CLINICAL ROUNDS

HYPERTROPHIC OSTEOARTHROPATHY AND RHEUMATOID ARTHRITIS

SIMULTANEOUS OCCURRENCE IN ASSOCIATION WITH DIFFUSE INTERSTITIAL FIBROSIS

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A patient is described who was treated with high-dose prednisone in an attempt to halt progressive respiratory insufficiency associated with diffuse interstitial fibrosis. On cessation of steroid therapy the patient was noted to have radiologic manifestations of hypertrophic osteoarthropathy (HOA) as well as clinical and laboratory features of rheumatoid arthritis (RA). Subsequently a diffuse vasculitis developed with bowel perforation and sepsis leading to death.

The association of digital clubbing with several pulmonary diseases, including diffuse interstitial fibrosis (DIF), is well established (1). Similarly pulmonary disease, especially bronchogenic carcinoma, has been associated with hypertrophic osteoarthropathy (HOA) with or without the accompanying skin findings of pachydermoperiostosis (Primary HOA) (2). One case of DIF associated with HOA including both clubbing and roentgenographic evidence of periosteal new bone growth has been reported (3).

The association of DIF with rheumatoid factor (RF) has been noted. In one series positive latex tests for RF were found in 32% and positive sheep cell agglutination tests in 46% (4). Furthermore there is good evidence for an association between DIF and clinical rheumatoid arthritis (RA). Several investigators have concluded that DIF is a clinical manifestation of rheumatoid disease (5–8). Recent studies employing pulmonary function tests have demonstrated that interstitial pulmonary abnormalities in patients with RA may be more common than previously presumed (9). Diffusion abnormalities have been found in RA patients with normal chest x-rays and these patients have been noted to have fibrotic changes on lung biopsy (10). Temporally, DIF has been reported to precede, coincide with, or follow the onset of joint symptoms (11–14).

This case is believed to represent the simultaneous occurrence of HOA and RA in the presence of DIF.

CASE REPORT

GT, a 53-year-old black woman, was well until April 1970, when she developed fever, chills, and purulent sputum. Pneumonia was diagnosed and treated with intramuscular

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penicillin. She demonstrated minimal improvement and had persistent shortness of breath and cough with dyspnea. A chest film in January 1972 showed a pattern consistent with DIF, and in February 1972 she was admitted to University Hospital for the first time. Physical examination was unremarkable except for the finding of clubbing of the fingers and toes with the presence of "cellophane-like" rales at both lung bases. She had a positive tuberculin reaction but sputa for acid-fast bacilli were negative on smear and culture. A test for antinuclear factor was positive in an unspecified pattern. Latex fixation test for RF and several lupus erythematosus preparations were negative. Pulmonary function studies were consistent with restrictive disease showing decreased lung volumes and diffusion capacity with normal flow rates. An open lung biopsy showed hyperplastic alveolar lining cells with proliferation of bronchiolar epithelium. Occasional periarteriolar fibrosis was present. No polarizable material, asbestos bodies, or granulomas were seen. These findings were interpreted as being consistent with idiopathic DIF.

Upon discharge, therapy was begun with prednisone, 120 mg every other day, in an effort to arrest progression of her respiratory disease. Isoniazid and pyridoxine were also administered. The patient was followed with serial pulmonary function tests and the prednisone dosage was gradually tapered over a 7-month period. Despite this therapy her respiratory status deteriorated. In July 1974 the prednisone dosage had been reduced to 4 mg/day and the patient first complained of pain and swelling around the left ankle. The discomfort was greatly increased on weight bearing. In August 1974, when she had been off steroid therapy for 3 weeks, the patient noted the gradual onset of pain in both wrists and the left shoulder. Additionally she had lost 11.8 kg (26 lb) in 3 months. These symptoms led to her second hospital admission in September 1974.

On admission the blood pressure was 140/100 mm Hg, pulse rate 100/minute, respirations 24/minute, and temperature 37.8°C. Pulmonary examination was unchanged from the previous admission. The joint examination revealed active synovitis and limited range of motion in a symmetric distribution involving the ankles, knees, and wrists. Small joint synovitis was present in the metacarpal–phalangeal and proximal interphalangeal joints of the hands. Grip strength was poor and there was marked decreased range of motion of the cervical spine, shoulders, elbows, and hips. There was exquisite tenderness to palpation over both the tibiae and fibulae. "Cylindrical" soft tissue thickening was present over the distal third of the left lower extremity.

