Parathyroid Carcinoma

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- Parathyroid hormone

Parathyroid carcinoma is an uncommon endocrine malignancy that was first described in 1904 by de Quervain.\textsuperscript{1} de Quervain described a metastatic, nonfunctioning parathyroid carcinoma; subsequent descriptions of functioning parathyroid carcinoma were reported in the 1930s.\textsuperscript{2} Since that time, only a few hundred cases have been reported in the literature.

The natural history of parathyroid carcinoma is described as slow but progressive. This entity has a tendency for spread to local lymph nodes with eventual metastasis to the lung and less commonly to the liver and bone.\textsuperscript{3–5} The majority of tumors are functional (ie, they secrete parathyroid hormone [PTH] with resulting elevated serum calcium levels). Morbidity and mortality usually result from unremitting hypercalcemia and its complications rather than mass effect from tumor burden.\textsuperscript{6,7} Nonfunctional tumors present as an expanding neck mass; typically, they are diagnosed at a more advanced stage and subsequently have a generally poorer prognosis. Mortality also is associated with regional disease and metastasis.\textsuperscript{8} The cause of parathyroid carcinoma is unknown and at present there are no data describing causal relationships between parathyroid carcinoma and any risk factors.\textsuperscript{9}

EPIDEMIOLOGY

The frequency of parathyroid carcinoma is reported as greater than 1% of patients with primary hyperparathyroidism,\textsuperscript{10,11} although a higher rate of 5% is reported from Japan.\textsuperscript{4,12} It is the least common endocrine malignancy,\textsuperscript{10,13–16} with a prevalence of 0.005%\textsuperscript{17} of all cancers. According to a report from the National Cancer Data Base,
the estimated incidence is 30 new cases per year in the United States.\textsuperscript{17} Most reports indicate an equal gender distribution.\textsuperscript{10,17} The typical age at presentation is reported to be from the 40s to the mid-50s, slightly younger than the average age of patients with primary hyperparathyroidism.\textsuperscript{3–5,16,17} Parathyroid carcinoma may occur as a sporadic event or as part of a syndrome; relationships are described with hyperparathyroidism–jaw tumor (HPT-JT) syndrome, multiple endocrine neoplasia types 1 and 2A, and familial hypocalciuric hypercalcemia.\textsuperscript{18–21}

CASE STUDIES

Case studies can be a helpful tool in expanding understanding of rare diseases seldom encountered in clinical practice. From the surgical experience of the senior author (BCS) with 8 cases, the following 2 cases are presented.

\textit{Patient 1}

A 50-year-old man was referred to the authors’ clinic with a chief complaint of dyspnea of more than 1 year’s duration and a right-sided neck mass. Ultrasound (his only preoperative imaging) demonstrated a large, noncystic, right-sided neck mass, which was initially thought a benign colloid goiter. The patient’s preoperative calcium level was incidentally noted as 10.6 mg/dL. Hemithyroidectomy was performed; however, operative findings revealed an exceptionally large right inferior parathyroid mass with mediastinal extension just behind and intimately associated with the thyroid lobe. After this discovery, a blood sample was sent and intraoperative measurement of the patient’s PTH (ioPTH) was 415 pg/dL (normal range, 10–65 pg/mL). Parathyroidectomy with dissection of the tracheoesophageal groove was undertaken. After dissection, his ioPTH level fell to 86 pg/dL and hypercalcemia normalized postoperatively. Histopathologic examination of surgical specimens revealed extensive necrosis and vascular and perineural invasion, leading to a diagnosis of parathyroid carcinoma. During the surgery, there was a concern that residual disease might have been left in the mediastinum. A postoperative neck and chest CT scan with contrast was ordered. A right mediastinal lesion was noted. Approximately 1 month later, after the initial surgery, the patient underwent right thoracotomy for excision of a mediastinal mass. Gross findings on thoracotomy included a soft, well-encapsulated mass with necrosis and mustard brown–colored debris that encompassed the right vagus nerve; the involved nerve was sacrificed. Histopathologic examination revealed no evidence of malignancy.

