Benign Bone Conditions That May Be FDG-avid and Mimic Malignancy

Kwee, Thomas C.; de Klerk, John M. H.; Nix, Maarten; Heggelman, Ben G. F.; Dubois, Stefan V.; Adams, Hugo J. A.

Published in:
Seminars in Nuclear Medicine

DOI:
10.1053/j.semnuclmed.2017.02.004

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 17-09-2023
Benign Bone Conditions That May Be FDG-avid and Mimic Malignancy

Thomas C. Kwee, MD, PhD,* John M.H. de Klerk, MD, PhD,† Maarten Nix, MD,‡ Ben G.F. Heggelman, MD,‡ Stefan V. Dubois, MD,§ and Hugo J.A. Adams, MD, PhD||

Positron emission tomography with the radiotracer $^{18}$F-fluoro-2-deoxy-D-glucose (FDG) plays an important role in the evaluation of bone pathology. However, FDG is not a cancer-specific agent, and knowledge of the differential diagnosis of benign FDG-avid bone alterations that may resemble malignancy is important for correct patient management, including the avoidance of unnecessary additional invasive tests such as bone biopsy. This review summarizes and illustrates the spectrum of benign bone conditions that may be FDG-avid and mimic malignancy, including osteomyelitis, bone lesions due to benign systemic diseases (Brown tumor, Erdheim-Chester disease, Gaucher disease, gout and other types of arthritis, Langerhans cell histiocytosis, and sarcoidosis), benign primary bone lesions (bone cysts, chondroblastoma, chondromyxoid fibroma, desmoplastic fibroma, enchondroma, giant cell tumor and granuloma, hemangioma, nonossifying fibroma, and ostoid osteoma and osteoblastoma), and a group of miscellaneous benign bone conditions (post bone marrow biopsy or harvest status, bone marrow hyperplasia, fibrous dysplasia, fractures, osteonecrosis, Paget disease of bone, particle disease, and Schmorl nodes). Several ancillary clinical and imaging findings may be helpful in discriminating benign from malignant FDG-avid bone lesions. However, this distinction is sometimes difficult or even impossible, and tissue acquisition will be required to establish the final diagnosis.

Semin Nucl Med 47:322–351 © 2017 Elsevier Inc. All rights reserved.

Introduction

FDG-PET/CT has evolved into an important and increasingly used imaging modality in clinical practice, most notably in oncology. One of the well-recognized advantages of FDG-PET/CT over CT alone is its increased sensitivity for the detection of malignant lesions. Malignant lesions, and particularly the ones that are clinically and histologically aggressive, generally have an increased FDG uptake. However, FDG is not a cancer-specific agent, because several physiological and benign conditions may also exhibit increased FDG uptake. Correlation with CT on fused FDG-PET/CT data may improve the characterization of FDG-avid foci and obviate the need for further evaluation or biopsy. Several previous reviews have discussed the spectrum of physiological uptake, normal variants, and benign conditions that can be encountered at FDG-PET/CT. However, one major organ that has been relatively overlooked and usually only briefly discussed in this context is the bone. The bone marrow is the most common organ to be affected by metastatic cancer and the site of disease that produces the greatest morbidity. Accurate diagnosis of malignant bone disease is important because of its potential prognostic and therapeutic implications. Although FDG-PET/CT plays an important role in this setting, it cannot always reliably classify a bone lesion as malignant. This is due to the fact that benign lesions may show both increased FDG uptake and aggressive morphologic imaging characteristics. One recent study investigated the malignancy rate of suspicious bone lesions at FDG-PET/CT that underwent CT-guided biopsy. In the 102 included patients with FDG-avid bone lesions, CT-guided bone biopsy with subsequent histologic examination showed a malignant lesion in 91 patients, which resulted in a positive predictive value for malignancy of 89.2%. Thus, a...
non-negligible proportion of suspicious FDG-avid bone lesions at FDG-PET/CT proves to be benign upon biopsy. Knowledge of the differential diagnosis of FDG-avid bone alterations that may resemble malignancy is important for correct patient management, including the avoidance of unnecessary additional invasive tests such as bone biopsy. The aim of this review was therefore to summarize and illustrate the spectrum of benign bone conditions that may be FDG-avid and mimic malignancy, and the potential ancillary clinical and imaging findings that may be helpful in discriminating the former from the latter. For that purpose, osteomyelitis, and a variety of benign systemic, benign primary, and benign miscellaneous bone conditions, will be reviewed separately in alphabetical order.

Osteomyelitis

Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism, Staphylococcus aureus being the most commonly involved.\(^\text{10}\) Osteomyelitis may be classified into three types: osteomyelitis due to local spread from a contiguous contaminated source of infection following trauma, bone surgery, or joint replacement; osteomyelitis secondary to vascular insufficiency (predominantly in diabetic people with a foot soft-tissue infection that spreads to bone); and hematogenous osteomyelitis (which is seen mostly in prepubertal children and in elderly patients).\(^\text{10}\) In prepubertal children, hematogenous osteomyelitis mostly involves the metaphysis of long bones (particularly tibia and femur), in most cases as a single focus.\(^\text{10}\) If hematogenous osteomyelitis occurs in adults, it most frequently involves the vertebral bodies.\(^\text{10}\)

Subacute hematogenous osteomyelitis (ie, duration of 2 weeks to 3 months) may mimic hematogenous metastatic disease and primary malignant bone tumors (particularly Ewing sarcoma in children) both clinically (both may present with fever, increased serum inflammatory markers, and bone pain) and at imaging (both can appear aggressive at radiographic, CT, and MRI studies with bone marrow and cortical destruction, articular involvement, periosteal reaction, increased enhancement, and an accompanying soft-tissue mass).\(^\text{10-12}\) In osteomyelitis, the presence of inflammatory cells (eg, neutrophils, lymphocytes, and macrophages) with heightened metabolic activity also results in increased FDG uptake.\(^\text{13}\) It has been estimated that about 50% of subacute osteomyelitis cases in children are initially mistaken to represent tumor.\(^\text{14}\) Although the presence of gas or fat-fluid levels in the bone marrow is very specific for osteomyelitis outside of a context of trauma, it is only occasionally found.\(^\text{15}\) MRI findings have been reported that be may be useful to discriminate osteomyelitis from malignant bone tumors. The penumbra sign has been described as an area of relatively hyperintense signal between the intermediate to low signal intensity of the intraosseous abscess cavity and the adjacent edematous or sclerotic bone marrow on unenhanced T1-weighted images, which enhances intensively following contrast medium administration and represents the thin layer of granulation tissue that lines the abscess cavity in subacute osteomyelitis.\(^\text{11,15-17}\) This sign has been reported to be highly specific for osteomyelitis but is not present in all cases and less common in nonmetaphyseal osteomyelitis.\(^\text{11,15-18}\) Persistent fatty signal within the bone as well as soft tissues at MRI, which is thought to be due to increasing intramedullary pressure that leads to septic necrosis with death of the lipocytes and release of free fatty globules, has also been reported as a characteristic, but not pathognomonic, MRI finding for osteomyelitis.\(^\text{19,20}\) However, this finding may be uncommon in subacute osteomyelitis.\(^\text{19}\)

Osteomyelitis due to tuberculosis deserves to be mentioned separately. Isolated tuberculous osteomyelitis in the absence of associated tuberculous arthritis is relatively rare.\(^\text{21}\) When it does occur, however, the femur, tibia, and small bones of the hands and feet are most commonly affected.\(^\text{21}\) Typically, the metaphyses are involved, with radiographic features that include osteopenia and poorly defined lytic lesions with minimal surrounding sclerosis.\(^\text{21}\) Cystic tuberculosis is an unusual pattern of osteomyelitis that occurs more commonly in children than in adults.\(^\text{21}\) It is characterized by multiple small, well-defined oval lytic lesions of variable size that usually lack sclerotic margins.\(^\text{21}\) In children, the metaphyses of the long bones tend to be affected, whereas in adults, the axial skeleton (skull, shoulder, and pelvis) is involved.\(^\text{21}\) Tuberculous osteomyelitis may be highly FDG-avid and mimic metastatic disease that cannot be differentiated from the latter based on imaging criteria.\(^\text{22,23}\)

With regard to spondylitis, for which MRI is the imaging test of choice, evidence of involvement of two consecutive vertebrae and the intervening disc is virtually diagnostic of infectious spondylitis.\(^\text{24}\) In the early stage of infection, however, imaging appearances are entirely nonspecific.\(^\text{24}\) Early spinal infection may manifest as involvement of an isolated vertebral body without disc involvement or involvement of one vertebral body and one disc.\(^\text{24}\) Furthermore, two vertebral bodies may be involved but not the intervening disc.\(^\text{24}\) In these situations, differentiation between infectious spondylitis and neoplastic conditions is difficult.\(^\text{24}\) Unfortunately, it is not uncommon that imaging findings, including FDG-PET/CT and MRI, cannot differentiate between osteomyelitis and malignant bone disease, and that tissue acquisition is required to make a final diagnosis (Figs. 1 and 2).\(^\text{22,23,25-27}\)

