Parathyroid carcinoma: a diagnostic and treatment challenge

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Abstract
Parathyroid carcinoma (PC) is a rare endocrine tumor, accounting for less than 1% of primary hyperparathyroidism (pHPT) cases. The clinical presentation is often indistinguishable from other causes of pHPT, leading to a delay in diagnosis and less than optimal surgical management. Early en bloc surgical resection is the recommended surgical procedure, but because the diagnosis of PC is usually made retrospectively, the most common surgical technique performed is a simple parathyroidectomy, which results in an increase in recurrence and mortality. Some centers routinely perform intra-operative histological examination of all parathyroid tissue. Hypercalcemia is the principal cause of morbidity and mortality in PCs and can be treated with repeated surgeries, bisphosphonates, calcimimetics, or newer therapies such as denosumab. There is little evidence that supports the role of chemotherapy or radiotherapy in the treatment of PC. This review will focus on the diagnosis and management of PC and will provide a diagnostic and treatment algorithm.

Keywords: parathyroid carcinoma, presentation, diagnosis, treatment
1. Introduction

Parathyroid carcinoma (PC) is a rare endocrine tumor accounting for less than 1% of primary hyperparathyroidism (pHPT) cases [1]. The majority of PCs are functional tumors, while 10% are nonfunctional and associated with a worse prognosis [2]. The clinical presentation of PC is often indistinguishable from other causes of pHPT, presenting with signs and symptoms of hypercalcemia. This leads to a delay in diagnosis and less then optimal surgical management. Patients are typically diagnosed at the time of surgery, after histologic analysis, or months to years later after initial surgery when relapses in hypercalcemia are noted. The only potential curative option is en bloc surgical resection; however, because the diagnosis is usually made retrospectively, the most common surgical technique is a simple parathyroidectomy [3]. This often inadequate and incomplete surgical resection is associated with an increase in recurrence and mortality [4–6]. Therefore, clinical suspicion prior to surgery is of paramount importance. Patients will typically have multiple recurrences throughout the disease course and will require reoperations to control hypercalcemia. PC-related morbidity and mortality is directly related to the persistent and severe hypercalcemia as opposed to tumor burden [2]. This review will focus on the diagnosis and management of PC and will provide a diagnostic and treatment algorithm.

2. Epidemiology

The prevalence of PC in the general population is extremely low; therefore, the incidence is commonly presented as a percentage of pHPT cases. The incidence of PC shows geographic variation. This was shown in a retrospective study of two European cohorts, were PC accounted for 0.3 to 2.1% of sporadic pHPT [7], while a national Japanese survey reported an incidence of 5.1% [8]. The reasons behind these geographic variations are unknown. In contrast to the female predominance of pHPT (3:1), PC occurs equally in males and females. Mean age at diagnosis is between 45-55 years, slightly earlier than parathyroid adenoma, which generally occurs in post-menopausal women [9,10].

3. Risk factors

The etiology of PC is unknown, however, several possible environmental and genetic risk factors have been identified. Prior exposure to radiation therapy and end stage renal disease with secondary hyperparathyroidism have been associated with parathyroid neoplasia, but the association with PC development is weak [4,11].

3.1. Genetic association and molecular and pathogenesis

Although PC can occur sporadically, it has been associated with various genetic syndromes. These include hyperparathyroidism-jaw tumor syndrome (HPT-JT), an autosomal dominant type of familial hyperparathyroidism, and multiple endocrine neoplasia 1 (MEN1) [12,13]. In a series of 348 MEN1 cases, only one case of PC was reported [14]. In contrast, PC is reported in 15% of patients with HPT-JT [15]. The presence of hypercalcemia in patients with a known genetic predisposition (HPT-JT, MEN1) should always raise the clinical suspicion for PC.

