Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation

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- **BACKGROUND** Parathyroid carcinoma is rare, with a reported prevalence of 0.6% to 4.0% in patients presumed to have primary hyperparathyroidism. This study examines the long-term results of surgical therapy and combination chemotherapy.
- **PATIENTS** From 1938 to 1988, 1260 operations for primary hyperparathyroidism were performed; only six patients (0.47%) were subsequently found to have parathyroid carcinoma. A seventh patient was referred to our institution after the diagnosis of parathyroid carcinoma had been made.
- **RESULTS** All patients had excessive hypercalcemia (serum calcium concentration > 12.0 mg/dL) with a range of 12.3 to 18.3 mg/dL. Locally recurrent tumors causing recurrent hypercalcemia were managed by repeated neck exploration and tumor resection. Six of the seven patients (85%) survived 5 years, while four patients (57%) survived 10 years.
- **CONCLUSIONS** Diagnosis of parathyroid carcinoma rests upon postoperative surveillance of patients who have undergone previous neck exploration and resection of apparently benign adenomas. Long-term survival is possible with repeated resection of locally recurrent tumors.

■ INDEX TERMS: PARATHYROID NEOPLASMS; CARCINOMA; HYPERPARATHYROIDISM; HYPERCALCEMIA ■ CLEVE CLIN J MED 1993; 60:331–335

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ONLY 0.6% TO 4.0% OF patients presumed to have primary hyperparathyroidism have parathyroid carcinoma.[1–3] From 1938 to 1988, 1260 operations were performed for primary hyperparathyroidism at The Cleveland Clinic Foundation: the diagnosis of parathyroid carcinoma was made in six of these cases, while a single patient was referred to our institution after this diagnosis had been made.

This report reviews the clinical and biochemical profile of these patients, discusses the difficulty in diagnosis of parathyroid carcinoma, describes our operative strategy in parathyroid surgery, and investigates the long-term results of surgical therapy and combination chemotherapy for this rare endocrine malignancy.

METHODS AND PATIENTS

Methods

The seven patients with parathyroid carcinoma included in this study had at least one of the follow-

TABLE 1
CHARACTERISTICS OF A GROUP OF PATIENTS WITH PARATHYROID CARCINOMA

Patient	Sex	Age (years)	Serum calcium (mg/dL)	Serum PTH* (pg/mL)	Total number of operations	Survival (years)	Associated conditions
1	F	43	12.3	NA†	3	20‡	Pulmonary metastasis, renal insufficiency
2	F	20	18.3	NA	5	12	Acute pancreatitis, renal insufficiency
3	M	56	17.3	213	2	3	Pulmonary metastasis, renal insufficiency, bone cysts
4	M	64	14.0	1941	2	11‡	None
5	M	48	13.6	NA	1	15	Renal insufficiency, myocardial infarction
6	F	44	13.5	2100	5	5	Pancreatitis, renal insufficiency
7	M	54	16.3	740	4	9	Pulmonary metastasis, renal insufficiency

*PTH, parathyroid hormone
†NA, not available
‡Alive

ing three characteristics: (1) evidence of metastasis to cervical lymph node(s) or distant sites; (2) evidence of local invasion of adjacent tissues; and (3) characteristic histopathology as described by Schantz and Castleman.[4]

The majority of the 1260 patients who underwent exploratory surgery for primary hyperparathyroidism at our institution were referred by their primary physicians. Postoperative surveillance of these patients was performed at our institution, or by the primary referring physician. Due to our extensive communication with these referring physicians, we are confident that all cases of recurrent hypercalcemia—and, therefore, potential cases of parathyroid carcinoma—were returned to our center for further evaluation.

Patient information

The characteristics of the patients in this study are listed in *Table 1*. Six of 1260 patients (0.47%) who underwent bilateral neck dissections for primary hyperparathyroidism were found to have parathyroid carcinoma, and another patient was referred to our institution after the diagnosis had been made, for a total of seven. Four were men and three were women, with a mean age of 45 years (range 20 to 65 years). All patients had hypercalcemia documented preoperatively on at least three occasions. Although not diagnostic of malignancy, hypercalcemia was excessive, with a mean of 15.3 mg/dL (range 12.3 to 18.3 mg/dL). Parathyroid hormone (PTH) levels were determined using either total PTH or *N*-terminal PTH assays at different time periods covered by this study. PTH levels were elevated in the four patients for whom this information was available, and in two cases were greater than 1000 pg/mL. Symptomatic nephrolithiasis or osteitis fibrosa cystica was diagnosed preoperatively in over 40% of patients.

In the six patients seen preoperatively at our institution, at the initial presentation, physical examination revealed no cervical masses, and chest radiography showed no abnormalities.