Benign Systemic Diseases

Brown Tumor

Brown tumors, which are benign osteolytic processes, are found in less than 5% of patients with hyperparathyroidism.\(^\text{28}\) Note that hyperparathyroidism is more frequently secondary than primary, and secondary hyperparathyroidism is most commonly due to chronic renal disease.\(^\text{29}\) The elevated levels of parathyroid hormone lead to increased bone turnover.\(^\text{28}\) The effects of this increased turnover can be either catabolic or anabolic, at cortical and cancellous sites, respectively.\(^\text{28}\) The most common skeletal finding is diffusely decreased bone
Brown tumors are a severe and much less common manifestation of hyperparathyroid-related bone disease. Brown tumors are the result of microfractures and secondary hemorrhages that result in an influx of multinucleated macrophages and the growth of reactive fibrous tissue. Brown tumors are most commonly found in long bones, but also occur in the mandible, clavicles, ribs, and pelvis. Brown tumors can show markedly increased FDG uptake and appear as expansile, osteolytic lesions, whereas internal septations or sclerosis can be seen in later stages of disease. Therefore, brown tumors can be confused with malignant disease, particularly when a typical history such as chronic renal disease is absent or when a patient with a known malignancy undergoes FDG-PET for staging or radiation therapy planning (Fig. 3). Note that MRI can show susceptibility artifacts (ie, signal loss, which is particularly pronounced on gradient-echo sequences with long echo times) due to hemosiderin deposition, which can give a clue toward the correct diagnosis. Laboratory investigations should be ordered to support the diagnosis of a brown tumor, which will reveal

---

Figure 1 Radiographs of the left humerus in 51-year-old man who presented with pain in the left upper arm since 8 weeks show a large osteolytic lesion with endosteal scalloping and cortical thinning (A and B, arrows). FDG-PET/CT was performed for further evaluation. The morphology of the lesion is also nicely demonstrated on the CT part of the FDG-PET/CT examination (C, arrow). The lesion was highly FDG-avid (D and E, arrows). FDG-PET/CT also showed a few slightly hypermetabolic left axillary lymph nodes (F-H, encircled). A primary malignant bone tumor with possible locoregional lymph node metastases was strongly considered, and the patient was referred to another institution with expertise in orthopedic oncology. The lesion was biopsied and proved to be osteomyelitis.

Figure 2 A 32-year-old asymptomatic woman was referred by the Area Health Authority because of an abnormal chest radiograph (not shown). FDG-PET/CT was performed, which showed a 4-cm mass in the left upper lobe with central necrosis (A-C, continuous arrows). PET also showed a focal FDG-avid lesion in the right ilium (A and D, dashed arrows) without any clear substrate at CT (E). Note hypermetabolic brown fat in the lower neck and shoulder regions (A, arrowheads). Although metastatic cancer was considered, biopsies of both the lung mass and the right iliac bone lesion revealed tuberculosis.
hypercalcemia, hypophosphatemia, and increased parathyroid hormone levels.

**Erdheim-Chester Disease**

Erdheim-Chester disease is a rare non-Langerhans cell histiocytosis characterized by the xanthomatous or xanthogranulomatous infiltration of tissues by spumous histiocytes, lipid-laden macrophages, or histiocytes, and surrounded by fibrosis. This disease usually occurs in middle-aged to older patients, with a strong male predominance. Although almost all patients with Erdheim-Chester disease have skeletal involvement, bone pain, which is the most common clinical feature of Erdheim-Chester disease, is only present in 50% of patients. More than 50% of cases have at least one associated extraskeletal involvement, namely, the kidney, skin, central nervous system, or heart. Typical skeletal findings in Erdheim-Chester disease are bilateral and symmetrical cortical thickening and osteosclerosis of the diaphyseal and metaphyseal regions in the long bones (the epiphyses are classically spared), especially of the lower limbs (tibia and fibula). As opposed to Langerhans cell histiocytosis, the axial skeleton and the mandible are classically spared in Erdheim-Chester disease. The bone abnormalities in Erdheim-Chester disease can show symmetrical increased FDG uptake (Fig. 4). Although the imaging findings are generally typical and considered pathognomonic due to the rarity of this disorder it may be confused with other diseases including diffuse osteoblastic metastases.

**Gaucher Disease**

Gaucher disease is a rare and extraordinarily heterogeneous inborn error of metabolism that exhibits diverse manifestations, a broad range of age of onset of symptoms, and a wide clinical spectrum of disease severity, from lethal disease during infancy to first age of onset of symptoms in octogenarians. The deficiency of glucocerebrosidase in this entity leads to the accumulation of glucosylceramide primarily in cells of mononuclear-macrophage lineage. Clinical alterations are hematologic, visceral, and skeletal. Almost all patients with symptoms present with anemia and thrombocytopenia, whereas the most commonly involved viscera are the liver and spleen, which can become markedly enlarged. Bone marrow infiltration generally follows the distribution of cellular red marrow progressing from the axial to the peripheral skeleton and from the
proximal to the distal aspects of the long bones with a tendency to spare the epiphyses. An array of skeletal manifestations can be seen in Gaucher disease, including bone pain, medullary cavity expansion with cortical thinning and endosteal scalloping, Erlenmeyer flask deformity of the distal femurs, osteopenia or osteoporosis, osteolytic lesions, bone infarcts, avascular necrosis, fractures, and acute osteomyelitis. Interestingly, a preliminary report has shown that FDG-PET may be very sensitive in detecting bone marrow infiltration in this disease. In a patient in whom the diagnosis has not been established yet, increased FDG uptake in the bone marrow should not be confused with malignant disease. The diagnosis of Gaucher disease should be considered if any of the above-mentioned bone alterations is seen in combination with hematologic and visceral manifestations.

Gout (and Other Types of Arthritis)

Gout is a common arthritis caused by deposition of monosodium urate crystals within joints after chronic hyperuricemia. The prevalence of gout is much higher in men than in women and rises with age. Gout affects 1%-2% of adults in developed countries, where it is the most common inflammatory arthritis in men. Acute gouty arthritis most often begins with one joint affected in the lower limbs (85%-90% of cases), usually the first metatarsophalangeal joint. The next most frequent locations are the midtarsis, ankles, knees, and arms. The initial attack is rarely polyarticular (3%-14% of cases), and acute attacks seldom affect the shoulders or hips. High FDG uptake can be seen around affected joints, which is related to macrophage activity in response to the deposition of monosodium urate crystals. Polyarticular gout in unusual locations may resemble metastatic disease at FDG-PET (Fig. 5). However, the periarticular location and concomitant typical radiological changes such as well-defined juxta-articular erosions with sclerotic rims and overhanging margins are highly suggestive of gout. Note that symptoms of arthritis may result from metastatic tumor in bone adjacent to a joint. Primary malignancies that have been reported to present in the latter fashion include lung, colon, breast, melanoma, and rhabdomyosarcoma. Therefore, other types of arthritis than gout that cause bony erosions (eg, septic arthritis, rheumatoid arthritis, and various seronegative spondylarthropathies such as psoriatic arthritis, reactive arthritis, Crohn’s disease, and anklyosing spondylitis may also mimic malignant bone disease) (Fig. 6). Although the radiographic abnormalities and clinical findings are usually suggestive of a nonmalignant cause of the arthritis, biopsy may be necessary in atypical presentations to excluding bone malignancy.

Figure 4 FDG-PET and CT in a patient with Erdheim-Chester disease show typical bilateral symmetrical increased intramedullary uptake of FDG in the femurs and tibiae (A) with diffuse osteosclerosis (and also several lytic changes) as well as marked cortical thickening of the tibiae (B). (Reproduced with permission from Mazor et al. 34)
Langerhans Cell Histiocytosis

Langerhans cell histiocytosis refers to a spectrum of disease characterized by idiopathic proliferation of histiocytes producing focal or systemic manifestations. The three classic syndromes may have considerable clinical overlap: eosinophilic granuloma, in which the disease is limited to bone in patients usually 5-15 years old (often monostotic); Hand-Schüller-Christian disease, characterized by multifocal bone lesions and extraskeletal involvement of the reticuloendothelial system usually seen in children 1-5 years old; and Letterer-Siwe disease, in which there is disseminated involvement of the reticuloendothelial system with a fulminant clinical course in children less than 2 years old. Osseous involvement is the most common manifestation of Langerhans cell histiocytosis and is typically seen in the flat bones, with lesions of the skull, pelvis, and ribs accounting for more than half of all lesions. About 30% of lesions are in long bones. Radiographic appearance of osseous Langerhans cell histiocytosis depends on site of involvement and phase of the disease. Early lesions appear aggressive with osteolysis, poorly defined margins, and lamellated periosteal reaction. Late lesions appear well-defined and may show sclerotic margins and expanded remodeled appearance. The MRI manifestations are nonspecific, especially during the early stages. The metabolically active histiocytes appear FDG-avid at PET. Early, metabolically active skeletal Langerhans cell histiocytosis may have a similar appearance to that of malignant bone tumors, and biopsy or surgical excision is sometimes required to establish the diagnosis (Fig. 7).