The patient’s PTH levels remained elevated for 10 months after surgery (97 to 160 pg/dL, normal range 12 to 88). During this time, his calcium levels were consistently low to low normal (8.2 to 8.9 mg/dL, normal range 8.7 to 10.5); subsequently, a 25-hydroxy (OH) vitamin D level was obtained and was 14 ng/mL (normal range, 30 to 80 ng/mL). The patient was determined to have vitamin D–deficient secondary hyperparathyroidism and he was repleted. On correction of vitamin D levels (44 ng/mL), his calcium and PTH levels normalized (9.0 mg/dL and 68.2 pg/mL, respectively). PTH and chorioembryonic antigen (CEA) levels were used for surveillance of disease recurrence; although PTH levels fluctuated, his CEA levels remained consistently normal (1.3–2.1 ng/mL, normal range 0.5–10). He refused radiation therapy and has since been only sporadically compliant with follow-up.

\textit{Patient 2}

A 63-year-old man was referred to the authors’ clinic for evaluation of a neck mass that had gradually increased in size over a 2-year time period. During this time the patient developed progressive back pain, kyphoscoliosis (Fig. 2), a 50-lb weight loss, and
a pathologic fracture of the left scapula while attempting to start his lawn mower. Initial workup revealed a PTH level of 5578 pg/dL, elevated serum calcium and bone alkaline phosphatase, and decreased activated (25-OH) vitamin D. The findings of a palpable neck mass along with massively elevated PTH led to a high index of suspicion for parathyroid carcinoma. Before his scheduled surgery, he was admitted to the hospital in acute renal failure and his hypercalcemia was treated with aggressive hydration. Results of soft tissue CT scan of the neck with contrast were consistent with a malignant neoplasm arising from the right inferior parathyroid (Fig. 3). CT scanning also detected the presence of a mass on the right third rib that was suspicious for a metastasis (Fig. 4).

Right-sided inferior parathyroidectomy, hemithyroidectomy, modified neck dissection, and rib resection were performed by a team effort of otolaryngologists and cardiothoracic surgeons. Histopathologic examination of surgical specimens confirmed diagnosis of parathyroid carcinoma with lymphovascular invasion.

Fig. 1. Mediastinal mass, 2-mm transverse view. Patient 1’s parathyroid mass had extended into the mediastinum, requiring thoracotomy.

Fig. 2. Kyphoscoliosis due to severe osteoporosis, a late sequela of parathyroid carcinoma. This is also seen in Fig. 4.
Examination of the rib mass revealed a fibrohistiocytic lesion with abundant giant cells, which, given the context of hypercalcemia, was identified as a brown tumor of hyperparathyroidism. This is a classic association but rarely encountered in clinical practice (Fig. 5). After resection, his PTH level normalized but hypocalcemia developed due to severe osteoporosis. Unfortunately, the patient’s recovery was complicated by acute tubular necrosis, acute renal failure requiring dialysis, bacteremia, and respiratory insufficiency. Attempts to wean him off the ventilator were unsuccessful. Palliative care was initiated, and he was discharged to hospice care.

PRESENTATION

Parathyroid carcinoma is often misdiagnosed preoperatively as primary hyperparathyroidism due to parathyroid adenoma or hyperplasia. Clinical and laboratory findings may suggest carcinoma, but these findings are nonspecific. At this time, there is no external independent reference standard for the diagnosis of parathyroid carcinoma, and histopathologic diagnosis can be equivocal. A palpable neck mass has been reported in approximately half of patients with parathyroid carcinoma but in less than 1% of patients with primary hyperparathyroidism. The degree of hypercalcemia is

