Hypertrophic Osteoarthropathy: Clinical and Imaging Features

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Abbreviations: AP = anteroposterior, HOA = hypertrophic osteoarthropathy, PA = posteroanterior, PGF = prostaglandin E2, VEGF = vascular endothelial growth factor

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

• Understand the potential pathophysiologic mechanisms causing HOA and the differences between the primary (pachydermoperiostosis) and secondary forms.
• Describe the clinical and imaging features of HOA at radiography, CT, MR imaging, and bone scintigraphy and the array of pulmonary and extrapulmonary causes.
• Differentiate the findings of HOA from other potential causes of multifocal periostosis.

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Hypertrophic osteoarthropathy (HOA) is a medical condition characterized by abnormal proliferation of skin and periosteal tissues involving the extremities and characterized by three clinical features: digital clubbing (also termed Hippocratic fingers), periostosis of tubular bones, and synovial effusions. HOA can be a primary entity, known as pachydermoperiostosis, or can be secondary to extraskeletal conditions, with different prognoses and management implications for each. There is a high association between secondary HOA and malignancy, especially non–small cell lung cancer. In such cases, it can be considered a form of paraneoplastic syndrome. The most prevalent secondary causes of HOA are pulmonary in origin, which is why this condition was formerly referred to as hypertrophic pulmonary osteoarthropathy. HOA can also be associated with pleural, mediastinal, and cardiovascular causes, as well as extrathoracic conditions such as gastrointestinal tumors and infections, cirrhosis, and inflammatory bowel disease. Although the skeletal manifestations of HOA are most commonly detected with radiography, abnormalities can also be identified with other modalities such as computed tomography, magnetic resonance imaging, and bone scintigraphy. The authors summarize the pathogenesis, classification, causes, and symptoms and signs of HOA, including the genetics underlying the primary form (pachydermoperiostosis); describe key findings of HOA found at various imaging modalities, with examples of underlying causative conditions; and discuss features differentiating HOA from other causes of multifocal periostitis, such as thyroid acropachy, hypervitaminosis A, chronic venous insufficiency, voriconazole-induced periostitis, progressive diaphyseal dysplasia, and neoplastic causes such as lymphoma.

Introduction

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by abnormal skin proliferation at the distal parts of the extremities as well as periosteal proliferation of the long bones. Three clinical features are often present: digital clubbing, periostosis of tubular bones, and synovial effusions (1,2).

Clubbing is characterized by a focal bulbous deformity of the tips of the digits and often portends serious disease (3). It is one of the oldest clinical signs to be recognized: Hippocrates described a patient with empyema and curved nails in the 5th century BC (4), hence lending the terms Hippocratic fingers and Hippocrates fingers. There is evidence for the ubiquity of HOA throughout time and among mammalian species. Paleopathologic studies have demonstrated changes consistent with HOA in human skeletal remains from pre-Hispanic Mesoamerica (5) and medieval Hungary (6). HOA has even been reported in canine and bovine species (7,8), apparently in response to the same illnesses as those reported for humans.
Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by abnormal skin proliferation at the distal parts of the extremities as well as periosteal proliferation of the long bones. Three clinical features are often present: digital clubbing, periostosis of tubular bones, and synovial effusions.

Although secondary HOA is most commonly associated with intrathoracic disease, it is important to be aware of its link to nonpulmonary diseases and avoid the pitfall of labeling all cases of secondary HOA as hypertrophic pulmonary osteoarthropathy.

Periostosis is the imaging hallmark of HOA and manifests along the shafts of tubular bones and usually spares the epiphyses in the earliest phases. Epiphyseal involvement is more common in primary HOA. Symmetric and widely distributed osseous involvement is a typical finding in primary and generalized secondary HOA, given its systemic mediation.

The presence of symmetric periostosis in the extremities, especially in the absence of an underlying osseous abnormality such as cortical destruction or fracture, should alert the radiologist to consider secondary HOA at the differential diagnosis and recommend a chest radiograph to look for a suspected thoracic abnormality, especially bronchogenic carcinoma. Extrathoracic pathologic conditions should also be considered if the results of thoracic imaging are negative.

Secondary HOA can also be further classified into the primary or secondary form, is also referred to as Bamberger-Marie syndrome or Pierre Marie–Bamberger syndrome. Nevertheless, many authors use these two eponyms to refer to secondary HOA. Pierre Marie and Eugen von Bamberger described the syndrome in 1890 and 1891, respectively, distinguishing it from acromegaly.

The term acropachy (Greek for “thick extremity”), by itself, may refer to either clubbing or the syndrome of HOA. Thyroid acropachy, on the other hand, specifically refers to HOA in the setting of thyroid disease, especially after treatment of Graves disease.

