CASE REPORTS

Hyperfunctioning carcinoma of the parathyroid gland

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Summary

Carcinoma of the parathyroid gland is rare, constituting about 1% of most series of patients with hyperparathyroidism. In 1969 a collective review identified forty-six unequivocal cases, and since then a further seven cases have been described in the literature.

A brief review of the condition is presented, and one further case of hyperfunctioning adenocarcinoma of the parathyroid gland is reported in detail. Primary treatment is discussed, together with postoperative biochemical problems, and the therapeutic manoeuvres available to deal with recurrences are presented.

Introduction

Hyperfunctioning carcinoma arising in the parathyroid gland is rare, as shown by the last extensive review of the subject (Holmes *et al.*, 1969). At that time only forty-six cases were considered to fulfil the required criteria, and since then only seven further cases (Mansour & Letton, 1967; Kelly, 1969; Newton & Sumich, 1968a; Saunders, 1970; Singer *et al.*, 1970; Sherif *et al.*, 1970; Rossi *et al.*, 1971), have been described in the English language medical literature. Carcinoma accounts for approximately 0.5-1% of cases of primary hyperparathyroidism (Pyrah *et al.*, 1966) and presents a metabolic rather than a neoplastic threat to life before excision, and a stormy postoperative period afterwards, but the response to effective treatment is rewarding. A brief review is presented together with a case history highlighting many of the management problems.

Case report

Mrs P. V., a 43-year-old Cypriot, was referred by her general practitioner complaining of muscle pain in the arms and legs, unaffected by exercise, noted for 8-9 months and worse for 10 weeks. She had noted loss of her appetite and of 1 st in weight over 10 weeks, and vomiting after food for 4 weeks. There was dysphagia, with a sensation of solid food sticking in the throat about the level of the thyroid gland. There was no definite history of polydipsia or

polyuria, but there was an inability to sleep due to a dry mouth. There was no relevant past medical history, or family history.

On examination she was apparently in a severe, agitated anxiety state. In the neck there was a mobile, spherical, firm, non-cystic, non-tender nodule about 2 cm in diameter closely connected with the left lobe of the thyroid gland, but not obviously adherent to adjacent tissues. There was no cervical lymphadenopathy. Indirect laryngoscopy showed both vocal cords moved normally. She had minimal bilateral medial corneal calcification. There was no bony tenderness, no muscle tenderness or wasting, no limitation of joint movement, and no obvious abnormalities in the cardio-vascular, respiratory, lymphatic or central nervous system. Blood pressure 140/70 mmHg, pulse rate 100/min, sinus rhythm.

Laboratory investigations: Hb 76%, ESR 73 mm/hr (35 mm/hr 1 month previously in OPD) WBC 7900, differential normal. Plasma urea 54 mg/100 ml; bicarbonate 21 mEq/l, chloride 99 mEq/l, fasting calcium (not corrected) 15.2 and 17.1 mg/100 ml, phosphate 2.9 mg/100 ml, alkaline phosphatase 28 KAU, 24-hr urine (1700 ml) calcium 290 mg, phosphate 460 mg. Creatinine clearance 33 ml/min. Faecal fat 2.5 g/day. Thyroid scan normal, PBI 5.4 µg/100 ml, 48-hr uptake 31% (normal 25-55%) T3 uptake 94% (normal 92-125%). Total serum protein 6.8 g/100 ml, albumin 4.4 g/100 ml, strip normal. ECG: ST interval 0.08 sec. Hydrocortisone, 40 mg 8-hourly, failed to suppress serum calcium level below 15.4 mg/100 ml (SG 1027). X-ray changes typical of hyperparathyroidism were seen in the hands, skull and teeth, and there were bilateral renal calculi. The chest X-ray and barium meal were normal.

Operation. On surgical exploration of the neck (Mr J. M. Davis, Whittington Hospital) under 240 mg hydrocortisone cover because of the recent suppression test, a tumour mass was found situated behind and adherent to the left upper pole of the

thyroid gland, and closely adherent to the oesophagus. No regional lymph nodes were palpably involved. Two normal parathyroid glands were identified on the right, the lower parathyroid on the left was not identified. A left hemithyroidectomy was performed, including sharp dissection down to the oesophageal mucosa. Macroscopically the tumour was a hard, well circumscribed pale grey mass $4 \times 2 \times 2$ cm, weight 10 g. Microscopic examination showed a well differentiated adenocarcinoma of the parathyroid gland with local invasion into the thyroid gland, and also into the oesophageal muscle. Malignant cells were seen in neighbouring lymphatic vessels.

