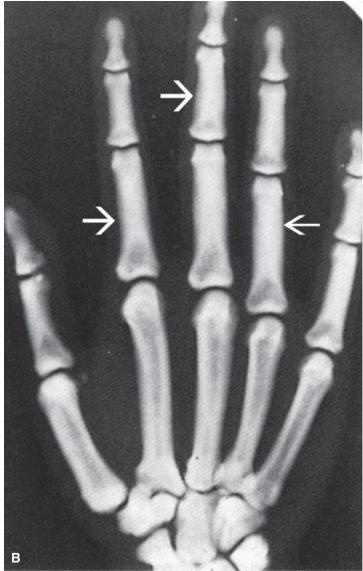
Figure 6. Drug-induced cause of diffuse sclerotic bone lesions. Fluorosis. Frontal radiograph of the lumbar spine in a 24-yearold woman shows widespread sclerosis (*arrows*) within lumbar vertebrae.



Figure 7. Developmental causes of diffuse sclerotic bone lesions. *A*: Pyknodysostosis. Frontal radiograph in a 12-year-old boy reveals widespread sclerosis within metacarpals (*closed arrows*). Note preservation of trabecular structure of underlying bone and acro-osteolysis (*open arrow*) of first distal phalanx. *B*: Osteopetrosis. The frontal radiograph of the hand of a 9-year-old boy demonstrates diffuse increased opacity within phalanges (*arrows*). Note characteristic lack of cortical or trabecular structure in the phalanges, a finding that differentiates osteopetrosis from pyknodysostosis.

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- 1. Which one of the following primary malignancies in adults is *least* likely to cause sclerotic bone metastases?
 - A. Breast cancer
 - B. Prostate cancer
 - C. Bladder cancer
 - D. Thyroid cancer
 - E. Carcinoid tumor

See Reference 3 for further study.

- 2. Which one of the following is a developmental cause of multifocal sclerotic bone lesions?
 - A. Osteopoikilosis
 - B. Paget disease of bone
 - C. Myelofibrosis
 - **D.** Fluoride toxicity
 - E. Hypervitaminosis D

See Reference 4 for further study.

- 3. Osteoblastic metastases most frequently involve
 - A. calvarium
 - B. spine
 - **C.** upper extremity
 - D. pelvis
 - E. lower extremity

See Reference 3 for further study.

- Figure 8 is an AP radiograph of the lumbar spine in an adult. All of the following conditions should be included in the differential diagnosis, *except*
 - A. osteoblastic metastasis
 - B. Paget disease of bone
 - C. lymphoma
 - D. secondary hyperparathyroidism

See Reference 5 for further study.



Figure 8.

- 5. Radiographs of the left femur in a 21-year-old woman reveal irregular, sclerotic, periosteal, cortical thickening with a "candle wax" configuration. The *most* likely diagnosis is
 - A. pyknodysostosis
 - B. melorheostosis
 - C. osteopoikilosis
 - D. tuberous sclerosis
 - E. hypervitaminosis D
- See Reference 4 for further study.
- 6. A 32-year-old African-American woman with mediastinal and hilar lymphadenopathy on chest radiographs also has lytic lesions in multiple phalanges of the hands and multifocal sclerotic lesions in the distal left radius. The *most* likely diagnosis is
 - A. osteopoikilosis
 - B. melorheostosis
 - C. sarcoidosis
 - **D.** tuberous sclerosis

See Reference 2 for further study.

- 7. All of the following are radiographic features in a patient with pyknodysostosis, *except*
 - A. diffuse osteosclerosis
 - **B.** absent trabecular structure of involved phalanges
 - C. pathologic fractures of long bones with minimal trauma
 - **D.** acro-osteolysis
- E. hypoplastic clavicles

See Reference 7 for further study.

- 8. Radiographic features of an adult man include diffuse osteosclerosis, absent cortical and trabecular structure of dense bones, broadened metaphyses, a pathologic fracture of an involved phalanx, and the sandwich appearance of vertebral bodies. The *most* likely diagnosis is
 - A. osteoblastic metastasis
 - B. pyknodysostosis
 - **C.** hypervitaminosis D
 - **D.** osteopetrosis
 - E. fluorine intoxication

See Reference 1 for further study.

- **9.** Which one of the following statements concerning fluoride toxicity is *false*?
 - A. It causes generalized osteopenia.
 - **B.** It can cause ligamentous calcification.
 - C. Its skeletal abnormalities can affect all age groups.
 - **D.** Its skeletal abnormalities have a predilection for the spine and pelvis.
 - E. It can be caused by industrial exposure to aluminum manufacture.

See Reference 6 for further study.

- **10.** All of the following are causes of diffuse sclerotic bone lesions, *except*
 - A. mastocytosis
 - B. osteopetrosis
 - C. healing nonossifying fibroma
 - D. renal osteodystrophy
 - E. osteoblastic metastases

See Reference 3 for further study.