Mutations of HRPT2 (or CDC73), a tumor suppressor gene that is located on chromosome 1 is involved in the molecular pathogenesis of PC. HRPT2 encodes for the protein parafibromin and these mutations lead to the loss of parafibromin expression. Although the exact role of this protein is still being investigated, it is involved in the regulation of gene expression and inhibition of cell proliferation [15]. HRPT2 mutations occur in sporadic PC as well as in HPT-JT and isolated familial hyperparathyroidism. This mutation is found more commonly in sporadic PCs than in parathyroid adenomas.

3.2. HRPT2 mutations in HPT-JT and sporadic PC

Patients with HPT-JT have inactivating germline mutations of HRPT2. These patients are at an increased risk of developing ossifying fibromas of the jaw, cystic and neoplastic renal lesions, uterine tumors, and parathyroid neoplasia including PC.

HRPT2 mutations also occur in sporadic PCs. Combined results from three studies showed that
HRPT2 mutations occurred in 77% of patients (20/26) with sporadic PC [16–18]. In one study, 10 of 15 patients with sporadic PC had HRPT2 mutations [17]. Somatic mutations were found in six patients and three patients had HRPT2 germ-line mutations, suggesting that these patients may have unrecognized HPT-JT or a phenotypic variant. Germline HRPT2 mutations in sporadic PCs suggest that family members of patients with sporadic PC may benefit from genetic testing [16,17]. In contrast, HRPT2 mutations in parathyroid adenomas occur less commonly with a prevalence between 0-1.8% [16,18–20].

3.3. Genetic testing

Genetic testing for HRPT2 mutations is indicated in patients with PC and known familial hyperparathyroidism or when HPT-JT is present in the index patient [21]. As already mentioned, some patients with sporadic PC may have germline mutations in HRPT2 suggesting that family members of the index patient may benefit from genetic testing as well [17]. However, the role of HRPT2 genetic testing in atypical parathyroid adenomas that may have clinical or pathological features of carcinoma is unknown [20]. Benefits of genetic testing include reassurance of family members when a negative result is obtained and decreased medical costs due to prolonged screening. However, a negative test in the index patient cannot guarantee that he/she is HRPT2 mutation-free because even families with HPT-JT have no detectable mutations in up to 40% of cases [19,21]. Occult HRPT2 mutations may be undetectable when inactivating mutations occur in regulatory regions as opposed to coding regions (which are usually sequenced) [22]. Another limitation of genetic testing is that it is not widely available in most centers and is expensive. Furthermore, for family members that inherited the mutation, guidelines for the follow-up and management of these patients are still unclear due to the rarity of these tumors.

3.4. Others genes involved

Somatic mutations of other genes have also been linked to PC including the retinoblastoma gene (Rb) [23] and the p53 gene [24]. Furthermore, overexpression of cyclin D1 (CD1) has been associated with PC [25]. Further investigations are required to determine the clinical significance of these findings [26].

4. Clinical and biochemical presentation

It is of paramount importance to distinguish benign parathyroid disease from malignant because PC-related morbidity and mortality depends on the type of surgical procedure performed initially. However, the clinical presentation of PC is often indistinguishable from other causes of hypercalcemia and include fatigue, muscle weakness, nervousness, depression, weight loss, abdominal pain, polyuria, bone disease, nephrolithiasis, peptic ulcer disease, and pancreatitis [27–29]. Although there are no specific signs and symptoms that can reliably distinguish benign parathyroid disease from PC, some clinical manifestations are more indicative of PC (Figure 1). Patients with PC will more likely be symptomatic, have severe hypercalcemia (>3.5 mmol/L) and may present with hypercalcemic crisis, present at a younger age, and have a palpable neck mass (>3 cm). Bone disease (bone pain, osteopenia, osteofibrosis, and pathological fractures) and renal involvement are also more common in PC than in benign parathyroid disease. Hoarseness, resulting for recurrent laryngeal nerve injury is rarely seen in benign parathyroid disease and should point to malignancy [30,31].

