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Hypertrophic pulmonary osteoarthropathy in association with pulmonary metastases from extrathoracic tumours

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Three cases of pulmonary osteoarthropathy secondary to pulmonary metastases from extrathoracic tumours are described. Analysis of the reported cases shows that most of them were secondary to osteosarcoma, nasopharyngeal tumour, fibrosarcoma, and uterine tumour. Fibrous tumours and tumours with a predominantly fibrous stroma tend to be associated with osteoarthropathy more than others. This suggests that the fibrous stroma may be a factor in the stimulation of the reflex mechanism responsible for osteoarthropathy.

Pulmonary osteoarthropathy was first described by Bamberger (1889) and Marie (1890) in association with intrathoracic inflammatory lesions. A few years later Virchow (1895) described a patient suffering from pulmonary osteoarthropathy secondary to lung metastases from chondrosarcoma of the humerus. The association of osteoarthropathy with bronchial carcinoma was first reported by Thompson (1904). With the marked increase in the incidence of bronchial carcinoma, this condition has become recognized as the main cause of pulmonary osteoarthropathy (Craig, 1937; Van Hazel, 1940; Berg, 1949; Editorial, 1954; Vogl, Blumenfeld, and Gutner, 1955; Semple and McCluskie, 1955; Coury, 1960; Yacoub, 1965b). That metastatic tumours of the lung can also be associated with osteoarthropathy is not widely recognized (Aufses and Aufses, 1960). The relationship between the site of the primary tumour and the incidence of pulmonary osteoarthropathy has not been described before. The purpose of this paper is to report three cases of pulmonary osteoarthropathy secondary to pulmonary metastases from extrathoracic tumours and to analyse the previously reported cases.

CASE REPORTS

CASE 1 D. H., a man aged 29, had a mole on the right thigh which had been getting bigger for the last few months. This was treated by local excision in May 1960. Histological examination showed 'an intradermal melanoma with some junctional activity'. In July 1960 he had a local recurrence which measured 2 cm. in diameter with two small satellite nodules. These were treated by wide excision of the mole and the surrounding tissues, including the deep fascia. He also had an enlarged hard lymph node in the right groin; this was treated by block dissection of the groin in August 1960. Histological examination of the excised mole showed a 'malignant melanoma infiltrating the subcutaneous tissue'. A chest radiograph showed no evidence of pulmonary metastasis.

In July 1961 a local recurrence was treated by regional perfusion using melphalan (phenylalanine mustard).

In July 1962 he complained of severe pain in the left elbow with effusion into the joint. Repeated radiographs showed no bony metastasis. In April 1963 he was found to have gross clubbing of the fingers and toes with painful swelling of the ankles and wrists. A chest radiograph (Fig. 1) showed two round opacities, one in the right upper lobe and the other in the left mid-zone. A few months later the joint pains became very severe and incapacitating. The chest radiograph showed multiple bilateral pulmonary metastases. He died in September 1965 from cerebral metastases. Post-mortem examination showed disseminated metastases; histologically the tumours in the lungs resembled the primary tumour except for the absence of pigment (amelanotic metastasis).

CASE 2 W. S., a man aged 42, was admitted to hospital on 21 June 1948. He had had painful swellings of the ankles and knees for three months. He was found to have marked clubbing of the fingers and toes with swelling of the distal thirds of the arms and legs. He also had bilateral effusions in the knee