![Fig. 4. (A) Rib mass of patient 2, coronal view. (B) Rib mass of patient 2, transverse view.](image)
often more pronounced in parathyroid carcinoma. Calcium levels above 14 mg/dL (normal, 8.5 to 9.9 mg/dL) are common, in contrast to the elevations of 1 to 2 mg/dL above normal levels typically seen in primary hyperparathyroidism.\textsuperscript{22,24,25} PTH levels are frequently 2 to 10 times the normal values in parathyroid carcinoma (normal intact PTH [iPTH], 10 to 65 pg/mL), whereas PTH levels approximately twice the normal range are more commonly seen in primary hyperparathyroidism.\textsuperscript{22,24,25} Alkaline phosphatase is also more commonly elevated in parathyroid carcinomas compared with adenomas and hyperplasia; this finding is thought to result from the higher incidence of concomitant bone disease.\textsuperscript{25,26} Hypophosphatemia is not a common feature of the disease.\textsuperscript{27} Curiously, parathyroid cancers seem to have a predilection for the inferior parathyroid glands, a finding noted by several investigators.\textsuperscript{3,28–30}

The most commonly affected organ systems in patients with primary hyperparathyroidism are the renal and skeletal systems.\textsuperscript{3,10,24} Parathyroid adenomas and hyperplasia are reported to cause renal impairment (nephrolithiasis, nephrocalcinosis, or impaired glomerular filtration) in fewer than 20% of patients. Renal involvement in parathyroid carcinoma is reported as higher, affecting 32% to 84% of patients.\textsuperscript{5,26} Radiologic signs of skeletal abnormalities secondary to hyperparathyroidism (osteitis fibrosa cystica, absent lamina dura, diffuse spinal osteopenia, subperiosteal bone resorption, or salt-and-pepper skull) have been reported in 44% to 91% of patients with parathyroid carcinoma, whereas specific radiologic findings have been reported in less than 10% of patients with benign primary hyperparathyroidism.\textsuperscript{4,5,26,31} Patients with parathyroid carcinoma are also at a higher risk for developing complications, such as severe pancreatitis, peptic ulcer disease, and anemia, in other organ systems.\textsuperscript{4,5}

None of these findings is specific to the diagnosis of parathyroid carcinoma. For this reason, a high index of preoperative suspicion and the intraoperative recognition of malignant features are of fundamental importance.\textsuperscript{32}

**OPERATIVE FINDINGS**

The appearance of parathyroid carcinoma during surgical resection varies, but the appearance can be different from that of parathyroid adenoma, which typically has a red/brown color, soft texture, and lack of attachments to the surrounding tissue.\textsuperscript{3} The classic description of a parathyroid carcinoma is a hard, lobulated mass that is

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**Fig. 5.** Brown tumor of hyperparathyroidism, also known as osteitis fibrosa cystica. A rare finding (H and E, original magnification \( \times200 \)).
fibrous in texture. The color ranges from tan to grayish. The tumor also frequently adheres to the surrounding structures, including the thyroid gland, strap muscles, and recurrent laryngeal nerve. The recurrent laryngeal nerve should be sacrificed only in the case of a locally aggressive tumor. There are several reports of parathyroid carcinoma being indistinguishable from parathyroid adenoma at the time of excision, with diagnosis made after pathologic analysis.

**PATHOLOGY**

Shantz and Castleman established a set of criteria for the pathologic diagnosis of parathyroid carcinoma in 1973, which includes

1. Presence of a fibrous capsule or fibrous trabeculae
2. Trabecular or rosette-like cellular architecture
3. Presence of mitotic figures
4. Presence of capsular or vascular invasion.

Subsequent studies have reflected the difficulty of diagnosing parathyroid carcinoma based on histopathologic analysis. McKeown and colleagues indicate that cellular pleomorphism and atypia are not reliable indicators of malignancy in endocrine tumors. Stojadinovic and colleagues described the morphologic features of parathyroid carcinoma as

1. Trabecular growth pattern
2. Thick fibrous bands (Fig. 6)
3. Adjacent skeletal muscle invasion by tumor
4. Vascular invasion with tumor attached to vessel wall (Fig. 7)
5. Capsular invasion with tongue-like protrusions.

