METASTATIC BONE DISEASE

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Skeletal metastases are the most common variety of bone tumors and should always be considered in the differential diagnosis, particularly in older patients.

Cancers of the breast, prostate, lung, and kidney account for 80% of all metastatic cancers to bone.
In children aged 5 years and younger, neuroblastoma is usually the primary tumor responsible for metastatic disease.

- Tumor cells seem to acquire a special “genetic signature” that enables them to metastasize. In addition, the microenvironment in bone, especially marrow stem cells, supports cancer cells in homing, differentiation, and survival.
cancer cells influence osteoblasts and osteoclasts by secreted factors such as parathyroid hormone–related peptide (PTHrP) or endothelin 1. This leads to osteolytic or osteoblastic metastases in bone; however, even osteoblastic metastases are accompanied by increased bone resorption, as is clinically evident by the treatment response to bisphosphonates in osteoblastic metastases of prostate cancer.
Stimulated tumor cells release factors that induce osteoblasts to secrete RANK (receptor activator of nuclear factor kappa b)–ligand or RANKL, which is a potent factor for osteoclast formation and activity. Osteoclasts, in turn, resorb bone and thus release additional growth factors that enhance the accumulation of cancer cells.
Clinical Presentation

- Metastases are relatively rare in patients younger than the age of 40. Therefore, patient age is an important discriminating factor in the diagnosis.

- Unlike primary bone tumors, metastases usually involve the axial skeleton (skull, spine, and pelvis) and the most proximal segments of limb bones.
Most metastatic lesions are found in the vertebrae, ribs, pelvis, skull, femur, and humerus.

The majority of skeletal metastases are silent.

When metastases are symptomatic, pain is the main clinical feature, although rarely a pathologic fracture through the lesion may focus attention on the disease.
Clinical and laboratory examinations frequently disclose other signs of malignancy, such as weight loss, anemia, fever, and an elevated erythrocyte sedimentation rate. In addition, serum calcium and alkaline phosphatase levels are usually elevated.
It has been estimated that 30% to 50% of normal bone mineral must be lost before a bone metastasis becomes visible on a radiograph.

Radionuclide bone scan is the best screening method for early detection of metastatic tumors.

(PET) scanning, being the most sensitive. On radiography, a metastatic lesion may resemble any of the benign or malignant lesions.
- There are no radiographic characteristics of metastasis. The type of bone destruction may be geographic, moth-eaten, or permeative, and the margins may be well or poorly defined.

- A periosteal reaction and a soft tissue mass may or may not be present, although the latter situation is more common.
Metastases can be solitary or multiple, and they can be further subdivided into purely lytic, purely sclerotic, and mixed lesions.

Lytic lesions. Osteolytic metastases are the most common, representing about 75% of all metastatic lesions. The primary source is usually a carcinoma of the kidney, lung, breast, gastrointestinal (GI) tract, or thyroid.
Osteolytic metastases. A: Osteolytic metastasis to the proximal femur from carcinoma of the colon in a 52-year-old woman. B: Osteolytic metastasis to the left ilium from carcinoma of the thyroid in an 83-year-old man.
Osteoblastic metastases represent approximately 15% of all metastatic lesions. In men they are caused mainly by a prostatic gland cancer or a seminoma. In women the primary source is usually carcinoma of the breast, uterus (particularly cervix), or ovary. In both genders, metastases may originate from carcinoid tumors, bladder tumors, certain neurogenic tumors, including medulloblastoma, and osteosarcoma.
Sclerotic metastases. A: Multiple sclerotic foci are scattered through the ilium, pubis, ischium, and proximal femur of a 55-year-old man with carcinoma of the prostate. B: Sclerotic metastases to the pubis, ischium, and proximal femur in a 57-year-old woman with breast carcinoma
Mixed lesions. Mixed osteoblastic and osteolytic lesions represent approximately 10% of all metastatic lesions. Any primary tumor can give rise to mixed metastases, the most common primaries being breast and lung tumors.

