

Parathyroid Carcinoma: A Case Series

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Abstract

Introduction: We present 3 patients with parathyroid carcinoma and describe their presentations, clinical profiles, and management. **Materials and Methods:** A case series review of medical records. **Results:** Two women and 1 man (age range, 32 to 57 years) had parathyroid cancer and primary hyperparathyroidism (PHPT). One patient presented with osteitis fibrosa, 1 with renal stone and a neck mass, and 1 with recurrence of PHPT after excision of supposedly benign parathyroid adenoma 4 years ago. All had severe hypercalcaemia and elevated parathyroid hormone levels that ranged from 4 to 43 times above the normal range. Exploration of the neck clearly identified 1 parathyroid tumour with local invasion; 2 other specimens showed capsular and vascular invasion on frozen section and final histology. All 3 patients underwent parathyroidectomy and ipsilateral hemithyroidectomy. Parathyroid size ranged from 1.3 to 4 cm and no lymph node metastasis was identified. No patient had tumour recurrence after a follow-up period of 1 year. **Conclusion:** Parathyroid carcinoma is a rare endocrine malignancy. Suspicious features include marked hypercalcaemia, neck mass, and local recurrence. Parathyroidectomy with ipsilateral hemithyroidectomy and nodal clearance gives the best chance of reducing local tumour recurrence.

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Introduction

Parathyroid carcinomas account for 1% to 3% of patients with primary hyperparathyroidism (PHPT).¹ Patients usually present with a severe form of hyperparathyroidism at diagnosis, such as bone disease, renal disease, or hypercalcaemic crisis, in contrast to the relatively asymptomatic presentation of benign parathyroid disease.² Problems encountered include difficulty in establishing accurate preoperative diagnosis and intraoperative recognition, local invasion of adjacent structures in the neck, local recurrence that require re-operation, metastatic disease commonly to the lung and liver, and death from uncontrollable hypercalcaemia.^{2,3} The aetiology of parathyroid carcinoma is unclear, although it has been associated with neck irradiation in sporadic tumours.¹ Carcinomas have also been reported in familial

hyperparathyroidism such as hereditary hyperparathyroidism jaw tumour (HPT-JT) syndrome,⁴ which carries an increased risk of parathyroid cancer.

This case series describes the presentation modes of 3 patients with sporadic parathyroid cancer and their surgical management.

Materials and Methods

Three patients with a diagnosis of parathyroid carcinoma were included for review. They had 1 or more absolute criterion of malignancy – pathological lymphatic or vascular invasion, capsular breach to invade adjacent neck structures, local recurrence, or regional/distant metastasis. None had any family history of hyperparathyroidism.

PHPT was confirmed biochemically by elevated serum calcium and parathyroid hormone (PTH). Neck imaging

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was performed by computed tomography (CT) scan, ultrasound, and sestamibi scintigraphy. Immediate medical management consisted of intravenous saline infusion and diuretic therapy to restore fluid volume and to enhance urinary calcium excretion. Surgery consisted of parathyroidectomy and ipsilateral hemithyroidectomy and clearance of central neck nodes.

Results

All 3 patients had PHPT. Their clinical features, including serum calcium, PTH levels, and surgical management are listed in Table 1.

Patient 1

A 32-year-old Chinese man presented with bone pain, constipation and severe hypercalcaemia. Bone marrow examination detected osteitis fibrosa and bone cysts, consistent with the classical bone disease of hyperparathyroidism. The serum alkaline phosphatase was elevated at 375 U/L, indicating a high rate of bone turnover. Serum total calcium was markedly elevated at 4.24 mmol/L and intact PTH was 43 times above the normal range. Examination of the neck was normal. Surgical exploration revealed an enlarged left inferior parathyroid mass; the remaining 3 glands were normal in size and shape. Parathyroidectomy of the tumour was performed; histology revealed a 3.4-cm tumour with foci of capsular and vascular invasion, and numerous mitoses. The patient underwent reoperation 2 weeks later for left hemithyroidectomy and central (paratracheal) compartment lymph node clearance. Histology revealed a residual 0.8-cm nodule of parathyroid cancer attached to the thyroid gland. No lymph node metastasis was detected. Postoperatively, the patient

developed hypocalcaemia that required treatment with intravenous (IV) calcium therapy. Follow-up at 6 months revealed normal serum calcium, intact PTH and normal neck CT imaging.

Patient 2

A 42-year-old Chinese woman presented with renal stones and pyonephrosis. PHPT was confirmed by elevated serum calcium and PTH levels. Preoperatively, a left superior neck mass was palpable, and CT scan suggested a parathyroid mass. At neck exploration, a 4-cm superior parathyroid mass was resected; frozen section showed capsular invasion, which led to ipsilateral hemithyroidectomy and central compartment nodal clearance. Pathology was consistent with parathyroid cancer. Postoperatively, the patient required IV calcium for hypocalcaemia and, at review at 6 months, she was free from tumour recurrence, with the calcium level returning to normal.

