Hypercalcaemia due to hyperparathyroidism in a patient with chronic renal failure and renal carcinoma

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SUMMARY A 65-year-old woman with a history of a left heminephrectomy for renal carcinoma developed hypercalcaemia 11 years after the operation. The same kidney was found to contain a recurrent renal carcinoma. After the radical nephrectomy of the left kidney, hypercalcaemia remitted but reappeared 11 months later. The right kidney was small but functioned at a level of creatinine clearance of 10-15 ml/min. Metastatic work-up was negative, and secondary causes of hypercalcaemia were excluded. A neck exploration revealed a parathyroid adenoma. With parathyroid resection the serum calcium declined to normal, and the risk of hypercalcaemic nephropathy in the remaining kidney was precluded.

Hypercalcaemia is a common manifestation of malignancy of numerous organs, including the kidney (Albright and Reifstein, 1948; Connor *et al.*, 1956; Plimpton and Gellhorn, 1956; Gold and Shnider, 1959; Lucas, 1960; David *et al.*, 1963; Noenickx *et al.*, 1962; Moses and Spencer, 1963; Samuelsson and Werner, 1963; Goldberg *et al.*, 1964). Primary hyperparathyroidism is a relatively common disorder, usually benign, with a frequency of 1 case per 1000 persons per year. The most common manifestation of this disorder is hypercalcaemia (Thorn *et al.*, 1977). The association of renal carcinoma and hyperparathyroidism in the same patient is uncommon and has rarely been diagnosed before the death of the patient (Bernstein *et al.*, 1965; Salama *et al.*, 1971; Nemoto *et al.*, 1977).

This report describes a patient with chronic renal failure, who had had a total left nephrectomy for a recurrent renal carcinoma accompanied by hypercalcaemia and, 11 months later, was found to have recurrent hypercalcaemia. The recurrent hypercalcaemia was not due to recurrent renal carcinoma but rather to a parathyroid adenoma. After removal of a parathyroid adenoma the hypercalcaemia remitted.

Case report

The patient is a woman who was found to have a carcinoma of the left kidney during evaluation of vaginal prolapse in 1965 at age 54. The physical examination was normal except for obvious vaginal prolapse. The full blood count, urine analysis, serum electrolytes, serum calcium and phosphate, and creatinine clearance were normal. She underwent segmental resection of the left kidney (Fig. 1). On microscopic examination the tumour was a renal carcinoma. There were no metastases nor was there evidence of local invasion. At the time of the operation the patient was described as being quite 'irritable' by several physicians. She was discharged from hospital and followed with yearly intravenous pyelograms.

In July 1976, 11 years after the first operation, she was found to have progressive dilatation and clubbing of upper pole calyces, and an angiogram (Fig. 2) showed a 7 × 4 × 5 cm tumour mass involving one-half to two-thirds of the upper pole of the left kidney. The right kidney appeared to be small but without gross tumour involvement. Investigation revealed that the haemoglobin was 12.0 g/dl, WBC 7.8 × 10⁹/l with a normal differential. The urine was clear with pH 6.0 and SG 1.010; there were 10-20 RBCs/hpf, 5-10 WBCs/hpf, and no casts nor bacteria. Urine cultures were negative on three

Fig. 1 A graph depicting the patient's course by following serum calcium, phosphate, PTH, and creatinine clearance.

separate occasions. Serum electrolytes were: sodium 135 mEq/l (135 mmol/l), potassium 4.1 mEq/l (4.1 mmol/l), chloride 99 mEq/l (99 mmol/l), carbon-dioxide combining power 26 mEq/l (26 mmol/l). Total serum proteins 6.3 g/dl (63 g/l) with albumin 3.6 g/dl (36 g/l). Serum calcium levels of 11.2 mg/dl (2.8 mmol/l), 11.0 mg/dl (2.75 mmol/l), and 11.5 mg/dl (2.88 mmol/l) (normal range: 8.4-10.0 mg/dl; 2.1-2.5 mmol/l) were found with corresponding serum phosphate levels of 3.2 mg/dl (0.03 mmol/l), 3.0 mg/dl (0.07 mmol/l), and 2.8 mg/dl (0.09 mmol/l). The ionised serum calcium was 2.54 mEq/l (1.27 mmol/l) preoperatively, falling to 2.22 mEq/l (1.11 mmol/l) postoperatively (normal range: 1.78-2.28 mEq/l; 0.89-1.14 mmol/l), creatinine clearance was 100 ml/min. All other laboratory or radiological investigations were normal.

The remainder of the left kidney was resected in September 1976 and found to contain a well-encapsulated neoplasm measuring 5.5 × 6.0 cm. On section it had a yellow, vascular cut surface with areas of haemorrhagic necrosis and microscopically was composed predominantly of polygonal clear cells (Fig. 3). No evidence of metastases was found at operation. The renal vessels and ureter were free of

disease. Postoperatively the urine output ranged from 50 to 100 ml/day for 48 hours and then rose to 1500 ml/day; creatinine clearance stabilised at 10-15 ml/min during the next 10 days. The serum calcium level was 9.0 mg/dl (2.25 mmol/l) and serum phosphate was 3.0 mg/dl (0.07 mmol/l) at discharge in October 1976.