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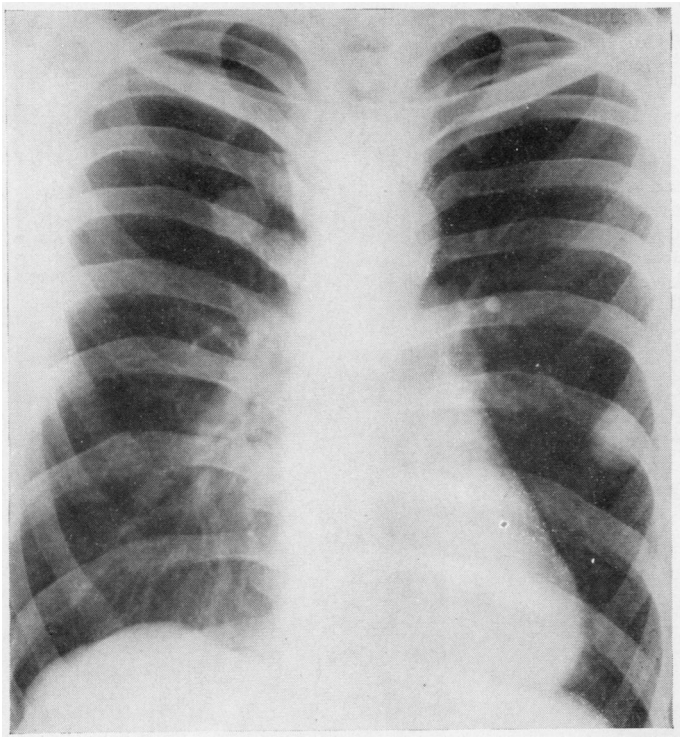

FIG. 1. *Case* 1. *Chest radiograph shows two round opacities, one in the right upper lobe and the other in the left mid-zone.*

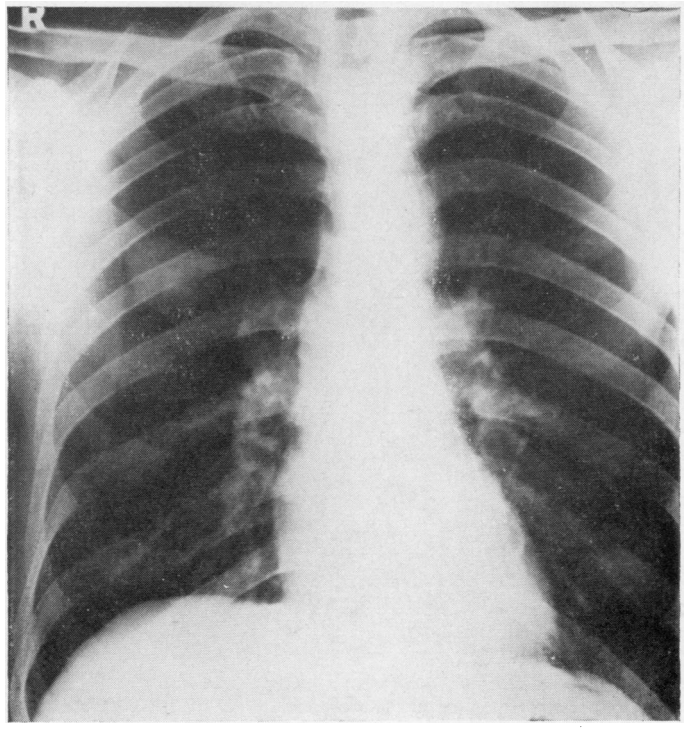

FIG. 2. *Case* 2. *Chest radiograph shows a round opacity in the right upper lobe.*

joints. A chest radiograph (Fig. 2) showed a round opacity in the right upper lobe ; radiographs of the long bones showed subperiosteal new bone formation. Right pneumonectomy was performed on 24 June 1948. Histological examination of the excised specimen showed a columnar-cell adenocarcinoma, suggesting a metastasis from the gastro-intestinal tract. The joint pains were immediately relieved after operation, but his general condition continued to deteriorate and he complained of anorexia. A firm mass was felt in the right hypochondrium. A barium meal on 11 October 1948 (Fig. 3) showed an advanced carcinoma of the pyloric end of the stomach. He died on 28 January 1949.

COMMENT The lesion in the upper lobe of the right lung was thought to be a primary carcinoma ; histological examination suggested a secondary deposit from the gastro-intestinal tract. This was confirmed by the clinical and radiographic evidence of carcinoma of the stomach.

CASE 3 A. M., a woman aged 27, was found to have advanced pulmonary osteoarthropathy with extensive subperiosteal new bone formation (Fig. 4). Osteosarcoma of the tibia had been treated by above-knee amputation a few months previously. The chest radiograph (Fig. 5) showed multiple bilateral pulmonary metastases.