Laboratory findings included a homoglobin level of 15.4 g/100 ml, hematocrit of 45%, and white blood count of 6,500/mm^3 with a normal differential. Urinalysis was normal. Antinuclear factor was positive in a 1:10 dilution in a homogeneous and speckled pattern. Latex test for RF was positive at a 1:5,120 dilution. Erythrocyte sedimentation rate (Westergren) was 74 mm/hour and three lupus erythematosus preparations were negative. Chest roentgenogram (Figure 1) showed a pattern of DIF unchanged from that of February 1972. Roentgenograms of the long bones of the lower extremities (Figures 2 and 3) demonstrated periosteal new bone formation and cortical thickening of the tibiae, fibulae, and femoral shafts in a symmetrical distribution. Roentgenograms of the upper extremities showed only soft tissue swelling at the wrists. A joint survey revealed no erosive changes indicative of RA. However a diagnostic arthrocentesis performed on the right knee yielded synovial fluid with a white blood count of 29,300/mm^3 containing 64% polymorphonuclear cells. Mucin clot in the fluid was fair. No crystals were seen and a culture grew out no pathogens. Synovial fluid complement level was not determined, and the patient refused to have a synovial biopsy performed.

During her hospitalization the patient complained of significant morning stiffness as well as pain in both temporomandibular joints. Conservative treatment with physical therapy, salicylates, and indomethacin resulted in modest improvement of her arthritis. She was discharged but re-ad-

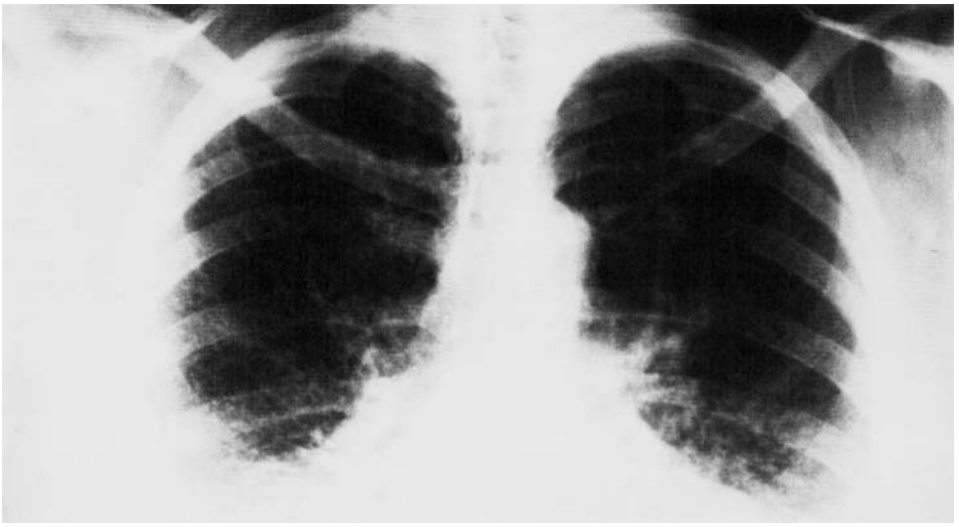

Fig 1. *Admission chest roentgenogram (September 1974) demonstrating pattern of diffuse interstitial fibrosis, most prominent in the lower lobes.*