Sarcoidosis

Sarcoidosis is a systemic disease of unknown cause that is characterized by the formation of immune granulomas in various organs, mainly the lungs and the lymphatic system. Seventy percent of patients are aged 25-45 years, whereas the disease is rare in people younger than 15 years or older than 70 years. Bone involvement in sarcoidosis has been reported to occur in about 5% of cases and to account for less than 5% of extrapulmonary manifestations of this disease. Importantly, bone involvement rarely occurs without other concomitant clinical or radiographic manifestations of
Any bone can be involved, but the small bones of the hands or feet are most frequently affected. Sarcoid bone lesions are characterized by their bilateral distribution, the fact that they usually affect the ends of the bones, and their cystic or lacelike shape (although sclerosis can be seen in advanced phases and in lesions in the spine and pelvis). In sarcoid bone lesions, the cortical borders of the bones are well preserved. Because the lesions occur mostly in non–weight-bearing bones (hands), they show features of increased bone resorption with thin cortices, and sharp, widely spaced, often palisading trabeculae. However, sarcoid bone lesions in early phases may have no visible changes on radiographs or CT. As a rule, the recognition of typical cystic or lacelike shape lesions is relatively easy if the patient presents with multisystem features of sarcoidosis. However, diagnosis may be difficult if bone lesions occur in the absence of the typical pulmonary and extrapulmonary features of sarcoidosis. In addition, there are no known MRI features that can discriminate osseous sarcoidosis lesions from metastatic bone disease. Furthermore, sarcoid bone lesions may show strong FDG uptake, probably due to macrophage activation (Fig. 8). As such, sarcoid bone lesions may mimic malignant bone lesions, and biopsy will be the only method to establish their true nature in such settings.

**Benign Primary Bone Tumors**

**Bone Cysts**

Simple and aneurysmal bone cysts are benign, well-defined solitary lytic bone lesions, usually encountered in children and adolescents. A simple bone cyst may be unicameral or partially separated. Unicameral bone cyst can involve any bone, but usually the long bone metaphysis (90%-95%) and primarily the proximal humerus and proximal femur. Aneurysmal bone cysts are metaphyseal, eccentric, bulging, have fluid-fluid levels, and may show strong FDG uptake, probably due to macrophage activation. The classic aneurysmal bone cyst is an expansive and hemorrhagic tumor, usually showing characteristic translocation. About 30% of aneurysmal bone cysts are secondary, without translocation, and occur in reaction to another, usually benign, bone lesion. Aneurysmal bone cysts are metastatic, except for tumors, which may show fluid-fluid levels.
multicameral, and may develop in all bones of the skeleton. Simple bone cysts may unexpectedly exhibit markedly increased FDG uptake according to some reports, but findings on anatomical imaging studies allow for a confident diagnosis and exclusion of malignant disease.

Chondroblastoma
Chondroblastoma is a rare benign chondral tumor characterized by an epiphyseal or apophyseal location in long bones. Most patients are less than 20 years of age, and men are more commonly affected than women. Approximately 75%-80% of all cases involve the long bones, most commonly the proximal tibia, distal femur, proximal humerus, and proximal femur. After the long bones, the foot is the second most common site of occurrence, most commonly in the talus and calcaneus. The tumor is classically located adjacent to the growth plate with almost half the cases limited to the epiphysis, but the majority extends for a variable degree into the metaphysis. A chondroblastoma classically appears as a 1- to 4-cm lucent lesion with a thin, sclerotic, geographic margin, a lobular contour, and matrix mineralization in approximately 30% of cases on radiographs or CT. A thick, solid periosteal reaction is present in almost 60% of long bone chondroblastomas, occurring in the metaphysis adjacent to the epiphyseal lesion. Tumors arising in the foot have similar characteristics but, in addition, commonly result in bone expansion. CT may demonstrate features such as extraosseous extension, sclerotic margin, and matrix mineralization that are not appreciated radiographically. At MRI, the lesion typically demonstrates intermediate T1-weighted signal intensity and, in the majority of cases, either complete or partial T2-weighted hypointensity, which is related histologically to abundant immature chondral matrix, hypercellularity of chondroblasts, calcifications, and hemosiderin. A lobular, thin hypointense margin is seen and the vast majority of cases show marked periosteal bone marrow edema. Periostitis, soft-tissue edema, reactive joint effusion, and synovitis are also commonly seen. Following contrast medium administration, either lobular or peripheral and septal enhancement is...
Although the clinical presentation and imaging findings can be highly suggestive for the correct diagnosis, chondroblastomas in unusual locations such as in the axial skeleton may mimic malignancy, also because they can be highly FDG-avid (Fig. 9).\textsuperscript{64,65}

**Chondromyxoid Fibroma**

Chondromyxoid fibroma is a very rare benign cartilaginous tumor accounting for significantly less than 1% of all primary bone neoplasms.\textsuperscript{62} Mean age at presentation is around 25 years with an age range of 3-70 years.\textsuperscript{62} The tumor may arise in a variety of locations but most commonly involves the medullary cavity of the lower limb long bones.\textsuperscript{62} Within the long bones, chondromyxoid fibroma is (eccentrically) located in the metaphyseal region in just over 50% of cases and in a predominantly diaphyseal location in approximately 40% of cases, whereas an epiphyseal location is very rare.\textsuperscript{62} A geographic pattern of bone destruction with a well-defined, sclerotic rim and commonly a round or elongated, lobular border is the classic appearance.\textsuperscript{62} Cortical thinning and expansion are also very common features, and complete cortical destruction may be seen in almost one-third of cases.\textsuperscript{62} Internal trabeculation is present in two-thirds of patients, but radiographically evident matrix mineralization is uncommon.\textsuperscript{62} MRI features are not very specific, although a peripheral intermediate signal band and a central hyperintense signal on T2-weighted images have been described in most cases.\textsuperscript{66} Chondromyxoid fibromas may show high FDG uptake and mimic malignancy such as chondrosarcoma (Fig. 10).\textsuperscript{67-70} Biopsy or surgical resection is usually necessary to establish the diagnosis.

**Desmoplastic Fibroma**

Desmoplastic fibroma is a very rare, locally aggressive, solitary tumor, accounting for significantly less than 1% of all primary bone neoplasms.\textsuperscript{71} Mean age at diagnosis is around 20 years, although the tumor can be seen at any age.\textsuperscript{71} Histologically, desmoplastic fibroma is the intraosseous counterpart of soft-tissue desmoid or fibromatoses.\textsuperscript{71} Commonly affected sites (in order of decreasing frequency) are the long tubular bones, mandible, and pelvis.\textsuperscript{71} On radiographs, desmoplastic fibromas typically show a geographic pattern of bone destruction, with a narrow zone of transition, and nonsclerotic margins. Internal pseudotrabeulation and widening of the host bone due to gradual apposition of periosteal new bone are also commonly seen.\textsuperscript{71} Cortical breach is seen in a minority of patients.\textsuperscript{71} Cross-sectional imaging features of desmoplastic fibroma are nonspecific, although some MRI characteristics, such as inhomogeneous contrast enhancement, the presence of low-intensity regions on T2-weighted images, and cystic changes have been described to occur in this entity.\textsuperscript{72-74} One report described a case of desmoplastic fibroma that showed moderate FDG uptake that could not be differentiated from
malignancy before wide surgical excision was performed (Fig. 11).75

**Enchondroma**

Solitary enchondromas are common benign cartilaginous tumors typically located in the medullary canal of a single bone.76 Solitary enchondroma is typically first discovered in the third or fourth decade.76 Most enchondromas are located in the metaphyseal or metadiaphyseal region, and they have a predilection for short tubular bones, the proximal femur, and humerus.76 Phalangeal enchondroma is almost always discovered following pathologic fracture. About half the cases in long bones are incidental findings on imaging studies performed for unrelated complaints.76 Enchondromas may have variable appearances, but the classical radiographic appearance is that of an oval, well-circumscribed, lytic, metaphyseal-to-metadiaphyseal lesion with densities.76 The densities are small and punctate to short, “ring-like,” and “arc-like” forms.76 At MRI, the lesion has high signal intensity on T2-weighted images intermixed with areas of low signal intensity, probably due to matrix mineralization. The cortex can show narrow scalloping to focal thinning. Small and thin bones can show expansion due to limited medullary contents.76 Fractures are common in phalangeal lesions, but not in long and flat bones.