Patient 3

The third patient was a 52-year-old Chinese woman who presented with chronic abdominal pain and hypercalcaemia. Nine years ago, she had had acute pancreatitis and a common bile duct stricture that required a biliary bypass. She was diagnosed with PHPT and she underwent preoperative imaging that revealed a left inferior parathyroid tumour; at surgery, a well-defined parathyroid tumour was removed. The histology confirmed a benign parathyroid adenoma measuring 2.5 cm and weighing 4.2 g, without any features of malignancy reported. Follow-up serum calcium and PTH returned to the normal range but she developed a recurrence 4 years later. Ultrasound showed 3

Table 1. Clinical and Pathological Features of 3 Patients with Parathyroid Cancer

	Patient 1	Patient 2	Patient 3
Age (years)	32	42	57
Gender	Male	Female	Female
Presentation	Osteitis fibrosa	Renal stone, neck mass	Recurrence
Serum calcium	4.24 mmol/L	4.0 mmol/L	3.02 mmol/L
Intact PTH (iPTH)	330.1 pmol/L	142.3 pmol/L	30.6 pmol/L
iPTH above normal level	43 times	18 times	4 times
Size of parathyroid cancer (cm)	3.4	4.0	1.3
Invasion	Capsular and vascular	Capsular	Capsular and vascular
Fibrous bands	Yes	Nil	Yes
Lymph node metastasis	Nil	–	Nil
Thyroid gland	Normal	Normal	Normal
Operation	Parathyroidectomy Hemithyroidectomy	Parathyroidectomy Hemithyroidectomy	Parathyroidectomy Hemithyroidectomy
Postoperative result	Normocalcaemic	Normocalcaemic	Normocalcaemic

Normal range serum total calcium: 2.15 mmol/L to 2.55 mmol/L; normal range intact parathyroid hormone: 1.3 pmol/L to 7.6 pmol/L



Fig. 1. Parathyroid cancer (arrow) invading thyroid lobectomy specimen with central compartment lymph nodes (left of picture).

nodules measuring 0.4 to 1.3 cm in size on the left thyroid gland, parathyroid scan showed uptake in the left inferior aspect, and ultrasound-guided fine needle aspiration cytology (FNAC) of the largest nodule revealed parathyroid cells. At operation, a hard 1.3-cm nodule and 2 smaller nodules were adherent to the thyroid lobe surface. Parathyroidectomy and ipsilateral hemithyroidectomy with central nodal clearance was performed; intraoperative PTH test showed a decline of 94% from a pre-excision level of 56 pmol/L to a post-excision level of 3.6 pmol/L (normal range, 1.7 pM to 7.6 pM; Roche Elecsys 2010). The postoperative serum calcium level dropped significantly to 1.74 mmol/L. Final histology revealed a tumour with fibrous bands and nuclear pleomorphism, with capsular and vascular invasion, and invasion into adjacent skeletal tissue (Figs. 1 & 2). None of the 10 lymph nodes showed tumour involvement. (The initial pathology was reviewed and showed features consistent with a benign parathyroid adenoma). She had a normal follow-up at 1.5 years.

Discussion

The causes of PHPT include parathyroid adenoma (in more than 85% of cases), multigland hyperplasia (in 5% to 10%), and carcinoma (less than 3%). Carcinoma results in severe PHPT and complications from recurrence and metastatic spread. Hence, its detection is vital to the overall management of patients. However, differentiating carcinoma from benign parathyroid disease is difficult in the preoperative and intraoperative stages, and even after histopathologic evaluation. Often, the diagnosis is made in retrospect, as shown in Patients 1 and 3.

A review of the literature of over 400 cases of parathyroid cancers reported since 1920 suggests that the following pertinent clinical features should lead one to suspect

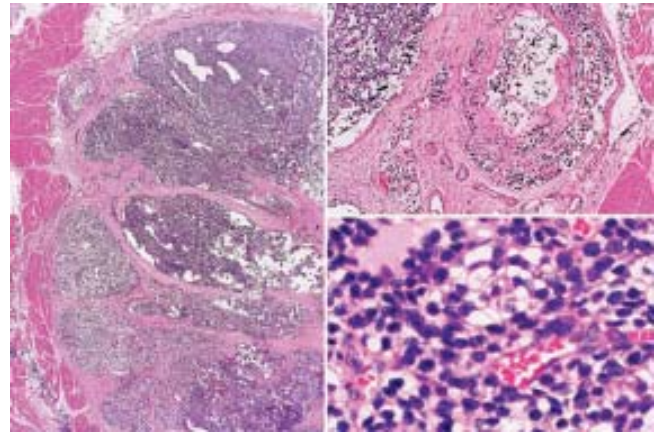


Fig. 2. (left) There are lobules of parathyroid carcinoma with intervening thick fibrous bands infiltrating into the skeletal muscle tissue. (H&E, x30) (top right) Medium power view of infiltrating parathyroid carcinoma with surrounding sclerosis and adjacent skeletal muscle. (H&E, x120) (bottom right) High power view of parathyroid carcinoma composed of closely packed cells with nuclear atypia and mild pleomorphism. (H&E, x400).