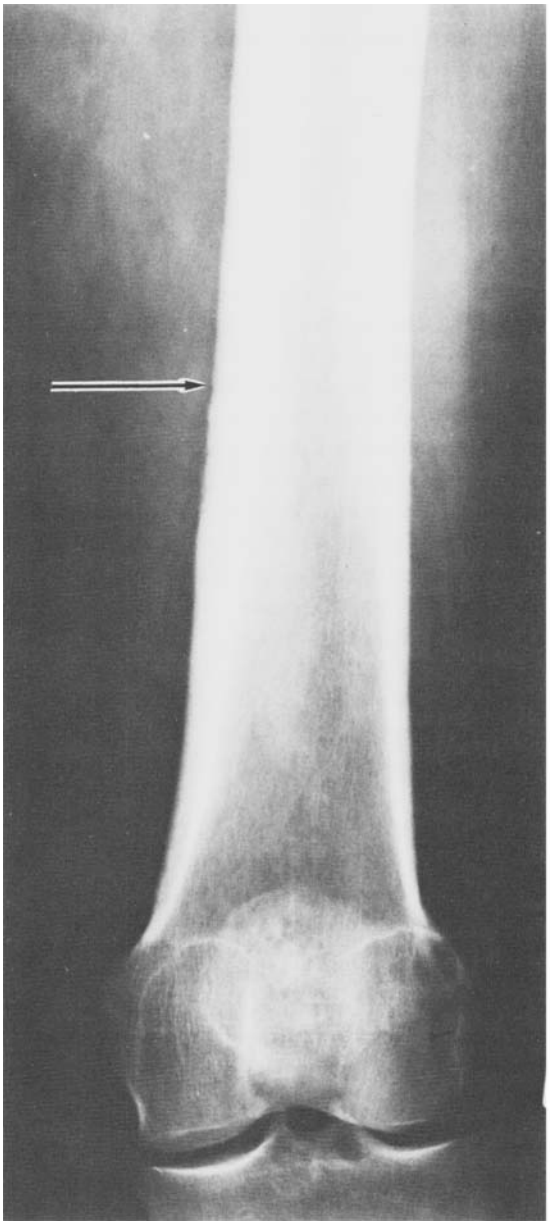

Fig 2. *Study of left femur demonstrating irregular periosteal surfaces and marked cortical thickening.*

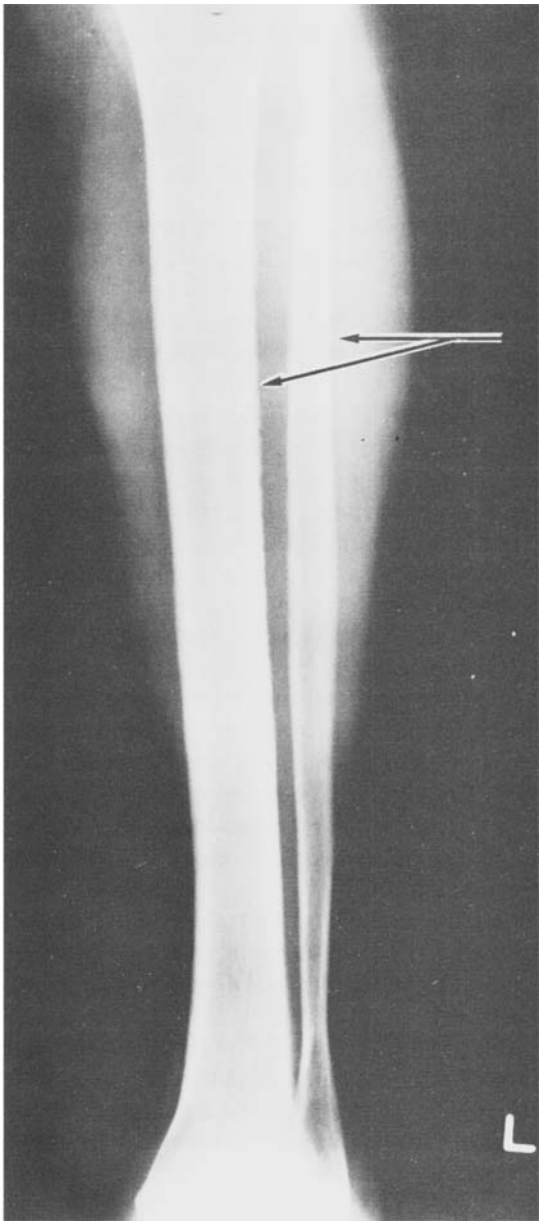

Fig 3. *Study of left tibia and fibula demonstrating irregularity of periosteal surfaces (lateral aspect of proximal tibia) and cortical thickening of both bones.*

mitted in November 1974 for treatment of cor pulmonale accompanied by a flare of her joint symptoms. The latter responded dramatically to 5 mg of prednisone two times a day with resolution of active synovitis.

In early January 1975 the patient was re-admitted with weakness and wasting of the musculature of the right hand. Hypoesthesia was present in the distribution of the ulnar and median nerves. Electromyogram and nerve conduction studies showed absent evoked response of the right median and ulnar nerves. Also denervation was noted in both legs, consistent with a peripheral neuropathy. Rectal biopsy was negative for amyloid. Sural nerve biopsy was refused and the patient was discharged.

The development of an acute abdomen led to the patient's final admission in late January 1975. An exploratory celiotomy revealed a small bowel perforation. Pathologic examination of the resected segment showed diffuse necrotizing vasculitis. Postoperatively the patient developed dry gangrene

of the second right digit. Subsequently her small bowel anastomosis broke down, and she became septic and died shortly after a second celiotomy was performed. Permission for an autopsy was not granted.

DISCUSSION

HOA and RA may be confused clinically and in fact HOA is listed as one of the exclusions in the American Rheumatism Association's revised diagnostic criteria for rheumatoid arthritis (15). The joint manifestations of HOA may mimic those of RA with morning stiffness, painful and warm swollen joints, limitation of motion, and even deformity and ankylosis in advanced cases (16). In HOA however large joint involvement including ankles, knees, and wrists is most common, whereas the interphalangeal joints are usually spared or only minimally involved (3).

