HYPERPARATHYROIDISM DUE TO PARATHYROID CARCINOMA

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Carcinoma of a parathyroid gland is an uncommon cause of hyperparathyroidism. Black (1954) was able to collect twelve cases of parathyroid carcinoma with hyperparathyroidism and distant metastasis. He considered that another group of four cases undoubtedly represented carcinoma, because a tumour found to be densely adherent or locally invasive at operation recurred later. Cope, Nardi and Castleman (1953) reported four cases in a series of 148 cases of hyperparathyroidism. Three of the patients were found to have metastases at necropsy, but in the fourth neither recurrence nor hyperparathyroidism had occurred four years after removal. Wray (1953) reported a further case in which the tumour was found to be locally invasive at operation. The growth recurred and proved to be inoperable because of infiltration. Although distant metastases were not present at necropsy, the malignant nature of the tumour is beyond doubt. Recently Weissman, Worden and Christie (1957) reported a case of mediastinal parathyroid carcinoma which, three years after surgical removal, recurred with multiple metastases and hyperparathyroidism. Thus the sixteen cases reported by Black, the three cases of Cope, Nardi and Castleman, Wray's case, that of Weissman, Worden and Christie, and the case here reported, bring the total of indisputable functioning parathyroid carcinomata to twenty-two.

CASE REPORT

The patient, a married woman of fifty-six, noticed a lump in the right upper jaw in July 1955. This was curetted, and proved to have the histology of an osteoclastoma. Further investigation showed that the serum calcium was increased and serum inorganic phosphate diminished. On these findings a diagnosis of hyperparathyroidism was made. Seven years before, in 1948, she had had five stones removed from the right kidney, followed by right nephrectomy for non-functioning kidney associated with hypertension. She had suffered from recurrent bouts of dyspepsia since adolescence. Treatment with diet and alkalies had produced symptomatic relief of variable duration.

Physical examination revealed, behind the sterno-clavicular joint, a small mobile swelling which moved on swallowing. Several soft, smooth tumours of the arms and axillae were thought to be neurofibromata. The blood pressure was 240/130 millimetres of mercury; there was no clinical evidence of left ventricular hypertrophy or heart failure.

Investigations (November 1955)—The serum calcium was 12.8 milligrams/100 millilitres; the serum inorganic phosphate 2.2 milligrams/100 millilitres; alkaline phosphatase 32.5 K.A. units; urinary calcium excretion 312 milligrams in twenty-four hours; blood urea 54 milligrams per cent; serum proteins and electrolytes were normal.

Operation—Mr R. Marnham explored the neck and removed a tumour about two centimetres in diameter in relation to the lower pole of the left lobe of the thyroid. The tumour was adherent and difficult to remove. No local metastases were discovered.

Histology—Histological examination revealed parathyroid tissue with mainly clear cells. There was evidence of capsular invasion and there were large numbers of nuclear mitoses. On these grounds a diagnosis of parathyroid carcinoma was made. After operation there was a fall in serum calcium with tetany (Fig. 1).

Further treatment and progress—Calciferol was given for the next five months (50-100,000 units daily). It was hoped that this would assist in the maintenance of the serum calcium
level and minimise any stimulus to hypertrophy falling upon remaining parathyroid tissue. The patient was without symptoms until August 1956, when she complained of increased urinary frequency, extreme tiredness and vague pains in the back and legs. She was admitted to hospital for further study.

Investigations (November 1956)—The serum calcium was 13·7 milligrams/100 millilitres; serum inorganic phosphate 2·4 milligrams/100 millilitres; serum alkaline phosphatase 10·7 K.A. units; plasma proteins total 6·2 grammes (albumin 3·7 grammes; globulin 2·5 grammes; albumen-globulin ratio 1·5); plasma chloride 106 m.eq./l; plasma sodium 139 m.eq./l; plasma CO₂ combining power 24·5 m.eq./l; blood urea 47 milligrams; urea clearance test 38 per cent of average normal; blood count Hb. 93 per cent (13·8 grammes), P.C.V. 41 per cent; erythrocyte sedimentation rate 7 millimetres/1 hour (Wintrobe); fractional test meal—marked hyperchlorhydria (free HCl≡84 millilitres N/10 HCl in one specimen).

![Diagram showing the variations in serum calcium (solid line) and serum inorganic phosphate (interrupted line). The values are expressed as milligrams/100 millilitres. The fall in serum calcium after the first operation is well shown. A similar result does not occur after the second operation.](image)

Radiographic examination—Skeletal survey showed generalised osteoporosis. The trabecular pattern in several bones was coarsened. There was slight cortical absorption in the phalanges as evidence of active hyperparathyroidism. The skull was normal.

Intravenous pyelography showed poor excretion from the remaining (left) kidney. Barium meal showed some persistent tenderness over the duodenum, which was deformed. The appearances suggested duodenal ulcer.

Electrocardiographic studies were within normal limits except for some shortening of the QT interval.

Balance studies—Balance studies were carried out for six periods of six days. The diet was constant with a calcium intake of 910 milligrams a day. Faecal and urinary estimations of calcium, phosphorus and nitrogen were made. The patient was in a strongly negative balance for calcium. Average urinary calcium was 400 milligrams a day and faecal calcium 900 milligrams a day.