This study found capsular invasion in 92% of patients, vascular invasion in 81%, and perineural invasion in 19%. In their meta-analysis of the parathyroid carcinoma literature, Obara and colleagues stated that the finding of fibrous bands was the most sensitive histopathologic feature, whereas trabecular growth pattern, capsular invasion, and vascular invasion carried the highest specificity. Tumor size does not seem to play a role in prognosis. Currently, no staging system exists for the evaluation of parathyroid carcinoma.

**Fig. 6.** Thick fibrous bands, a typical feature of parathyroid carcinoma (H and E, original magnification ×200).
Nuclear content analysis has also been studied in patients with parathyroid carcinoma. Mean nuclear DNA content is greater, and an aneuploid DNA pattern is more common in parathyroid carcinoma than in parathyroid adenomas. The presence of aneuploidy in parathyroid carcinomas is a poor prognostic indicator.\textsuperscript{11,37}

With immunohistochemical staining, several cellular proteins have been determined to occur more commonly in specimens of parathyroid carcinoma than in parathyroid adenoma.\textsuperscript{36,38,39} Ki-67 is present in 27\% of patients with parathyroid carcinoma in contrast to 2\% of those with a parathyroid adenoma.\textsuperscript{36} Retinoblastoma (Rb) protein expression is present in most patients with parathyroid adenoma and significantly reduced or entirely absent in patients with parathyroid carcinoma.\textsuperscript{36,39} Stojadinovic and colleagues\textsuperscript{36} tested several molecular phenotypes and determined that 76\% of patients with a parathyroid adenoma and no patients with carcinoma had the phenotype p27\((+\)) bcl-2\((-\)) Ki-67\((-\)) mdm2\((+\)). The phenotypes p27\((+\)) bcl-2\((-\)) Ki-67\((+\)) mdm2\((-\)), p27\((-\)) bcl-2\((-\)) Ki-67\((-\)) mdm2\((-\)), and p27\((-\)) bcl-2\((+\)) Ki-67\((+\)) mdm2\((-\)) were present in 9\%, 27\%, and 18\% of patients with parathyroid carcinoma, respectively, but were not present in any patients with parathyroid adenoma. Although these immunohistochemical markers show potential to discriminate between benign and malignant parathyroid disease, they do not yet exceed the accuracy of surgical findings and conventional histopathology.

**GENETICS**

Recent genetic research has analyzed possible molecular explanations for tumor development in parathyroid carcinoma. In 2009, Westin and colleagues\textsuperscript{40} performed a comprehensive literature review of studies describing the molecular genetics of parathyroid diseases. Of their presented studies, several investigators had determined that somatic HRPT2 mutations with biallelic inactivation are seen in 15\% to 100\% of sporadic parathyroid carcinomas.\textsuperscript{41–45} Parafibromin, the protein product encoded by the HRPT2 gene, is proposed as regulating transcription by interacting with the Wnt/\(\beta\)-catenin and cyclin D1 signaling pathways.\textsuperscript{40} Negative immunostaining for parafibromin is considered highly suspicious for parathyroid carcinoma, unless a patient has HPT-JT syndrome.\textsuperscript{46,47} The incidence of HRPT2 mutations in parathyroid carcinoma, however, is variable (15\% to 100\%), and inactivation may also be caused by methylation.\textsuperscript{42,43,46–51}

