Parathyroid carcinoma: a review

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Keywords: parathyroid carcinoma, hyperparathyroidism

The first successful removal of a parathyroid adenoma was reported to the Viennese Medical Society by Mandl in 1925. During the next 50 years primary hyperparathyroidism was considered to be a very uncommon condition. In 1959, McGeown and Morrison[1] reported 53 cases from Northern Ireland who had been operated on successfully for primary hyperparathyroidism, and had the foresight to note that 'it is not a rare disease'. More recent studies have confirmed that primary hyperparathyroidism due to a benign adenoma is a relatively common entity, particularly when actively sought[2]. In the past 10 years, its incidence and clinical presentation have changed dramatically[2,3].

In contrast, parathyroid carcinoma remains an infrequent cause of primary hyperparathyroidism: since 1948 about 120 cases have been reported in the literature[4,5]. Opinions as to its exact incidence have differed from 0.5%[6-8] to around 5%[9,10] of cases of primary hyperparathyroidism. The morphological criteria for diagnosis, the prognosis and the optimal management of the disease remain controversial, and individual experience is limited. The histological characteristics that are useful in determining malignancy in other organs seem less applicable to endocrine tumours – especially tumours of the parathyroid glands – and differing diagnostic criteria, coupled with limited experience, have almost certainly contributed to the differing incidence cited by various authors. Despite the considerable Northern Ireland experience in parathyroid disease[1,11], a biopsy review of parathyroid histology in cases of primary hyperparathyroidism in Northern Ireland from 1930 to 1985 revealed 195 cases of parathyroid adenoma, 94 of hyperplasia and only one (see below) parathyroid carcinoma – an incidence of carcinoma of around one in 300 cases of hyperparathyroidism (0.3%). Since the increased diagnosis of primary hyperparathyroidism during the last two decades has not resulted in any increase in reports of parathyroid carcinoma, it seems probable that the true incidence of carcinoma is less than one in 100 cases of hyperparathyroidism[6,7,12].

Aetiology

There are a few reports of carcinoma in association with familial hyperparathyroidism[13]. There have also been reports, despite earlier views to the contrary[9], of carcinoma occurring within an adenoma or in a hyperplastic gland[14-16]. Parathyroid carcinoma has been described in several patients receiving dialysis, and attention has recently been drawn to the possibility of radiation-induced malignant change in hyperplastic tissue[17]. Several cases have been reported of apparently benign 'parathyroid adenomas' associated with distant metastases[18,19], but the original diagnosis of the benign adenoma must be in doubt.

Symptoms and diagnosis

The diagnostic differences between benign and malignant functioning parathyroid tumours have been clarified by the modern clinical profile of benign hyperparathyroidism[3,9,12,19-22]. Symptoms of hyperfunctioning parathyroid carcinoma are mainly those of hypercalcaemia, as the serum calcium levels are usually much higher than those seen in patients with benign parathyroid disease, and the symptoms are more severe[3,12]. Schantz and Castleman[9], in a review of 70 patients with parathyroid carcinoma, found an average initial serum calcium of 3.8 mmol/l, 62% of the patients showing levels above 3.5 mmol/l. Corresponding figures reported by Holmes *et al.*[20] were 3.98 mmol/l and 75%, and those of Shane and Bilezikian[12] were 3.88 and 70% respectively. These figures should be compared with the milder elevations of serum calcium usually seen in benign disease. There are much higher levels of circulating immunoreactive parathyroid hormone (two to five-fold increases) in carcinoma[12,22].

In contrast to the benign parathyroid adenoma, which has a 3:1 preponderance in women, parathyroid carcinoma affects men and women with equal frequency[12,20]. Patients with carcinoma are often younger than those with benign parathyroid disease – the mean age in two independent reviews was 44–48 years[12,19,20]. Of 41 patients reviewed by Shane and Bilezikian[12], all but one were clearly symptomatic. The most common symptoms were polyuria and polydipsia occurring in 35% of patients, followed by general weakness, fatigue, anorexia, nausea, vomiting and weight loss. The kidneys and the bones, classical targets for parathyroid hormone, were affected more frequently and more severely than in benign primary hyperparathyroidism. Renal disease was present in 37 of 47 patients; 72% of these had nephrolithiasis, 21% nephrocalcinosis and 55% impairment of renal function. Holmes *et al.*[20], in an earlier review of 46 patients, found renal disease in 15, many with symptoms of renal colic. Skeletal disease is found in between 55% and 73% of cases, including osteoporosis, subperiosteal bone resorption and osteitis fibrosa cystica, with symptoms of bone pain and pathological fracture. Concomitant renal and skeletal disease occurred frequently, which is a rarity in benign hyperparathyroidism. Acute, often recurrent, pancreatitis has been reported in several patients, and anaemia is more common than in patients with benign parathyroid disease[12,15,19,20].

