53-year-old Bahraini businessman, known to have hypertension and diabetes, presented with complaints of cough with scanty white sputum, bilateral knee pain and painful bilateral ankle swelling, all of 2-months duration. He also had streaky hemoptysis of 2 days duration. He was a chronic smoker who had smoked about 30 cigarettes a day for the past 30 years and also complained of weight loss of about 5 kilograms over the past few months. General examination revealed clubbing of the fingers of both hands and bilateral symmetric tender pitting edema of the lower limbs. There was no thickening of the skin of the face. The breath sounds were reduced over the right mammary and inframammary region with dullness on percussion. Examination of other systems were normal.

Figure 1 is an anteroposterior [AP] radiograph of both knees and Figure 2 is a lateral radiograph of both ankles. What do these radiographs show? Figure 3 is a frontal radiograph of the chest and Figure 4 is a selected image from a CT scan of the chest. Do these lead you to a specific diagnosis?

Answer on page 489.
Figure 3. Frontal radiograph of the chest.

Figure 4. CT scan of the chest.
**WHAT'S YOUR DIAGNOSIS?**

**DIAGNOSIS:** Hypertrophic pulmonary osteoarthropathy due to carcinoma of the right lung

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The radiograph of the knees (Figure 1) shows periosteal thickening at the metadiaphysis of the distal femur and proximal tibia and fibula on both sides. The knee joint space is maintained and there are no periarticular erosions. The radiograph of ankles (Figure 2) reveals a similar periosteal reaction in the distal tibia and fibula, which is most conspicuous along the dorsal aspect with a normal appearance of the joints. The differential diagnosis for this pattern of bilateral periosteal reaction includes hypertrophic pulmonary osteoarthropathy (HOA), pachydermoperiostosis, thyroid acropachy and vascular insufficiency. The chest radiograph (Figure 3) reveals a mass without air bronchogram in the right paracardiac region and right pleural effusion. CT of the chest (Figure 4) shows the mass as a lobulated lesion in the right middle and lower lobe abutting the mediastinum associated with right pleural effusion. The features in chest imaging are those of a lung carcinoma. The combination of all radiological findings leads us to the diagnosis of hypertrophic pulmonary osteoarthropathy (HOA) due to carcinoma of the right lung. Biopsy of the lung mass revealed the lesion to be a moderately differentiated adenocarcinoma.

**Discussion**

HOA is a syndrome characterized by digital clubbing and periostosis of the tubular bones. The syndrome occurs in two forms—primary and secondary. The primary form, also termed pachydermoperiostosis, is an autosomal dominant condition characterized by coarsening of facial features,
mild bone and joint involvement and early onset of disease, usually in the second decade of life. Secondary HOA occurs mostly in adults and is associated with an underlying disease, usually an intrathoracic malignancy or infection. Pulmonary causes for HOA include bronchogenic carcinoma, pleural mesothelioma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, and pneumoconiosis. Though the syndrome was originally referred to as pulmonary hypertrophic osteoarthropathy, the term “hypertrophic osteoarthropathy” is becoming more common as there are many extrapulmonary diseases that cause HOA. These include cardiovascular diseases like cyanotic congenital heart disease, bacterial endocarditis and aortic aneurysm; gastrointestinal diseases like inflammatory bowel disease, Whipple’s disease, gastrointestinal tract malignancies and amebic dysentery; hepatobiliary diseases, thyroid acropachy, acquired immune deficiency syndrome, cystic fibrosis and sarcoidosis. HOA may be associated with any cell type of lung cancer, most frequently with squamous and adenocarcinoma and least frequently with small cell lung carcinoma. In our patient, biopsy of the lung tumor revealed it to be a well differentiated adenocarcinoma. Hypertrophic osteoarthropathy may affect up to 10% of patients with adenocarcinoma of the lung.

Clinically, HOA presents as clubbing of the digits, oligoarthritis or polyarthritis of the distal joints, tender periostitis of the distal long bones, and noninflammatory synovial effusions. Positive laboratory findings in HOA include an elevated erythrocyte sedimentation rate and if there is considerable new bone formation, elevated serum alkaline phosphatase. Rheumatoid factor and antinuclear antibody are negative. The exact etiology of HOA is unknown. Roles have been proposed for reflex vagal stimulation, growth factors, hormonal and immune mechanisms. It has been suggested that vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) released after platelet clusters impact in the distal vasculature may induce the stromal and vascular changes present in digital clubbing.

The primary and secondary types of HOA display similar radiographic changes. The radiographic findings of HOA may occur in the absence of any clinical findings, and uncommonly, radiographs are normal in the presence of florid clinical disease. Periosteal proliferation is the hallmark of HOA. Changes are most often seen in the tibia, radius, ulna, fibula, and femur. The short and flat bones are involved in about 18.5% of patients and show less pronounced periosteal reaction than in the long bones. A three-dimensional pattern of evolution of periostosis has been described in HOA, with the three dimensions being (1) the number of bones affected (2) the area of involvement of a given bone and (3) the shape of the periostosis. In early and mild cases few bones are affected and the periosteal bone apposition is limited to the diaphysis with a monolayer configuration. Advanced cases are characterized by involvement of practically all tubular bones with an irregular periosteal reaction that extends to involve the metaphysis and even the epiphysis. The...
adjacent joints characteristically do not show any narrowing of the joint space, in particular osteoporosis or erosions. Radiographic changes described in the terminal phalanges include osteolysis with truncation, overgrowth with mushrooming of the tuft and tapering of the bones. In our patient, advanced changes of periostosis were seen in the leg bones while the forearm bones showed mild involvement. Radionuclear scans are more sensitive than radiographs and reveal the bone involvement by HOA at an earlier stage. Radionuclide scintigraphy shows diffuse symmetrical increased uptake along the cortical margins of the diaphysis of the involved bones, referred to as the tramline sign, parallel tract sign or ‘double stripe’ sign. Associated synovitis may produce increased uptake in juxta-articular bone and increased uptake is also seen in the distal phalanges affected with marked clubbing. The most effective treatment for the pain and discomfort of secondary HOA is cure of the underlying condition. Tumor ablation or chemosuppressive therapy of an associated malignancy often results in prompt reversal of symptoms and resolution or disappearance of the radiographic and radionuclide imaging findings.

References