Other molecular associations have been made in the context of parathyroid cancer. Juhlin and colleagues\textsuperscript{52} revealed absent immunostaining for the Wnt pathway

\[\text{Fig. 7. (A) Parathyroid carcinoma exhibiting lymphovascular invasion (H and E, original magnification } \times 100). (B) Parathyroid carcinoma exhibiting lymphovascular invasion (H and E, original magnification } \times 100).\]
component adenomatous polyposis coli in 75% of parathyroid carcinomas, indicating that this pathway abnormality may be useful in recognition of parathyroid carcinoma when used alongside immunohistochemistry staining for parafibromin and the proliferation index. A Ki-67 proliferation index greater than 5% may indicate increased risk for cancer in a parathyroid tumor, although a high Ki-67 index can be seen in parathyroid adenomas. A high Ki-67 index may also be associated with a poorer prognosis for patients with parathyroid carcinoma.53

Overexpression of cyclin D1 is encountered in up to 90% of parathyroid carcinomas.44,53 Additionally, allelic loss on chromosome 13q and absent nuclear staining for the Rb protein is found in parathyroid carcinomas but rarely in parathyroid adenomas.41,44,53 Other allelic losses, including 1q25, 7q13, 10q23, 13q14, and 11p15, are prevalent in these carcinomas, where frequently deleted areas have included HRPT2, PTEN, Rb, HRAS, and p53 genes.42–44,53,54 Carcinomas show more proximal losses on chromosome 1p than adenomas, and it is suggested that there may be 2 different parathyroid tumor-suppressor genes at this location.45,54 Research in this field is dynamic, and new findings may offer novel therapeutic modalities for future treatment of parathyroid carcinoma.

DIAGNOSTIC IMAGING

Nuclear medicine studies, including technetium-99m sestamibi and 201thallium, have proved useful in localizing most hyperfunctional parathyroid glands as well as parathyroid carcinomas.13,55 Ultrasound also is used. Distinguishing features of parathyroid carcinoma on ultrasound include a length/width ratio greater than 1 in 94% of patients, contrasting with 5% of patients with adenoma. An ultrasound scan may also indicate the lobulated appearance and inhomogeneous echogenicity often associated with parathyroid carcinoma.56 Bone mineral density scans are used to detect significant skeletal abnormalities and, when correlated with grossly abnormal laboratory values of calcium, PTH, and alkaline phosphatase, are helpful in distinguishing patients with parathyroid carcinoma from those with adenoma.25 In patients with suspected parathyroid carcinoma, MRI with gadolinium and fat suppression is useful in preoperative identification of the tumor.57 PET has also recently been described in detection of these malignant tumors.31

MANAGEMENT

Several reports have stressed the importance of an en bloc resection, including thyroid lobectomy with the isthmus and paratracheal and central neck nodal dissection.4,5,12,13,31,55 This procedure, when performed as the initial therapeutic step, offers patients the best chance for cure. Unfortunately, the diagnosis of parathyroid carcinoma is frequently made after permanent pathologic review. Controversy exists as to whether or not patients without obvious tumor extension should be taken back to the operating room for ipsilateral thyroidectomy, isthmusectomy, and excision of paratracheal and central neck nodes after the diagnosis is obtained from the pathology report. Some practitioners advocate close observation of calcium levels for evidence of recurrence, holding en bloc excision in reserve in the event of recurrence.4,11 Most agree that recurrent tumors that can be identified and are amenable to resection should be excised, even multiple times if necessary, for palliative relief from hypercalcemia.4,5,11,13,24,56 Because parathyroid carcinoma patients are at a relatively high risk of multiple relapses over prolonged time periods, they should be monitored for life using serum calcium and iPTH levels. If elevations of these disease markers are noted, signs of recurrence should be evaluated with localizing imaging studies, such as
Surveillance for parathyroid carcinoma principally depends on monitoring calcium and iPTH levels. Caution should be used in interpreting modest elevations in iPTH as they may be indicative of secondary hyperparathyroidism due to vitamin D deficiency rather than recurrence.\textsuperscript{58,59} If this is of concern, given the widespread prevalence of vitamin D deficiency, a 25-OH vitamin D level should be measured. If deficient, this should be corrected through repletion to a level greater than 30 ng/mL.\textsuperscript{58} CEA levels may also be used for surveillance.\textsuperscript{58,59}

