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The effect of adrenergic blockade in hypertrophic pulmonary osteoarthropathy (HPOA)

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Summary

A case of hypertrophic pulmonary osteoarthropathy (HPOA) is described, together with synovial fluid cytology and synovial histology. A new approach to therapy is described using adrenergic blockade. The effectiveness of this regime was assessed by quantitative thermography. The successful results support the neurogenic hypothesis for the aetiology of HPOA.

Introduction

Hypertrophic osteoarthropathy was described over 80 years ago (Bamberger, 1889; Marie, 1890). There have been several series and case reports published since, but the aetiology remains obscure. Furthermore, therapy aside from treatment of the primary lesion is usually disappointing. A case is presented of hypertrophic osteoarthropathy, secondary to carcinoma of the lung, with objective assessment by quantitative thermography. This was used to demonstrate diminution in limb hypervascularity when treatment by sympathetic blockade was initiated. Synovial fluid and histology findings are also reported.

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Case report

A 63-year-old female, a chronic cigarette smoker, presented with a 10-month history of painful swelling of both legs and arms, with accompanying morning stiffness. She had initially been treated as a case of probable rheumatoid arthritis, with non-steroidal anti-inflammatory agents and, more recently, with weekly injections of 1 mg tetracosactide (synacthen; Ciba). Following injection she symptomatically and objectively improved for 2 days, with almost complete disappearance of joint swelling, followed by relapse to the previous state.

Examination revealed small effusions in both knee joints, and swelling in the metatarsophalangeal and proximal interphalangeal joints of both hands. In addition there was marked tenderness and local warmth along the shin and forearm, particularly near the joints, together with gross clubbing of the fingers and toes. Other examination, including that of the respiratory system, revealed no abnormality. X-rays of her chest revealed a localized opacity near the hilum of the right lung. Peripheral films demonstrated extensive characteristic periostitis of hypertrophic osteoarthropathy, most marked near the diaphysis, but involving the entire length of the long bones of the upper and lower limbs.

A right lower lobectomy was performed revealing a well defined neoplasm with an anaplastic small cell

type of histology. There were no secondaries evident and no pleural involvement, and it was considered that the whole tumour had been removed.

Investigations and therapy before surgery

Routine blood tests were normal, including haemoglobin (13·3 gm %). ESR (Westergren) was 51 mm/hr. The latex test for rheumatoid factor was negative. Synovial fluid aspirated from the knee contained 300 leucocytes/mm^3, all mononuclears, and synovial needle biopsy showed thickening up to two cells wide, but no cellular infiltration in the scanty stroma (Fig. 1). Other investigations included estimation of 24-hr urine oestrogens: oestrone 25 μg/ml (normal range 2–10 μg/ml), oestriol not detected (normal range 2–55 μg/ml), and oestradiol 2 μg/ml (normal range 2–4 μg/ml).

Pre-operative therapy included continuation of weekly tetracosactide injections. Adrenergic blockade was initially achieved with propranolol (inderal, I.C.I.: daily 320 mg) in a dose adjusted to just below that which produced postural hypotension in this subject. This produced minor symptomatic, but little objective, improvement. After a short break, propranolol was reintroduced with phenoxybenzamine (dibenyline, SK & F), 10 mg, and then 20 mg daily, added. This regime induced definite clinical and objective evidence of improvement.

Throughout the period of therapy, ring sizes and grip strengths were measured daily, and intermittently quantitative thermograms (Collins *et al.*, 1974) were performed on both hands and both knees (Fig. 2). There was little alteration in hand measurements throughout this period, but a marked drop in the thermographic index occurred while on the combined adrenergic blocking drugs. There was further improvement after thoracotomy. However, the index following surgery is within the limits of normal established by the above authors.

Discussion

Multiple hypotheses have been advanced over the years for the aetiology of hypertrophic arthropathy, including absorption of toxic material from neoplasms, peripheral concentration of toxic products by venous stasis, and peripheral hyperaemia caused by compression of lung capillaries. There is little evidence for any of these mechanisms. There are now two main theories advanced, the neurogenic and the humoral, and there is some supporting evidence for both of these.

The neurogenic theory suggests that the presence of extensive vascular anastomoses occurs as a reflex response to ischaemia. Extensive anastomoses between the bronchial and pulmonary circulations were demonstrated by radio opaque dye injected at post-mortem examination by Cudkowicz and Armstrong (1953). They suggested that ischaemia of pulmonary nerves and plexi leads reflexly to the development of these anastomoses and postulated a similar mechanism to explain the development of the arteriovenous anastomoses in the limbs in hypertrophic pulmonary osteoarthropathy described earlier (Lovell, 1950). Overgrowth of vascular

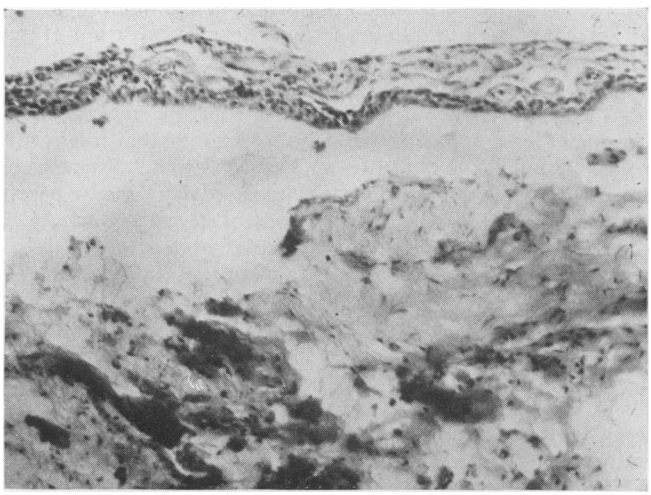

FIG. 1. A needle biopsy of synovium from the knee (H & E × 28). The section shows:
(a) Minimal hyperplasia of synovial lining layer, up to two cells in thickness.
(b) Absence of cellular infiltration in the underlying stroma.