All patients underwent bilateral neck exploration for parathyroid pathology, as previously described.[5] At our institution, following gross identification of both parathyroid glands on the first side explored, biopsy of each gland is performed and the specimens are submitted for frozen-section confirmation, but only if the gland's gross appearance is normal. Open biopsy is contraindicated if features suggestive of malignancy are apparent, such as adherence to adjacent structures, hard consistency, gray-white appearance, or gross muscle invasion. In this instance, meticulous dissection of the gland and resection without violation of the capsule are necessary to avoid tumor "spillage." Typical benign adenomas are excised. Every attempt is made to identify all four glands and to submit biopsy specimens for frozen-section analysis.

RESULTS

All seven patients in this study underwent bilateral neck exploration for primary hyperparathyroidism as described. In a single patient (patient 5) the diagnosis of parathyroid carcinoma was made intraoperatively when gross muscle in-

vasion was found. In this case the operation included en bloc resection of the tumor, the ipsilateral thyroid lobe, and the isthmus.

In the remaining six patients, the diagnosis of parathyroid carcinoma was established as outlined in *Table 2*. All six patients developed recurrent hypercalcemia after a period of postoperative eucalcemia. In none of these cases had the diagnosis of parathyroid carcinoma been entertained at the time of the initial operative procedure. However, at the time of the subsequent operation, histopathologic examination of the operative specimen was consistent with parathyroid carcinoma.

TABLE 2
CHARACTERISTICS LEADING TO THE DIAGNOSIS OF PARATHYROID CARCINOMA IN SEVEN PATIENTS

Patient	Recurrent hypercalcemia after eucalcemia	Gross tumor invasion at initial operation	Histopathology	
			Initial operation	Subsequent operation
1	Yes	No	No	Yes
2	Yes	No	No	Yes
3	Yes	No	No	Yes
4	Yes	No	No	Yes
5	No	Yes	Yes	No
6	Yes	No	No	Yes
7	Yes	No	No	Yes

Control of locally recurrent tumors required subsequent operations. Six patients required at least one subsequent operation to resect recurrent tumors: one patient required a third operation, one required a fourth, and two required a fifth operation for control of hypercalcemia. In three patients, radiographic findings consistent with pulmonary metastasis developed 3 to 20 years after the initial operation. These patients were confirmed to have pulmonary metastases at autopsy. Six patients experienced renal insufficiency during the long-term follow-up period, as evidenced by progressive elevation of blood urea nitrogen and serum creatinine. At autopsy, five of these patients had histologic evidence of nephrocalcinosis.

During the follow-up period, serum calcium concentration was determined every 3 months. In addition, when hypercalcemia recurred, a chest roentgenogram was obtained to rule out pulmonary metastasis.

Six of the seven patients (85%) survived 5 years, and four patients (57%) survived 10 years. A single patient (14%) continues to survive 20 years after her diagnosis. In no case was death directly related to local complications of recurrent parathyroid carcinoma. Two patients died as a result of myocardial infarction, and a single patient died of pneumonia. In three cases the cause of death is unknown, and no information is available about these patients' serum calcium concentrations at the time of death.

In addition to surgical resection for locally recurrent parathyroid carcinoma, adjuvant treatments were attempted at various times during the 50-year period of this study. These included external-beam irradiation of either the site of local recurrence or a presumed pulmonary metastasis, and combination chemotherapy. In the two patients who received external-beam irradiation, no objective response was apparent.

We have previously reported the case of one patient who received combination chemotherapy for pulmonary lesions with a radiographic appearance consistent with pulmonary metastasis.[6] This 54-year-old black man presented with a 1-month history of nausea, arthralgia, anorexia, and weight loss. His initial serum calcium concentration was 16.3 mg/dL and the serum PTH level was 740 pg/mL (normal 0 to 40 pg/mL). Bilateral neck exploration revealed three normal-looking parathyroid glands and a 1-cm intrathyroidal parathyroid adenoma discovered upon sectioning the left lobe specimen. Postoperatively, the patient became normocalcemic, but 4 years later he experienced a recurrence of his initial symptoms and his serum calcium concentration rose to 16.2 mg/dL. He underwent a second operation, and a hyperplastic-appearing parathyroid gland was excised. Postoperatively, he again became normocalcemic.

One year later, he presented a third time with his previous symptom complex; his serum calcium concentration was 12.9 mg/dL. At reoperation an apparent sixth parathyroid gland was removed, and the results of histopathologic examination were consistent with parathyroid carcinoma. The patient underwent subsequent exploratory surgery of the neck for control of hypercalcemia, at which time multiple nodules were seen on chest radiography

consistent with pulmonary metastasis. The patient remained hypercalcemic for the next 2 years, despite intensive medical therapy with salmon calcitonin, steroids, and intermittent peritoneal dialysis.