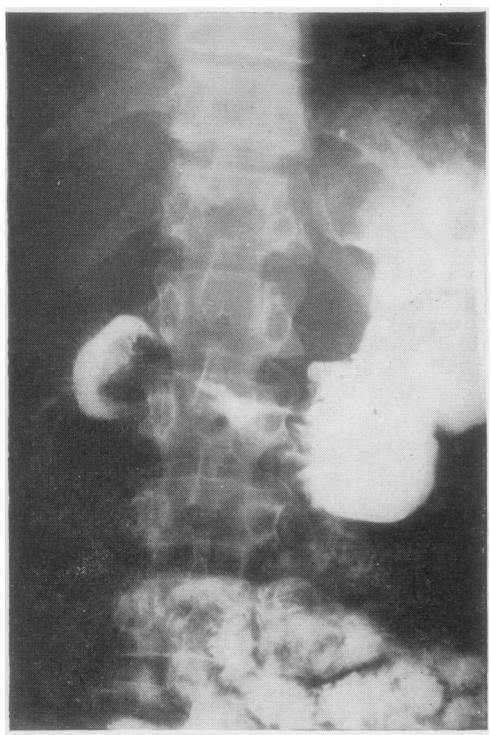

FIG. 3. *Case 2. Barium meal shows an irregular filling defect in the pyloric region of the stomach.*

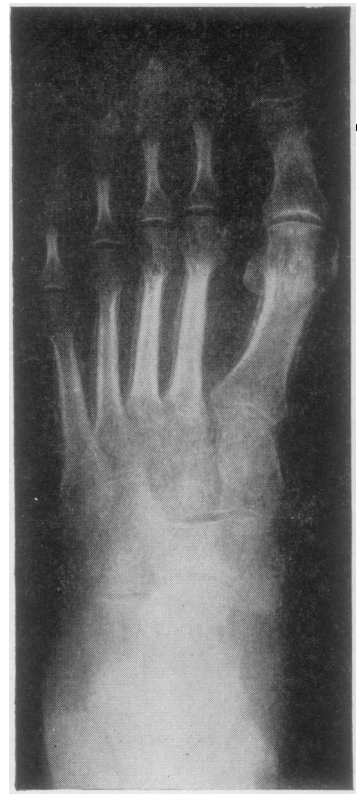

FIG. 4. *Case 3. Radiograph of left foot shows extensive subperiosteal new bone formation.*

DISCUSSION

Pulmonary osteoarthropathy is a syndrome characterized by painful symmetrical arthropathy with swelling of the distal thirds of the arms and legs. Severe clubbing of the fingers and toes and subperiosteal new bone formation are usually present. Gynaecomastia is present in some cases (Hammarsten and O'Leary, 1957 ; Bariéty and Coury, 1950 ; Yacoub, 1965a). The pathological changes have been described by Gall, Bennett, and Bauer (1951). Increased blood flow to the affected limbs has been demonstrated (Charr and Swenson, 1946 ; Mendlowitz, 1941 ; Ginsburg, 1958). All the available evidence suggests that the syndrome is produced by a reflex mechanism with the afferent impulses carried from the chest by the vagus

