Hypertrophic Pulmonary Osteoarthropathy in Four Patients with Interstitial Pulmonary Disease*


The association between digital clubbing and idiopathic pulmonary fibrosis has been well established; however, the simultaneous occurrence of hypertrophic pulmonary osteoarthropathy and interstitial fibrosis, in the absence of neoplastic disease, has only been described in two case reports and was not mentioned in any of 336 patients described in several recent reviews. Among 70 patients referred for investigation of pulmonary infiltrates, four were found to have hypertrophic pulmonary osteoarthropathy associated with interstitial pulmonary disease, in the absence of malignant disease. We conclude that the use of bone scans and roentgenographic examination of the extremities may draw attention to an association between hypertrophic pulmonary osteoarthropathy and idiopathic pulmonary fibrosis.

The most common pulmonary associations of digital clubbing are primary intrathoracic malignant neoplasms, chronic suppurative pulmonary disease, and diffuse infiltrative diseases such as fibrosing alveolitis. Hypertrophic pulmonary osteoarthropathy comprises digital clubbing and the additional features of proliferative periostitis of the long bones and polyarthritis, but is not generally associated with fibrosing alveolitis. A computer-assisted search of the world literature revealed only two cases of interstitial fibrosis associated with hypertrophic pulmonary osteoarthropathy. Four further cases of hypertrophic pulmonary osteoarthropathy appearing in association with biopsyped interstitial pulmonary disease are presented, unassociated with underlying malignant disease or suppuration.

CASE REPORTS

CASE 1

A 58-year-old woman experienced gradual onset of dyspnea and dry cough. In the previous seven years, she had lived in a house containing 20 canaries and a pigeon. Poor expansion of the chest, diffuse bilateral crackles on auscultation, and clubbing of the digits were found. A chest roentgenogram showed diffuse bilateral interstitial infiltrates. Studies of pulmonary function showed a restrictive pattern, and the diffusing capacity for carbon monoxide (Dco) was 60 percent of predicted. Avian precipitins and intradermal cutaneous test results to birds were positive, and the antinuclear factor was negative. Open lung biopsy showed diffuse chronic interstitial pneumonia with fibrosis, areas of bronchiolitis obliterans, and granulomatous inflammation. The patient was treated with prednisone at 40 mg (0.7 mg/kg) per day, without significant improvement. Within a year, she changed residences, and therapy with prednisone was reduced to 10 mg/day, but symptoms, pulmonary function, and chest x-ray films were unchanged for eight years, until she experienced two weeks of increasing dyspnea, nonproductive cough, fever, and pain in the bones.

On examination, the patient was obese, hirsute, and dyspneic at rest, with drumstick clubbing of the fingers and toes. Movement of the chest wall was restricted, and there were diffuse inspiratory crackles on auscultation. The anterior aspects of the legs were erythematous, warm, and tender to light palpation. No tenderness in the calves, lymphangitic streaking, or prominent inguinal nodes was noted, nor objective signs of arthritis. The results of routine laboratory studies were normal, except for a hemoglobin level of 10.3 g/dl and an erythrocytic sedimentation rate of 100 mm/hr. The antinuclear antibodies were positive in a homogeneous pattern at 1:40, the rheumatoid factor was 99.4 IU/ml, the lupus erythematosus cell preparation was negative, the total hemolytic complement was 1:50 with a control of 1:90, and normal, and antidouble-stranded DNA by indirect immunofluorescence was negative. Cold agglutinins were present in a titer of 1:16 at 4°C, and results of direct and indirect Coombs' tests were negative. Studies of pulmonary function showed a restrictive pattern with a Dco of 64 percent of predicted. Total lung capacity and vital capacity showed a 30 percent reduction in three years. The chest x-ray film was unchanged. A gallium scan showed increased uptake in both pulmonary fields. No evidence of malignant disease was noted in multiple bronchial washings. Bone roentgenograms demonstrated periosteal reaction and new bone formation in the distal portion of the humeri, radius, ulnae, tibiae, and hands (Fig 1), and feet, along with the metatarsals and metacarpal joints. A bone scan showed activity in the shafts of both tibiae, distal portion of the radii, and hands, consistent with hypertrophic pulmonary osteoarthropathy. Four months later, the patient's symptoms, pulmonary function, and chest x-ray film findings were unchanged, despite therapy with anti-inflammatory medications.

