Successful Removal of Single Metastasis in Recurrent Parathyroid Carcinoma

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When a remote metastasis is found after removal of a primary carcinoma it is usually assumed that further surgery is unlikely to effect a lasting cure, and therefore radiotherapy or more conservative chemotherapeutic measures are adopted. However, in the case of a few tumours—for instance, hypernephroma—the removal of a single metastasis has produced long-lasting cure and is, therefore, always worth consideration. In the case of parathyroid carcinoma tumours commonly recur even after radical surgery, usually by the local spread of multiple seedling tumours, although circumscribed metastases also occur, often many years after an apparently completely successful operation.

In a review of published cases of parathyroid carcinoma Holmes *et al.* (1969) gave data on 46 cases with unequivocal evidence of malignancy and hyperparathyroidism. They quoted a 10-year survival of 13%. None appears to have been cured by resection of a solitary remote deposit. They note that resection of pulmonary metastases can make hypercalcaemia easier to control. In one case (Goepfert *et al.*, 1966) wedge resection of a solitary lesion in the left upper lobe was followed within a year by the appearance of metastases in the right lung. Details of the biochemical response to resection were not provided. One report describes the finding at postmortem examination of what appeared to be a solitary distant metastasis in liver (Albertini *et al.*, 1953). A patient under our care was found at postmortem examination to have a single bony metastasis in the spine, leading us to regret that we had not considered its direct surgical removal. Forewarned in this way, we approached the problem described here with a little more optimism.

Case History

An 18-year-old woman was first admitted to hospital in 1961 with right-sided abdominal pain for which appendicectomy was carried out. In November a renal stone was found, which was passed. Plasma calcium was determined and found to be 13·0 mg/100 ml. In September 1962 she was symptomless but radiographs of her hands showed hyperparathyroid changes. Her neck was explored for the first time (Mr. C. H. Talbot) and a large parathyroid tumour was found behind the upper pole of the thyroid on the right. Two normal glands were identified on the left. Histology of the tumour showed it to be an adenoma without evidence of malignancy. Plasma calcium six months postoperatively was 9·9 mg/100 ml.

She remained well until January 1965 when her plasma calcium was found to be 12·0 mg/100 ml, and by September it was 14·4 mg/100 ml. At this time a second exploration was carried out and a nodule was removed from the midline below the isthmus. Histology suggested for the first time that this was possibly a carcinoma. Left upper and right lower parathyroid glands were identified. Postoperatively the plasma calcium remained raised.

In January 1966 a third exploration including the mediastinum failed to reveal any parathyroid tissue, and there was no biochemical improvement. She subsequently developed bone pain and tenderness. At this point she was admitted to this hospital in November, aged 24. She had lost her appetite and was losing weight, but she was not thirsty and had no symptoms arising from renal stones. There was no lymphadenopathy and no corneal calcification. Her blood pressure was normal. An ill-defined mass was palpable on the right side of the neck lateral to the thyroid gland. Examination was otherwise negative.

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INVESTIGATIONS

Results of investigations were: Plasma calcium 14·8 mg/100 ml (specific gravity 1·025-6), phosphorus 1·7 mg/100 ml, alkaline phosphatase 66 King-Armstrong Units. Plasma chloride 110 mEq/l. and bicarbonate 21 mEq/l. Plasma urea was normal but there was a defect of urine concentration, maximal specific gravity being 1·010. There was a moderate aminoaciduria present. Twenty-four-hour urinary calcium was 950 mg and total hydroxyproline 371 mg. A urinary tract infection with *Escherichia coli* was present.

Skeletal *x*-ray pictures showed widespread subperiosteal bone resorption pathognomonic for hyperparathyroidism. Bone biopsy showed extensive bone resorption and fibrous tissue replacement (Dr. P. D. Byers).

In November a fourth neck exploration was carried out by one of us (D.R.D.), and a large parathyroid carcinoma was removed from the right side measuring 7 cm by 4 cm. It was adherent to the oesophagus and trachea and involved the recurrent laryngeal nerve on that side. The sternum was also split and the upper mediastinum was explored. No other parathyroid tissue was found. All thymus and lymphoid tissue was removed as well as the entire thyroid gland, and a thorough search was made for more parathyroid tissue. A tracheostomy was performed. The histology later confirmed infiltrating parathyroid carcinoma (Professor J. F. Smith). Postoperatively she was given a full course of radiotherapy to the neck and mediastinum.