Figure 9 A 21-year-old man presented with a 6-month history of pain on movement in the right buttock and on radiography of the pelvis, an abnormal lucency in the right ischium was found. FDG-PET showed the lesion to be highly FDG-avid (A and B, arrows). Its appearance on radiography and CT was that of a well-defined lytic lesion with cortical erosion (C and D, arrows). The differential diagnosis included giant cell tumor of bone, chondroblastoma, and malignant bone tumor, such as osteosarcoma or chondrosarcoma. Open curettage was performed following biopsy. Histopathology revealed chondroblastoma. (Reproduced with permission from Hamada et al.)

Figure 10 A 15-year-old girl presented with mild chronic back pain. Initial spine radiographs revealed a mass in her upper right chest. CT showed an expansile soft-tissue mass in the lateral aspect of the right second rib with cortical destruction (not shown). Bone scintigraphy showed low-grade tracer uptake in the location of the right lateral second rib (not shown). FDG-PET showed the mass in the right second rib to be hypermetabolic (arrow). The differential diagnosis included Ewing sarcoma, nerve sheath tumor, and neuroendocrine tumor. Biopsy and subsequent resection revealed chondromyxoid fibroma. (Reproduced with permission from Long et al.)
unless the stress is fairly severe. Differentiation between enchondroma and chondrosarcoma is essential. Importantly, chondrosarcoma in the hands and feet (phalanges, metacarpals, and metatarsals) are exceedingly rare, whereas chondrosarcomas are common in the axial skeleton (spine and pelvis) and typically present with large associated soft-tissue masses. However, differentiation of enchondroma from chondrosarcoma in the other appendicular bones is often difficult clinically, radiologically, and pathologically. Pain related to the lesion, depth of scalloping greater than two-thirds of cortical thickness, cortical destruction, soft-tissue mass (at CT or MRI), periosteal reaction (at radiography), and greater uptake than the anterior iliac crest at bone scintigraphy have been reported to strongly suggest the diagnosis of chondrosarcoma. However, imaging is still insufficiently accurate to discriminate enchondroma from low-grade (grade I) chondrosarcoma. In addition, although grade II and III chondrosarcomas have been reported to have a higher FDG uptake than low-grade

![Figure 11](image.png)
cartilage tumors, FDG-PET cannot discriminate between benign enchondroma and grade I chondrosarcoma. Enchondromas may have either low FDG uptake or high FDG uptake and mimic malignancy (Fig. 12). Giant Cell Tumor and Granuloma

Giant cell tumor is a relatively common bone neoplasm. It is generally a benign and solitary tumor composed of mononuclear stromal cells and characteristic multinucleated giant cells that exhibit osteoclastic activity. The vast majority of giant cell tumors affect skeletally mature patients (ie, those with closed physes), with approximately 80% occurring in patients between 20 and 50 years of age. Giant cell tumor is thought to arise from the metaphyseal side of the epiphyseal plate, and usually develops in long bones, with most lesions (in order of decreasing frequency) occurring in the distal femur, proximal tibia, distal radius, sacrum, and proximal humerus. The typical appearance is a lytic lesion with a well-defined but nonsclerotic margin that is eccentrically located in the meta-epiphysis and extends to the subchondral bone with expansile remodeling, but lacks internal mineralization. However, giant cell tumor may have aggressive features, including a wide zone of transition, and cortical expansion or destruction with a soft-tissue mass. Fluid-fluid levels, consistent with secondary formation of aneurysmal bone cysts, are seen in around 14% of cases. The solid components demonstrate low-to-intermediate signal intensity on T2-weighted MRI, a feature that can be helpful in diagnosis. Giant cell tumor may also occur in flat bones or an apophysis, but is less likely to demonstrate the classic appearance of a lytic lesion with a well-defined, nonsclerotic margin in these locations. Rarely, giant cell tumor is associated with histologically benign lung metastases or undergoes malignant degeneration. Giant cell granuloma is a related but uncommon lesion that is not a true neoplasm, but rather a reactive process. The reported patient age range is wide, but most patients are under 30 years of age at presentation, and women are more frequently affected than men. Giant cell granuloma most frequently affects the mandible, maxilla, and small bones of the hands or feet. The radiographic features of giant cell granuloma are similar to those of giant cell tumor, although extension to subchondral bone in lesions of the appendicular skeleton is uncommon. Note that the histologic appearance of giant cell tumor and granuloma is similar to that of brown tumor of hyperparathyroidism, and the latter should be excluded with laboratory analysis. Because of their radiological appearance and FDG avidity, giant cell tumor and granuloma may mimic lytic bone metastases and multiple myeloma (Fig. 13), and the latter two should be included in the differential diagnosis if there are multiple lesions and in patients over 40 years of age.

Hemangioma

Skeletal hemangioma is a benign hamartomatous vascular tumor with a female predominance that most frequently involves the skull and vertebrae. Hemangiomas in the
skull and spine are usually asymptomatic, can present a typical polka-dot or honeycomb appearance at CT, have high signal at T1-weighted and T2-weighted images, and low FDG uptake. 87-89 Skeletal hemangiomas in the peripheral, tubular, and flat bones, however, are very rare, and among them, the tibia and femur are the most common sites. 87-89 Solitary skeletal hemangioma of the extremities can occur at any age, but is rare in those younger than 10 years of age. 87 Unlike their counterparts in the skull and vertebrae, hemangiomas in the peripheral and pelvic bones are often symptomatic (they can present with pain, soft-tissue swelling, and pathologic fracture), have a diversity of radiological appearances (they can appear aggressive with osteolysis, cortical destruction, and an extraosseous mass), and can be highly FDG-avid. 87-89 Therefore, and unfortunately, skeletal hemangiomas in the peripheral, tubular, and flat bones can usually not be differentiated from bone malignancies before surgical resection (Fig. 14). 87-89

**Nonossifying Fibroma**

Nonossifying fibromas are benign fibrous proliferations thought to be caused by a developmental defect and have been reported using many different names, including fibrous cortical defect, metaphyseal fibrous defect, and cortical desmoid. 90,91 Nonossifying fibromas are usually discovered incidentally in children, particularly in the lower extremities, and are rarely found in adults. Nonossifying fibromas are typically located in the metaphysis (adjacent to the physis) and appear as eccentric, well-defined, lucent lesions with smooth lobulated edges and surrounding sclerotic bone. 90,91 The lesions may be multilocular, and there may be cortical expansion and thinning present. 90,91 Radiographs are usually sufficient to establish the diagnosis. Distinguishing MRI features of nonossifying fibroma are hypointensity and septation on T2-weighted images. 92 Nonossifying fibromas fill in by normal bone during adolescence. Although nonossifying fibromas may exhibit increased FDG uptake, their anatomical imaging characteristics are usually characteristic and are not to be confused with malignant disease (Fig. 15).

**Osteoid Osteoma and Osteoblastoma**

Osteoid osteoma and osteoblastoma are commonly seen benign osteogenic bone neoplasms. 94 Both tumors are typically seen in the second decade of life, with a notable predilection in men. 94 Histologically, these tumors resemble each other, with characteristically increased osteoid tissue formation surrounded by vascular fibrous stroma and periosteal sclerosis. 94 Both osteoid osteoma and osteoblastoma can appear hypermetabolic at FDG-PET, 95 and may sometimes mimic a malignant bone tumor (Fig. 16). 96,97 However, clinical findings, location, and particularly CT findings may give clues toward the correct diagnosis. Osteoid osteoma most commonly occurs in the long bones (femur and tibia) and typically causes night pain that is relieved with salicylates. 94 Osteoblastoma, on the other hand, is most frequently located in the axial skeleton (particularly spine and mandible), and the pain is usually not worse at night and is less likely to be relieved with salicylates. 94 Osteoid osteoma
lacks growth potential, whereas osteoblastoma can be locally aggressive. Osteoblastomas are larger than osteoid osteomas, and exhibit greater osteoid production and vascularity.

At imaging, osteoid osteoma is characterized by an intracortical nidus with a variable amount of calcification, as well as cortical thickening, sclerosis, and bone marrow edema. When these findings are present, a diagnosis of osteoid osteoma is easily made. Note that, compared to CT, MRI has been reported to be of limited value in depicting the nidus. Osteoblastoma usually appears more expansile, is larger than 2 cm, and has less reactive sclerosis surrounding the mass than osteoid osteoma does.

Benign Miscellaneous Bone Conditions

Post Bone Marrow Biopsy or Harvest Status

Bone marrow biopsy is often performed for diagnostic or staging purposes, whereas bone marrow harvest is increasingly being performed for stem cell transplantation. After bone marrow biopsy or harvest, the targeted bone may exhibit increased FDG uptake (although this is not a common finding after biopsy, which should not be mistaken for malignancy (Fig. 17). Knowledge of the fact that bone marrow biopsy or harvest was performed before FDG-PET will avoid this pitfall.