The role of radiation therapy in the treatment of this disease is described in the literature, albeit with limited data and nondefinitive results.\textsuperscript{24} Although parathyroid carcinoma has traditionally been considered a radioresistant tumor, recent retrospective studies have suggested that adjuvant radiotherapy may produce a positive benefit on survival.\textsuperscript{33,60} In a 2004 retrospective cohort, Busaidy and colleagues\textsuperscript{27} found that adjuvant radiation therapy decreased the risk of localized disease recurrence, although formal statistical analysis was precluded due to the small study population. Additionally, other studies\textsuperscript{61,62} have reported that treatment groups receiving adjuvant radiation therapy after surgical excision where margins were positive or close have also shown evidence of possible improvement in preventing recurrence of disease.

Data are limited for the treatment of parathyroid carcinoma with chemotherapy. No defined treatment regimen exists at this time. Dacarbazine alone was shown to provide a brief reduction of a hypercalcemia in 1 report.\textsuperscript{63} A remission of hypercalcemia for 13 months has been reported with a regimen of dacarbazine, 5-fluorouracil, and cyclophosphamide.\textsuperscript{64} Several other regimens have been tried with poor results.\textsuperscript{24}

Profound hypercalcemia can also be a problem for patients with end-stage parathyroid carcinoma. In patients with persistent hypercalcemia and those with unresectable tumors, medical treatment aimed at reducing calcium levels should be implemented. Conservative treatment with saline infusion and loop diuretics is typically not sufficient, and more aggressive medical therapy is usually required.\textsuperscript{5} Medications used with some success include pamidronate (bisphosphonates), mithramycin, and calcitonin.\textsuperscript{10,64–66}

Schott and colleagues\textsuperscript{67} described a case of tumor vaccination with antigen-loaded dendritic cells that demonstrated significant in vitro and in vivo immune responses to the antigens in a patient with disseminated parathyroid carcinoma, although there was no observed clinical improvement. Bradwell and Harvey\textsuperscript{68} immunized a metastatic parathyroid carcinoma patient with human and bovine PTH peptides to induce antibodies that block PTH binding to its receptors. This patient showed rapid improvements in serum calcium level and clinical condition. Betea and coworkers\textsuperscript{69} reported the long-term hormonal, biochemical, and antitumor effects of anti-PTH immunotherapy in a patient with refractory metastatic parathyroid carcinoma. Further research efforts are needed to elucidate these novel therapeutic techniques.

**OUTCOME**

Recurrence after surgical excision of parathyroid carcinoma is common, with rates ranging from 33% to 78%.\textsuperscript{11,13,24,55} The reported time from surgery to the first recurrence (disease-free interval) varies greatly, from 1 month to 20 years, with the mean most commonly reported as between 2 and 5 years.\textsuperscript{11,13,24} Studies reporting statistical estimates of disease-specific survival in patients with parathyroid carcinoma have yielded 5- and 10-year survival rates that range between 20% and 90% and
42% and 86%, respectively. Variation of the survival rates reported in these studies may reflect the differences in histopathologic definitions, the proportions of unequivocal versus equivocal cases, and initial therapeutic interventions used.9

SUMMARY
Parathyroid carcinoma is a rare tumor that is prone to recurrence and poor local-regional control. Despite advances in technologies that have shown promise for accurate diagnosis, the mainstay of initial diagnosis remains pathologic analysis and clinical assessment. A surgeon’s intraoperative analysis is important in identifying those patients with a high likelihood of parathyroid carcinoma. If parathyroid carcinoma is suspected intraoperatively, a more aggressive surgical strategy should be implemented. As continued advances in diagnosis and treatment develop, medical therapies may provide an alternative to what is currently a surgical disease.

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REFERENCES
1. de Quervain F. Parastruma maligna aberrata [Malignant aberrant parathyroid]. Deutshe Zeitschr Chir 1904;100:334–52 [in German].