Severe and persistent postoperative hypocalcaemia followed as a result of the removal of her parathyroid glands and the healing of her widespread bone resorption. She was maintained on 4 mg dihydrotachysterol daily for eight weeks and Aludrox (dried aluminium hydroxide gel) 30 ml four times daily intermittently during the same period; this regimen controlled her tetany. She was discharged on half the dose of dihydrotachysterol—namely, 2 mg daily and Aludrox 15 ml four times daily. On follow-up she was normocalcaemic on her first attendance but thereafter she became hypercalcaemic and all treatment was stopped. This was attributed to intoxication with vitamin D, to which patients with hyperparathyroidism seem particularly sensitive. Her plasma calcium level fell to normal in March 1969 but thereafter slowly climbed once more. Nevertheless, symptomatically she remained well, earning her living as a shop assistant.

By December 1971, however, plasma calcium had risen to 14·1 mg/100 ml indicating recurrence of her carcinoma. She was readmitted in January 1972 having in the meantime been placed on a low calcium diet and ethane hydroxy diphosphonate 500 mg three times daily. Apart from some lethargy and depression she was symptom free, and physical examination was negative. Plasma calcium had fallen to 12·8 mg/100 ml (specific gravity 1·024-5) but subsequent studies indicated that this appeared to be due to lowering of dietary calcium intake. Balance studies were carried out and she was shown to be in strongly negative calcium balance. Radiographs of hands and other bones showed no evidence of osteitis fibrosa, which went well with her normal plasma alkaline phosphatase levels on this admission. Attempts were made to locate the site of recurrence of the parathyroid cancer by selective venous catheterization (Dr. D. G. Shaw) and parathyroid hormone assay (D.R.I.). Only the venous system on the right side could be cannulated because of severe scarring. "Background" levels (1 ng/ml) of parathyroid hormone were found on all samples and no local increase in hormone concentration was identified. She was discharged on a low calcium diet and cellulose phosphate 5 g three times daily.

On readmittance in April a faint circular opacity was noted in the lower left lung field on a chest *x*-ray film (Dr. C. M. Hall) taken for investigation of a mild pneumonia. Bilateral whole lung tomography showed an isolated circular lesion in the left lower lobe (see fig. 1). This was presumed to be a metastatic deposit of parathyroid carcinoma. As the size of this seemed sufficient to account entirely for her recurrence of hypercalcaemia there was now no need to suppose that local metastatic spread of the cancer had occurred in the neck, as we had feared. Thoracotomy was carried out (Miss D. Nightingale) and the nodule was resected with surrounding lung tissue. Histology showed it to consist of parathyroid carcinoma.

The postoperative course was complicated by severe and prolonged hypocalcaemia despite the absence of radiological bone disease, and she required treatment with large doses of dihydrotachysterol and Aludrox once more. The whole course of her biochemical changes and the relevant therapy are summarized in fig. 2. She

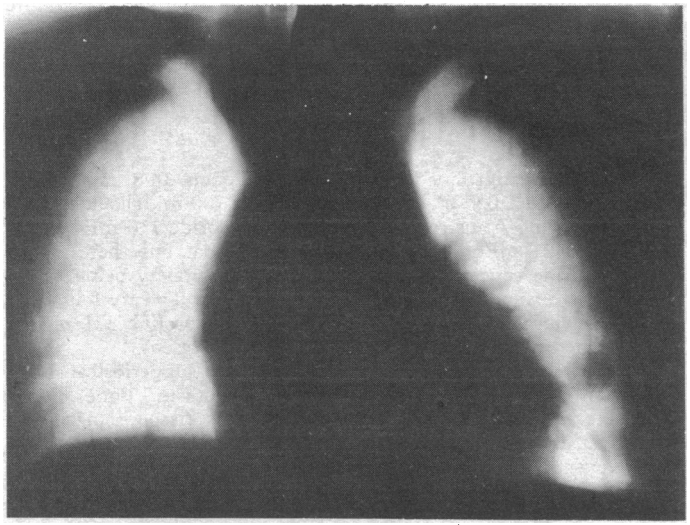

FIG. 1—Chest tomogram on 12 April 1972. There is a round opacity, 1 cm in diameter, in left lower lung field.