Bone Marrow Hyperplasia

Under normal conditions, the red (hematopoietic) bone marrow shows slight FDG uptake that decreases with advancing age. In patients with cancer, diffuse homogeneously increased bone marrow FDG uptake after granulocyte colony-stimulating factor (G-CSF) administration is a well-known phenomenon that reflects red bone marrow hyperplasia and is usually not confused with diffuse metastatic bone disease. However, red bone marrow hyperplasia may unusually also appear heterogeneous, mimicking (progressive) multifocal bone metastases (Fig. 18), particularly when FDG-PET scanning is performed very early after G-CSF administration. Awareness of the fact that G-CSF was administered may suggest the presence of stimulated islands of red bone marrow, although there is not always an association with G-CSF administration. When in doubt, additional MRI (including in- and opposed-phase chemical shift imaging, with red bone marrow showing signal dropout on out-of-phase images), bone marrow scintigraphy, or follow-up FDG-PET (bone marrow FDG uptake usually

Figure 14 A 22-year-old woman presented with a gradually increasing pelvic mass with tenderness for 1 month. The patient underwent multiple imaging examinations for further evaluation. FDG-PET showed an FDG-avid mass in the left ilium (A and B, arrows). Morphologically, this mass in the left ilium appeared as a geographic lytic lesion with a thick and irregular sclerotic rim on radiography (C, arrow). CT showed extraosseous soft-tissue mass formation and intralestional stippled calcifications (D, arrow). The lesion appeared to have irregular low signal septa, intermediate signal on T1-weighted images (E, arrow), and heterogeneous high signal on fat-suppressed T2-weighted images (F, arrow). After gadolinium administration, the mass appeared to be enhancing heterogeneously, with nonenhancing soft-tissue components and septal structures (G, arrow). Based on the imaging features, a malignant cartilaginous tumor was considered. Complete removal of the tumor was performed. Histopathology revealed cavernous hemangioma. (Reproduced with permission from Ko and Park)
Figure 15  An 8-year-old girl underwent FDG-PET because of fever of unknown origin and an elevated erythrocyte sedimentation rate (82 mm/h). FDG-PET showed locally increased FDG uptake in the right distal medial tibial metaphysis (A, arrow) and no other lesions in the body. Note focal FDG contamination around the right buttock (A, arrowhead). Osteomyelitis and bone tumor were included in the differential diagnosis. Radiographs (with “R” indicating the right lower leg/ankle) showed an eccentric, well-defined lucent lesion in the right distal tibial metaphysis (B and C, arrows) with smooth lobulated edges, surrounding sclerotic bone, and cortical thinning, characteristic for a nonossifying fibroma. Additional MRI showed this nonossifying fibroma to be T1 hypointense (D, arrow), T2 hypointense (not shown), and with some small internal foci of enhancement after gadolinium administration (E, arrow).

Figure 16  FDG-PET/CT shows a hypermetabolic well-defined soft-tissue mass in the left sacrum with marginal bone sclerosis (A and B, arrows) in a 9-year-old girl who had presented with left hip pain radiating to the left thigh. Excisional biopsy revealed osteoblastoma. This research was originally published in the Journal of Nuclear Medicine Technology, © by the Society of Nuclear Medicine and Molecular Imaging, Inc.
Figure 17  FDG-PET/CT in a 63-year-old man with mantle cell lymphoma and lymphadenopathy on both sides of the diaphragm shows focally increased FDG uptake in the left posterior iliac crest (A-C and E, arrows), without any clear structural changes at corresponding CT (D). Consultation with the treating hematologist revealed that bone marrow biopsy was performed at this site 4 days earlier. Therefore, the increased FDG uptake in the left posterior iliac crest could be attributed to postbiopsy inflammatory changes.

Figure 18  A 69-year-old woman presented with persistent coughing, shortness of breath, and mucus production. A chest radiograph (not shown) demonstrated a right hilar mass. FDG-PET/CT was performed, which revealed a 3-cm lesion in the right upper lobe with surrounding atelectasis and adjacent ipsilateral hilar and mediastinal lymphadenopathy (A, arrowheads). Biopsy of the right upper lobe lesion showed squamous cell carcinoma. FDG-PET/CT also showed several FDG-avid bone marrow foci, including involvement of the medial left clavicle (A, B, D, continuous arrows) and the anterior right iliac spine (A, F, H, dashed arrows). Corresponding CT scans showed no clear abnormalities in the medial left clavicle (C) and anterior right iliac spine (G). Bone biopsies were performed at both locations (E and I), which revealed islands of red marrow hyperplasia without any sign of malignancy. Laboratory examination showed a hemoglobin level of 7.1 mmol/L (normal values: 7.8-10.0 mmol/L), consistent with anemia. Note that this patient had not received any granulocyte colony-stimulating factors.
returns to the pretreatment situation within 5 days after discontinuation of G-CSF therapy\textsuperscript{104} may be performed to avoid misdiagnosis. Bone marrow biopsy may also be performed but may suffer from sampling errors. Heterogeneously increased bone marrow FDG uptake may also be seen in patients who have both areas of G-CSF-induced hypermetabolic red marrow and areas of successfully treated bone disease that have become hypometabolic.\textsuperscript{110}

**Fibrous Dysplasia**

Fibrous dysplasia is a relatively common, benign skeletal disorder, typically encountered in adolescents and in young adults, but may present at any age.\textsuperscript{111} Fibrous dysplasia is a developmental anomaly in which the normal medullary space of the affected bone is replaced by fibro-osseous tissue.\textsuperscript{111} The process may affect a single bone or many bones (although the latter is six times less common than the mono-ostotic form).\textsuperscript{111} Polyostotic fibrous dysplasia typically presents earlier in life, and one-third to one-half of patients have so-called cafe-au-lait spots.\textsuperscript{111} Fibrous dysplasia has been reported in association with several endocrine dysfunctions such as precocious puberty in girls (McCune-Albright syndrome), hyperthyroidism, hyperparathyroidism, acromegaly, diabetes mellitus, and Cushing syndrome.\textsuperscript{111} Fibrous dysplasia can affect any bone in the skeleton.\textsuperscript{111} Lesions may involve only a small segment of a bone or extend from one end of the affected bone to the other.\textsuperscript{111} Generally, the lesions encountered in polyostotic fibrous dysplasia are more extensive (ie, larger and longer).\textsuperscript{111} The most common sites of skeletal involvement in monostotic fibrous dysplasia are (in order of decreasing frequency) the ribs, proximal femurs, and craniofacial bones.\textsuperscript{111} Symptomatology depends on lesion extent and location.\textsuperscript{111} Fibrous dysplasia has a variable FDG uptake,\textsuperscript{112} and FDG-avid lesions may mimic malignant disease (Fig. 19).\textsuperscript{113,114} Nevertheless, and although fibrous dysplasia has a wide spectrum of radiological appearances, findings on radiographs and CT are frequently sufficient for diagnosis,\textsuperscript{111} with fibrous dysplasia characteristically appearing as a well-circumscribed

![Figure 19](image_url) **Figure 19** A 71-year-old man with a history of abdominal endovascular aneurysm repair and extreme localized pain above the umbilicus underwent FDG-PET/CT to detect vascular graft inflammation or infection. FDG-PET/CT did not show any signs of vascular graft complications. However, slightly increased FDG uptake was observed in the left 10th rib (A and B, arrows). Corresponding CT shows a well-circumscribed medullary lesion with some “ground-glass” consistency and endosteal scalloping (C, arrow). The lesion appeared morphologically similar on a CT scan that was performed 3 years earlier (not shown). Based on its location, morphologic appearance, and stability over time, fibrous dysplasia is the most likely diagnosis.
medullary lesion with "ground-glass" consistency and expansive bone remodeling, with or without endosteal scalloping and surrounding reactive sclerosis.\textsuperscript{111} The MRI characteristics of fibrous dysplasia are variable.\textsuperscript{115,116}