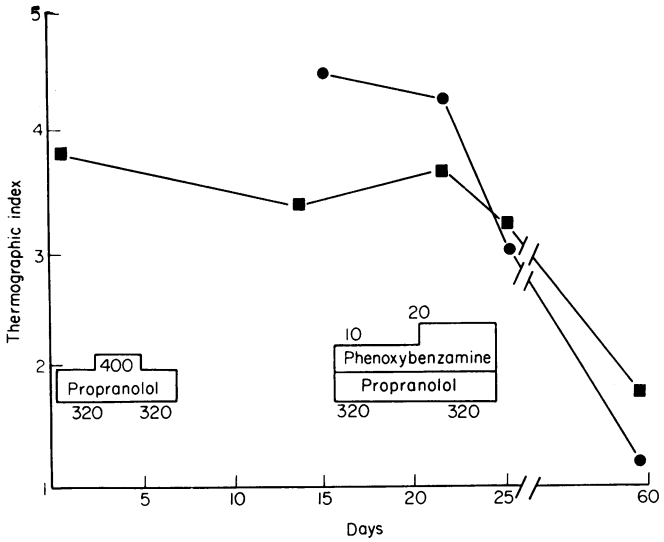

FIG. 2. Effect of therapy on the thermographic index. Little response is seen with tetracosactide or with propranolol alone, but a fall in the thermographic index is seen on combined adrenergic blockade, particularly marked in the hands. A further fall, to within the normal range, is seen after surgery (time of operation is shown by broken line). ●—●, Hands; ■—■, Knee.

connective tissue is the earliest demonstrable abnormality in HPOA. The increased limb blood flow reflects not only arteriovenous anastomoses, but also dilation of these vessels.

Adrenergic blockade has not been previously used to treat HPOA. The rationale for using this therapy in the case described here was to reverse the hypervascularity discussed above. The measurable response to this treatment tended to support the neurogenic hypothesis, although the subjective response was inferior to that seen with tetracosactide. It is possible that this was due at least in part to the euphoriant effect of steroids. Certainly the objective thermographic measurements showed that sympathetic blockade had a definite effect on the vascularity of HPOA, and this was superior to the response to tetracosactide. Thermography, which reflects the vascularity of the region examined (Draper and Boag, 1971), appears to be an excellent method to assess response of HPOA to therapy, as it is in the inflammatory arthritides such as rheumatoid arthritis (Ring *et al.*, 1974).

The response to surgery in this case was more pronounced, both clinically and on thermographic measurement, in agreement with the rapid and complete relief of limb symptoms following removal of the neoplasm noted by several previous authors (Wierman, Clagett and McDonald, 1954; Pattison *et al.*, 1951).

Alternative humoral theories for HPOA have been advanced for a number of reasons. The superficial resemblance of the large hands to those seen in acromegaly received some support when three or four cases of HPOA associated with bronchogenic carcinoma showed definite eosinophilic cell hyperplasia of the anterior lobe of the pituitary at post-mortem examination (Fried, 1943). However, six other patients were later reported who had a miniature basophilic adenoma (Pattison *et al.*, 1951).

A role for oestrogens was postulated from the observations that a number of cases had coexistent gynaecomastia. Urine oestrogen excretion was increased in a series of cases with HPOA to twice the control levels (Ginsburg and Brown, 1961), but further investigation failed to delineate a role for oestrogen in this condition (Ginsburg, 1963). Raised urinary oestrogens could merely be an incidental finding, and only a minimal increase in oestrogen levels was seen in the case described here. A humoral mechanism involving bradykinin was postulated by Kunkel (1971) from results of arterial and venous blood gases, while Hall (1959) had suggested that incomplete blood oxygenation secondary to pulmonary shunts might itself lead to opening of the digital anastomoses.

The synovial findings have been included in this report since there have been very few descriptions of the joint pathology in the literature, although

Collins (1966) mentioned changes of an inflammatory character causing joint enlargement. Our patient had definite recurrent synovial effusions, but the cytology proved that this was not an inflammatory fluid. Synovial biopsy also revealed an absence of cellular infiltration and only minimal synovial cell hyperplasia. Thus, in this case, in spite of effusions in multiple joints, there was no pathological evidence of inflammatory arthritis. It is possible that the effusion was an oversecretion due to the increased vascularity of the synovium where it is in contact with the underlying hypervascular periosteum.

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Progressive systemic sclerosis and autoimmune haemolytic anaemia

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Summary

The development of progressive systemic sclerosis (PSS) in a patient with established autoimmune haemolytic anaemia is described. Points favouring an immunological aetiology for PSS are reviewed and discussed.

SINCE the first report by Fundenberg and Wintrobe (1955) describing the association between progressive systemic sclerosis (PSS) and autoimmune haemolytic anaemia, other similar cases have been reported (Steiner, Haeger-Aronsen and Nielson, 1967; Westerman *et al.*, 1968; Chaves *et al.*, 1970; Ivey *et al.*, 1971; Rosenthal and Sack, 1971). All reported cases presented initially with features of PSS and were only later complicated by autoimmune haemo lytic anaemia. In 1973, Loft and Olsen described a case which presented with autoimmune haemolytic anaemia but had on examination features of PSS as well. In none of the previously reported cases had autoimmune haemolytic anaemia preceded the development of PSS.

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