This patient was believed to have HOA because of the physical findings of clubbing of the fingers and toes associated with the roentgenographic findings of periosteal new bone formation with thickening of the tibiae, fibulae, and femorae. Historically there was insidious onset of ankle swelling and pretibial pain increased on weight-bearing, features classically described in HOA. The marked thickening of the cortices suggests that the causative process was long-standing, perhaps dating to the initial roentgenographic appearance of DIF in January 1972.

Adequate clinical findings also support the diagnosis of definite RA. The patient gave a history of joint pain that affected the cervical spine. Similar discomfort symmetrically involved the temporomandibular, knee, and ankle joints, as well as the metacarpal-phalangeal and interphalangeal joints of the hands. Physical examination in September 1974 demonstrated tender, hot joints with acute symmetrical synovitis of the knees, ankles, wrists, and hands including the metacarpal-phalangeal and proximal interphalangeal joints. Morning stiffness of 4 hours duration was prominent during her hospitalization. A latex fixation for RF was negative in February 1972 when DIF was diagnosed. This test was positive in a dilution of 1:5,120 with the onset of acute symmetrical arthritis in September 1974. The symmetrical interphalangeal small joint involvement in this case is more consistent with RA than HOA, in which large joint involvement is most common. Finally the synovianalysis results were characteristic of the Class II inflammatory type fluid typical of RA and atypical for HOA. In the latter condition synovial fluids have all been reported to be of noninflammatory character (Class I), similar to nonhemorrhagic traumatic fluids (17). Similarly low white blood counts of less than 1,000/mm^3 with a small percentage of polymorphonuclear cells have been described in other forms of HOA (18–21). If the HOA exclusion is ignored, the patient fulfills six of the American Rheumatism Association's revised diagnostic criteria consistent with definite RA (15).

Worthy of note is the clinical appearance of both HOA and RA upon discontinuation of corticosteroid therapy. One could speculate that the steroid therapy suppressed the clinical manifestations of each of these entities. Both RA and HOA have been shown to respond symptomatically to such treatment (3). It would appear that, when the lowest effective suppressive dose of prednisone had been withdrawn, clinical signs and symptoms of HOA and RA became manifest. The significant degree of improvement of the rheumatic signs and symptoms with reinstitution of prednisone therapy at a dosage of 10 mg a day supports this hypothesis. The patient went on to develop a diffuse vasculitis manifested by a peripheral neuropathy, dry gangrene, and bowel perforation. This condition most likely represented a complication of her rheumatoid disease, though a contributing role may have been played by her steroid therapy.

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DISCUSSION

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Any report of association of hypertrophic osteoarthropathy (HOA) with some previously unrecognized disease is especially welcome because of the possibility for new clues to pathogenesis. Because it has been recently speculated that circulating materials are important in pathogenesis (1, 2), the possible role of circulating immune complexes in this patient with pulmonary fibrosis, polyarthritis, and vasculitis is intriguing. Serum complement determinations and immunofluorescent and electron microscopic studies of lesions in any future patients will be of interest. Periostitis or periosteal new bone formation without full-blown HOA has also been seen in other patients with arteritis (3–5) as well as in association with incompletely explained dysproteinemia (6).

The fact that hypertrophic osteoarthropathy has so rarely been reported in association with pulmonary fibrosis or rheumatoid arthritis (RA) may of course mean that it has been overlooked, but it must also suggest that isolated cases may merely be coincidental. As Schechter and Bole mention, there is a syndrome termed pachydermoperiostosis (often without dramatic skin changes) that begins early in life and is often familial. Such a coincidental syndrome might also account for their patient's apparently long-standing periosteal changes (7). It is often difficult to ascertain the duration of clubbing from patients—the woman in the case presented is described only as having clubbing at the time of her first examination at University Hospital in 1972.

Joint effusions believed to be related to pachydermoperiostosis have not yet been seen. The patient reported here had inflammatory effusions that can be attributed to her suspected rheumatoid disease. Even if a syndrome as described in this report emerges as a cause for hypertrophic osteoarthropathy, the very common association of HOA with tumor should still be kept in mind (8,9). Reports have described pulmonary carcinoma developing in patients with rheumatoid lung disease (10,11). Lung tumors need not be radiographically apparent when osteoarthropathy is first noted.

The authors make the important distinction between simple clubbing and full-blown HOA. Clubbing

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