Fractures

PET scans may show FDG uptake at the site of a fracture, potentially resembling the presence of a malignant bone lesion. First, a fracture at FDG-PET may present as an FDG-avid focus without a clear pattern (such as the Honda sign in sacral insufficiency fractures) and without a clearly identifiable fracture line or callus formation at low-dose CT. Clinical history, such as previously diagnosed osteoporosis or exposure to previous radiation therapy, may suggest (insufficiency) fracture. When in doubt, additional full-dose CT or MRI may demonstrate the fracture line and explain the increased FDG uptake (Figs. 20 and 21). Second, both benign and pathologic fractures exhibit increased FDG uptake, and PET alone may not be able to discriminate between these two entities. Anatomical imaging with CT or MRI may be helpful in distinguishing benign fractures from pathologic fractures.\textsuperscript{117} CT findings that may suggest an underlying malignancy include the presence of an aggressive periosteal reaction, a bone marrow pattern of destruction, endosteal scalloping, mineralized matrix, and a large soft-tissue mass.\textsuperscript{117,118} At MRI, well-defined low signal marrow alterations on T1-weighted images have been reported to indicate an underlying malignancy, in addition to the above-mentioned CT findings.\textsuperscript{117,118} Discriminating osteoporotic from malignant vertebral fractures is a similar issue in which additional CT and MRI findings may indicate the correct diagnosis. CT findings suggestive of benign fractures include intravertebral gas (which is considered very specific)\textsuperscript{119} and distinct fracture lines (Fig. 21), whereas osteolytic destruction and a focal paraspinal mass suggest a malignant cause.\textsuperscript{120,121} MRI findings suggestive of benign fractures include preservation of normal bone marrow signal, intravertebral fluid collection or fluid signal, and a continuous black line representing the posterior vertebral body margin at T2-weighted imaging, whereas a focal paraspinal

![Figure 20](image)

**Figure 20** FDG-PET/CT in a 64-year-old man after eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy because of stage IV, intermediate-risk diffuse large B-cell lymphoma, showed a new FDG-avid lesion in the right sacrum (A, arrow) without any visible changes at corresponding low-dose CT (B). The interpreting nuclear medicine physician considered this new lesion suspicious for lymphoma, and bone biopsy was scheduled. However, sacral insufficiency fracture was considered by the radiologist who was assigned to perform the biopsy, and MRI was ordered for further evaluation. MRI shows enhancement in the right sacrum after gadolinium administration (C, arrow) and edema at fat-suppressed T2-weighted imaging (D, arrow), but also a distinct hypointense fracture line, which is best appreciated on fat-suppressed T2-weighted and non–contrast-enhanced T1-weighted images (D and E, arrows). The diagnosis of sacral insufficiency fracture was confirmed and biopsy was canceled.
An 82-year-old man with known emphysema underwent FDG-PET/CT because of an abnormality in the right upper lobe on chest radiography (not shown). FDG-PET/CT showed a tumor in the right upper lobe (A, arrow), which was proven to be squamous cell carcinoma on biopsy. FDG-PET/CT also showed some FDG avidity in vertebra T8 (B and C, arrowheads), without any clear abnormalities on corresponding low-dose CT (D). The FDG avidity of vertebra T8 was less than that of the right upper lobe tumor, which may suggest a different nature of the former. MRI was performed for further characterization, which showed T1 hypointensity (E, arrowhead), T2 hyperintensity (F, arrowhead), and enhancement in vertebra T8 after administration of gadolinium (G, arrowhead). Also note some T2 hyperintensity and enhancement just below the cranial end plate of vertebra T9 (F, G). MRI findings were considered equivocal and biopsy of vertebra T8 was scheduled. Full-dose planning CT just before biopsy showed a distinct fracture line and intravertebral gas in vertebra T8 (H, arrowhead), highly specific for a benign fracture. Retrospective close-up view of the low-dose CT part of the FDG-PET/CT examination (I, same as D) shows none of these findings in vertebra T8 (I, arrowhead). Despite the full-dose CT findings of a benign fracture, biopsy of vertebra T8 was performed by the attending radiologist, which, as expected, showed only reactive changes without any signs of malignancy.
mass and deposit-like appearance of pedicle involvement are more likely to be associated with malignancy.\textsuperscript{120,121} Age and other compression deformities without bone marrow edema have also been reported to be negatively correlated with vertebral compression fractures.\textsuperscript{121}

**Osteonecrosis**

Osteonecrosis is common and represents loss of blood supply to a region of bone.\textsuperscript{122} There are numerous causes of osteonecrosis most commonly related to trauma, corticosteroids, and idiopathic.\textsuperscript{122} Common sites affected include the femoral head, humeral head, knee, femoral and tibial metaphysis, scaphoid, lunate, and talus.\textsuperscript{122} Unlike epiphyseal osteonecrosis (also known as avascular necrosis), metadiaphyseal osteonecrosis (also known as bone infarction) is often occult and asymptomatic.\textsuperscript{122}

Osteonecrosis can show increased FDG uptake due to vascularized, inflammatory granulation tissue at the reactive interface between the affected and surrounding bone (Fig. 22).\textsuperscript{122} This may cause diagnostic confusion in patients with cancer who undergo staging or follow-up FDG-PET.\textsuperscript{123,124} Concomitant CT may show a serpentine rim of sclerosis, but is insufficiently sensitive in early osteonecrosis.\textsuperscript{122} MRI is generally considered the most sensitive and specific imaging modality for early diagnosis (which shows maintained yellow marrow with a serpentine rim of high signal intensity on fat-suppressed T2-weighted images), and should be ordered to avoid misdiagnosis or unnecessary biopsy.

**Paget Disease of Bone**

Paget disease of bone is a chronic skeletal disorder whose cause remains largely unknown.\textsuperscript{125} Paget disease has a slight male predilection and its frequency increases remarkably in both sexes with advancing age.\textsuperscript{125} Although most patients are asymptomatic, overall abnormal bone formation results in osseous weakening, with deformity and fractures and associated pain being common manifestations of the disease.\textsuperscript{125}

The primary event in Paget disease is intense focal bone resorption followed by disorderly bone formation that results in overall abnormal bone remodeling.\textsuperscript{125} Three major phases are recognized: the lytic phase (incipient active), in which osteoclastic resorption predominates; the mixed phase (active), in which there is both osteoclastic and osteoblastic hyperplasias with predominant osteoblastic activity; and finally, the blastic phase (late inactive), in which osteoblastic activity gradually declines.\textsuperscript{125} As a result of this anarchic bone behavior that produces disorganized new bone, an increased or decreased external bone contour and a narrowed or enlarged marrow cavity are seen.\textsuperscript{125} The anatomical distribution of Paget disease usually is asymmetrical and (in order of decreasing frequency) most commonly affects the lumbar spine, pelvis, sacrum, femur, and cranium.\textsuperscript{125} There is a preference for the

---

*Figure 22*  
FDG-PET/CT in a 64-year-old woman who was treated for bilateral non–small cell lung cancer 3 years earlier showed several suspicious pleural lesions (A, arrowheads) that were proven to represent recurrent disease. There was also increased FDG uptake in and around both femoral heads (A and B, arrows). Corresponding CT image shows bilateral proximal epiphyseal sclerosis and partial destruction and collapse (most prominently on the left side), in keeping with avascular necrosis.
lower extremities and a tendency for right-sided alterations.\textsuperscript{125} Polyostotic disease is more frequent than monostotic disease.\textsuperscript{125} Typical anatomical changes on radiographs or CT such as mixed lysis and sclerosis, trabecular and cortical bone thickening, bone expansion and deformity, and a coarsened trabecular pattern may indicate the correct diagnosis.\textsuperscript{125} The MRI characteristics in Paget disease are variable, reflecting the natural course of the disease process in different phases.\textsuperscript{125} Active Paget disease may demonstrate increased FDG uptake (Fig. 23), which may mimic metastatic bone disease when typical anatomical changes are absent.\textsuperscript{126-128} Note that about 1\% of cases of Paget disease of bone undergo sarcomatous change\textsuperscript{129} and that FDG-PET alone is not able to differentiate the former from the latter.

**Particle Disease**

Activity-related wear and tear of a joint prosthesis sheds particles (mostly from the polyethylene liner within the prosthetic cup), which induce bone resorption by activating macrophages.\textsuperscript{130} Among the joint replacements, this
phenomenon of particle disease is more often seen with hip arthroplasties, ultimately leading to aseptic loosening of the prosthesis requiring revision surgery.\textsuperscript{130} Particle disease appears as a lytic and sometimes expansile osseous abnormality located in close proximity to the prosthesis, occasionally associated with a soft-tissue mass.\textsuperscript{130} Associated high FDG uptake can be seen in these patients, and all these imaging findings may mimic a bone malignancy (Fig. 24).\textsuperscript{130,131} However, the diagnosis of particle disease can be suggested by the presence of hardware and the fact that abnormal lucencies are seen on both sides of the joint.\textsuperscript{131}

Schmorl Nodes
A Schmorl node is the herniation of nucleus pulposus through the cartilaginous and bony end plate into the body of the adjacent vertebra.\textsuperscript{132} No consensus on pathogenesis exists.\textsuperscript{132} Schmorl nodes are more frequent in men than in women, and there may be a positive association with age, although there is no consensus on the latter issue.\textsuperscript{132} Schmorl nodes are mostly localized to the lower thoracic area, between the T8 and T12 vertebrae.\textsuperscript{132} Schmorl nodes are common findings on imaging, and although most Schmorl nodes are asymptomatic, some have been shown to become painful lesions.\textsuperscript{132} Symptomatic Schmorl nodes are thought to be due to the inflammatory response solicited by the herniation of the nucleus pulposus into the well-vascularized vertebral body.\textsuperscript{132} Schmorl nodes demonstrate low-to-moderate FDG uptake,\textsuperscript{133} but higher FDG uptake can be seen in those with perifocal enhancement at MRI (which is thought to be due to inflammation)\textsuperscript{133} and in giant Schmorl nodes.\textsuperscript{134,135} Schmorl nodes with high FDG uptake can mimic malignancy (Fig. 25), but their typical location at CT or MRI should avoid misdiagnosis.