Before operation in 1976 the patient's parathyroid hormone level had been 916 pg/ml. Postoperatively, the level declined to 800 pg/ml and has remained at approximately the same elevated level to the present time. While the patient's renal function gradually improved with hypertrophy of the remaining kidney, the serum calcium began to rise again and in August 1977 reached values of 10.5-11.5 mg/dl (2.63-2.88 mmol/l); the ionised calcium was also elevated at 2.60 mEq/l (1.3 mmol/l). Initially, the hypercalcaemia was thought to be due to the renal carcinoma, but the postoperative rise in 1977 suggested that the patient had a recurrence of tumour or had another, occult cause of hypercalcaemia. After another work-up for metastatic neoplasm was found to be negative radiologically and biochemically, secondary causes of hypercalcaemia were evaluated. Bone marrow and serum protein electrophoresis were both normal and

Fig. 2 *Renal angiogram demonstrating large tumour of the left kidney and the small right kidney.*

Fig. 3 *Renal cell carcinoma showing typical clear cells with highly vascular stroma (Haematoxylin and eosin $\times 100$).*

Fig. 4 *Functioning parathyroid adenoma containing chief cells growing in sheets and glandular pattern (H and E $\times$ 100).*

excluded the largest group of multiple myelomas, that is, secretory myelomas. Thyroid function studies were normal. Sarcoidosis was not suggested by either history, physical findings, or radiological examination. The patient was taking no vitamins nor diuretics, nor was she ingesting any milk products or antacids in large quantities to our knowledge. It was, therefore, concluded that a parathyroid adenoma might be present, although this diagnosis was supported only by the patient's chronic irritability, noted by many observers, and her hypercalcaemia.

Since the renal function was slowly improving with one kidney, it was decided to explore her neck for a possible parathyroid adenoma. While the level of serum calcium was not life-threatening, the residual kidney was at risk and its function could deteriorate if the hypercalcaemia persisted. At operation three parathyroid glands were identified. A mass removed from the right superior region of the thyroid gland measured $1.8 \times 1.0 \times 0.5$ cm in its greatest dimensions. It had a thin, connective tissue capsule and a greyish-brown cut surface. Microscopically, it was an encapsulated lesion composed mainly of chief cells, which were growing in sheets and in a glandular pattern (Fig. 4). The adenoma was separated by a fibrous band from a definite rim of normal parathyroid. No mitosis was present. Three normal parathyroid glands were identified microscopically. The patient recovered uneventfully, and

the serum calcium levels returned to the 9.5-10.0 mg/dl (2.38-2.5 mmol/l) range with a serum phosphate reading 3.0-3.4 mg/dl (0.97-1.10 mmol/l) two months after surgery. The patient now feels well, but her irritability persists. Her renal function continues to improve gradually and her creatinine clearance is now 45 ml/min.

Discussion

The relationship between malignancy and increased parathyroid hormone (PTH) levels can be ascribed to the production of PTH by tumour tissue. The development of hypercalcaemia and hypophosphataemia in patients with malignant neoplasms has been reported. On the basis of histological studies, reasonably convincing evidence has been produced that a PTH-like substance can be formed in patients with tumours and hypercalcaemia (Kohout, 1966). In a series of 128 consecutive patients with malignant disease studied at necropsy, 34 had hypercalcaemia and all were found to have parathyroid hyperplasia on microscopic examination, with an increase in chief cells and eosinophilic cells. In 16 of the 34, the weight of the parathyroid glands was slightly above normal. Therefore, the relationship between parathyroid hyperplasia, PTH levels, and hypercalcaemia is such that true primary hyperparathyroidism can be mimicked by malignancy.

In the Uppsala University Hospital study (Johansson and Werner, 1975), co-existing malignant disease was found in 13 of 350 patients with histologically proven parathyroid adenomas. The association, if any, between parathyroid disease and malignancy is unclear. However, they suggest three possible mechanisms for a direct relationship between hyperparathyroidism and malignancy.

First, the malignant process and 'primary' hyperparathyroidism might have a causative factor in common so that, for example, parathyroid tissue might be sensitive to a viral agent inducing myeloproliferative disease. There are no data to support this theory.

Secondly, the malignancy may cause hyperparathyroidism by a variety of possible mechanisms. For instance, the malignant cells may produce protein or proteins that directly stimulate the parathyroid gland, or bind the parathyroid hormone or block its effect, for example, on the kidney tubules. The protein might also bind serum calcium more or less specifically. It is interesting that such calcium-binding proteins have been identified (Lindgärde and Zettervall, 1973).

The third possibility is that primary hyperparathyroidism might cause malignancy, though there is no direct evidence to support such a theory. Clubb *et al.* (1964) reported a case in which a serum 'paraprotein' fraction disappeared after the removal of a hyperactive parathyroid adenoma, though they reported later that the paraprotein reappeared in the serum two and a half years after the operation. Furthermore, several cases of monoclonal IgG gammopathy associated with hyperparathyroidism have been reported (Dexter *et al.*, 1972). Though hypercalcaemia disappeared in all three cases after parathyroidectomy, the monoclonal gammopathy persisted with no evidence of malignancy. No matter what the true pathophysiological interactions are among parathyroid disease, hypercalcaemia, and malignant disease, the implication remains that hypercalcaemia in patients with a malignancy should not be accepted as an inevitable sign of recurrent tumour.

In our patient with resected renal carcinoma and parathyroid adenoma, the situation was complicated by the fact that there was also chronic renal failure. Since this lowers total serum calcium levels, the parathyroid-induced hypercalcaemia failed to become apparent until postoperatively the renal function improved. The only symptom that the patient had for many years was 'irritability', and though this may be a clue to the duration of her hyperparathyroidism, it is impossible to ascertain whether parathyroid disease was present in 1965. Moreover, it is interesting that the irritability still

persists. Eight months postparathyroidectomy the patient continues to do well. The creatinine clearance is 45 ml/min and the serum calcium is normal.

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