Pulmonary Hypertrophic Osteoarthropathy and Its Resolution

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A 67-YEAR-OLD MAN with type II diabetes mellitus, hypertension, and chronic obstructive pulmonary disease underwent bronchoscopic biopsy because of a nodular lesion in the right lung observed on a computed tomography of the chest; the biopsy showed adenocarcinoma of the right lung. A Tc-99m HMDP bone scan (Fig 1) showed increased uptake in the elbows, wrists, joints of the hands, knees, ankles, and diffusely increased uptake in the tibiae and radii; an anterior image of the lower legs showed diffusely increased uptake in both fibulae and tibiae and linear periosteal uptake along the tibial shafts (Fig 1).

After presurgical clearance, the patient underwent a right middle lobectomy and radical node resection, which confirmed the diagnosis of moderately differentiated papillary adenocarcinoma of the right lung. The patient’s postoperative course was uneventful, and he was discharged on the 10th postoperative day. A follow-up bone scan, performed 4 years later (Fig 2), showed normal uptake in the elbows, wrists, joints of the hand, knees, ankles, radii, and tibiae as compared with the first bone scan.

DISCUSSION

The hallmark of hypertrophic pulmonary osteoarthropathy is bilateral periosteal new bone formation that predominantly affects the long bones and is also associated with increased uptake in the joints. This condition has been associated with pulmonary tumors that include bronchial carcinoid,1 adenocarcinoma,2,3 large cell carcinoma,3,4 squamous cell carcinoma,3,5,6 and small cell carcinoma.3 Approximately 17% of bronchogenic carcinoma patients were observed to have hypertrophic osteoarthropathy, which had no prognostic significance.3 The tumors in the lung were predominantly located in the periphery.3 With adenocarcinoma of the lung, our patient’s hypertrophic osteoarthropathy on his first bone scan (Fig 1A and B) was apparent.

The term hypertrophic pulmonary osteoarthropathy (HPOA) has been used because the disease entity is most often associated with primary lung disease, but it may be associated with nonpulmonary conditions, which include abnormalities in the gastrointestinal, cardiovascular, hepatobiliary, and endocrine systems. Hypertrophic pulmonary osteoarthropathy also has been called hypertrophic osteoarthropathy (HOA).

The common pathway of pathogenesis on HOA is thought to be bone remodeling with tuft hypertrophy and osteolysis7 and irregular deposition of cancellous bone on the lateral aspect of the long bone.8 Two theories of the causation of HOA are of mechanical and biochemical etiology. The mechanical theory is based on pulmonary arterovenous shunting, as in some cyanotic heart lesions and in severe cirrhosis of the liver.9 When arterovenous shunting in the lung occurs, vasoactive compounds are not deactivated in the pulmonary circulation. Such megakaryocytes escape the filtering effect of the pulmonary capillaries and reach the systemic circulation, leading to degranulation and the production of platelet-derived growth factors. Shunting of blood in primary lung carcinoma produces a similar effect to other forms of shunting.10

For the biochemical or humoral theory, endotoxins from patients who may have an infected aortic graft or aortic graft and aortoenteric fistula may account for unilateral HOA in a lower extremity.11-13 Vasoactive compounds, predisposed to platelet aggregation and thrombosis in veins draining the inflamed areas,14 lead to HOA. Activation of endothelial cells and platelets occurring with

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0001-2998/04/$30.00/0
doi:10.1053/j.semnuclmed.2004.01.001
neovascular proliferation contributes to osteoclastic activity.\textsuperscript{15} This theory would not be applicable in the current patient.

Ectopic growth hormone or growth hormone-releasing hormone also has been suggested as one of the mechanisms of hypertrophic osteoarthropathy.\textsuperscript{3,5,16,17} Our patient’s electron microscopic examination showed dense granules of various sizes in the apical cytoplasm, suggesting secretary granules. The granules proved to contain ectopic growth hormone. It was postulated that after surgical resection of the primary lung tumors, secretion of the hormone from the tumor no longer existed and resulted in resolution of the HOA.\textsuperscript{18,19}

In this patient, after surgical resection of the right lung tumor, the HOA (Fig 1A and B) resolved as shown in the follow-up bone scan (Fig 1B). HOA also has been shown to resolve after radiation therapy of lung tumor,\textsuperscript{20,21} chemotherapy,\textsuperscript{22} and specific therapy with pentamidine for \textit{Pneumocystis carinii} Pneumonia,\textsuperscript{23} or after resection of a lung mass caused by exanthgranulomatous inflammation.\textsuperscript{19} Reversible HOA in a patient with adenomacarcinoma after surgical resection has been
reported as well. This patient’s HOA resolved after removal of the primary pulmonary cancer. The causes of HOA and the reasons for their resolution are shown below.

**Possible Causes of HOA**

- **Primary pulmonary malignancies**
  - Small cell carcinoma of the lung
- **Benign pulmonary conditions**
  - Bronchial carcinoid
  - Cystic fibrosis
  - Lung mass of xanthogranulomatous inflammation
  - Sarcoïdosis
  - Lipid pneumonia
  - Plasma cell granuloma of the lung
  - Bronchiectasis
  - Pulmonary tuberculosis
  - Pulmonary alveolar microlithiasis
  - Pleural mesothelioma
- **Extrapulmonary malignancies**
  - Nasopharyngeal carcinoma
  - Esophageal carcinoma
  - Esophageal leiomyoma
  - Breast cancer
  - Thymic carcinoma
  - Soft tissue sarcoma
  - Malignant fibrous histocytoma
  - Hodgkin’s disease
  - Undifferentiated thyroid cancer
  - Renal cell carcinoma with pulmonary metastasis
- **Cardiac disease**
  - Cyanotic congenital heart disease
  - Subacute bacterial endocarditis
- **Chronic liver disease**
  - Biliary atresia
  - Primary sclerosing cholangitis
  - Wilson’s disease, primary biliary cirrhosis
- **Benign gastrointestinal lesions**
  - Gastrointestinal polyposis
  - Crohn’s disease
  - Ulcerative colitis
  - Regional enteritis
  - Gastro-esophageal reflux and esophagitis
  - Infected graft with endotoxin: infected aortic graft
  - Neurogenic origin: vagotomy
  - AIDS
  - Docetaxel chemotherapy for breast cancer

**Causes for Resolution or Reversible HOA**

- Resection of lung cancer
- Resection of lung mass of xanthogranulomatous inflammation

![Fig 2. Anterior total body bone image 4 years after surgical resection of the right lung tumor shows normalized skeletal uptake in the elbows, wrists, radius, femora, knees, tibiae, and ankles.](image)
Renal metastasis
Chemotherapy
Radiation therapy
Treatment of an infected endocarditis
Biphosphonate therapy (Pamidrone), an inhibitor of osteoclastic bone absorption
Octreotide, an analogue of somostatin, well recognized as an inhibitor of growth hormone and gastropancreatic peptide secretion
Hepatic transplantation for biliary atresia, primary sclerosing cholangitis, Wilson’s disease, primary biliary cirrhosis
Removal of a celestin tube
Usage of PGE1 in a patient with congetive heart failure

ACKNOWLEDGMENT
The author expresses his appreciation to Mark Ingram, MSLS, reference librarian, for his excellent and diligent search of the literature during the preparation of this paper.

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