Arising from case presentation to Section of Endocrinology, 23 April 1986

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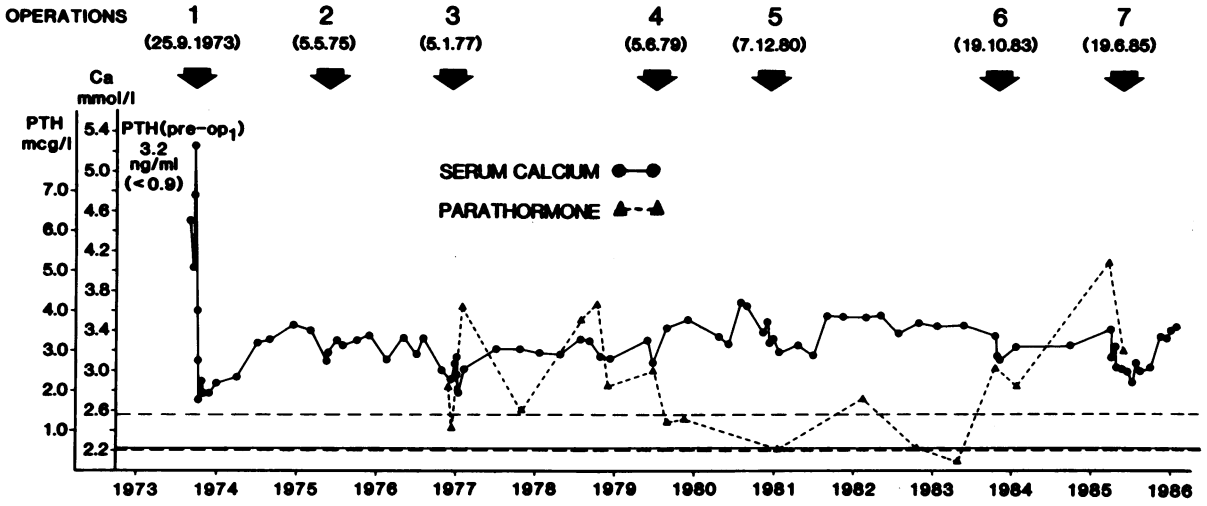

Figure 1. Serum calcium (normal range 2.2–2.55 mmol/l) and parathormone (normal range < 0.53 μg/l) profile from the original presentation in 1973 to death in 1986. Exploratory operations are represented by arrows.

Another striking difference from benign parathyroid disease is the presence of a palpable neck mass. In benign parathyroid disease, a neck mass can be felt in less than 10% of patients[8]. According to reviews by Schantz, Shane and Holmes, a neck tumour can be felt in 30–50% of patients with parathyroid carcinoma[9,12,20]. Unilateral paralysis of the recurrent laryngeal nerve in connection with hyperparathyroidism is another sign suggestive of cancer – as is late recurrence after surgery[20], particularly if a single large gland was removed, and the operation resulted in interim relief for a significant period of time. A propensity for inferior gland involvement has been described[8].

Unfortunately, despite an appropriate index of suspicion, some tumours will continue to present diagnostic difficulties. We recently encountered such difficulty in a patient with a 13-year history of persistent hyperparathyroidism, in whom the diagnosis of parathyroid carcinoma ultimately was confirmed at necropsy (Figure 1).

Case report

TS first presented to the ENT department at the Royal Victoria Hospital in 1953 aged 53, with a six-week history of vertigo. She was otherwise asymptomatic, with no palpable neck masses. Hypercalcaemia was diagnosed incidentally on biochemical screening, the serum calcium being as high as 5.2 mmol/l (normal range 2.2–2.5), serum phosphate 2.0 mmol/l and serum parathyroid hormone (PTH) 3.2 μg/l (normal <0.53). Intravenous calcitonin therapy reduced the serum calcium to 3.3 mmol/l, and at surgery three days later a 3 × 2 × 1 cm parathyroid adenoma was removed from the left superior region of the neck. This was initially reported as a chief cell parathyroid adenoma. All other usual sites in the neck were explored, and no other parathyroid tissue was identified. Postoperatively the calcium fell to a minimum of 2.65 mmol/l by discharge, but had risen again to 2.75 at one month, and was 3.2 mmol/l three months postoperatively. Hypercalcaemia persisted for the next 12 years.