Postoperative management. The plasma calcium fell steadily to 8.6 mg/100 ml by the fourth postoperative day when the patient experienced tingling with weakness in the arms and legs and mental confusion. Carpo-pedal spasm was marked but Chvostek's sign was negative. Initially this was relieved with 20–40 ml 10% calcium gluconate by slow intravenous injection on several occasions, but by the eighth day the weakness was severe, laryngeal stridor was present and spasm of the back, arm and leg muscles was marked. In contrast to her initial postoperative lethargy the patient was extremely agitated and restless. 60 ml of 10% calcium gluconate i.v. only partially relieved the tingling and stridor, but there was no other improvement. However, 15 min after 4 ml 50% magnesium sulphate i.m. (serum magnesium 1.6 mg/100 ml at this time, but level not available during the attack) there was clear improvement, with abolition of the tingling, relaxation of muscle spasm and distinct calming and re-orientation. Chvostek's sign remained negative until the eleventh postoperative day (calcium 8.0 mg/100 ml, phosphate 3.5 mg/100 ml, phosphatase 72 KAU) and then remained positive until the thirty-second day when increased oral calcium and Maalox (magnesium aluminium hydroxide) had elevated the serum calcium to 8.5 mg/100 ml and phosphate to 3.1 mg/100 ml (Fig. 1). The patient was discharged home after 42 days, and subsequently received a course of super-voltage radiotherapy (Dr J. N. Godlee, University College Hospital, London) to her neck and mediastinum, with a total dose of 5400 rad over 5 weeks. She continued to take a low phosphate diet, effervescent calcium 6 g four times a day, Maalox 15 ml 6-hourly, and AT 10 (0.25 mg/ml) 5 ml 8-hourly for 6 weeks, but then she chose to cease medication. Six weeks later she again developed tetany, which responded to DHT 1 mg/day. Investigations at that time were as follows: Hb 10.5 g/100 ml; ESR 25 mm/hr; plasma calcium 6.4 mg/100 ml (SG 1025–6); phosphate 4.8 mg/100 ml; alkaline phosphatase 14 KAU; magnesium 1.63 mg/100 ml; urea 67 mg/100 ml; sodium 140 mEq/l; potassium

FIG. 1. The course and management of a case of parathyroid carcinoma (Mrs. P. V., aet 43).

4.4 mEq/l; chloride 103 mEq/l; bicarbonate 22 mEq/l. 24-hr urinary calcium 33 mg; phosphate 1034 mg; magnesium 82 mg.

Discussion

Because definitely invasive tumours of the parathyroid gland are rare, stringent criteria have been established to make the diagnosis of carcinoma, in order to differentiate from adenoma and hyperplasia (Holmes *et al.*, 1969; Black, 1954; Cope *et al.*, 1953; Kelly, 1969). The electron microscope has demonstrated ultra-structural differences (Faccini, 1970). These criteria vary with different authors but in general the following are accepted:

- (1) The tumour must be biochemically hyperfunctioning. This is a requirement because of the similar histological appearance of various thyroid and thymic tumours, and pathological lymph nodes, to that of carcinoma of the parathyroid.
- (2) The tumour must be locally invasive, or have local or distant metastases at the time of the original

surgery, or develop them later. This is required because the usual microscopic findings suggestive of malignancy (e.g. mitoses) are not valid when applied to tumours of the parathyroid gland, and frozen section is notoriously unreliable. A most reliable clue to the presence of malignancy at operation is a fibrous inflammatory-like reaction which surrounds the tumour and binds it firmly to the adjacent structures. Parathyroid carcinoma, in contrast to the smooth, soft, reddish-brown adenoma, has a hard consistency and is pale whitish-yellow. In the present case, as described above, there was local invasion into the thyroid gland, and into the oesophagus.

The incidence of parathyroid carcinoma varies in different series from 3/400 (Beahrs *et al.*, 1963), 4/148 (Cope *et al.*, 1953), 15/343 cases (Cope, 1966) to 9/284 (Faccini, 1970) of hyperparathyroid states, and cases reported in the literature rose only from twenty to forty-six between 1954 and 1969 (Black, 1954, Holes *et al.* 1969). Early diagnosis is vital and rewarding, because the tumour is slow-growing and metastases by lymphatic and venous paths occur late. Generally symptoms are more marked and of shorter duration in carcinoma compared with adenoma, and the tumour is larger and more likely to be palpable (Table 1). Features of presentation are summarized in Table 1, comparing carcinomas with adenomas

TABLE 1. Clinical manifestations of carcinomas and adenomas

	Carcinoma* (%)	Adenoma and hyperplasia†‡§ (%)
Calcium:		
More than 13 mg/100 ml	82	50
Less than 12 mg/100 ml	6	50
Bone disease	73	30-54
Palpable neck mass	52	14
Pancreatitis	15	2
Metastases:		
Local (neck)	32	-
Distant (e.g. lung)	16	-
Cervical recurrence	52	-
Sex preponderance	1 : 1	F 3-6 : 1

* From Table 2, and Holmes *et al.* (1969).