Occasionally, some primary neoplasms may give rise to both lytic and sclerotic metastases.
Osteolytic and sclerotic metastases. Osteolytic metastasis in the medial end of the clavicle (arrows) and sclerotic metastasis in the humeral head (open arrow) in a 27-year-old woman with a bronchial carcinoid tumor.
The spread of malignant cells to involve the skeleton usually takes place via the hematogenous route. In such instances, the bulk of the tumor lodges in the marrow and spongy bone. Therefore, the initial radiography of metastatic lesions in the skeleton reveals the destruction of cancellous bone; only after further tumor growth is the cortex affected.
Primary carcinomas of the kidney and bladder and melanoma may also give rise to cortical metastases. It is of interest that the majority of cortical metastases affect the femur.

Sometimes the morphologic appearance of a metastasis may suggest a specific site of origin. For example, bubbly, highly expansive, so-called blow-out metastatic lesions originate from a primary carcinoma of the kidney or thyroid. Multiple round, dense foci or diffuse increases in bone density are often seen in metastatic carcinoma of the prostate.
In general, metastatic bone disease is characterized by a combination of bone resorption and bone formation. Radiographic imaging of the lesions will reveal the predominant process. When osteolysis predominates, the lesions appear lytic, and when bone formation is dominant, they appear sclerotic. Multiple sclerotic metastases may present either in a focal pattern (multiple snowball appearance) or may have a diffuse pattern (generalized radiopacity of bones).
Bone destruction is always mediated by tumor-induced osteoclastic resorption.
It must be pointed out, however, that after treatment (radiation therapy, chemotherapy, or hormonal therapy), purely lytic lesions may become sclerotic. Scintigraphy is almost invariably positive in bone metastases, and increased uptake is observed in both sclerotic and lytic lesions. This phenomenon is secondary to the increased bone turnover and reactive repair at the periphery of the lesion. Radionuclide bone scan is helpful for distinguishing metastatic disease from multiple myeloma because the latter usually presents with a normal uptake of a tracer.
Occasionally, widespread metastatic disease produces a diffusely increased uptake throughout the skeleton rather than discrete hot spots. This so-called superscan appearance is identified by the abnormally intense bone uptake.

Sometimes metastases cause cold spots (photopenic defects) when there is bone destruction but insignificant reactive bone formation; this may be observed in metastases from lung and breast carcinoma.
Metastases distal to the elbows and the knees. A: Diffuse osteolytic metastases to the ulna in a 66-year-old woman with breast carcinoma. B: Osteolytic metastasis to the midshaft of the right fibula of a 41-year-old woman with hypernephroma.
Acrometastases. A: Osteolytic metastasis to the proximal phalanx of the left thumb in a 63-year-old man with bronchogenic carcinoma. B: Osteolytic metastasis to the distal phalanx of the right thumb (arrow) in a 50-year-old woman with breast carcinoma.
Cortical metastases. **A:** Osteolytic cortical metastasis to the femur (*arrow*) in a 62-year-old man with bronchogenic carcinoma. **B** and **C:** Osteolytic cortical metastases to the femur of an 82-year-old man with bronchogenic carcinoma. Note characteristic cookie-bite appearance of the lesion on the lateral radiograph (*arrows*). In three different patients, a 70-year-old man (**D**), a 46-year-old woman (**E**), and a 72-year-old woman (**F**), all with bronchogenic carcinoma, computed tomography sections demonstrate cortical metastases in the femora.
**Skeletal metastases.** A 52-year-old man with renal cell carcinoma (hypernephroma) developed a solitary metastatic lesion in the acromial end of the left clavicle. A: Radiograph of the left shoulder shows an expansive blown-out lesion associated with a soft tissue mass destroying the distal end of the clavicle. C: In another patient, a 59-year-old woman with hypernephroma, a blown-out lesion is associated with a soft tissue mass destroying the acromial end of the right clavicle, acromion, and glenoid.
Skeletal metastasis: (CT). **A:** An anteroposterior radiograph of the left hip of a 50-year-old man with hypernephroma shows an osteolytic lesion almost completely destroying the ischium (*arrows*). **B:** CT section demonstrates the extent of bone destruction and a soft tissue extension of metastasis.
**Skeletal metastasis: magnetic resonance imaging (MRI).**  
**A:** Anteroposterior radiograph of the left hip shows a diffuse osteolytic metastatic lesion in the proximal femur of a 60-year-old woman with breast carcinoma.  
**B:** Coronal T2*-weighted (MPGR, TR 550, TE 15, flip angle 15 degrees) MRI demonstrates increased signal of the lesion. The uninvolved bone marrow remains of low signal intensity.
MRI is more sensitive than technetium scans for detection of metastatic disease. Focal lytic metastases are characterized by a low signal on T1-weighted sequences, becoming bright on T2-weighting.