Six further exploratory operations (5 cervical and one mediastinal) were performed between 1973 and 1985 after various attempts to localize abnormal parathyroid tissue including thallium scintigraphy, CT scanning, neck and internal mammary venous sampling and angiography. Surgery included exploration of the usual ectopic sites, a left total thyroid lobectomy and removal of a normal thymus gland. Two further parathyroid glands were identified, the first at the fifth operation in 1980, consistent with the right inferior gland (small chief cell adenoma), and a small hyperplastic fragment of parathyroid tissue at the left inferior site at the sixth operation in 1983. No changes in serum calcium followed any of these procedures, and serum parathormone remained measureable throughout. Chest radiology was normal. A variety of pharmacological measures failed to reduce calcium levels below 3.0 mmol/l. She finally died of advanced Von Recklinghausen's disease, following fracture of both femoral necks and collapse of the vertebral column with a complicating deep venous thrombosis and pulmonary embolus.

Histopathology

Opinions differ about the diagnosis of parathyroid carcinoma by histological examination in the absence of infiltration or metastasis. Some consider this is not possible[6,20], but Castleman and associates have always maintained that with attention to detail the correct interpretation may be made. The importance of mitoses, a trabecular architecture, adherence to surrounding tissues and to some extent capsular invasion and the extension of fibrous trabeculae from the capsule into the tumour was emphasized in the diagnosis of carcinoma[23]. In the revised AFIP Fascicle in 1978[24], in addition to these features, the grey/tan colour, the hard consistency and the lobulated cut surface of many carcinomas were stressed. The presence of mitoses within parenchymal cells was considered to be the single most valuable criterion[18,24], while cellular atypia and variation were not helpful.

Subsequent authors have largely adopted these criteria, although reservation has been expressed regarding the significance of vascular and capsular invasion[18,25,26], and some feel that mitotic activity alone is an unreliable indicator of aggressive potential in parathyroid tissue. Snover and Foucar[27] found increased mitotic figures in the parenchymal cells of 12 of 17 adenomas, and 8 of 10 hyperplasias. Even when mitotic figures are absent, 'benign adenomas' may metastasize[18,27], and Schantz and Castleman[9] described 10% of cases of parathyroid carcinoma with metastases which lacked mitoses. It is important to consider the overall picture, rather than a single criterion[26].

In the case reported here, prompted by the autopsy findings, a reappraisal of the original 1973 tissue blocks was made which indicated that the lesion was parathyroid carcinoma from the onset. Histology revealed a cellular tumour with a thick fibrous capsule and prominent fibrous septae (Figure 2). Mitotic figures were absent, but the tissue was very vascular, and there were some areas showing capsular

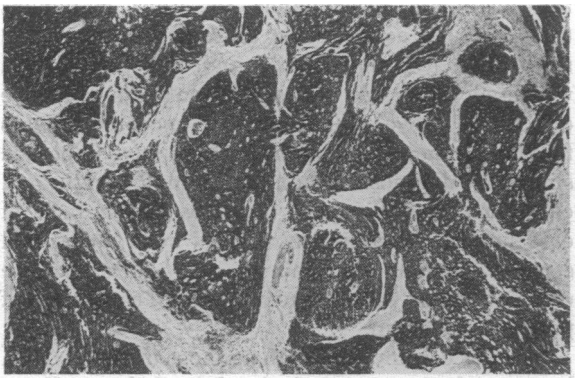

Figure 2. Section of the original parathyroid tumour removed in 1973. Low-power view showing prominent septation of the tumour by thick fibrous bands. (H&E × 15.)

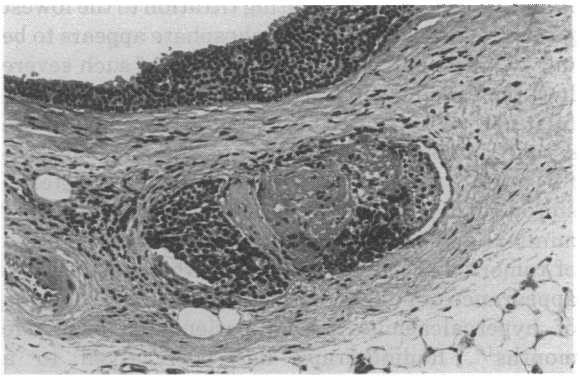

Figure 3. Capsular section of the original parathyroid tumour removed in 1973, showing small endothelial-lined vessel occluded by clumps of tumour cells with overlying fibrin thrombus. (H&E × 150.)