At that time, 2 years after his third operation and 7 years after his initial diagnosis, combination chemotherapy was started, consisting of the following: fluorouracil, 500 mg/m^2 body surface area intravenously daily for 4 days; cyclophosphamide, 500 mg/m^2 body surface area on day 1; and dacarbazine, 200 mg/m^2 body surface area intravenously daily for 4 days. The chest roentgenogram was unremarkable, with disappearance of the presumed pulmonary metastasis after 5 months of chemotherapy. During this period, the patient's serum calcium concentration remained normal (8.6 mg/dL to 10.0 mg/dL), and his serum PTH level was only slightly elevated (74 pg/mL). However, 15 months after chemotherapy was started, the patient was noted to have a mass measuring 6 to 8 cm in the left side of his neck. His serum calcium concentration was 11.4 mg/dL, and PTH was extremely elevated (2700 pg/mL). Interestingly, roentgenography and computerized tomography of the chest showed nothing remarkable. On repeat operation, the entire neck mass was excised. Histopathologic examination revealed poorly differentiated sarcomatous carcinoma, consistent with parathyroid carcinoma.

DISCUSSION

Parathyroid carcinoma is a rare malignancy, and in our series was diagnosed in 0.47% of patients presumed to have primary hyperparathyroidism. Other authors have reported the prevalence to be 0.6% to 4.0%.[1–3] As more patients are evaluated for asymptomatic hypercalcemia, the true prevalence of parathyroid carcinoma may be revealed to be higher than previously appreciated.

A preoperative diagnosis of parathyroid carcinoma is rarely possible, although certain preoperative criteria may suggest the presence of malignant disease. In our series, the mean age of patients with parathyroid carcinoma was 45 years, approximately 10 years younger than patients with benign parathyroid adenomas. This has been confirmed in other reported series.[4,7]

Although hypercalcemia was certainly not diagnostic of malignancy, serum calcium concentrations were much higher in patients with parathyroid carcinoma than in those with benign adenomas. This finding has also been confirmed in other series.[7–9] Perhaps more substantial is the occurrence of nephrocalcinosis, nephrolithiasis, and osteitis fibrosa cystica in association with parathyroid malignancy. This association has also been reported in other large series.[2,4,9–11]

In our series, no patient presented with a palpable cervical mass prior to initial neck exploration for presumed primary hyperparathyroidism. However, other authors describe this finding in 31% to 64% of patients.[4,7] This may be explained by the small size of the parathyroid carcinomas in our series, and by the early stage of these tumors at the time of initial presentation.

Intraoperative diagnosis of parathyroid carcinoma is simplified if gross muscle invasion is found. In the absence of frank invasion, a number of macroscopic features suggest malignancy. These include a hard consistency, a thick fibrous capsule, gray-white color, or adherence of the gland to adjacent structures.[4,10,11]

There appears to be no agreement on the histologic findings that best support the diagnosis of parathyroid carcinoma. The various microscopic patterns that support this diagnosis include fibrous bands, a trabecular pattern, and the presence of mitotic figures. The last of these may be the most valuable criterion of malignancy.[4,10]

In our series, parathyroid carcinoma was most often diagnosed with a combination of clinical and histologic criteria. As shown in *Table 2*, in six of the seven patients, recurrent hypercalcemia following a period of postoperative eucalcemia led to repeated neck exploration. The histologic diagnosis of the tissue specimens at subsequent operations supported the diagnosis of parathyroid malignancy. In these cases, histologic features consistent with parathyroid carcinoma included a trabecular pattern and mitotic figures. Histologic confirmation was essential, since recurrent hyperparathyroidism secondary to rupture of a benign adenoma, with subsequent seeding of the operative field, has been described.[12,13] This emphasizes the need for meticulous dissection in parathyroid surgery. The evaluation of all four glands at initial neck exploration for primary hyperparathyroidism is advisable, since the simultaneous occurrence of parathyroid carcinoma with one or more hyperplastic glands has been reported.[14]

Palliation of recurrent parathyroid carcinoma causing symptomatic hypercalcemia is based upon

repeated resection of locally recurrent tumor.[15–17] The extent of resection required may include the ipsilateral thyroid lobe or sacrifice of the recurrent laryngeal nerve.[4,8] Combination chemotherapy was believed to be effective in the control of pulmonary metastasis, with radiographic resolution and a 10-month period of eucalcemia. However, 15 months after the initiation of chemotherapy, local recurrence of parathyroid carcinoma with associated hypercalcemia was noted. Chemotherapy has been reported to be effective in the resolution of a pulmonary mass believed to be a nonfunctioning parathyroid carcinoma metastasis.[17]

SUMMARY

Parathyroid carcinoma remains a difficult malignancy to diagnose and treat. Diagnosis rests upon postoperative surveillance of patients who have undergone previous neck exploration and resection of apparently benign adenomas. In the majority of our patients, diagnosis was confirmed by the finding of recurrent, not persistent, hypercalcemia and histologic examination of tissue obtained at repeated neck exploration.

These patients were approximately 10 years younger than those with parathyroid adenomas. The occurrence of renal and bone disease prior to initial exploration was more common in patients with malignant parathyroid disease than in patients with benign parathyroid disease. Long-term survival is possible; with repeated resection of locally recurrent tumor causing symptomatic hypercalcemia, 5- and 10-year survival rates of 85% and 57% were achieved.

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