Primary HOA is a rare hereditary disease, usually with an early onset during childhood or adolescence, a male predilection (male-to-female ratio, approximately 7:1), and is more common in African Americans (9). It is also known as idiopathic HOA, pachydermoperiostosis, Touraine-Solente-Golé syndrome, and Friedreich-Erb-Arnold syndrome. Between 33% and 73% of patients have a close relative with the same illness. Disseminated skin hypertrophy is characteristic of primary HOA, hence the term pachydermoperiostosis. In 1868, Nikolaus Friedrich, Wilhelm Heinrich Erb, and Julius Arnold described “hyperostosis of the entire skeleton” in two brothers (10). In 1935, Albert Touraine, Gabriel Solente, and Laurent Golé distinguished primary HOA from the secondary form and detailed three clinical subtypes of the disease (10).

Secondary HOA is overwhelmingly more common than primary HOA, comprising 95%–97% of all cases, and is associated with a wide spectrum of extraskeletal conditions. The term hypertrophic pulmonary osteoarthropathy, which Marie had coined, may be applied instead if the underlying condition, such as non–small cell lung carcinoma or cystic fibrosis, is pulmonary in origin. It is important to note, however, that cardiovascular, pleural, and mediastinal causes have also been described, and even extrathoracic diseases such as cirrhosis and inflammatory bowel disease can be causes of secondary HOA (Table 2).

Secondary HOA can also be further classified into generalized forms due to systemic diseases and localized forms limited to one or two extremities (Fig 1), usually due to prominent endothelial injury (eg, arterial aneurysm). In addition, HOA may be limited to the cyanotic limb in the setting of a patent ductus arteriosus complicated by pulmonary hypertension, and may manifest unilaterally in the setting of arterial graft infection (11–13) or a functioning arteriovenous fistula (14).

Classification and Nomenclature of HOA
Confusion often exists surrounding the terminology and nomenclature regarding both digital clubbing and HOA (Table 1), especially because HOA can be a primary or secondary entity (Fig 1).

Synonyms for clubbing include Hippocrates fingers, Hippocratic fingers, and drumstick fingers.

HOA, in its broadest sense, without specifying the primary or secondary form, is also referred to as Bamberger-Marie syndrome or Pierre Marie–Bamberger syndrome. Nevertheless, many authors use these two eponyms to refer to secondary HOA. Pierre Marie and Eugen von Bamberger described the syndrome in 1890 and 1891, respectively, distinguishing it from acromegaly.

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and vascular endothelial growth factor (VEGF), have been implicated at the molecular level. Many of these humoral factors are hypoxia-induced agents, which may account for the presence of clubbing in different hypoxic and malignant illnesses (17). The humoral pathway model is further supported by the fact that neonates with congenital heart disease given prostaglandins to maintain patency of the ductus arteriosus often develop periosteal new bone formation (prostaglandin-induced periostitis) involving the diaphyses of the long bones within 2–8 weeks of starting the infusion in a pattern that can be identical to that seen with HOA, with resolution of this finding 1–5 months after discontinuation of the infusion (18).

Table 1: Nomenclature of Clubbing and HOA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Synonyms and Eponyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clubbing</td>
<td>Hippocratic or Hippocrates fingers, drumstick fingers, acropachy*</td>
</tr>
<tr>
<td>HOA</td>
<td>Bamberger-Marie syndrome†, Pierre Marie–Bamberger syndrome†, acropachy*</td>
</tr>
<tr>
<td>Primary HOA</td>
<td>Idiopathic HOA, pachydermoperiostosis, Touraine-Solente-Golé syndrome, Friedreich-Erb-Arnold syndrome</td>
</tr>
<tr>
<td>Secondary HOA</td>
<td>Hypertrophic pulmonary osteoarthropathy (HPOA) (if underlying cause is pulmonary), Bamberger-Marie syndrome†, Pierre Marie–Bamberger syndrome†</td>
</tr>
</tbody>
</table>

*Acropachy, by itself, may refer to either clubbing or the fully developed syndrome of HOA. Thyroid acropachy, on the other hand, specifically occurs in the setting of thyroid disease, especially after initiating treatment for Graves disease.

†Bamberger-Marie syndrome and Pierre Marie–Bamberger syndrome have been used by different authors to refer to both HOA in its broadest sense and secondary HOA.

Figure 1. Classification of HOA. MSK = musculoskeletal.

Pathogenesis and Etiology of HOA

The exact mechanism underlying the pathogenesis of HOA is still unclear. Two models currently exist: a neurogenic pathway and a humoral pathway.

In the neurogenic pathway model of HOA, diseased organs innervated by the vagus nerve may induce a neural reflex leading to vasodilatation and increased blood flow to the extremities (15). Chemical vagotomy with atropine and surgical vagotomy as attempts for symptomatic relief have been reported with varying success (16).

