Parathyroid carcinoma: Diagnostic criteria, classification, evaluation

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Abstract

Parathyroid carcinoma is a little-known cancer, difficult to diagnose. We focus this short review on the current diagnostic criteria, the classification and the evaluation tools for this cancer based on latest publications.

Keywords: Parathyroid carcinoma; Presentation; Diagnosis; Classification; Pathology

1. Introduction

Parathyroid carcinoma (PRTC) is a rare, slow growing and lethal endocrine cancer. As regards symptoms, PRTC mimics a parathyroid adenoma of severe phenotypic expression. Few cases are recognized pre- or intra operatively, excepted when local invasion is obvious. However, early suspicion of PRTC would allow for an en bloc resection with lymph node dissection, a surgical procedure proven beneficial to prevent recurrence and reduce mortality [1]. Even at histopathological examination, malignancy is sometimes challenging to establish. Molecular biology and genetics may be complementary tools to enhance diagnostic accuracy with the consistent findings of the loss expression of tumor suppressor \textit{HRPT2} gene in PRTCs compared to adenomas. The first classification of PRTC provided in 2010 and validated in 2012 should improve prediction of outcome and therapeutic guidance [2].

2. Incidence

PRTC accounts for 0.5–5% of cases of primary hyperparathyroidism [3]. It affects middle-aged adults with an equal sex ratio. Median age varies from 45 to 55 years [4,5]. The incidence is extremely low, at about 4 to 6 cases per 10 million population a year [6]. Nonetheless, changes in diagnostic pathology criteria since 2004 may have favored the slight increasing incidence figure for the last decade [6].

3. Risk factors

Prior neck irradiation has been suggested to be a risk factor for parathyroid adenomas but its role as risk factor for
PRTC is more controversial [7,8]. Longstanding secondary hyperparathyroidism in end-stage kidney disease may promote PRTC occurrence though causality has not been clearly established given the rarity of these cases [6,9]. Hereditary hyperparathyroidism-jaw tumor syndrome (HPT-JT) is an autosomal-dominant disease that affects predominantly male young adults. It is due to germline mutations in HRPT2 gene (1q21-q32) also called CDC73. The condition is characterized by primary hyperparathyroidism including PRTC in 10–15% of cases, cystic parathyroid adenomas, ossifying jaw fibromas, renal cystic or solid tumors, and uterine tumors. In apparently sporadic cases of PRTC, 20% of germline mutations in HRPT2 gene are present. This implies that genetic testing should be considered for HRPT2 in every patient with PRTC [10]. Interestingly, a high rate (55–100%) of HRPT2 somatic mutations in sporadic PRTC tissue samples has been detected [11]. PRTC occur much less frequently in association with other genetic and molecular alteration. PRTC can develop in familial isolated hyperparathyroidism. To date, five cases of PRTC in multiple endocrine neoplasia type 1 or type 2 have been reported [8]. In older studies, loss of expression or function of tumor suppressor genes like Rb1, BRCA2, p53, CCND1 and APC, involved in cell cycle regulation, has been suspected to be linked to PRTC [10].

### 4. Clinical presentation

A summary of characteristics of PRTC in comparison to adenomas is provided in Table 1. PRTC can be found in the neck at initial clinical evaluation, as a palpable painless mass sometimes adherent to the thyroid gland or to the adjacent structures (soft tissues, muscle, and recurrent laryngeal nerve). The average tumor size is approximately 3 cm [5], larger than for adenomas. There are no specific clinical features of PRTCs that distinguish them from large adenomas, but the expected signs and symptoms of hyperparathyroidism are generally more severe in case of malignancy. A higher level of preoperative serum calcium is reported in PRTC compared to adenoma, directly dependant on the larger amount of parathyroid hormone (PTH) secretion. Renal and bone complications related to the severity of primary hyperparathyroidism are usually present at the time of diagnosis (nephrolithiasis, nephrocalcinosis, renal colic, impaired renal function, osteitis fibrosa cystica, osteoporosis, bone pain, pathologic fractures…). Patients may also have gastrointestinal symptoms such as nausea, abdominal pain, constipation, peptic ulcer and acute pancreatitis. However, not every PRTC causes PTH-related symptoms. Non-functioning PRTCs have been reported that do not secrete active PTH resulting in normal calcium level [12].