Other biochemical parameters associated with PC include higher parathyroid hormone (PTH) levels, higher alkaline phosphatase (ALP) levels as well as α and β sub-units of human chorionic gonadotropin (HCG) [31,32]. In one study, PTH levels 10 times above the upper limit of normal had a positive predictive value of 81% for PC [6]. Another study found that when PTH was <4 times the upper limit of normal and tumor weight was <1.9 g, the probability of PC was zero [33]. PC over-secrets the amino form of PTH, which is modified in the 15-20 amino acid region, and can be detected by third generation but not second-generation PTH immunoassays [34]. This finding has lead to the development of the PTH ratio (third generation/second generation). In normal individuals, this ratio should be less than 1, and several studies have found that a high third generation/second generation PTH is associated with PC [35,36]. An inverted PTH
ratio (<1) has been shown to have a PC sensitivity and specificity of 78.5% and 98.9%, respectively [34,35,37,38].

5. Diagnosis

5.1. Imaging studies

Whether or not PC is suspected prior to surgery, all patients with pHPT undergo imaging studies for tumor localization. These imaging modalities include ultrasonography (US), Technetium-99m sestamibi scanning with single-photon emission computed tomography (SPECT), computed tomography (CT), magnetic resonance imaging (MRI), and more recently, C-11 methionine positron emission tomography (methionine PET-CT) [26].

Neck US and Technetium-99m (Tc-99m) sestamibi scans are usually the first imaging modalities used. US features suggestive of malignancy include: lobulated hypoechoic appearance, large parathyroid gland with ill-defined borders [39], local infiltration, calcification, suspicious vascularity, thick capsule, or cervical lymph node enlargement [40]. It should be noted that fine needle aspiration (FNA) cannot reliably distinguish benign parathyroid disease from malignant and due to the potential risk of seeding and dissemination, should be avoided at the initial tumor site. However, because dissemination is less of a concern in metastatic disease, if there is doubt regarding the etiology of a potential metastatic lesion, FNA can be used to identify parathyroid tissue by cytology or by a PTH aspirate-hormone test [41]. Tc-99m sestamibi is a radionucleotide with a high affinity for parathyroid mitochondria. Because most PCs are functional, Tc-99m sestamibi scans are used for tumor localization, but will not provide additional information to distinguish benign parathyroid lesions from malignant. These scans are helpful when relapses in hypercalcemia are noted and metastatic disease is suspected [42].

CT and MRI can additionally be used when US and Tc-99m sestamibi scans do not provide sufficient information. These imaging modalities provide additional anatomical information including local invasion and are also helpful in identifying metastatic disease, which are most frequently seen in the lungs, liver and bones. In a retrospective study including 18 patients treated for PC, the sensitivity of sestamibi scans, MR imaging, CT scans, US, and selective venous catheterization with PTH measurement was 79%, 93%, 67%, 69%, and 83% respectively [43]. In addition, the combinations of at least two imaging modalities increased the sensitivity of metastatic disease detection. More recently, Methionine PET-CT has been shown to correctly localize single gland adenomas in 79-91% of cases. The use of this imaging modality holds potential and should be investigated in patients with PC as well [44]. It is important to note that if fluorodeoxyglucose PET-CT (FDG-PET) is used, lytic lesions or Brown tumors may be mistaken for bone metastases because they can be FDG-avid [9]. When other noninvasive imaging methods fail to localize the tumor, selective venous catheterization may be used [43].

5.2. Pathological diagnosis

At the time of initial surgery it may be difficult to differentiate parathyroid adenoma from PC because unless massive local invasion or regional metastases are seen, even experienced surgeons cannot differentiate these two clinical entities. Furthermore, pathological features of PCs and adenomas often overlap [30]. Therefore, it is important to examine all clinical, biochemical and histological features when considering PC in the differential diagnosis of pHPT [45]. Furthermore, an intra-operative histological examination of all parathyroidal tissue should be considered.