In the humoral pathway model of HOA, cytokines and growth factors, including platelet-derived growth factor (PDGF), prostaglandin E₂ (PGE₂) and vascular endothelial growth factor (VEGF), have been implicated at the molecular level. Many of these humoral factors are hypoxia-induced agents, which may account for the presence of clubbing in different hypoxic and malignant illnesses (17). The humoral pathway model is further supported by the fact that neonates with congenital heart disease given prostaglandins to maintain patency of the ductus arteriosus often develop periosteal new bone formation (prostaglandin-induced periostitis) involving the diaphyses of the long bones within 2–8 weeks of starting the infusion in a pattern that can be identical to that seen with HOA, with resolution of this finding 1–5 months after discontinuation of the infusion (18).
Primary HOA
Genomic studies in families with primary HOA have identified mutations involving the 15-hydroxyprostaglandin dehydrogenase gene (HPGD) and solute carrier organic anion transporter family member 2A1 gene (SLCO2A1), both of which are responsible for the degradation of PGE₂ (19–21) (Fig 2). Affected individuals demonstrate chronically elevated levels of PGE₂, which may result in overexpression of VEGF and its effect on osteoblasts, leading to excessive new bone formation. The disease demonstrates variable expressivity, and both autosomal dominant and recessive inheritance of pachydermoperiostosis have been suggested (22).

Secondary HOA
Most cases of generalized secondary HOA are related to alteration of lung function, either by a lung tumor, injury to the lung parenchyma (eg, interstitial lung disease), or exclusion of the lungs from the circulation (eg, cyanotic heart disease). High levels of growth factors may accumulate in the peripheral circulation in two hypothetical ways (Fig 3).

First, in the presence of intracardiac shunting (eg, tetralogy of Fallot) or intrapulmonary shunting (eg, hepatopulmonary syndrome), platelet precursors fail to fragment within the pulmonary circulation and instead enter the systemic circulation (23). As platelet fragments are entrapped in the peripheral capillaries in the extremities, the release of growth factors promotes vascularity and fibroblast activity and therefore leads to soft-tissue and bone formation. Shunting may also explain how an arteriovenous fistula in an arm for hemodialysis access can divert these growth

Table 2: Causes of HOA

<table>
<thead>
<tr>
<th>Category</th>
<th>Pulmonary</th>
<th>Pleural/Mediastinal</th>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>Bronchogenic carcinoma*</td>
<td>Mesothelioma</td>
<td>Atrial myxoma</td>
<td>Liver</td>
<td>Hematologic malignancies</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
<td>Solitary fibrous tumor of the pleura</td>
<td></td>
<td>Esophageal</td>
<td>Osteosarcoma</td>
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<tr>
<td></td>
<td></td>
<td>Thymoma</td>
<td></td>
<td>Gastric</td>
<td>Nasopharyngeal carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Hodgkin disease</td>
<td></td>
<td>Pancreatic</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Infections</td>
<td>Abscess*</td>
<td>Empyema</td>
<td>Bacterial endocarditis*</td>
<td>Subphrenic or liver abscess</td>
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<tr>
<td></td>
<td>Tuberculosis*</td>
<td></td>
<td>Infected arterial grafts*</td>
<td>Amebiasis</td>
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<td></td>
<td>Fungal* (Pneumocystis)</td>
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<td></td>
<td>Tuberculosis</td>
<td>Polyarteritis nodosa</td>
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<td></td>
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<td>Whipple disease</td>
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<td>Inflammatory</td>
<td>Sarcoidosis</td>
<td>...</td>
<td>Aortic aneurysm</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Chronic</td>
<td>COPD</td>
<td>...</td>
<td>...</td>
<td>Ulcerative colitis</td>
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<td>hypoxia</td>
<td>Emphysema</td>
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<td>Crohn disease</td>
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<td>Bronchiectasis</td>
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<td>Celiac sprue</td>
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<td>Cystic fibrosis</td>
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<td></td>
<td>Pulmonary fibrosis</td>
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<td></td>
<td>Pulmonary AVM</td>
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<tr>
<td>Other</td>
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<td>...</td>
<td>...</td>
<td>Cirrhosis</td>
<td>Primary HOA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatic</td>
<td>Myxedema</td>
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<td></td>
<td>Biliary (PBC)</td>
<td>Thyrotoxicosis (thyroid acropachy)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Achalasia</td>
<td>Polycythemia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POEMS syndrome</td>
</tr>
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</table>

Sources.—References 1, 2.
Note.—AVM = arteriovenous malformation, COPD = chronic obstructive pulmonary disease, PBC = primary biliary cirrhosis, POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes.

*Most common causes.
Figure 3. Illustrations demonstrating the hypothesized mechanisms underlying the pathogenesis of HOA in congenital heart disease with right-to-left shunt (a) due to failure to fragment platelet precursors within the pulmonary circulation or with pleural or pulmonary disease (b) resulting in the release of growth factors and trophic effects on capillary beds, in both cases promoting vascularity and stimulation of fibroblasts and osteoblasts, and leading to periostitis and finger clubbing.