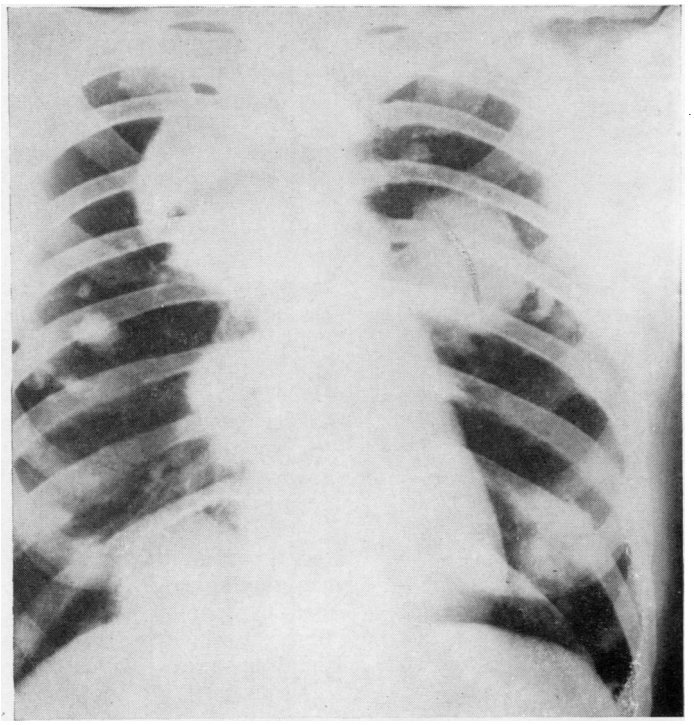

FIG. 5. *Case* 3. *Chest radiograph shows bilateral multiple secondary deposits.*

nerve; the efferent pathways are not known (Flavell, 1956; Huckstep and Bodkin, 1958; Coury, 1960; Holling, Brodey, and Boland, 1961; Yacoub, 1965a).

Although pulmonary osteoarthropathy can occur with a wide variety of intrathoracic conditions, certain diseases tend to be associated with it more commonly than others. Osteoarthropathy can be secondary to intrathoracic inflammatory conditions, including empyema, lung abscess, pulmonary blastomycosis, and pulmonary aspergillosis (Locke, 1915; Compere, Adams, and Compere, 1935; Yacoub and Simon, 1966). Pulmonary tuberculosis is sometimes associated with clubbing of the fingers (Poppe, 1947; Kaplan and Munson, 1941; Neufeld and Wallbank, 1952), but osteoarthropathy is rarely secondary to it (Skorneck and Ginsburg, 1958; Yacoub and Simon, 1966).

Intrathoracic tumours are the commonest cause of pulmonary osteoarthropathy. According to Coury (1960) lung cancer (primary or metastatic) accounts for 80% of the cases, pleural tumours for 10%, and other intrathoracic tumours for 5%. The reported incidence of pulmonary osteoarthropathy in bronchial carcinoma varies in different series; in a group of 200 patients studied by one of us the incidence was 4% (Yacoub, 1965b). In an attempt to determine the incidence of pulmonary osteoarthropathy in cases of metastatic tumours of the lung, Aufses and Aufses (1960) examined the records of 883 patients with pulmonary metastases at the Montefiore Hospital, New York. None of these patients had clinical evidence of pulmonary osteoarthropathy; one had periosteal new bone and 34 had clubbing of the fingers. Fibrous tumours of the pleura are associated with pulmonary osteoarthropathy in 66% of cases (Clagett, McDonald, and Schmidt, 1952; Price Thomas and Drew, 1953; Benoit and Ackerman, 1953).

The incidence of pulmonary osteoarthropathy in association with bronchial carcinoma is related to the cell type (Yacoub, 1965b). No similar relationship has been described in cases of metastatic pulmonary tumours. This is probably due to the rarity of the condition and the paucity of reported cases; 41 cases, including the patients described here, have been reported (see Table). Analysis of these showed that metastasis from osteosarcoma accounts for 30% of cases, from

