

Hypertrophic osteoarthropathy in adults with cystic fibrosis

M. A. MATTHAY, R. A. MATTHAY, D. M. MILLS,
S. LAKSHMINARAYAN, and E. COTTON

*Department of Medicine, Pulmonary and Arthritis Divisions, and the Department of Pediatrics,
University of Colorado Medical Center, Denver, Colorado, USA*

Matthay, M. A., Matthay, R. A., Mills, D. M., Lakshminarayan, S., and Cotton, E. (1976). Thorax, 31, 572-575. Hypertrophic osteoarthropathy in adults with cystic fibrosis. Three adult patients with cystic fibrosis presented with arthralgia, and investigation for the usual causes of arthritis proved negative. Radiographs of long bones revealed periostitis and new bone formation characteristic of hypertrophic osteoarthropathy. Symptomatic improvement occurred after analgesic and anti-inflammatory therapy. In patients with cystic fibrosis and bone or joint pain, the diagnosis of hypertrophic osteoarthropathy should be considered and long bone radiographs obtained.

A 24-year-old man with cystic fibrosis presented to the University of Colorado Medical Center with arthralgia and joint effusions of unknown cause. Initial evaluation, including joint fluid analysis, failed to yield a diagnosis. Long bone radiographs revealed typical changes of hypertrophic osteoarthropathy, a syndrome characterized by ossifying periostitis of long bones, arthritis, and clubbing (Bamberger, 1889; Hammarsten and O'Leary, 1957). A delay in diagnosis occurred due to lack of awareness of an association between hypertrophic osteoarthropathy and cystic fibrosis in adults. Subsequently, two more adults with cystic fibrosis have been diagnosed as having hypertrophic osteoarthropathy. These three cases are described in detail to emphasize this association.

CASE REPORTS

PATIENT 1 A 24-year-old man, in whom a diagnosis of cystic fibrosis had been made at the age of 3 years, was admitted to the hospital in January 1974 with a three-week history of arthralgia in the ankles, knees, and wrists and bilateral knee swelling. His past history included progressive dyspnoea, productive cough, recurrent pneumonitis, chronic diarrhoea, and liver disease due to cystic fibrosis. Two years before

admission he had an upper gastrointestinal haemorrhage due to oesophageal varices.

The blood pressure was 118/78 mmHg, pulse 90, respirations 28, and temperature 37.3°C. Clubbing of the toes and fingers with tenderness of the ankles, knees, and wrists was present. Effusions were noted in both knees. Chest examination revealed diffuse rhonchi and basal crepitations. A loud pulmonary second sound and a right ventricular lift were found, but the jugular venous pressure was not raised. The liver was enlarged with a span of 13 cm; the spleen was palpable 3 cm below the left costal margin. The sweat chloride was 100 mEq/l¹. Clear yellow fluid aspirated from the right knee revealed 850 WBC/mm³ (all mononuclear cells) with a good mucin clot but no crystals and no growth on culture. Arterial blood gases while breathing ambient air were pH 7.45, Pco₂ 31 mmHg (Denver normal 34-38), Po₂ 60 mmHg (Denver normal 65-75). Pulmonary function tests revealed a moderate obstructive defect. An electrocardiogram showed right axis deviation and right atrial and right ventricular enlargement. Alkaline phosphatase was 555 IU/l (normal less than 280), serum aspartate aminotransferase 13 IU/l (normal 6-21), and total bilirubin 0.3 mg/100 ml. A chest radiograph demonstrated diffuse interstitial and nodular infiltrates (Fig. 1). Radiographs of the extremities showed periosteal elevation in the fifth metatarsal bilaterally and periosteal elevation and

¹Normal values for adults less than 70 mEq/l (Jones, Steige, and Logan, 1970)

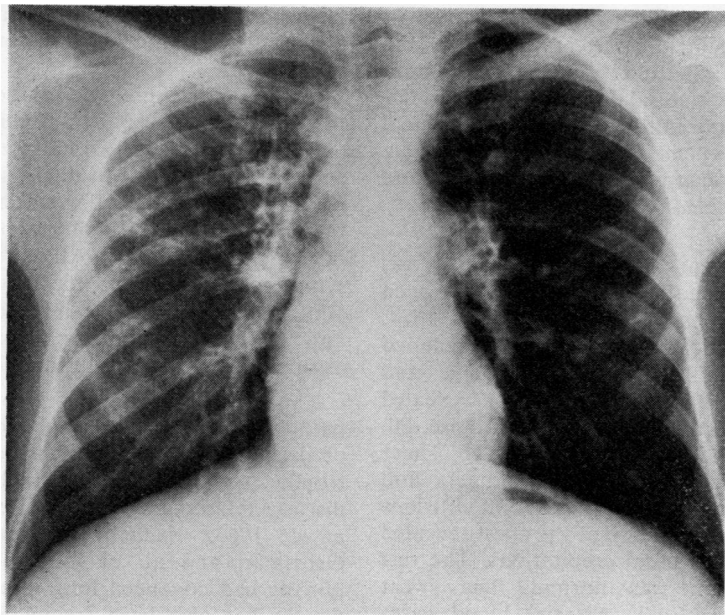


FIG. 1. Chest radiograph of patient 1 showing diffuse interstitial and nodular infiltrates.