Second, in the setting of pulmonary fibrosis, lung cancer, or solitary fibrous tumor of the pleura, growth factors may be released by abnormal tissue and enter the systemic circulation to induce acropachy (2). Systemic dissemination of vasoactive factors produced or activated by a local pathologic process may also play a role in the humoral pathway of HOA. Endotoxins produced by bacteria in an infected vascular graft may account for unilateral HOA in a lower extremity (24).

At the histologic level, excessive collagen deposition, vasodilatation, vascular hyperplasia, and interstitial edema contribute to the bulbous deformity of digits seen in clubbing (25). Excessive connective tissue in the outer portion of the bones leads to elevation of the periosteum and deposition of new osteoid matrix underneath.

HOA can be secondary to a variety of conditions involving different organ systems (Table 2). Although secondary HOA is most commonly associated with intrathoracic disease, it is important to be aware of its link to nonpulmonary diseases, and avoid the pitfall of labeling all cases of secondary HOA as hypertrophic pulmonary osteoarthropathy. The most common cause of HOA is non–small cell lung carcinoma (NSCLC). The incidence of HOA in lung cancer has been reported to be between 4% and 17% (26). HOA can also be a paraneoplastic syndrome due to other tumors, including solitary fibrous tumor of the pleura (27,28). In fact, HOA has been reported as a paraneoplastic syndrome.
Methods to diagnose digital clubbing at physical examination include the hyponychial angle (angle abc < 188° is normal, left, and >192° for clubbing, right), Lovibond or profile angle (angle abd < 165° is normal, left, and >180° for clubbing, right), phalangeal depth ratio (distal phalangeal depth [DPD]/interphalangeal depth [IPD] ratio <1 is normal, left, and >1 for clubbing, right), Schamroth sign (loss of normal diamond-shaped window between nailbeds when nails are placed together), and digital index (sum of nail bed circumference [NB]/distal interphalangeal circumference [DIP] ratios for all fingers, >10 for clubbing).

In up to 22% of patients with solitary fibrous tumor of the pleura, compared with a prevalence of only approximately 5% with lung carcinoma, although lung carcinoma remains the most common cause of secondary HOA given its increased overall prevalence (28). It has been reported that periostitis or HOA can precede these underlying diseases by several months (17).

HOA in children is more commonly related to nonneoplastic causes, such as bacterial endocarditis and congenital heart diseases, as well as cystic fibrosis, chronic airway infection, and other chronic lung diseases. To our knowledge, neoplastic diseases have been reported as a cause of pediatric HOA in only 34 patients to date: 12 with nasopharyngeal carcinoma, nine with Hodgkin lymphoma, eight with osteosarcoma, three with thymic carcinoma, one with periosteal sarcoma, and one with pleural mesothelioma (29).

**Clinical Presentation of HOA**

Patients with HOA present with a continuum of signs and symptoms and rarely present with the complete triad of digital clubbing, periostosis, and synovial effusions. In fact, patients with HOA can often present with periostosis without clubbing or joint pain (26).

At one end of the spectrum, patients may be asymptomatic and unaware of their digital deformities. On the other end, some individuals, particularly those with lung malignancies, may present with burning sensation and bone pain in the digits in advance of clubbing (2). Pain involving the bones in addition to the adjacent joint should incline the clinician away from a potential misdiagnosis of inflammatory arthritis in these patients (1).

Clubbing of the fingers demonstrates a distinctive bulbous deformity of the fingertips and may be the only manifestation in the majority of HOA cases (2). Edema and increased soft tissue produce rocking of the nail bed, leading to a drumstick appearance. Several methods exist for diagnosing clubbing (Fig 4). A Lovibond or profile angle between the skin proximal to the cuticle and proximal takeoff of the nail exceeding 180°, a hyponychial angle between the skin proximal to the cuticle and distal nail exceeding 192°, and a phalangeal depth ratio (between the DPD and IPD) greater than 1 are all considered diagnostic of clubbing (30). The Schamroth sign (or Schamroth window test) is defined as the loss of the diamond-shaped window between two juxtaposed nailbeds (31). Additionally, the digital index is computed by first measuring the perimeter of each finger at the DIP joint and at the nail bed and then adding the 10 nail bed–to–distal interphalangeal ratios. If the digital index is greater than 10, clubbing is likely present (2). These physical examination maneuvers and measurements demonstrate interobserver variability, however (30).

Although not required for the diagnosis, effusions in large joints may manifest in HOA, but there is neither synovial membrane hypertrophy nor inflammatory cell exudation into the synovial fluid. These reflect the fact that HOA is neither an inflammatory joint disease nor a proliferative synovial disease (2). On occasion, the bilateral symmetric distribution of joint pain symptoms
can mislead the clinician to a misdiagnosis of early or atypical rheumatoid arthritis (17,32).