Focal sclerotic metastases, such as those from a primary carcinoma in breast or prostate, induce an osteoblastic reaction with new bone formation. Therefore, both T1- and T2-weighted images reveal a low signal intensity.
Metastatic tumor is often histologically identical or very similar to the primary, thus enabling accurate identification.

On microscopic examination, two aspects must be considered. The first is that of the tumor tissue itself.

The second histologic aspect is the effect of the metastasis on the bone, which constitutes a combination of reactive bone destruction and reactive proliferation.
**Skeletal metastasis:** (CT). Anteroposterior (A) and lateral (B) radiographs of the distal arm of a 78-year-old man with bronchogenic carcinoma show an osteolytic lesion in the posterolateral cortex of the distal humerus associated with periosteal reaction. C: CT section shows cortical destruction, periosteal reaction, and a soft tissue mass.
Differential Diagnosis

- There are no characteristic radiologic features of metastasis. A metastatic lesion may look like a primary benign or malignant tumor, like a focus of infection, like a metabolic disease, or even like a post-traumatic abnormality.

- The length of the lesion is often a helpful clue because long lesions (10 cm or greater) frequently represent a primary malignant tumor, whereas most metastatic lesions are smaller, between 2 and 4 cm in length.
A recent study evaluated the usefulness of MRI in discriminating osseous metastases from benign lesions. The so-called bull's eye sign (a focus of high signal intensity in the center of an osseous lesion) proved to be a sign of a benign disease, whereas a halo sign (a rim of high signal intensity around an osseous lesion) proved to be a sign of metastasis.
A single metastatic bone lesion must be distinguished from primary benign lesions and malignant tumors.

In addition to the length of the lesion, which can help in distinguishing a primary from a metastatic tumor, other helpful features are the presence (or absence) of a periosteal reaction and a soft tissue mass. A metastatic lesion usually presents without or with only a small soft tissue mass.
A periosteal reaction is usually absent unless the mass breaks through the cortex.

In the spine, metastatic lesions usually destroy the pedicle, a useful feature for distinguishing this lesion from myeloma or neurofibroma eroding the vertebral body.
Skeletal metastasis with soft tissue mass. A 70-year-old woman with breast carcinoma developed a skeletal metastasis to the thoracic vertebra. Note a large associated soft tissue mass.
**Skeletal metastases.** Metastases from bronchogenic carcinoma in a 45-year-old woman destroyed the right pedicles of vertebrae T8 and T10 (*arrows*).
A solitary osteoblastic metastasis should be differentiated from the bone island (enostosis).

On radiography, bone islands exhibit characteristic thorny radiations that blend imperceptibly with the normal trabeculae of the host bone, a feature not present in metastasis.
Further confirmation is provided by the radionuclide bone scan, which is invariably positive in metastatic disease but is usually normal in bone islands.

At times, a sclerotic metastasis with exuberant sunburst periosteal reaction, such as metastasis from a prostatic carcinoma, can simulate the appearance of osteosarcoma.
A single sclerotic lesion at the medial (sternal) end of the clavicle, which often is mistaken for a metastasis, may in fact represent condensing osteitis of the clavicle.