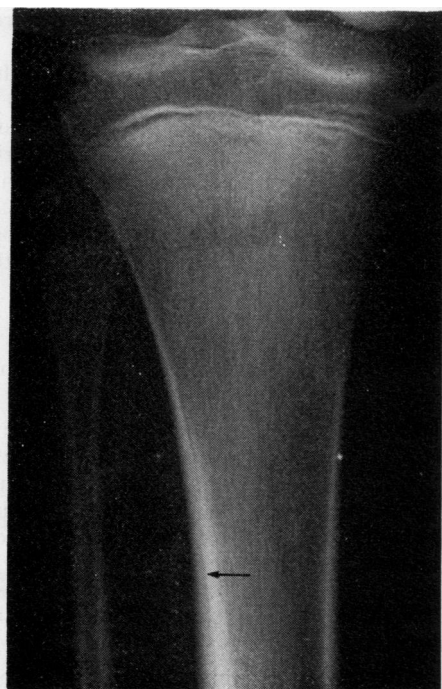


FIG. 2. Radiograph of left tibia and fibula of patient 1 demonstrating periosteal elevation and new bone formation (arrow).

new bone formation in the left tibia (Fig. 2). The joint pains and knee effusions resolved after treatment for four weeks with acetaminophen and indomethacin. Although the radiographic abnormalities of the bones persist, the arthralgia has not recurred.

PATIENT 2 A 23-year-old man with cystic fibrosis diagnosed at the age of 5 years was admitted to the hospital in April 1974 with painful knees and ankles for the previous two months. Manifestations of the disease before this admission included dyspnoea at rest with a chronic productive cough, recurrent pneumonia, and chronic diarrhoea. The blood pressure was 120/80 mmHg, pulse 92, respirations 24, and temperature 37.4°C. There was finger and toe clubbing with warmth and tenderness over the ankles and knees bilaterally, but no joint effusions were present. Examination of the chest revealed diffuse bilateral crepitations and the cardiac examination was within normal limits with the exception of a loud pulmonary component of the second sound. The rest of the examination was normal. The sweat chloride was 118 mEq/l. Arterial blood gases while breathing ambient air were pH 7.43, PCO_2 40 mmHg, and PO_2 40 mmHg. Pulmonary function tests showed a severe obstructive defect.

Right axis deviation and right atrial and right ventricular enlargement were present on the electrocardiogram. The chest radiograph demonstrated bilateral interstitial infiltrates, and radiographs of the extremities showed periosteal elevation and new bone formation in the tibiae. The patient was treated with acetaminophen and the bone pain subsided with no recurrence.

PATIENT 3 A 21-year-old man with a diagnosis of cystic fibrosis since the age of 4 years developed bilateral ankle and knee pains in February 1974. Previous manifestations of cystic fibrosis included dyspnoea at rest, recurrent pneumonia, and chronic diarrhoea. Physical examination revealed a blood pressure of 110/80 mmHg, pulse 80, respirations 24, and temperature 37.4°C. There was marked clubbing of toes and fingers and bilateral knee and ankle tenderness. Joint effusions were not found. Examination of the chest revealed bilateral rhonchi and basal crepitations. The rest of the examination was normal. The sweat chloride was 117 mEq/l. Arterial blood gases while breathing ambient air were pH 7.39, PCO_2 48 mmHg, and PO_2 38 mmHg. Pulmonary function tests showed a severe obstructive defect. An electrocardiogram revealed right axis deviation and right atrial and right ventricular enlargement. The chest radiograph showed bilateral interstitial infiltrates, and radiographs of the long bones revealed periosteal elevation and new bone formation over both tibiae. After acetaminophen and indomethacin therapy for three weeks the knee and ankle pains disappeared and have not recurred.

DISCUSSION

The syndrome of hypertrophic osteoarthropathy was described by Bamberger (1889) and Marie (1890). Subsequently, hypertrophic osteoarthropathy has been reported in association with a wide variety of diseases, including neoplasms of the lungs, oesophagus, thymus, and stomach, and intrathoracic Hodgkin's disease (Fischer, Singer, and Feldman, 1964; Shapiro and Zvaifler, 1973). In the pre-antibiotic era, hypertrophic osteoarthropathy was commonly observed in individuals with tuberculosis, bronchiectasis, and empyema (Fischer *et al.*, 1964; Hammarsten and O'Leary, 1957). It has also been reported in patients with inflammatory bowel disease, hepatic cirrhosis, cyanotic congenital heart disease, bacterial endocarditis, and hyperthyroidism (Trever, 1958; Fischer *et al.*, 1964; Stanley and Woodgate, 1971).