**Primary HOA**
In addition to the aforementioned osteoarticular symptoms, patients with primary HOA or pachydermoperiostosis tend to present with disseminated cutaneous overgrowth but can also demonstrate a continuum of symptoms. Different subtypes of pachydermoperiostosis with varying degrees of skeletal and cutaneous involvement have been described: the classic or complete form, with skin and skeletal changes; an incomplete form, with isolated periostosis without skin changes; and a forme fruste, with pachydermia but no skeletal effects. Of these three subtypes of primary HOA, the incomplete form is the most common.

Cutaneous manifestations of pachydermoperiostosis are diverse. Pachydermia, or thickening of the skin, forehead, and dorsum of the hands, is common. Ptosis, as well as coarsening and furrowing of the face, can contribute to a leonine facies appearance. The most advanced stage of skin hypertrophy, cutis verticis gyrata, is characterized by cerebriform cranial skin folds leading to a bulldog scalp appearance, although this finding is not specific to pachydermoperiostosis (33). A cylindrical leg deformity (called elephant leg), hyperhidrosis, and seborrhea may be present too.

**Secondary HOA**
Additional clinical findings associated with secondary HOA may reflect disease in an internal organ and assist in identifying the cause of HOA. Patients with thyroid acropachy, in particular, tend to also demonstrate exophthalmos and pretibial myxedema after initiating treatment of Graves disease. Cyanosis points to the presence of congenital cyanotic heart disease and, less commonly, pulmonary diseases such as cystic fibrosis, pulmonary fibrosis, and chronic obstructive pulmonary disease.

**Imaging Features of HOA**
Due to the lack of reliable serologic tests for HOA, imaging evaluation plays a central role in the diagnosis of HOA.

**Radiography and CT**
Plain radiographs of the extremities are often the first imaging modality used to evaluate the pain with which HOA often manifests, and may demonstrate abnormalities even in asymptomatic patients. Soft-tissue findings such as bulbous deformities at the distal fingers, abnormal nail curvature, and soft-tissue swelling can be present on radiographs.

Bone remodeling in the setting of long-standing clubbing can result in osseous resorption at the terminal phalanges of the fingers and toes, known as acro-osteolysis, traditionally associated with primary HOA and congenital cyanotic heart disease. A less frequent radiographic pattern, tuftal overgrowth, has also been described in the phalanges, supposedly more commonly in patients with malignancy. However, recent studies have demonstrated considerable overlap between these two patterns (34,35). These two osseous changes usually manifest in the toes first, before the fingers (2).

Periostosis is the imaging hallmark of HOA and manifests along the shafts of tubular bones and usually spares the epiphyses in the earliest phases. Epiphyseal involvement is more common in primary HOA (36). Symmetric and widely distributed osseous involvement is a typical finding in primary and generalized secondary HOA, given its systemic mediation (Fig 5) (37). The tibia, fibula, radius, and ulna are the most commonly affected bones (Fig 6), followed by the phalanges of the fingers (Fig 7). The periosteal reaction may be solid, linear, dense, or layered.

The periostosis in HOA appears at radiography to progress in stages with respect to three factors: the number of affected bones, the site of involvement within a given bone, and the shape of the tuftal overgrowth periostal reaction (Table 3). In mild cases, few bones are affected (usually the tibias and fibulas); periostosis is limited to the diaphysis and demonstrates a linear monolayer configuration, increasing the bone circumference without altering its shape (Fig 8). In moderate cases, periostosis can extend into the epiphyses and appear laminated or multilayered (Fig 9). Advanced cases can affect all tubular bones: in addition to the diaphysis, the metaphysis and epiphysis can also be involved and the periostosis acquires an irregular configuration. The stage of periostosis may correlate with the disease duration, rather than the primary or secondary nature of HOA (38).

Joint involvement in HOA is characterized radiographically by the presence of synovial effusion without evidence of joint space narrowing, erosions, or periarticular osteopenia. In fact, as arthritis is often the presenting complaint in HOA, initial radiographs will often be centered on the joint space, and it is imperative for the radiologist not to overlook the radiograph’s periphery and thereby miss periostosis in the long bones adjacent to the joint of concern.

The presence of symmetric periostosis in the extremities, especially in the absence of an underlying osseous abnormality such as cortical
destruction or fracture, should alert the radiologist to consider secondary HOA at the differential diagnosis and recommend a chest radiograph to look for a suspected thoracic abnormality, especially bronchogenic carcinoma. Extrathoracic pathologic conditions should also be considered if the results of thoracic imaging are negative.