Grossly, PCs are firm, grayish-white in appearance, shaped spherically and may be adherent to surrounding structures. In contrast, parathyroid adenomas are generally red-brown in appearance, soft and flattened, and round or oval in shape [26,46].

There are no pathognomonic features of PC; however, several features are suggestive of malignancy. Although earlier reports suggested that the presence of fibrous trabeculae, mitotic figures, and capsular and vascular invasion were suggestive of malignancy [47], mitotic activity as well as a trabecular pattern can be seen in adenomas as well and none of these criteria are sensitive or specific enough to diagnose PC [45]. However, gross invasion
beyond the capsule correlate best with PC [48].

When there are insufficient criteria to diagnosis PC, these tumors are referred to as atypical adenomas, and the diagnosis of PC is made retrospectively after local recurrence or distant metastases are found during follow-up [49].

The different frequencies of HRPT2 mutations in PCs and parathyroid adenomas indicate that immunohistochemical staining for parafibromin may be a valuable diagnostic tool to differentiate these two conditions. This was shown in a study that examined parafibromin immunostaining in PCs and parathyroid adenomas [50]. While parafibromin immunostaining showed strong positivity in 17 of 18 adenomas, the loss of parafibromin expression (characterized by negative or weak positivity) had a specificity of 94.4% for PC. However, negative staining is not automatically consistent with PC and cannot be used alone to diagnose PC [51]. The distinction between PC and atypical parathyroid adenomas is less clear. A retrospective analysis of aggressive parathyroid tumors (18 parathyroid carcinomas and 34 atypical adenomas) showed no significant difference in loss of parafibromin expression between the two groups [48]. Another study examined the diagnostic utility of a combination of markers, including parafibromin, Rb, galactin-3, p27 and mdm-2 [52]. Although no single diagnostic marker could distinguish whether a parathyroid tumor was malignant, loss of parafibromin and Rb expression, and overexpression of galactin-3 was associated with PC. A higher than 10% Ki-67 index has also been associated with an increased risk of PC and possibly recurrence. Furthermore, in a small series, when a panel of immunohistochemistry markers (parafibromin, galactin-3, PGP9.5, and Ki67) were used to supplement classical histopathology they were found to be superior to any single marker used alone, with a sensitivity and specificity of 80% and 100% respectively [53].

The rarity of this tumor represents a major limitation in the development of novel biochemical and molecular methods used to diagnose PC. The combination of various classical histopathological and immunohistochemical markers seems to be the best option until additional evidence becomes available.

6. Treatment

Surgery is the mainstay of PC treatment in order to decrease disease burden and control hypercalcemia. Not only is it indicated for initial tumor resection, it is also indicated for tumor recurrence and metastases in order to palliate the effects of hypercalcemia. However, prior to surgery, optimal management of hypercalcemia must be accomplished. Furthermore, in disseminated disease, when surgery is no longer a viable option, management of hypercalcemia with medical therapy becomes the primary focus, although this effect is usually transient.

6.1. Surgical management

The treatment of choice, and the only potential curative treatment is enbloc tumor resection. Complete en bloc resection should include the ipsilateral thyroid lobe, paratracheal alveolar and lymphatic tissue, the thymus or some of the neck muscles, and sometimes, when indicted, the recurrent laryngeal nerve [27,54–56]. Goals of surgery include complete surgical resection with clear gross margins and leaving the capsule intact in order to avoid tumor seeding [2]. If cervical node involvement is present, ipsilateral cervical compartment lymph node resection should be performed. More extensive resection is usually not indicated due to the increased morbidity and minimal benefit to survival [56].

As mentioned previously, the diagnosis of PC is usually made retrospectively, and thus, the most common procedure performed is a simple parathyroidectomy. In the Surveillance, Epidemiology, and End Results (SEER) registry, 78.6% of patients had a simple parathyroidectomy while only 12.5% had en-bloc resection [3]. Patients that are diagnosed preoperatively and have en bloc resection performed have a recurrence rate of 33%. In contrast, patients that are diagnosed postoperatively and have only local excision performed have a recurrence rate of over 50%, which emphasizes the need for early diagnosis in order for appropriate surgical intervention to be undertaken [4,30].