CASE 2

A 58-year-old male hairdresser presented with a six-month history of increasing dyspnea and a cough productive of small amounts of white sputum. He noted progressive clubbing of the fingers and toes, intermittent bilateral pain in the knees and ankles, with warmth and swelling present at rest and aggravated by walking. There was a 70 pack-year history of smoking, which the patient had discontinued 13 years ago. The family history was remarkable for a paternal history of progressive pulmonary disease and digital clubbing.

Inspiratory and expiratory crackles were heard at both pulmonary...
erythematous cell preparation was negative. An assay for circulating immune complexes was positive. Studies of pulmonary function showed mild pulmonary restriction and a reduced Dco. The chest roentgenogram showed diffuse bilateral increased interstitial markings. The gallium scan showed no significant parenchymal pulmonary uptake. Bronchoalveolar lavage yielded 59 percent polymorphonuclear leukocytes, 8 percent lymphocytes, 31 percent macrophages, and 2 percent eosinophils. Bronchial washings were negative for malignant disease. The open lung biopsy showed interstitial pneumonitis. Although bone roentgenograms showed no periosteal reaction, bone scintiscans showed bilateral symmetrically increased activity over both tibiae, with more significant activity in the lateral cortical bone and small foci in both femurs and periarticular activity at knees and ankles (Fig 2). The patient was treated with prednisone at 40 mg daily, and the bony pain subsided gradually over several weeks.

Case 3

A 69-year-old man presented with an 18-month history of increasing dyspnea, severe burning pain in both legs, and intermittent pain and swelling of the knees. Ten years prior to admission, digital clubbing was noted, and a chest x-ray film showed diffuse interstitial infiltrates. Open lung biopsy showed marked interstitial fibrosis. Treatment with high doses of steroids was begun. Eighteen months prior to admission, the patient developed pain in the bones, and roentgenograms were interpreted as showing osteoporosis. He was started on therapy with vitamin D, prednisone (25 mg on alternate days), and aspirin. There was no significant improvement.

The patient was dyspneic at rest and had central cyanosis with clubbing of the fingers and toes. Coarse bibasilar end-inspiratory crackles were present. Tenderness was noted on light palpation of the legs. Signs of arthritis were absent.

The results of routine laboratory investigations were normal. The antinuclear antibody was weakly positive in a homogeneous pattern, and rheumatoid factor was less than 60 IU/ml. Arterial blood gas levels on room air showed an arterial carbon dioxide tension (PaCO₂) of 30 mm Hg and an arterial oxygen pressure (PaO₂) of 61 mm Hg, which fell to 43 mm Hg with mild exercise. Studies of pulmonary function showed mild pulmonary restriction and a D of 48 percent of predicted. A chest roentgenogram showed severe diffuse interstitial infiltrates. A gallium scan was negative, and bronchoalveolar lavage showed 79 percent macrophages, 17 percent polymorphonuclear leukocytes, and 4 percent lymphocytes. The cytology of pulmonary washings was negative. Bone x-ray films demonstrated cortical thickening in the tibiae, fibulae, and femora. A bone scan (Fig 3) demonstrated increased activity in these areas, consistent with
A 53-year-old man was admitted with increasing dyspnea on exertion, a cough productive of yellow sputum, bilateral pain in the knees and legs which was aggravated by weight bearing, and intermittent swelling of the ankles and knees. Four years prior to admission, he was admitted to another center with exertional dyspnea, digital clubbing, coarse crackles on chest auscultation, and diffuse bilateral interstitial infiltrates on the chest roentgenogram. Open lung biopsy showed fibrosing alveolitis. The patient was discharged on a tapering oral course of steroids.

Coarse inspiratory crackles were noted diffusely in both lungs. There was tenderness to light palpation of the forearms, lower legs, ankles, and feet, although joint pain was absent. The results of routine laboratory studies were normal. Arterial blood gas levels showed: pH of 7.41, PaCO₂ of 33 mm Hg, and PaO₂ of 60 mm Hg. Pulmonary function showed mild pulmonary restriction with a Dco of 45 percent of predicted.