**MR Imaging**

Periosteal reaction at MR imaging typically exhibits low-to-intermediate signal intensity on T1-weighted images and low signal intensity on T2-weighted images (Fig 10). Its appearance at MR imaging usually correlates with the radiographic findings and can manifest as simple periosteal elevation or laminated or onionskin periosteal reaction (39). Alternating bands of intermediate and low signal intensity at T1-weighted imaging, corresponding to immature and mature periosteum, respectively, have been reported (40).

Fluid-sensitive sequences such as T2-weighted, proton density–weighted, and short T1 inversion-recovery (STIR) imaging will often demonstrate a fine hypointense line, representing the elevated periosteum, surrounded by high signal intensity (41,42). Contrast enhancement of the thickened periosteum can also be seen (43). Osseous prolif-
eration at the ligamentous or tendinous insertion sites and the interosseous membrane can manifest in the later stages (40).

High signal intensity on T2-weighted images within the paraosseous soft tissues likely represents soft-tissue reactive changes and may correlate with the severity and location of periarthritis swelling reported by the patient. Muscular or septal edema may be present as well (41).

Although rare, endosteal new bone formation that can encroach on the medullary cavity has been reported (40,44). Regardless, the overall normal signal intensity of the bone cortex and medullary cavity at MR imaging is helpful for excluding an underlying osseous infection or malignancy. Bone marrow edema was reportedly present in at least one case of HOA secondary to lung carcinoma; however, this was thought to be due to biopsy-proven osseous metastases (45).

MR imaging is also helpful for identifying synovial effusions (46).

Digital clubbing can manifest at MR imaging as soft-tissue thickening underneath the nail bed and nail root with diffuse contrast enhancement and edema, indicative of hypervascularity in the nail bed (25,47).

The MR imaging findings of pachydermoperiostosis and secondary HOA in the extremities can be indistinguishable. Cutis verticis gyrata can manifest at MR imaging of the cranium as thickening of the diploë associated with diminished intradiploic fat signal intensity and thickening of the scalp with furrowing (33,44).

Bone Scintigraphy
Radionuclide bone scanning, usually with technetium 99m (\(^{99m}\text{Tc}\))–methylene diphosphonate (MDP), is usually more sensitive for the detection and characterization of the extent of HOA than radiography alone (48). In fact, HOA is often diagnosed serendipitously at bone scintigraphy in patients with known malignancy.

Typically, there is symmetrically increased tracer uptake at the periosteum in a linear fashion along the cortical margins of the diaphysis and metaphysis of the long tubular bones (32,49,50), termed the tram line or double stripe sign (Fig 11) (51,52). Prominent tracer uptake
HOA secondary to presumed bronchogenic carcinoma in a 58-year-old woman who presented with pain and swelling of the hands and feet. (a) Posteroanterior (PA) radiograph of the right hand demonstrates periosteal reaction (arrows) of the first metacarpal and some of the proximal and middle phalangeal shafts. (b) AP radiograph of the right foot demonstrates thick periosteal reaction (arrows) surrounding several metatarsal shafts. The left hand and foot (not shown) had similar radiographic appearances. (c, d) Frontal radiograph (c) and coronal CT reconstruction (d) of the chest demonstrate a left upper lobe mass (arrow).

Unilateral distribution in an extremity can point to a localized HOA secondary to an arterial graft infection (13). In addition to diagnosis, radionuclide bone scans can also be used to evaluate therapy response, as scintigraphic findings can resolve after treatment of the underlying secondary cause (54).

Although some authors have described a correlation between disease duration and the morphology and the extent of periostosis on radiographs, an analogous relationship at bone scintigraphy has not been found (24,38). Of note, negative follow-up radiographic evaluation of regions positive at scintigraphy is not uncommon and may reflect the increased sensitivity of radionuclide bone scanning (55).

Positron Emission Tomography
Similar to bone scintigraphy, positron emission tomography (PET) with bone-seeking $^{18}$F isotopes can also show symmetric hypermetabolic activity along the cortex of long tubular bones, especially in the lower extremities. Case reports utilizing both sodium fluoride (Na$^{18}$F) and $^{18}$F fluorodeoxyglucose (FDG) isotopes have reported uptake distributions

in the digits is reflective of digital clubbing (53).
corresponding to the periosteal thickening seen on the corresponding CT scan (56–59) (Fig 11). In some cases, high $^{18}$F tracer accumulation in a tumor or particular internal organ may point to the possible origin of secondary HOA.

**Differential Diagnosis of HOA**

Several conditions that also demonstrate multifocal periosteal reaction can mimic the radiologic appearance of HOA (Table 4). Although correlating with the patient’s age and symptoms is helpful, focusing on certain imaging traits can greatly assist the radiologist in narrowing the differential diagnosis of polyostotic periostitis. These characteristics include the type and anatomic distribution of the periosteal reaction, as well as the presence or absence of osseous destruction and soft-tissue and marrow abnormalities.