† Pyrah *et al.* (1966).

‡ Black, B.M. (1958).

§ Reinhoff *et al.* (1968).

and hyperplasia, showing the higher calcium levels, increased incidence of bone disease, pancreatitis, and of the presence of a palpable neck-mass in carcinomas, and the lack of a female sex preponderance. The age of incidence is between 12 and 72 years, with 60% of carcinomas between 40 and 50 years compared with only 21% of the adenomas. An associated laryngeal nerve palsy is strongly suggestive of malignancy.

In the eight cases (including the present case) reported in the literature since the last collective review, six were female, five had radiological changes, six had evidence of local invasion and five renal tract involvement. (Table 2). Cases may present, as here, with manifestations of neoplasia, i.e. tumour and dysphagia caused by direct oesophageal infiltration, or with clinical features of hypercalcaemia, e.g. psychiatric features of 'neurosis'. This in a patient unable to speak English, provided yet another example of 'metabolic madness' (Watson, 1968; Anderson, 1968; Peterson, 1968). Another feature was thirst, only partially relieved by repeated small drinks and yet sufficient to prevent sleep. It was not accompanied by polyuria (urine volume 1-1½ l/24 hr), thus suggesting that hypercalcaemia may stimulate thirst directly rather than cause a diuresis with secondary polydipsia.

The frequently stormy postoperative course of these patients follows the sudden withdrawal of hormone excess causing decreased calcium absorption and phosphate loss with resulting depression of calcium. The situation will be further aggravated with any pre-existing negative calcium and magnesium balance which is associated with the bone disease of primary hyperparathyroidism (Bulgar & Gusmann, 1933; Tibbets & Aub, 1937; Barnes *et al.*, 1957) and by phosphate retention related to the frequently associated renal failure. Normal parathyroid function may remain repressed from the effects of surgical trauma and the hyperfunctioning tumour (Ellis & Barr, 1951) and accelerated uptake of calcium and magnesium into the bones may finally precipitate tetany, convulsions occasionally with fractures of weakened bones (Davies & Friedman, 1966), or even death (Nicholson, 1969). The maximum danger is between the fourth and tenth day, and the patient and nursing staff should be warned of the significance of tingling or muscle twitching.

The patient's condition is best monitored with daily estimation of fasting levels of calcium (corrected for serum SG) and magnesium, if possible. Chvostek's sign, although a clinical guide is not an adequate indicator of the patient's well-being. It can be positive with normal serum levels of calcium and magnesium (Dent, 1962), may be positive following parathyroidectomy irrespective of calcium values (Hanna *et al.*, 1960) and occasionally intravenous calcium gluconate will correct a hypocalcaemia without reversing an associated positive sign (Newton & Sumich, 1968b). Both the latter authors suggest hypomagnesaemia is an important consideration.

Hypocalcaemia and hypomagnesaemia should be promptly corrected, as above, with appropriate parenteral supplements, but with marked renal failure urinary magnesium clearance is reduced and

TABLE 2.

Author	Sex	Age	Palpable neck mass	Calcium (mg/100 ml)	Skeletal changes	Local invasion	Local recurrence	Renal disease	Comments
Mansour & Letton (1967) Kelly (1967)	F	58	Yes	12.0	Yes	Thyroid	—	Yes	No recurrence at 1 year
	F	33	Yes	15.2	Yes	Muscles	Yes	Yes	Local recurrence at 42 months. Excision gave symptomatic relief
Newton & Sumich (1968a)	F	53	Yes	13.0	No	Muscles	—	Yes	Incomplete surgery plus radiotherapy. No recurrence at 1 year
Saunders (1970)	F	48	?	18.0	?	Capsule invasion	Yes	?	At 18 months (Ca 17.5) cervical metastases excised.
									At 42 months (Ca 16) pulmonary metastases excised after no response to calcitonin.
Sherif <i>et al.</i> (1970)	F	40	Yes	14.6	Yes	Thyroid	Yes	Yes	At 48 months (Ca 14) no evidence of recurrence
Singer <i>et al.</i> (1970)	M	53	?	?	Yes	?	Yes	Yes	4½ years pathological fracture of tibia, local recurrence, died
									Early local recurrence, ten surgical excisions over next 9 years. Then temporary response to calcitonin. Mithramycin for increased bone pain gave relief and fall in calcium. Died 2 months later with renal failure
Rossi <i>et al.</i> (1971)	M	51	? Yes	13.5	Yes	Muscles	—	?	18 months previously pathological fracture and mild hypercalcaemia. Recent rapid rise of Ca to 20, angiography showed large malignant parathyroid tumour. Died immediately post-operatively
The present case	F	43	Yes	15.2	Yes	Thyroid Oesophagus	No	Yes	Hemithyroidectomy and radiotherapy. No recurrence 18 months
Holmes <i>et al.</i> (1969) (forty-six cases)	F 20	—	24	> 14 in 34	34	29	24	?	
	M 26			< 13 in 5					
Total (fifty-four cases)	F 26	—	29	> 14 in 38	40	36	28	—	
	M 28			< 13 in 6					