parathyroid cancer in a patient with PHPT;¹ (a) age of less than 50 years; (b) markedly elevated serum calcium and PTH levels (more than 10 times above the upper limit of normal), including parathyroid crisis in 12% of patients;² (c) severe symptoms of bone (osteitis fibrosa cystica) disease in 40% to 70% of cases, and renal disease (renal stones, nephrocalcinosis) in 30% to 60% of cases (Patients 1 and 2); (d) recurrent laryngeal palsy from direct tumour invasion; and (e) a palpable (parathyroid) neck mass in 30% to 50% of cases (Patient 2). However, it is worth noting that most neck lumps in patients with PHPT are due to thyroid nodules rather than parathyroid cancer. Benign parathyroid adenomas are essentially non-palpable except for unusually large tumours. Preoperative imaging tests may demonstrate tumour invasion of adjacent neck structures or metastatic disease. FNAC in Patient 3 alerted the surgeon to the diagnosis of recurrent local disease; however, it should not be performed in patients undergoing initial neck exploration because of the risk of seeding tumour cells (although no report has documented parathyroid cell seeding from needle aspiration).

The intraoperative diagnosis of parathyroid cancer is also not easy. A National Cancer database of 286 cases in the US between 1985 and 1995⁵ found that up to 86% of cases had not been appreciated initially by the surgeon. Enucleative biopsy or piecemeal resection, with the risk of tumour seeding the surgical field, led to a high rate of local recurrence – 40% to 60% within 5 years in some studies.⁶ Frozen section may assist in the diagnosis, as shown in Patient 2, but subtle pathologic findings such as mitoses, nuclear pleomorphism, and fibrous septa, may overlap with benign disease, and should not be used alone for

diagnosis. As mentioned previously, the *sine qua non* of parathyroid cancer is capsular or vascular invasion, local invasion, and lymph node or distant metastases. Surgeons performing parathyroid surgery should be suspicious of cancer if, (a) the gland is large; a mean of 3.3 cm in diameter in some series,⁷ (b) the gland is firm or hard and appears pale in colour, (c) there is local invasion of adjacent structures, e.g., thyroid, strap muscle, recurrent laryngeal nerve, (d) there is lymph node involvement, present in about 15% of cases.¹ In such cases, en bloc resection that includes the ipsilateral thyroid gland, adjacent lymph nodes and adherent tissue is the only curative treatment. In a multivariate analysis, Sandelin et al⁶ showed that patients treated with more extensive surgery had a longer survival and a longer relapse-free period than patients treated with tumour resection alone. Patients with recurrent disease should also be treated surgically because other modalities of treatment such as radiotherapy or chemotherapy palliate poorly.⁸ The overall survival at 5 years and 10 years was 85% and 49%, respectively, in a series of 286 patients.⁵

Mutation of the HRPT2 gene has been found to be associated with parathyroid cancer, which was demonstrated in 10 of 15 patients with sporadic parathyroid carcinoma in a recent study.⁹ The tumour suppressor HRPT2 gene is linked to the chromosome region of 1q32-q21, and has been identified in the majority of kindreds with the HPT-JT syndrome,⁴ a rare autosomal dominant cause of parathyroid tumours and ossifying fibromas of the mandible and maxilla. Although most of the parathyroid tumours in HPT-JT syndrome are benign, the incidence of parathyroid carcinomas is markedly increased in these patients.¹⁰ The gene may be of pathogenetic importance and encodes the protein parafibromin, of which the mechanisms of action are still unknown. Study of the HRPT2 status in parathyroid specimens could add weight to the diagnosis of parathyroid carcinoma on a molecular level. Additionally, loss of parafibromin has recently been shown to be a predictor of parathyroid carcinoma.¹¹

Conclusion

Parathyroid carcinoma is an uncommon cause of PHPT. It manifests in a wide range of presentations and continues to pose diagnostic and therapeutic challenges for clinicians.

Certain features distinguish parathyroid carcinomas from benign adenomatous or hyperplastic disease; however, absolute criteria of malignancy include local, regional and distant spread. The ultimate prognosis depends on successful resection of the tumour at the time of the initial operation.

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