TABLE

Author	Age	Sex	Primary Tumour
Virchow (1895) ..	Young	M	Chondrosarcoma right femur
Hasbrouck (1898) ..	55	M	Sarcoma beneath right lower jaw
Cotterill (1901) ..	19	M	Periosteal sarcoma right femur
Schlagenhaufer (1904)	21	F	Carcinoma nasopharynx
Hall (1905)	14	M	Periosteal sarcoma right femur
Krüger (1906) ..	52	F	Carcinoma left breast
Schmidt (1913) ..	53	M	Primary sarcoma right side of neck
Oliver (1918) ..	28	M	Periosteal sarcoma left femur
Hoffmann (1919) ..	44	F	Carcinoma cervix uteri
Weinberg (1919) ..			Sarcoma of femur
Bryan (1920) ..	29	M	Spindle-cell sarcoma arising from scar on right arm
Bryan (1925) ..	25	M	Osteosarcoma right femur
Rijkmans (1928) ..			Breast
			Tonsil
Crump (1929) ..	50	F	Carcinoma simplex of breast
Blumensaat (1931) ..	49	F	Malignant melanoma of abdominal wall
Palugyay (1934) ..	13	M	Osteosarcoma right femur
Rypins (1935) ..	37	M	Fibrosarcoma of groin
Compere *et al.* (1935)	50	M	Carcinoma nasopharynx
Penitschka (1938) ..	37	M	Sarcoma left femur
Tobler (1939) ..	56	F	Sarcoma uterus
Barta (1939)	13	M	Periosteal sarcoma left femur
Martin (1939) ..	19	M	Transitional-cell carcinoma nasopharynx
	15	M	Transitional-cell carcinoma nasopharynx
Van Hazel (1940) ..	74	F	Fibrosarcoma of abdominal wall
Bénard, Rambert, Deparis and Pestel (1943)		F	Carcinoma uterus
Massachusetts General Hospital (1954) ..	65	M	Fibrosarcoma
Kollbrunner (1948) ..	47	M	Malignant giant-cell tumour of fibula
Bariéty and Coury (1950)	25	F	Chorionepithelioma of uterus
	66	M	Carcinoma kidney
Holmes, Bauman, and Ragan (1950) ..	32	F	Giant-cell tumour extensor tendon right middle finger
Ray and Fischer (1953)			Fibrosarcoma
Garcia de Lima (1955)			Myxochondrosarcoma
Baldry (1959) ..	51	M	Myxoma left rectus femoris
Gibbs, Schiller, and Stovin (1960) ..	49	F	Leiomyosarcoma of uterus
Alexander and Johnson (1962)	17	F	Osteosarcoma left tibia
Aufses and Aufses (1960)	57	M	Rhabdomyosarcoma muscles of left forearm
Barres, Garetta, Quintane, and Jeantet (1962)			Osteosarcoma
Diner (1962)	17	M	Lymphoepithelioma naso-pharynx
Ive (1963)	39	F	Carcinoma cervix
Papavasiliou (1963) ..	22	M	Lymphoepithelioma naso-pharynx
	23	M	Epidermoid carcinoma naso-pharynx
	25	M	Lymphoepithelioma naso-pharynx
Jaffee (1964)	21	F	Undifferentiated carcinoma nasopharynx
Present series ..	29	M	Malignant melanoma right thigh
	42	M	Carcinoma stomach
	27	F	Osteosarcoma of tibia

fibrosarcoma for 17%, from nasopharyngeal tumours for 19·1%, from uterine tumours for 12·7%, and from tumours of other regions for 21·2%. Together, osteosarcoma and fibrosarcoma account for 47% of cases. The relationship between pulmonary metastasis from nasopharyngeal tumours and osteoarthropathy has been pointed out by Papavasiliou (1963), who commented on the young age of the patients affected, the hilar position of the pulmonary metastases, and the regression of symptoms after irradiation of the pulmonary metastases. Out of four patients with pulmonary metastases from nasopharyngeal tumours seen by the same author, three had osteoarthropathy. Osteoarthropathy secondary to pulmonary metastases from nasopharyngeal tumours was reported as early as 1904 (Schlagenhaufer, 1904) and later by Compere *et al.* (1935), Martin (1939), Diner (1962), and Jaffee (1964).

The factors which determine the ability of a tumour to produce pulmonary osteoarthropathy are not known. The vascularity of the tumour has been suggested as an important factor (Mendlowitz, 1941 ; Aufses and Aufses, 1960). Against this theory is the fact that the very vascular oat-cell carcinoma is seldom if ever associated with osteoarthropathy (Yacoub, 1965b), whereas pleural fibroma, which has a lower vascularity, is commonly associated with osteoarthropathy. The rate of growth of the tumour is not a factor, since some of the most rapidly growing tumours are associated with osteoarthropathy which can develop in a very short time. Fibrous tumours (pleural fibroma, pulmonary metastasis from fibrosarcoma, and tumours with a predominantly fibrous stroma (pulmonary metastasis from osteosarcoma)) tend to be associated with osteoarthropathy more than other tumours. This suggests that the fibrous stroma may be a factor in stimulating the reflex responsible for osteoarthropathy. This is supported by the fact that oat-cell carcinoma, which lacks a fibrous stroma, is never associated with osteoarthropathy.

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