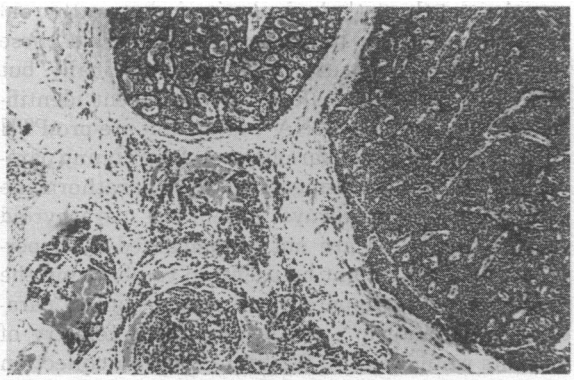

Figure 4. Section of nodule recovered from scar tissue in neck at autopsy. Tumour composed of nodules of parathyroid chief cells separated by broad fibrous septae. (H&E × 60.)

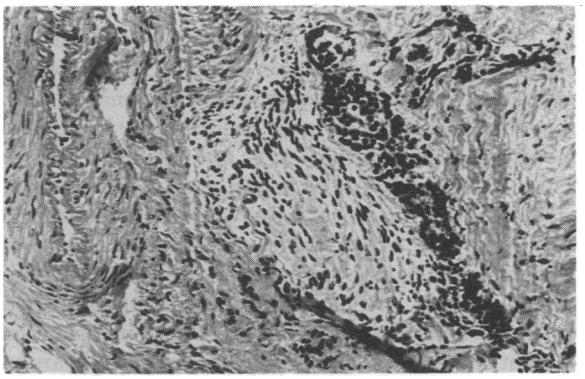

Figure 5. Fibrous tissue adjacent to nodule of tumour recovered from the neck at autopsy, showing neoplastic infiltration along the perineurium of a small nerve. (H&E × 150.)

invasion and infiltration of adjacent thyroid tissue with perineural and lymphatic infiltration. Tumour infiltration of a small vessel, with associated thrombosis, was seen (Figure 3).

At autopsy careful examination of the neck and mediastinum had revealed no recognizable parathyroid glands in usual or ectopic sites. Dissection of scar tissue revealed a firm, greyish-yellow nodule, 1.5 cm in maximum dimension, adherent to the right posterolateral aspect of the trachea, and multiple smaller nodules embedded in scar tissue on both sides of the upper trachea. Histology of all these nodules showed dense scar tissue containing irregular masses of cells, separated by thick hyalinized fibrous septae (Figure 4). In several of the nodules, there was evidence of perineural and lymphatic infiltration (Figure 5). Vascular invasion was not seen. No organized lymphoid tissue was seen in relation to any of the tumour nodules to suggest that these were lymph node metastases. The subpleural parenchyma of the posterior aspect of the lower lobe of the left lung contained multiple discrete greyish/brown nodules, ranging in diameter from 0.3 to 1.0 cm. Histologically, these nodules consisted of tumour similar in pattern and cellular morphology to that in the neck. Immunoperoxidase studies showed positive staining of both neck and lung tumour for neurone-specific enolase (a histological marker of neuroendocrine differentiation). Staining for the presence of parathormone using an indirect immunofluorescent technique was positive. The kidneys showed nephrocalcinosis with, in addition, the incidental diagnosis of a renal tubular adenoma showing oncocytic differentiation. Osteitis fibrosa cystica was present in several bones including the ribs, vertebrae and clavicle.

Treatment

Even if the primary operation is considered successful, 30–65% of the patients will eventually develop recurrent disease[9,20]. Local tumour recurrence is most common, but metastases also appear especially in cervical nodes (30–32%), lung (10–40%), liver (10%) and bone (7%)[7,9,12,20]. Recurrence manifests itself by a rising serum calcium. Since patients dying from parathyroid carcinoma usually succumb from the effects of hypercalcaemia, several authors have emphasized that resection of recurrent tumour or functioning metastases should be considered both in terms of palliation and in facilitating adjunctive medical therapy[8,20]. As parathyroid carcinoma is an indolent malignancy with marked tenacity[22], a significant palliation may be achieved for a considerable period of time by this approach, but only very rarely is a patient with recurrent disease cured. When surgical efforts at curative or palliative resection are unsuccessful or no longer possible, other methods of treatment should be tried, but in general these have met with little or only transient success.