Further course—An attempt was made to treat the patient with oral phosphate. (The dosage of di-sodium hydrogen phosphate was equivalent to 2 grammes of phosphorus a day.) It was hoped that this might raise the serum phosphorus and produce a secondary reduction in serum
calcium. In fact, serum inorganic phosphate increased from 3 milligrams to 5.5 milligrams/100 millilitres while the serum calcium continued to increase from 15 to 17 milligrams per cent. Phosphates caused diarrhoea and were discontinued. Balance studies while phosphate was being given showed a marked increase in faecal calcium (2-4 grammes a day) with little change in urinary calcium. A second exploration of the neck was carried out by Mr Marnham in December 1956 with the hope that any functioning tumour tissue might be removed in order to prolong life. Multiple grey, firm nodules about three millimetres in diameter were removed from the left side of the neck. A remnant of thymus containing two firm nodules was also removed. Histological examination of the nodules showed areas of clear cell tumour tissue, confirming the diagnosis of parathyroid carcinoma.

The patient recovered from the operation but there was no improvement. There was no post-operative tetany, nor any lowering of the serum calcium (Fig. 1). During the next few weeks the blood urea rose to 108 milligrams/100 millilitres, but fell to 56 milligrams/100 millilitres under the influence of a low protein, high caloric diet.

Professor Charles Dent suggested that an attempt to lower the serum calcium might be made with methyl thiouracil. Some evidence has been obtained (C. E. Dent, K. E. Halnan and E. E. Pochin, unpublished observations) that added thyroxin potentiates the effect of parathormone on the serum calcium level and that hypothyroidism decreases its action. In the period that the drug could be given (four weeks; 400 milligrams daily) no benefit was apparent, and it did not appear to influence serum calcium levels. As the patient's condition was deteriorating, cortisone was given (60 milligrams daily—total 960 milligrams) in the hope that it might have an anti-parathyroid effect, but its administration was also without benefit.

By this time (six weeks after the second operation) definite radiological evidence of hyperparathyroidism had developed. Cortical absorption was visible in the phalanges, with porosis and pseudo-cysts (Fig. 2). The patient died thirteen months after the diagnosis had been confirmed at the first operation.

Necropsy findings—Necropsy revealed the following significant findings. 1) Several minute grey nodules in the neck shown by histological examination to be carcinomata of the parathyroid gland (Figs. 4 and 5); 2) the right lobe of the thyroid was intact and two parathyroid glands of normal size were demonstrated on its postero-lateral surface; 3) a metastatic deposit in the lung (Fig. 6); 4) calcinosis of the remaining (left) kidney; 5) some metastatic calcification of the cranial dura mater; 6) cardiac hypertrophy (weight 460 grammes) with scattered plaques in the ventricular myocardium due to calcinosis; 7) a healed peptic ulcer on the posterior wall of the pylorus.

DISCUSSION

In benign hyperparathyroidism the histological appearances sometimes misleadingly suggest early carcinoma. The diagnosis of parathyroid carcinoma is established beyond all doubt if the tumour is associated with hyperparathyroidism and distant metastasis. If the tumour is locally invasive and recurs after surgical removal it may also be accepted as...
Low power view of recurrent parathyroid tumour. Note nodular masses of tumour cells with infiltration of surrounding tissue. (× 40.)

Higher magnification of recurrent tumour.
carcinomatous. This paper concerns a case with hyperparathyroidism, local recurrence after surgery and metastasis. Although non-functioning parathyroid carcinoma probably exists, it is a less definite entity.

The most common cause of death in carcinoma of the parathyroid with hyperparathyroidism is renal failure. There is no significant difference in the sex distribution, and the disease is commonest in the fifth decade.

Castleman (1952) based the pathological diagnosis of carcinoma upon evidence of capsular invasion, local infiltration, loss of the normal parathyroid pattern and a trabecular arrangement of the cells. The cells themselves are often cylindrical, and numerous mitoses are present. The nuclei are deeply staining and enlarged nucleoli are often visible. Tumour cells within blood vessels also support the diagnosis of malignancy, but are not confined to malignant tumours. In this case the tissues removed at both operations and from the neck and lung at necropsy fulfil these criteria. The tumours are locally invasive, which renders surgical removal difficult. Often this may be the first signal that the tumour is not a simple parathyroid adenoma. Regional lymph nodes and the liver are common sites for metastasis.

Treatment of the condition is unsatisfactory. If a carcinoma is suspected at operation a wide excision is indicated, together with a thorough search of the neck for lymphatic involvement or secondary nodules. The improvement after surgery commonly disappears with the onset of local recurrence or metastasis. A second operation under such circumstances is technically difficult, and in this case, as in others, was unsuccessful. Black (1954) makes a plea for post-operative irradiation, but any improvement from this form of treatment seems to be partial and temporary.

Treatment was attempted with oral phosphates, cortisone and methyl thiouracil without success. Radical surgical removal of neoplastic parathyroid tissue remains the only form of treatment with any hope of cure or improvement.
A further point of interest is the association between peptic ulcer and hyperparathyroidism reported by several authors (Rogers 1946, Lancet annotation 1955). In this case there was marked hyperchlorhydria, and the scar of a healed duodenal ulcer was demonstrated at necropsy. The symptoms of peptic ulcer had been present for more than thirty years. It is difficult to define the onset of hyperparathyroidism, but renal stones were removed nine years before death.

SUMMARY

A case of hyperparathyroidism from carcinoma of the parathyroid gland which recurred locally and metastasised to the lung is described. There was a history of renal lithiasis and peptic ulceration. Improvement followed initial surgical removal but the tumour recurred and death resulted from hyperparathyroidism.

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REFERENCES

LANCET (1955): Hyperparathyroidism and Peptic Ulcer (Annotation), i, 341.