Surgical success can be confirmed by a >50% reduction of PTH from baseline [10]. Intraoperative PTH assays can be used to test whether complete surgical resection
was performed. If PTH levels remain increased, additional localization studies and reintervention should be performed [45].

If the diagnosis of PC is made after the initial surgical procedure, re-exploration of the neck with resection of contiguous tissues is recommended [57]. Recurrences, which usually occur in the neck, should also be treated surgically as it results in significant palliation of hypercalcemia [58]. Furthermore, metastases, when possible, should be treated with surgery as it also results in palliation of hypercalcemia and increases survival [59]. Most patients will require repeated surgical intervention, which results in significant morbidity. The most common complications include laryngeal nerve injury, hypoparathyroidism, esophageal or tracheal injury, and neck hematoma. “Hungry bone syndrome” occurs when decreases in PTH results in cessation of osteoclastic bone resorption without affecting osteoblastic activity leading to increased bone uptake of calcium, phosphate, and magnesium. Therefore, postoperative calcium levels should be monitored with calcium supplementation provided as needed [10].

6.2. Non-surgical management

6.2.1. Chemotherapy and radiotherapy

There is little evidence that supports the role of chemotherapy or radiotherapy in the treatment of PC, most of which comes from small observational studies and case reports. A few case reports have shown some benefits with chemotherapy regimens that included dacarbazine alone or in combination with other drugs in patients with advanced metastatic disease; however, survival benefits are rarely reported [27,45,60].

PC is not considered to be radiosensitive but there is some evidence from small observational studies that it may be of some benefit. One small series that included 26 patients with PC that were followed for a median of 7.9 years showed that after initial surgery, only one of the six patients that received adjuvant radiotherapy had a local relapse, compared with 10 of 20 that did not receive radiation [28]. In a retrospective review of 57 patients from the Mayo Clinic that had surgical resection of PC, 25 patients had locoregional disease progression at a median follow-up of 27 months [61]. Four patients that were treated with adjuvant radiotherapy with doses of 66-70 Gy had no recurrence at 60 months follow-up. Some authors recommend adjuvant radiotherapy with 40-50 Gy in patients with a high risk of local recurrence [62]. However, due to the small patient samples, these results must be interpreted with caution. Unfortunately, the rarity of PCs makes it difficult to conduct larger randomized clinical trials.

7. Management of hypercalcemia

7.1. Bisphosphonates

Patients with hypercalcemia are initially treated with generous intravenous saline hydration, followed by loop diuretics and intravenous bisphosphonates. Bisphosphonates are inhibitors of osteoclastic bone resorption and can improve hypercalcemia, although their effect lasts from several days to months [31,63]. Zoledronate and pamidronate are the most potent and are administered intravenously. Bisphosphonates can cause renal impairment; therefore, renal function must be monitored [64].

7.2. Calcimimetics

Calcimimetics (namely cinacalcet) are allosteric modulators of calcium sensing receptors on the surface of parathyroid cells. They increase the sensitivity of these receptors to extracellular calcium and thereby decrease PTH secretion [65]. Cinacalcet was tested in a multicentric study that included 29 patients with inoperable PC [66]. Cinacalcet doses were titrated (30 mg twice daily to 90 mg four times daily) until serum calcium was no more than 10.0 mg/dl. Cinacalcet successfully reduced serum calcium concentration by at least 1 mg/dl in 62% of patients and the greatest reductions were observed in patients with the highest baseline calcium levels. The most common side effects included nausea and vomiting.