However, hypertrophic osteoarthropathy complicating cystic fibrosis has not been recognized widely.

Grossman, Denning, and Baker (1964) described the occurrence of symptomatic hypertrophic osteoarthropathy in two children (aged 9 and 12) with cystic fibrosis. In their series, three other patients with cystic fibrosis had clubbing and radiographic evidence of osteoarthropathy without bone or joint pains. All our patients developed symptomatic hypertrophic osteoarthropathy as adults. A review of the literature did not reveal any reference to hypertrophic osteoarthropathy in association with cystic fibrosis in adults.

The aetiology of hypertrophic osteoarthropathy has not been proven. However, a number of disease states has been associated with hypertrophic osteoarthropathy, including pulmonary diseases (Hammarsten and O'Leary, 1957; Fischer *et al.*, 1964). Each of the patients reported by Grossman and all of our patients with cystic fibrosis had advanced lung disease. Chronic liver disease has also been frequently associated with hypertrophic osteoarthropathy (Trever, 1958; Fischer *et al.*, 1964). Histological evidence of biliary cirrhosis has been reported in 5% of children and in 20% of adults with cystic fibrosis. Although none of Grossman's five patients had clinical evidence of liver disease, one had cirrhosis at necropsy. One of our patients (patient 1) had clinical evidence of liver disease manifested by hepatosplenomegaly and oesophageal varices. Diseases causing chronic diarrhoea, such as regional enteritis and ulcerative colitis, have also been reported in association with hypertrophic osteoarthropathy (Fischer *et al.*, 1964). All three of our patients and two of Grossman's had chronic diarrhoea. Thus, pulmonary, hepatic, and gastrointestinal disease may be related to the development of hypertrophic osteoarthropathy in cystic fibrosis.

All three subjects in the present series experienced improvement or disappearance of symptoms after analgesic and anti-inflammatory therapy and remained free of symptoms during a follow-up period of 10 to 14 months. However, the radiographic bone abnormalities persist and the long-term course of hypertrophic osteoarthropathy in patients with cystic fibrosis is unknown.

Since hypertrophic pulmonary osteoarthropathy has not been recognized widely in association with cystic fibrosis, the true incidence of this complication is not known. With early diagnosis and

improved maintenance therapy many patients with cystic fibrosis survive to adulthood (Coates, 1966; Goodman, 1967), and it is likely that in the future hypertrophic osteoarthropathy will be diagnosed with increasing frequency among adults with cystic fibrosis. The cases in this series suggest that in all patients with cystic fibrosis in whom bone or joint pains develop the diagnosis of hypertrophic osteoarthropathy must be considered and long bone radiographs obtained to make the diagnosis.

REFERENCES

- Bamberger, E. (1889). In Protokoll der k.k. Gesellschaft der Aerzte in Wien. *Wiener Klinische Wochenschrift*, **2**, 226.
- Coates, E. O., Jr. (1966). Characteristics of cystic fibrosis in adults. *Diseases of the Chest*, **49**, 195.
- Fischer, D. S., Singer, D. H., and Feldman, S. M. (1964). Clubbing: a review with emphasis on hereditary acropachy. *Medicine*, **43**, 459.
- Goodman, D. H. (1967). Adult mucoviscidosis. *Annals of Allergy*, **25**, 224.
- Grossman, H., Denning, C. R., and Baker, D. H. (1964). Hypertrophic osteoarthropathy in cystic fibrosis. *American Journal of Diseases of Children*, **107**, 1.
- Hammarsten, J. F. and O'Leary, J. (1957). The features and significance of hypertrophic osteoarthropathy. *Archives of Internal Medicine*, **99**, 431.
- Jones, J. D., Steige, H., and Logan, G. B. (1970). Variations of sweat sodium values in children and adults with cystic fibrosis and other diseases. *Mayo Clinic Proceedings*, **45**, 768.
- Kopel, F. B. (1972). Gastrointestinal manifestations of cystic fibrosis. *Gastroenterology*, **62**, 483.
- Marie, P. (1890). De l'ostéoarthropathie hypertrophique pneumonique. *Revue de Médecine*, **10**, 1.
- Shapiro, R. F. and Zvaifler, N. J. (1973). Concurrent intrathoracic Hodgkin's disease and hypertrophic osteoarthropathy. *Chest*, **63**, 912.
- Stanley, N. N. and Woodgate, D. J. (1971). The circulation, the lung, and finger clubbing in hepatic cirrhosis. *British Heart Journal*, **33**, 469.
- Trever, R. W. (1958). Hypertrophic osteoarthropathy in association with congenital cyanotic heart disease. *Annals of Internal Medicine*, **48**, 660.

Requests for reprints to: Dr. R. A. Matthay, Yale Lung Research Center, 333 Cedar Street, New Haven, Connecticut 06510, USA.