The chest roentgenogram showed diffuse interstitial infiltrates, and gallium scintigraphy demonstrated increased uptake at both pulmonary bases; bronchoalveolar lavage showed a neutrophilic predominance of 14 percent. Bone roentgenograms revealed periosteal new bone formation in the distal third of both tibiae (Fig 4). Bone scintigraphy showed increased uptake in the lower extremities. The patient was treated with methylprednisolone (2 g intravenously). Within 24 hours the pain in his legs had subsided. A repeat bone scan performed one week after the injection of methylprednisolone remained abnormal; however, isotopic uptake in the lower extremities was diminished.

**DISCUSSION**

Hypertrophic pulmonary osteoarthropathy consists of chronic proliferative periostitis of long bones, digital clubbing, and polyarthritis. This syndrome, of unknown etiology, is associated with neoplastic, infectious, and immunologic disorders of the lung. Whereas digital clubbing alone is asymptomatic, periostitis causes severe burning pain in the distal extremities, aggravated by dependency and weight bearing. Synovitis may be present in the metacarpophalangeal joints, wrists, elbows, knees, and ankles. Hypertrophic pulmonary osteoarthropathy can be distinguished from arthritis by the presence of clubbing and tenderness to palpation of the shafts of long bones in the former. Passive movement of the joint does not evoke pain. Autonomic disturbances including sweating, flushing, and blanching of the skin may be present. Radiographically, symmetrical periosteal thickening of bone shafts and flaring of the terminal phalanges confirm the presence of hypertrophic pulmonary osteoarthropathy. Bone scintiscans performed with diphosphonates demonstrate linear uptake along the cortical margins of the long bones and juxta-articular uptake associated with synovitis. Postulated mechanisms include the presence of a circulating vasodilator, hormonal causes such as elevated concentrations of growth hormone or estrogen, and neural...
medication via parasympathetic pathways.9

Interstitial pneumonitis associated with pain in the joints and extremities is often confused with “rheumatoid lung.” Twenty-five percent of the patients with interstitial pneumonitis have arthritis in the absence of a positive latex fixation test, while rheumatoid factor is frequently positive in idiopathic pulmonary fibrosis in the absence of arthritis. Strepton and Leemingt2 described two patients with idiopathic diffuse interstitial pulmonary fibrosis, digital clubbing, and positive sheep cell agglutination test without any joint symptoms. Gottlieb et al10 studied 19 patients with idiopathic pulmonary fibrosis and detected rheumatoid factor in five patients (26 percent). In four of these patients, transient arthritis manifestations were present. These investigators11 proposed that the diagnosis of “rheumatoid lung” be reserved for the combination of pulmonary fibrosis and clinical rheumatoid arthritis. Using this definition, patients 1 and 2 in our series, with pulmonary fibrosis, positive rheumatoid factor, and clinical and radiologic criteria for hypertrophic pulmonary osteoarthropathy do not fulfill the criteria for “rheumatoid lung” disease.

The association between digital clubbing and interstitial fibrosis has been well established; however, the occurrence of hypertrophic pulmonary osteoarthropathy and interstitial pulmonary disease appears to be unusual. A computer-assisted search of the literature spanning the last 20 years has uncovered only two cases2,3 of interstitial pulmonary disease associated with hypertrophic pulmonary osteoarthropathy, one of these in a patient with rheumatoid pulmonary disease.4 We have reviewed the clinical data presented in various reports by Carrington et al,12 Crystal et al,13 Livingstone et al,14 Louw et al,15 and Turner-Warwick et al.16 Hypertrophic pulmonary osteoarthropathy was not reported in any of the 336 patients with fibrosing alveolitis, despite the high incidence of clubbing, which ranged from 50 to 61 percent of all patients. We therefore wish to report and draw to the attention of clinicians that interstitial pulmonary disease may be associated with hypertrophic pulmonary osteoarthropathy in the absence of underlying pulmonary malignant disease.

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REFERENCES

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