7.3. Denosumab

Denosumab is a humanized monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B
ligand (RANKL). It is a potent inhibitor of bone resorption and can be given even when hypercalcemia is refractory to bisphosphonates and cinacalcet. Evidence is limited to case reports that showed that denosumab effectively controlled hypercalcemia in the short term in patients with PC previously treated with surgery, bisphosphonates, calcium receptor agonists, and dacarbazine [67–70].

7.4. Other therapies

Calcitonin inhibits osteoclast-mediated bone resorption and increases urinary calcium excretion [57]. Although calcitonin is rarely used today to control hypercalcemia and has only transient effects, it has been shown to have a synergistic effect when combined with steroids [71]. Other drugs that are less commonly used to control hypercalcemia in PC patients include plicamycin, mitramycin, octreotide, and gallium nitrate [26,57,72,73].

7.5. Novel and experimental therapies

Anti-PTH immunotherapy has been reported to control tumor growth and improve hypercalcemia but without any effects on tumor regression [10,74]. Evidence is provided from single case reports and further studies are needed to test this potential treatment strategy. Furthermore, biologic agents based on gene products including parafibromin have been investigated in addition to telomerase inhibitors, which have been tested in vitro [10,21,75,76]. Future studies are needed to test these potential novel therapeutic agents.

Figure 1. Diagnostic and treatment algorithm for parathyroid carcinoma
8. Disease outcome

Hypercalcemia is the principal cause of morbidity and mortality in functional PCs. As previously mentioned, nonfunctioning PCs are extremely rare and present with signs and symptoms of local invasion. In contrast to functional PCs, these patients die from tumor burden rather than hypercalcemia [77]. In general, PCs are slow growing tumors. One-third of patients with PC are cured at initial or follow-up surgery, one-third of patients have recurrences after a prolonged disease-free survival, and one-third of patients have a short and aggressive course [78]. At initial presentation, one-third of patients will have lymph node metastases and one-third will have distant metastases [28].

A retrospective study that included 37 patients with PC treated at a single tertiary care center reported a median overall survival of 14.3 years [41]. Factors associated with increased mortality included lymph node or distant metastases, number of recurrences, higher calcium level at recurrence, and a higher number of calcium-lowering medications being used. Another interesting finding was the lack of association between the extent of thyroid resection and mortality, even though en bloc resection with the thyroid is usually recommended. In contrast, a review of 286 cases from the National Cancer Data Base (NCDB) and results from the SEER registry did not show an association between lymph node metastases and mortality [3,30] and their overall 10-year survival rate was 49.1% with metastases and 67.8% without, respectively.

Although no universally accepted staging system for PC exists, several have been proposed [6,79]. Talet’s staging system focuses on the extent and type of tumor invasion and divides PCs into low-risk and high-risk [6]. Low-risk PCs are considered as having only capsular invasion, or invasion of surrounding structures. In contrast, high-risk PCs have vascular invasion, invasion of vital organs, lymph node metastases, and/or distant metastases. When this staging system was applied to 82 patients with PC, a “differentiated” classification system further classified high-risk PC patients into high-risk class II (vascular invasion), high-risk class III (lymph node metastases or organ invasion) and high-risk class IV (distant metastases) [80]. Low-risk PC was classified as class I. This classification system demonstrated a statistically significant overall survival difference between the classes thus validating this classification system.

9. Conclusion

The rarity of PCs introduces numerous limitations in designing larger longitudinal studies that could expand our knowledge on the pathogenesis, diagnosis, and treatment of PC. As such, most studies performed to date are retrospective and on small sample sizes. Therefore, results of these studies must be interpreted with caution. When considering PC in the differential diagnosis of pHPT, an intergraded and comprehensive multidisciplinary approach is needed in order to optimize patient outcome. In addition, all patients with suspected PC should be referred to a tertiary care center that has experience with PC prior to surgical management in order to optimize patient workup and management.

Author contributions

LSKB performed literature review, wrote the article and gave the final approval. DP gave the idea for the article, critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval. FK critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.
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