Theoretically, calcitonin should be the drug of choice because of its ability to inhibit parathormone-stimulated bone resorption and its lack of toxic effects. However, an encouraging initial effect of calcitonin is often difficult to sustain for more extended periods of time[12]. The administration of calcitonin in combination with prednisone may be more promising[28], and a combination with diphosphonate has been recommended for severe cancer-associated hypercalcaemia[29]. Mithramycin, a cytotoxic antibiotic, has been successful in a few patients with parathyroid carcinoma[15], but the drug has to be administered intravenously and toxicity (liver, kidney and bone marrow) which is dose-related

is quite common, necessitating titration to the lowest possible effective dose. Oral phosphate appears to be universally ineffective in the setting of such severe hypercalcaemia. Diphosphonates have been successful when administered intravenously, reducing the serum calcium in several patients, but are unsuccessful orally. Treatment with oestrogen and testosterone, tried in a few patients, resulted in only minimal and transient success[19,30]. A combination of tumoricidal agents resulted in the complete disappearance of pulmonary metastases and regression of hypercalcaemia in one patient for over five months[16]. Radiotherapy has been given to a limited number of patients, but without significant effect[12,14,20]. Perhaps the answer will lie with the parathyroid hormone antagonist[31] – a concept which is no longer hypothetical.

Survival and prognosis

As can be seen from our own case, the disease is compatible with prolonged survival, even when metastatic disease is present, making it amenable to repeated resection of local recurrences or distant metastases for palliation[8], but seldom cure[12]. Three patients have been reported alive with known metastases 15 or more years after initial surgery, including one of 33 years' duration[12]. Death in patients with parathyroid carcinoma is usually due to the cardiac and renal sequelae of uncontrolled hypercalcaemia rather than to local invasion or distant metastases. The five-year survival appears to be less than 50% and the 10-year survival less than 35% although figures vary, and recently a review of 8 cases noted only one patient who suffered a local recurrence, the only death being due to primary lung cancer[32]. Given the indistinct morphological and histological features of parathyroid carcinoma, it would seem likely that cases will continue to be suggested postoperatively by the pathologist and ultimately confirmed by recurrence of the disease[33].

Some have remarked pessimistically on how little progress has been made in diagnosis or therapy since the first series of parathyroid carcinoma was published in 1948[32]. Clarification of the problem will only be achieved by further standardization of the diagnostic criteria, continual review of all available histology and appropriation of the guidelines for optimal treatment which are now beginning to emerge. Firstly, the treatment of parathyroid carcinoma remains surgical[8]. Extensive yet meticulous *en bloc* resection at initial surgery offers the best chance for cure for patients with parathyroid carcinoma[22,32]. Most investigators now advocate excision of the lesion with ipsilateral thyroidectomy including the isthmus, if the tumour is confined within the capsule and there is no apparent lymph node involvement[7,10], in contrast to the original suggestion of more radical neck surgery involving ipsilateral lymph node dissection[20]. Secondly, the surgeon must be constantly aware of the possibility of parathyroid malignancy[8] and extreme care must also be taken to avoid capsular violation or tumour spillage[22]. Carcinoma of the parathyroid, if diagnosed early and treated adequately, might be expected to lead to more gratifying long-term results[7,8,10,25].

Non-functioning parathyroid carcinoma

The existence of this entity is controversial. The lack of clear-cut diagnostic histologic criteria and the histologic resemblance to other malignant tumours such as follicular thyroid carcinoma and metastatic hypernephroma, and the rarity with which such tumours will occur, make its existence difficult to prove. Holmes *et al.*[20] accepted 4 cases for the diagnosis and several others have appeared since. The diagnosis of non-functioning parathyroid carcinoma has generally been based on lack of evidence of hyperparathyroidism, such as normal serum calcium, phosphorus and parathormone concentrations, despite the presence of carcinoma of parathyroid origin.

In other carcinomas, such as those of the thyroid, breast and prostate, analysis of the DNA profile of tumour cells by the stage cell technique has successfully differentiated rapidly growing life-threatening malignancies from less aggressive lesions with similar morphology. Perhaps such an analysis would complement the pathological criteria in parathyroid carcinoma and help to clarify the prognosis of these tumours, which appear similar histologically but differ markedly in virulence[32]. The recent identification of messenger RNA coding for pre-pro-PTH (PTH mRNA) in an apparently non-functioning parathyroid carcinoma, suggesting that parathormone synthesis is not always absent in parathyroid carcinomas which are not accompanied by hyperparathyroidism, might be useful in establishing the diagnosis of an apparently non-functioning parathyroid carcinoma[34]. An international registry of patients would help to facilitate uniform collection and accurate interpretation of data on these rare tumours[32].

Acknowledgments: We are grateful to our many colleagues for their interest and cooperation in the protracted management of the case reported, in particular, Mr E Morrison FRCS who carried out the initial operations, Dr Mary G McGeown for consultative advice on many occasions, and Dr E M McIlrath for his repeated efforts at radiological localization.

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(Accepted 1 December 1986)

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