**Thyroid Acropachy**

Thyroid acropachy usually arises after treatment of Graves disease, including following thyroid ablation or resection. Patients will also present with digital clubbing, pretibial myxedema, and exophthalmos. The periosteal reaction in thyroid acropachy typically is lacy, fluffy, spiculated, and thick, involving the diaphyses of short tubular bones in the hands and feet, commonly involving the radial side of the first, second, and fifth metacarpals, and proximal and middle phalanges of the fingers (Fig 12) (37,60). Unlike with HOA, the tibia, fibula, radius, and ulna are usually not involved. MR imaging of the lower extremities may demonstrate changes related to thyroid dermopathy or myxedema: underlying a heaped-up morphology, a subcutaneous soft-tissue mass consisting of mixed components of isointense and hyperintense signal on fat-saturated T2-weighted images can be identified (61).

**Voriconazole-induced Periostitis**

Voriconazole is a second-generation triazole antifungal agent commonly used to treat immunocompromised (eg, organ transplant) patients for invasive aspergillosis and candidemia. Patients usually present with refractory joint pain. The periostitis induced by voriconazole usually has a patchier and more asymmetric extent than does HOA and can affect the clavicles, ribs, scapula, acetabulum, and hands. The periosteal reaction appears dense, focal, nodular, and irregular (Fig 8).
13), as opposed to the smooth or linear periostitis in HOA. Increased uptake at bone scintigraphy corresponds to the areas of periosteal reaction and may mimic diffuse osseous metastasis. The high fluoride composition of voriconazole likely correlates with the similarity in skeletal manifestations to those of fluorosis (62). Symptoms and periostitis will usually resolve on discontinuation of the medication (63).

**Venous Stasis or Insufficiency**

Long-standing impaired venous return may elicit periosteal reaction in the tibia and fibula due to increased pressure on the periosteum. Periosteal reaction due to chronic venous insufficiency can initially be separate from the cortex and usually appears thick, shaggy, and irregular but symmetric (Fig 14). Subcutaneous edema, superficial varicosities, phleboliths, and dystrophic soft-tissue calcifica-
tion are often present on radiographs (37). Bone scintigraphy will also show persistent tracer uptake in the lower extremity soft tissues due to impaired soft-tissue clearance (64).

**Leukemia and Lymphoma**
Both entities can be associated with an aggressive-appearing periosteal reaction that is commonly thin or lamellated in appearance. Radiographs may also show a permeative lytic lesion near the end of a long bone and a soft-tissue mass larger than the zone of bone destruction, although these findings may be subtle or inapparent, especially given the degree of involvement, and there may be little or no cortical destruction (37,60). MR imaging can definitively show any associated marrow and soft-tissue abnormality involved by tumor (Fig 15). More prominent bone destruction can be seen in Hodgkin lymphoma (65).

**Hypervitaminosis A**
This often stems from overuse of retinoids in adolescent and preadolescent children with acne, psoriasis, or burn injuries. Thick, dense, wavy periosteal reaction usually is greatest near the diaphysis and tapers toward the ends of the bone.
Long bones such as the ulna and metatarsals, followed by the clavicle, tibia, and fibula, are the most common locations. Cortical thickening of the tubular bones may also occur (66). Radiographs may also show cupping or splaying of the metaphyses and premature or asymmetric closure of the physis, leading to the appearance of coned epiphyses (37,60). Hypervitaminosis A may also cause tendon and ligament calcifications, including hyperostosis of the anterior cervical spine, which may mimic diffuse idiopathic skeletal hyperostosis and may be a cause of neck stiffness and dysphagia in these patients (67).

**Progressive Diaphyseal Dysplasia**

Progressive diaphyseal dysplasia (Camurati-Engelmann disease) is a rare autosomal dominant disorder characterized by bilateral symmetric cortical thickening (Fig 17). The diaphyses of the long bones are expanded due to endosteal as well as periosteal new bone formation. The presence of endosteal cortical thickening is an important differentiating feature from HOA, which will have only periosteal new bone formation. The metaphyses and epiphyses are typically not involved, as these regions are formed by endochondral ossification. Sclerosis of the skull base can cause cranial nerve compression, leading to sensory deficits, blindness, or deafness (68). Bone scintigraphy may show increased uptake in the entire thickened cortex in primary diaphyseal dysplasia, rather than just the periosteal distribution in HOA.

**Prognosis and Treatment of HOA**

**Primary HOA**

Primary HOA is generally self-limiting without effect on life span. Symptoms typically stabilize or even resolve by the third or fourth decades, with an average lapse of 10 years after the initial onset of symptoms. Patients may encounter sig-
significant comorbidities, however, such as myelofibrosis, anemia, and compressive neuropathy (22).

Primary HOA is usually treated symptomatically with analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs), interestingly, do not induce regression of the skeletal syndrome, despite the theorized role PGE$_2$ plays in the pathogenesis of HOA and the function of NSAIDs as potent prostaglandin inhibitors (2).