### 5. Evaluation

In the absence of preoperative accurate evaluation, half of the primary surgeries for PRTC are inadequate and under stage lymph node status [1]. Whenever PRTC is suspected, it is critical to undertake complete work-up so as to guide medical and surgical treatment. An additional benefit of tumor characterization prior to surgery is the ability to schedule long term follow-up with appropriate biological markers and pertinent radiographic imaging.

#### 5.1. Laboratory tests

To evidence primary hyperparathyroidism and help for discrimination between PRTC and large adenomas, the following biological measurements may be valuable: serum and urinary calcium, phosphorus, vitamin D, PTH, and if available serum or urinary human chorionic gonadotropin (HCG) and N-PTH, the amino terminal form of PTH. Usual laboratory tests are non-specific of PRTC but serum calcium, alkaline phosphatase and PTH have been found at significantly greater values in case of malignancy in contrast to benign primary hyperparathyroidism. However, it is necessary to remind the 5% (or less) cases of non-functioning PRTCs reported to be eucalcemic [1]. Other laboratory findings may be more specifically associated to PRTC condition. Elevation of serum and urinary HCG – in particular the hyperglycosylated isoform – has been described in PRTC patients, of both genders [13]. Overproduction of N-PTH has also been recognized in malignant tumors, best detected by measurement of the third-generation to second-generation PTH ratio [14].

#### 5.2. Imaging studies

Initial imaging should include neck ultrasonography and sestamibi scan. Ultrasonography can focus on the tumor, revealing typically a hypervascular solid hypoechoic mass, located immediately posterior to the thyroid gland. PRTC can appear inhomogeneous, lobulated, infiltrating the surrounding tissues with enlarged lymph nodes nearby. Fine-needle aspiration biopsy should be avoided to prevent tumor seeding. Sestamibi parathyroid scan, regularly performed to localize parathyroid adenoma, is also useful for detecting in situ PRTC as well as recurrent or metastatic PRTC. To assess accurately local invasiveness, a prerequisite to surgery, cervico-mediastinal
computed tomography (CT) scan and magnetic resonance imaging (MRI) are helpful tools notably in case of perivascular involvement. Finally, documentation of distant metastases is based on chest and abdominal CT, 18F-fluorodeoxyglucose-positron emission tomography and bone MRI covering the whole skeleton [15].

**6. Pathologic diagnostic criteria and classification**

The diagnosis of PRTC is challenging and distinguishing between parathyroid adenoma and PRTC can be difficult. On gross examination parathyroid carcinomas are large tumors with adherence to and invasion of the surrounding neck structures such as soft tissues of neck, thyroid and perioesophageal soft tissues. This infiltration into the neighbouring neck structures serve as an important surgical finding and may require an en bloc resection of the tumor mass with surrounding adherent structures [16]. The only reliable indicators of malignancy in PRTC are invasion of adjacent soft tissues or thyroid gland, blood vessels or perineural spaces and to the tumors with documented metastases [17,18]. Major histologic features diagnostic of malignancy include capsular invasion present in approximately 60% of carcinoma and vascular invasion in 10–15% [18]. From this analysis Schulte et al. validated two classifications schemes which are summarized in Table 2: the first differentiated classification based on system (TNM) classification by the Union for International Cancer Control, the second classification dissociating low-risk (defined by capsular and soft tissue invasion alone) versus high risk (defined by vascular invasion or organ invasion and/or lymph node or distant metastasis) [2]. However, some tumors may be totally encapsulated, lack gross invasion and resemble parathyroid adenomas. Large adenomas can show adherence and degenerative changes with fibrosis and “pseudoinvasion” of trapping cells in the capsule [16].

Other helpful features include mitotic activity, thick fibrous bands and necrosis. However mitotic activity like Ki67 in PRTC is extremely variable and shows broad overlap between adenoma and hyperplasia [17]. Parathyroid carcinomas usually have a relatively monotonous solid growth pattern with sheets of chief cells but mixtures of cell types can be seen. Proeminent nucleioli are seen in parathyroid carcinoma. Nuclear atypia are not diagnostic and may be seen in many benign endocrine tumors. None of these histological features are diagnostic of malignancy. That’s why a relatively new entity defined by Lewin in 1988 has been accepted by the WHO (2004) as atypical adenoma and considered of uncertain malignant potential [17] with some features of PRTC but lacking unequivocal capsular, vascular or perineural space invasion. These tumors have some features of PRTC such as adherence to adjacent structures, mitotic activity, fibrosis, trabecular growth and tumor cells within the capsule. A few available follow-up studies have shown that these tumors behave in a clinically benign fashion [19,20].