repeated i.m. magnesium should be given with care. Signs of intoxication include cerebral and neuromuscular depression with feelings of thirst and heat, the appropriate antidote being intravenous calcium gluconate. Biochemical estimation provides the only definitive assessment but deficiency may be suspected on physiological grounds. Low calcium and magnesium states increase muscular and neural irritability, but whereas hypomagnesaemia increases acetylcholine release, hypocalcaemia decreases it and slows neuromuscular transmission. This may explain why there is no tetany *per se* in hypomagnesaemia (Hanna, 1960; McIntyre, 1963) and Trousseau's sign is negative but Chvostek's sign is positive (Newton & Sumich, 1968b). Convulsions and psychiatric features, e.g. agitation and aggression (Davies & Friedman, 1966; Nicholson, 1969) occur in calcium and magnesium deficiency but tremor is less common in hypocalcaemia.

Postoperative vitamin D (preferably as pure DHT) should be given routinely as 8 mg, 8 mg, 4 mg, 4 mg, 2 mg, 2 mg, on successive days with intravenous calcium as necessary. Excess vitamin D was used in this case to overcome the more resistant postoperative tetany found when mild renal failure antagonises the action of vitamin D (Rasmussen, 1968). Up to 10 mg daily vitamin D can be used before operation if resistant hypocalcaemia is anticipated. Milk though convenient is an inefficient calcium supplement because of the high phosphate content, but absorption can be increased by giving up to 40 ml daily Aludrox (aluminium hydroxide) in divided doses to chelate the phosphate. In this present case Maalox (containing magnesium and aluminium hydroxide) was used. Low phosphate diets may also increase the serum calcium by less well understood mechanisms.

Close follow-up must continue until bone healing is complete and ideally until the serum calcium is stable. If rarefaction is demonstrated radiologically then at least half of the mineral is lost (Lachman, 1955) and needs replacement. Alkaline phosphatase activity is a good index of bone activity during the healing or 'bone-sucking' phase (Potts & Roberts, 1958).

In the treatment of this malignant tumour, most authors advise radical excision, including hemithyroidectomy and neck dissection to include especially the nodes in the tracheo-oesophageal groove (Hoehn, Beahrs & Woolner, 1969; Castleman, 1952) because of the great tendency towards local invasion. Radiotherapy used as an adjunct to operative measures is largely unsatisfactory, although there are a "few" reports of reduction in tumour size or serum calcium levels.

The optimal treatment of recurrence is not clear. Multiple excisions of cervical recurrences, charac-

teristic of this disease, generally result in reduction of the serum calcium level and hence facilitate the management of metabolic disturbances. Similarly resection of functioning pulmonary metastases should be considered as a palliative procedure. (Saunders, 1970; Holmes *et al.*, 1969). Oestrogens have also provided some temporary palliative benefit (Goepfert *et al.*, 1966; Ellis & Barr, 1951). Porcine calcitonin has been used with variable success (Saunders, 1970; Pak *et al.*, 1968), in one case serum calcium was reduced temporarily from 16 to 15 mg/100 ml but in another case there was marked reduction of serum calcium for several months. Complete restoration to normal would be unexpected since calcitonin possibly only antagonises the action of parathormone on bone, and not that on the gut and kidneys which probably also contributes to sustained hypercalcaemia (MacIntyre, 1970; Foster, 1968). Mithramycin, a cytotoxic antibiotic, has successfully lowered serum calcium levels in similar clinical situations (Singer *et al.*, 1970). It is important to re-emphasize that the present treatment of choice is surgical removal of the neoplastic tissue wherever possible.

Prognosis should be guarded, though initially optimistic, because times of recurrence vary from 3 months to 9 years (Holmes *et al.*, 1969; Hoehn *et al.*, 1969). Holmes had forty-three patients followed up for up to 12 years when 65% had died, 11% had recurrence, giving an overall cumulative survival rate of 50% at 5 years and 13% at 10 years, a mean survival of 4 years. Our patient has been followed for 18 months without evidence of recurrence (although the serum calcium is slowly rising). Three of the most recently published cases have been followed for less than 18 months, all are without signs of recurrence. Another case, alive after 6 years developed a cervical lymph gland metastasis after 18 months (excised) and 2 years later pulmonary metastases which, after porcine calcitonin treatment had failed, were excised with further metabolic remission.

Acknowledgments

We wish to thank Mr J. M. Davis for permission to publish details of this patient, Dr J. N. Godlee who arranged radiotherapy, and Dr L. C. A. Watson for providing biochemical follow-up data, together with encouragement and advice in the preparation of this paper.

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