Patients with pachydermoperiostosis may also consult with a plastic surgeon to remove excess skin or administer botulinum toxin type A for cosmetic purposes.

**Secondary HOA**

In contrast to pachydermoperiostosis, the prognosis and mortality of secondary HOA are related to the underlying disease itself. The significance of this fact is accentuated by the high prevalence (up to 90%) of malignancy in patients with secondary HOA. Definitive clinical management is therefore targeted at curative treatment of the underlying cause, with surgical options, including lung tumor resection, lung transplantation, and correction of cyanotic heart disease, aiming to definitively treat the underlying primary cause (69). Following surgical correction of the underlying cause, the symptoms and imaging abnormalities related to secondary HOA may dissipate. In one case, for example, periostosis and its corresponding scintigraphic changes in

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<th>Table 4: Differential Diagnosis of Multifocal Periosteal Reaction</th>
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<td><strong>Children</strong></td>
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<td>Child abuse</td>
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<td>Multifocal osteomyelitis</td>
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<td>Hypervitaminosis A</td>
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Figure 12. Thyroid acropachy in a 45-year-old woman. PA radiograph of the left hand demonstrates fluffy, nonlinear, thick periostitis (arrows) involving the diaphyses of the first, second, and fifth metacarpals as well as all the middle and proximal phalanges.

of HOA and the function of NSAIDs as potent prostaglandin inhibitors (2).

 suggesting the high prevalence (up to 90%) of malignancy in patients with secondary HOA. Definitive clinical management is therefore targeted at curative treatment of the underlying cause, with surgical options, including lung tumor resection, lung transplantation, and correction of cyanotic heart disease, aiming to definitively treat the underlying primary cause (69). Following surgical correction of the underlying cause, the symptoms and imaging abnormalities related to secondary HOA may dissipate. In one case, for example, periostosis and its corresponding scintigraphic changes in
Figure 13. Voriconazole-induced periostitis in a 46-year-old woman with cystic fibrosis and a long-term history of voriconazole use after bilateral lung transplantation who presented with bilateral elbow and left knee pain. (a, b) AP radiographs of the bilateral forearms (a) and lateral radiograph of the left knee (b) demonstrate focal nodular periostitis involving both proximal radial diaphyses (arrows in a), as well as the distal femur (curved arrow in b) and anterior proximal tibia (straight arrow in b). (c) Sagittal proton density–weighted MR image of the left knee demonstrates corresponding nodular foci of low-to-intermediate signal intensity in the distal femur just superior (curved arrow) to the femoral trochlea and anterior to the proximal tibia just proximal (straight arrow) to the tibial tuberosity.

Figure 14. Chronic venous stasis in a 67-year-old woman with severe tricuspid regurgitation who presented with right lower extremity pain and swelling. AP radiograph of the right ankle demonstrates thick irregular periostitis (arrows) involving the distal tibia and fibula, as well as shallow skin ulceration (arrowheads) overlying the lateral malleolus and diffuse soft-tissue swelling.
the lower extremity resolved after resection of the lung tumor (54).

HOA secondary to vascular graft infection is treated by surgical removal of the infected prosthesis and intravenous antibiotic therapy (13). The prognosis of vascular graft infection is reportedly poor, however, with an overall survival of only 58% and a posttreatment complication rate of 57% (11).

Functioning as VEGF inhibitors, bisphosphonates and octreotides have also been reported to provide effective symptomatic treatment of bone pain in secondary HOA (69). Alternatively, vagotomy, in which the vagus nerve is transected, may provide symptomatic pain relief for refractory cases (16).

**Conclusion**

Centuries after Hippocrates described clubbing, HOA remains an important disease to diagnose, given the high association between its secondary form and malignancy, especially non–small cell lung carcinoma. Its pathogenesis remains poorly understood, which limits the efficacy of existing therapeutic options and leaves management of the underlying primary disease as the mainstay treatment of secondary HOA. Although the manifestations of HOA are most commonly detected at radiography, abnormalities can also be identified at CT, MR imaging, and bone scintigraphy. It is also important to distinguish HOA from other causes of multifocal periostitis, including thyroid acropachy,
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Figure 17. Progressive diaphyseal dysplasia in an 18-year-old woman who presented with headache and bone pain. (a, b) PA radiograph (a) of the bilateral hands and AP radiograph (b) of the tibias and fibulas show bilateral symmetric periosteal and endosteal new bone formation (arrows) in the diaphyses of the metacarpals and second through fourth proximal phalanges, distal radial and ulnar diaphyses, as well as the tibial and fibular diaphyses. (c) Axial CT image of the head demonstrates sclerosis (arrows) of the skull base.

chronic venous insufficiency, and voriconazole-induced periostitis.

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References
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