Clinically, this condition manifests with pain, as well as local swelling and tenderness. Radiography reveals a homogeneously dense sclerotic patch, usually limited to the inferior margin of the medial end of the clavicle.
Condensing osteitis of the clavicle. A: Radiograph shows a sclerotic lesion in the inferior aspect of the right clavicle (arrow), originally thought to represent sclerotic metastasis. B: Trispiral tomography shows that the superior aspect of the clavicle is not affected. There is no evidence of periosteal reaction. C: Computed tomography section through the sternal ends of the clavicles shows homogeneous sclerosis of the right clavicular head and soft tissue swelling adjacent to it anteriorly.
A sclerotic vertebra ("ivory vertebra") resulting from metastasis should be differentiated from lymphoma, sclerosing hemangioma, and Paget disease.

Involvement by a lymphoma is usually indistinguishable from metastatic disease, although the clinical and laboratory data may be helpful.
In *Hodgkin lymphoma* there is an occasional anterior scalloping of the vertebral body, which accentuates the anterior vertebral concavity and thus provides a useful differentiating feature.

*Hemangioma* often presents with typical vertical striations or a honeycomb pattern. *Paget disease* characteristically enlarges affected vertebrae and causes disappearance or coarsening of the vertebral endplates.
If a picture frame appearance typical for Paget disease is present, metastasis can be safely ruled out. Conversely, in metastatic lesions to the vertebrae the endplates remain preserved.
**Skeletal metastasis.** Sclerotic metastasis to the lumbar vertebra of a 72-year-old man with prostatic carcinoma mimics Paget disease. Note, however, that the vertebral endplates are preserved and vertebral body is not enlarged.
Osteolytic metastases must be differentiated from multiple myeloma and brown tumors of hyperparathyroidism.

In younger patients, Langerhans cell histiocytosis must be considered.

Probably the best modality for distinguishing metastases from multiple myeloma is the radionuclide bone scan because
Helpful in distinguishing *brown tumors of hyperparathyroidism* are other hallmarks of this condition, such as diffuse osteopenia, loss of the lamina dura of the tooth sockets, subperiosteal bone resorption, and soft tissue calcifications.

Because of their expansive nature, multiple metastases from kidney and thyroid should be differentiated from *pseudotumors of hemophilia*.
Sclerotic metastases should be differentiated from *osteopoikilosis*. Osteopoikilosis is classified among the sclerosing dysplasias of endochondral failure of bone formation and remodeling.

Sclerotic foci in osteopoikilosis are typically distributed near the large joints, such as hips, knees, and shoulders.

osteopoikilosis, unlike sclerotic metastases, exhibits a normal radionuclide bone scan.
Erdheim-Chester disease, a rare form of histiocytosis, can radiographically mimic sclerotic metastases. This condition usually exhibits bilateral, symmetric, patchy, or diffuse sclerosis of the medullary cavity of the long bones, sparing the epiphyses.
**Osteopoikilosis.** Anteroposterior radiograph of the right shoulder of a 34-year-old man shows typical periarticular distribution of sclerotic foci of osteopoikilosis.
**Skeletal metastases.** Diffuse sclerotic metastases to the pelvis and left femur causing a pathologic fracture in a 68-year-old man with prostate carcinoma mimic sclerotic changes of Paget disease.
Erdheim-Chester disease resembling sclerotic metastases.
Diffuse sclerosis of the radius may be mistaken for blastic metastases.
A solitary cortical metastasis should be differentiated, among other possibilities, from osteoid osteoma, cortical bone abscess, plasmacytoma, hemangioma, and cortical osteosarcoma. Cortical involvement associated with a soft tissue mass must be differentiated from an aneurysmal bone cyst and a primary soft tissue tumor invading the bone, including synovial sarcoma.

Multiple cortical metastases should be differentiated from hemangiomatosis and any vascular lesion involving the cortex.
Histologically, metastatic tumors are easier to diagnose than many primary tumors because of their essentially epithelial pattern.

A metastatic lesion may exhibit a characteristic morphologic pattern that strongly suggests a primary tumor, such as the clear cells of renal carcinoma, follicular or giant cell carcinoma of the thyroid, or the pigment production of melanoma.