Summary
The present article reviewed a wide spectrum of relatively more common and less common benign bone conditions that may be FDG-avid and mimic malignancy, including osteomyelitis, bone lesions due to benign systemic diseases (Brown tumor, Erdheim-Chester disease, Gaucher disease, gout and other types
of arthritis, Langerhans cell histiocytosis, and sarcoidosis), benign primary bone lesions (bone cysts, chondroblastoma, chondromyxoid fibroma, desmoplastic fibroma, enchondroma, giant cell tumor and granuloma, hemangioma, nonossifying fibroma, and osteoid osteoma and osteoblastoma), and a group of benign miscellaneous bone conditions (post bone marrow biopsy or harvest status, bone marrow hyperplasia, fibrous dysplasia, fractures, osteonecrosis, Paget disease of bone, particle disease, and Schmorl nodes). Several ancillary clinical and imaging findings may be helpful in discriminating benign from malignant FDG-avid bone lesions. Table summarizes the key features of the benign and possibly FDG-avid bone conditions that may mimic malignancy. Note that this list may not be complete, that the exact incidence of increased FDG uptake in these benign bone conditions is not clear, and that the biological causes for the observed FDG avidity remain unclear in most cases. However, the information provided in this article is believed to be useful for establishing a differential diagnosis when encountering an FDG-avid bone lesion and when malignancy is in doubt. Nevertheless, the distinction between benign and malignant FDG-avid bone diseases remains sometimes difficult or even impossible, and tissue acquisition will be required to establish the final diagnosis.

Figure 25  An 89-year-old man with a history of carcinoid, hemihepatectomy, and aortic stenting underwent FDG-PET/CT because of suspicion of giant cell arteritis. FDG-PET showed slightly increased activity in the large vessel walls (including aortic arch branches and iliac and femoral arteries), which may suggest giant cell arteritis (note that this patient had already received prednisolone in therapeutic doses for 4 days). FDG-PET also showed focally increased FDG uptake in the S1 vertebra (A and B, arrows), which corresponded to the location of a Schmorl node at CT (C, arrow).
<table>
<thead>
<tr>
<th>Bone Condition</th>
<th>Typical Patient Spectrum</th>
<th>Typical Location(s)</th>
<th>Imaging and Clinical Characteristics of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteomyelitis</strong></td>
<td>Prepubertal children</td>
<td>Any site, but most frequently involves the metaphysis of long bones (particularly tibia and femur)</td>
<td>May appear aggressive with bone marrow and cortical destruction, articular involvement, periosteal reaction, and an accompanying soft-tissue mass. Presence of gas or fat-fluid levels in the bone marrow (without preceding trauma), the penumbra sign at MRI (area of relatively hyperintense signal between the intermediate-to-low signal intensity of the intraosseous abscess cavity and the adjacent edematous or sclerotic bone marrow on unenhanced T1-weighted images that enhances intensely after contrast medium administration), and persistent fatty signal within the bone as well as soft tissues at MRI are specific for osteomyelitis.</td>
</tr>
<tr>
<td>(subacute hematogenous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elderly patients</td>
<td>Any site, but most frequently involves the vertebral bodies</td>
<td>(Early) spinal infection may manifest as involvement of an isolated vertebral body without disc involvement, involvement of one vertebral body and one disc, or two vertebral bodies but not the intervening disc; in these situations, differentiation between infection and malignancy is difficult. Involvement of two consecutive vertebrae and the intervening disc is virtually diagnostic of infectious spondylitis.</td>
</tr>
<tr>
<td><strong>Bone lesions due to benign systemic diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown tumor</td>
<td>In less than 5% of patients with primary or secondary hyperparathyroidism</td>
<td>Long bones, but may also occur in the mandible, clavicles, ribs, and pelvis</td>
<td>Appears as an expansile, osteolytic lesion, whereas internal septations or sclerosis can be seen in later stages of disease. Bone mineral density of the skeleton can be diffusely decreased. MRI can show susceptibility artifacts (due to hemosiderin deposition). Laboratory investigations will reveal hypercalcemia, hypophosphatemia, and increased parathyroid hormone levels. Imaging findings are considered pathognomonic. More than 50% of cases have at least one associated extraskeletal involvement, namely, the kidney, skin, central nervous system, or heart.</td>
</tr>
<tr>
<td></td>
<td>Most commonly in secondary hyperparathyroidism due to chronic renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erdheim-Chester disease</td>
<td>Middle-aged to older patients</td>
<td>Long bones, especially of the lower limbs (tibia and fibula)</td>
<td>Bilateral and symmetrical cortical thickening and osteosclerosis of the diaphyseal and metaphyseal regions with classical sparing of the epiphyses. Imaging findings are considered pathognomonic. More than 50% of cases have at least one associated extraskeletal involvement, namely, the kidney, skin, central nervous system, or heart.</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Any age</td>
<td>Bone marrow infiltration generally follows the distribution of red marrow progressing from the axial to the peripheral skeleton and from the proximal to the distal aspects of the long bones with a tendency to spare the epiphyses.</td>
<td>An array of skeletal manifestations can be seen, including bone pain, medullary cavity expansion with cortical thinning and endosteal scalloping, osteopenia or osteoporosis, osteolytic lesions, bone infarcts, avascular necrosis, fractures, and acute osteomyelitis. Gaucher disease should be considered if bone alterations are seen in combination with hematologic (anemia and thrombocytopenia) and visceral (hepatosplenomegaly) manifestations.</td>
</tr>
<tr>
<td>Gout</td>
<td>Frequency increases with age, male predominance</td>
<td>Acute gouty arthritis mostly begins in one joint in the lower limbs (85%-90% of cases), usually the first metatarsophalangeal joint, whereas the next most frequent locations are the midtarsi, ankles, knees, and arms.</td>
<td>Polyrarticular gout (3%-14% of initial attacks) in unusual locations such as the shoulders or hips may resemble metastatic disease. The periarticular location and concomitant typical radiological changes such as well-defined juxta-articular erosions with sclerotic rims and overhanging margins are highly suggestive of gout.</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Bone Condition</th>
<th>Typical Patient Spectrum</th>
<th>Typical Location(s)</th>
<th>Imaging and Clinical Characteristics of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>5-15 y (eosinophilic granuloma), 1-5 y (Hand-Schüller-Christian disease), &lt;2 y (Letterer-Siwe disease)</td>
<td>Lesions of the skull, pelvis, and ribs account for more than half of all lesions, whereas about 30% of lesions are in long bones.</td>
<td>Early lesions appear aggressive with osteolysis, poorly defined margins, and lamellated periosteal reaction, whereas late lesions appear well defined and may show sclerotic margins and expanded remodeled appearance.</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Bone involvement occurs in about 5% of sarcoidosis patients.</td>
<td>Any bone can be involved, but the small bones of the hands or feet are most frequently affected.</td>
<td>Sarcoid bone lesions are characterized by their bilateral distribution, usually affect the ends of the bones, have a cystic or lacelike shape, and well-preserved cortical borders. Lesions in non–weight-bearing bones (hands) may show increased bone resorption. Sarcoid bone lesions in early phases may have no visible changes on radiographs or CT.</td>
</tr>
</tbody>
</table>

**Benign primary bone tumors**

| Bone cysts | Children and adolescents | Can involve any bone, but usually the long bone metaphysis (90%-95%) and primarily the proximal humerus and proximal femur | Well-defined solitary lytic bone lesion, may be unicameral or partially separated |

| Chondroblastoma | Most patients are less than 20 y of age, male predominance | Epiphyseal or apophyseal location. Approximately 75%-80% of all cases involve the long bones (tibia, distal femur, proximal humerus, and proximal femur). The foot is the second most common site of occurrence, most commonly in the talus and calcaneus. | Classically appears as a 1- to 4-cm lucent lesion with a thin, sclerotic, geographic margin, a lobular contour, and matrix mineralization in approximately 30% on radiographs or CT. A thick, solid periosteal reaction is present in almost 60% of long bone chondroblastomas, occurring in the metaphysis adjacent to the epiphyseal lesion. |

| Chondromyxoid fibroma | Mean age at presentation is around 25 y with an age range of 3-70 y. Very rare bone tumor | Most commonly involves the medullary cavity of the lower limb long bones. Metaphyseal or diaphyseal location (epiphyseal location is very rare) | A geographic pattern of bone destruction with a well-defined, sclerotic rim and commonly a round or elongated, lobular border is the classic appearance. Cortical thinning and expansion are also very common features, and complete cortical destruction may be seen in almost one-third of cases. |

| Desmoplastic fibroma | Mean age at diagnosis is around 20 y, but it can be seen at any age. Very rare bone tumor | Long tubular bones, mandible, and pelvis | Typically shows a geographic pattern of bone destruction, with a narrow zone of transition, and nonsclerotic margins |