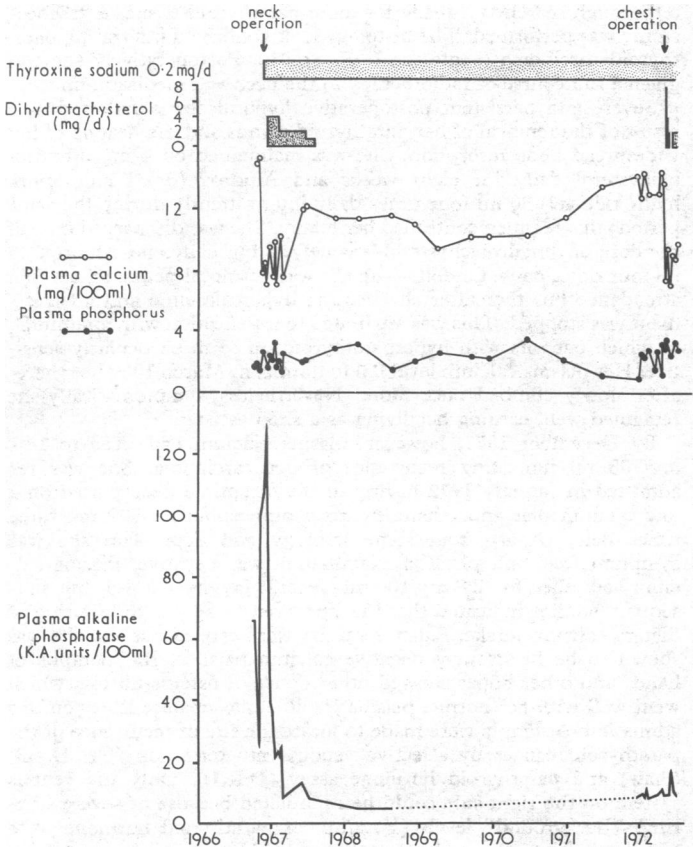

FIG. 2—Biochemical determinations. Note the high alkaline phosphatase on first admission to this hospital, and the normal level on second one.

returned home in good general health taking dihydrotachysterol 2·0 mg daily and Aludrox 15 ml four times daily. On later follow-up her plasma calcium had become normal and the Aludrox was therefore stopped.

Comment

Clearly, at the time of writing, this patient had little, if any, parathyroid cancer tissue remaining, as judged by the severity of the postoperative hypocalcaemia. If there are a few remaining tumour cells we presume that it will take many years for them once again to create trouble, during which time we expect her to enjoy normal health. We therefore recommend strongly that the possibility of there being a solitary metastasis, not necessarily local, accessible to surgery should always be kept in mind when recurrence of such a cancer is first detected. While we were alert to this possibility in this patient we must admit that the final discovery of the site of metastasis was accidental. Possibly the tumour deposit did by its presence contribute to the local chest infection which caused the *x*-ray film to be taken on which the opacity in her lung fields was discovered.

The diagnosis of parathyroid carcinoma is, of course, best made early, but nevertheless this diagnosis is mostly made at operation, and on histology, and often not at the first operation as in our case. The clinical history of the patient did, however, give indications that in retrospect could make us suspect on the second admission that the tumour was not benign. We have pointed out elsewhere (Dent, 1962) that the two forms of hyperparathyroidism—namely, that with and that without bone disease—usually remain true to type throughout their course when due to an adenoma. On the other hand when due to carcinoma this separation of the two clinical manifestations is not always maintained. The present case is an excellent illustration of this curious phenomenon. Her clinical history began with ordinary stone-forming hyperparathyroidism without bone disease. When the hyperparathyroidism later recurred she developed gross osteitis fibrosa and formed no more stones. With the recent, and we hope final, recurrence with the metastasis in her lung she reverted to the non-bone disease form despite the severe hypercalcaemia (fig. 3).

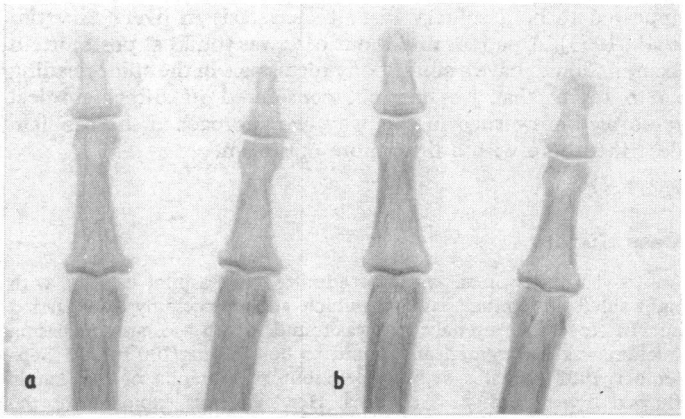

FIG. 3—*X*-ray pictures of index and middle fingers (left) in 1966 when she had gross osteitis fibrosa with subperiosteal erosions and erosion of phalangeal tufts, and (right) in 1972 when no signs of osteitis fibrosa can be seen.

We thank the nurses of the hospital for help in the care of this patient, at times critically ill. Most of the biochemical determinations were carried out in the metabolic ward laboratories. Dr. Roger Smith helped us with clinical care during the patient's first admission to this hospital. We are grateful to the Medical Research Council for support to one of us (D.R.I.).

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