(continued on next page)
<table>
<thead>
<tr>
<th>Bone Condition</th>
<th>Typical Patient Spectrum</th>
<th>Typical Location(s)</th>
<th>Imaging and Clinical Characteristics of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enchondroma</td>
<td>Solitary enchondroma is typically first discovered in the third or fourth decade.</td>
<td>The majority is located in the metaphyseal or metadiaphyseal region, with a predilection for short tubular bones, the proximal femur and humerus.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oval, well-circumscribed, lytic lesion with small and punctate to short, “ringlike” and “arclike” densities. Fractures are common in phalangeal lesions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Differentiation of enchondroma from chondrosarcoma in the long appendicular bones is often difficult clinically, radiologically, and pathologically, but pain related to the lesion, depth of scalloping greater than two-thirds of cortical thickness, cortical destruction, and soft-tissue mass, perioskeletal reaction, and greater uptake than the anterior iliac crest at bone scintigraphy strongly suggest chondrosarcoma.</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>Skeletally mature patients, with approximately 80% occurring in patients between 20 and 50 y of age</td>
<td>The lesion is thought to arise from the metaphyseal side of the epiphyseal plate, usually develops in long bones, most lesions in distal femur, proximal tibia, distal radius, sacrum, and proximal humerus.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lytic lesion with a well-defined but nonsclerotic margin that is eccentrically located and extends to the subchondral bone with expansile remodeling, but lacks internal mineralization. May have aggressive features, including a wide zone of transition, and cortical expansion or destruction with a soft-tissue mass.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The solid components typically demonstrate low-to-intermediate signal intensity at T2-weighted MRI.</td>
</tr>
<tr>
<td>Giant cell granuloma</td>
<td>Wide age range, but most patients are under 30 y of age at presentation, female predominance</td>
<td>Mandible, maxilla, and small bones of the hands or feet are most commonly affected.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiographic features are similar to those of giant cell tumor, although extension to subchondral bone in lesions of the appendicular skeleton is uncommon. Unlike their counterparts in the skull and vertebrae, hemangiomas in the peripheral and pelvic bones are often symptomatic (they can present with pain, soft-tissue swelling, and pathologic fracture), have a diversity of radiological appearances they can appear aggressive with osteolysis, cortical destruction, and an extraneous mass, and can be highly FDG-avid.</td>
<td></td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Female predominance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solitary skeletal hemangioma of the extremities can occur at any age but is rare under 10 y of age.</td>
<td>Most frequently involves the skull and vertebrae.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skeletal hemangiomas in the peripheral, tubular, and flat bones are very rare, and among them, the tibia and femur are the most common sites.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiographic features are similar to those of giant cell tumor, although extension to subchondral bone in lesions of the appendicular skeleton is uncommon. Unlike their counterparts in the skull and vertebrae, hemangiomas in the peripheral and pelvic bones are often symptomatic (they can present with pain, soft-tissue swelling, and pathologic fracture), have a diversity of radiological appearances they can appear aggressive with osteolysis, cortical destruction, and an extraneous mass, and can be highly FDG-avid.</td>
</tr>
<tr>
<td>Nonossifying fibroma</td>
<td>Usually discovered incidentally in children and rarely found in adults</td>
<td>Typically located in the metaphysis (adjacent to the physis), frequently found in the lower extremities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Characteristic imaging appearance allows for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Osteoid osteoma and osteoblastoma</td>
<td>Second decade of life, male predominance</td>
<td>Osteoid osteoma most commonly occurs in the long bones (femur, tibia).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoblastoma most commonly occurs in the axial skeleton (particularly spine and mandible).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distinguishing MRI features are hypointensity and septation on T2-weighted images. Osteoid osteoma typically causes night pain that is relieved with salicylates, but pain in osteoblastoma is usually not worse at night and is less likely to be relieved with salicylates. Typical clinical and imaging findings allow for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Benign miscellaneous bone conditions</td>
<td>Post bone marrow biopsy or harvest status</td>
<td>Posterior iliac crest is a common site for bone marrow biopsy and harvest.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any age</td>
<td>Shape of bone defect corresponds to bone marrow biopsy tract or osteotomy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Knowledge of the fact that bone marrow biopsy or harvest was performed before FDG-PET will avoid confusion with malignancy. (continued on next page)</td>
</tr>
<tr>
<td>Bone Condition</td>
<td>Typical Patient Spectrum</td>
<td>Typical Location(s)</td>
<td>Imaging and Clinical Characteristics of Interest</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bone marrow hyperplasia</td>
<td>Any age</td>
<td>Axial and proximal appendicular skeleton</td>
<td>Either homogeneously increased FDG uptake of the red bone marrow (most common) or heterogeneous FDG uptake (less common) due to scattered islands of hyperplastic red marrow or previously treated bone disease that has become hypometabolic relative to the surrounding hypermetabolic red marrow. Awareness of the fact that granulocyte colony-stimulating factor was administered suggests the presence of stimulated red bone marrow. When in doubt, additional MRI, bone marrow scintigraphy, or follow-up FDG-PET may be performed.</td>
</tr>
<tr>
<td>Fibrous dysplasia</td>
<td>Adolescents and young adults, although it may present at any age</td>
<td>Can affect any bone Mono-ostotic form six times more common than polyostotic form Monostotic fibrous dysplasia frequently affects the ribs, proximal femurs, and craniofacial bones.</td>
<td>Wide spectrum of radiological appearances, but characteristically appears as a well-circumscribed medullary lesion with “ground-glass” consistency and expansile bone remodeling, with or without endosteal scalloping and surrounding reactive sclerosis. Typical radiological findings allow for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Fractures</td>
<td>Any age</td>
<td>Any bone</td>
<td>Full-dose CT or MRI may demonstrate the fracture line that is not seen at low-dose CT. Presence of an aggressive periosteal reaction, a bone marrow pattern of destruction, endosteal scalloping, mineralized matrix, a large soft-tissue mass, and well-defined low signal marrow alterations at T1-weighted MRI are suggestive of a malignant fracture. CT findings suggestive of a benign vertebral fracture are intravertebral gas and distinct fracture lines, whereas osteolytic destruction and a focal paraspinal mass suggest malignancy. MRI findings suggestive of a benign vertebral fracture are preservation of normal bone marrow signal, intravertebral fluid collection or fluid signal, and a continuous black line representing the posterior vertebral body margin at T2-weighted imaging, whereas a focal paraspinal mass and deposit-like appearance of pedicle involvement suggest malignancy. MRI is the most accurate imaging modality for early diagnosis, which shows maintained yellow marrow with a serpentine rim of high signal intensity on fat-suppressed T2-weighted images. Typical radiological findings allow for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>Any age</td>
<td>Femoral head, humeral head, knee, femoral and tibial metadiaphysis, scaphoid, lunate, and talus</td>
<td>CT may show a serpentine rim of sclerosis but is insufficiently sensitive in early osteonecrosis. MRI is the most accurate imaging modality for early diagnosis, which shows maintained yellow marrow with a serpentine rim of high signal intensity on fat-suppressed T2-weighted images. Typical radiological findings allow for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>Frequency increases remarkably with age</td>
<td>Most commonly affects the lumbar spine, pelvis, sacrum, femur, and cranium</td>
<td>Mixed lysis and sclerosis, trabecular and cortical bone thickening, bone expansion and deformity, and a coarsened trabecular pattern are typical findings seen on radiographs or CT. MRI is the most accurate imaging modality for early diagnosis, which shows maintained yellow marrow with a serpentine rim of high signal intensity on fat-suppressed T2-weighted images. Typical radiological findings allow for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Particle disease</td>
<td>Patients with joint prosthesis</td>
<td>Most frequently seen in hip arthroplasties</td>
<td>Lytic and sometimes expansile osseous abnormality located in close proximity to the prosthesis, occasionally associated with a soft-tissue mass. Presence of hardware and abnormal lucencies on both sides of the joint suggests particle disease. Typical location at CT or MRI allows for a confident diagnosis and exclusion of malignancy.</td>
</tr>
<tr>
<td>Schmorl nodes</td>
<td>Possible positive association with age</td>
<td>Adjacent to vertebral end plate</td>
<td>Herniation of nucleus pulposus through the cartilaginous and bony end plate into the body of the adjacent vertebra. Typical location at CT or MRI allows for a confident diagnosis and exclusion of malignancy.</td>
</tr>
</tbody>
</table>