Parathyroid adenomas and carcinomas need to be differentiated from thyroid neoplasms especially in intratharyd localisation by positive immunohistochemistry for synapto-ophysin, chromogranin, and parathyroid hormone and negative for TTF1 and thyroglobulin. Parathyromatosis must be included in the differential diagnosis of PRTC. Small collections of parathyroid cells, mainly chief cells, rarely can be encountered embedded within the surrounding soft tissue of the neck and mediastinum outside the confines of parathyroid gland capsule. Parathyromatosis can occur in two situations: seeding of hypercellular parathyroid tissue during surgical excision of abnormal parathyroid tissue (usually hyperplasia) and over-growth of embryologic parathyroid rests.

As previously mentioned, inactivating mutation of tumor suppressor HRPT2 gene have been implicated in 70% of PRTC and in less than 1% of adenomas [11,21]. HRPT2 gene encodes parafibromin protein. Although some have found immunohistochemistry for parafibromin to be useful in both confirming a definitive diagnosis of malignancy and in triggering patients for germline mutation testing for HPT-JT [22,23] others like us have found the antibody difficult to deploy [3] with poor sensitivity (unpublished data). The reproducibility and variability in the interpretation of this immunostain needs to be confirmed. Loss of parafibromin expression in a subset of parathyroid adenomas with cystic change has also been identified and associated with HRPT2 mutation [3]. Thus the utilisation of parafibromin in some settings could be misleading. Negative staining for parafibromin is beginning to be validated both as biomarker of poor prognosis in definite PRCs as well as a marker of increase risk of recurrence in histological atypical parathyroid tumors which do not quite fulfill conventional histological criteria for carcinoma [24,25].

**Table 2**
Classification scheme [2].

| Differentiated classification derived from the TNM system classification | T | (Tx) | No information available | T1 | Evidence of capsular invasion | T2 | Invasion of surrounding soft tissues excluding the vital organs of trachea, larynx, and oesophagus | T3 | Evidence of vascular invasion | T4 | Invasion of vital organs, hypopharynx, trachea, oesophagus, larynx, recurrent laryngeal nerve, carotid artery |
| | | | | | | | | | | | |
| | N | (Nx) | Lymph node not assessed | N0 | No regional lymph node metastases | N1 | Region lymph node metastases |
| | M | (Mx) | Distant metastases not assessed | M0 | No evidence of distant metastases | M1 | Evidence of distant metastases |

| Classification histology criteria | | I | T1 or T2 N0M0 | II | T3 N0 M0 | III | Any T, N1, M0, or T4 | IV | Any N, M1 |
| | | Low | Capsular invasion combined with invasion of surrounding soft tissue | | | | | | | |
| | | High | Vascular invasion and/or lymph node metastases and/or invasion of vital organs and/or distant metastases | | | | | | |
7. Outcome and prognostic factors

Despite that PRTC can remain latent for years with slow growing metachronous metastases, their prognosis is poor. The overall 5-year and 10-year relative survival rates are respectively 85.5% and 49.1% in a large study [5]. After a median follow-up time of 6 years, two thirds of patients usually experience recurrence while one third of patients can die from cancer progression or refractory hypercalcemia [1]. Local recurrence with involvement of regional lymph node is frequent. Synchronous metastases are rare, evidenced in 1% of cases in a large series of PRTCs [1]. The most common sites of metastases are the upper mediastinum, lung, pleura and bone. Unfavorable prognostic factors include clinical features, surgical treatment modality, vascular invasion and pathological TNM stage. Male gender, younger age and higher calcium level appear as clinical factors of metastases [1]. The most common sites of metastases are the upper mediastinum, lung, pleura and bone. Unfavorable prognostic factors include clinical features, surgical treatment modality, vascular invasion and pathological TNM stage. Male gender, younger age and higher calcium level appear as clinical factors associated with a poor prognosis [1]. Greater recurrence and death also occur when primary surgical procedure is not oncological [1]. Vascular invasion found at pathological examination may promote metastatic spread and worsen outcome [1].

8. Conclusion

PRTC is a challenging entity representing the rare malignant counterpart of parathyroid neoplasia. Recognition of atypical adenomas, an intermediate category between the very common parathyroid (typical) adenoma and the PRTC reflect the diagnostic uncertainties, suggesting a continuum of pathologic changes among these lesions. The expected development of molecular biology tools and a better understanding of the role of HRPT2 gene may overcome the current diagnostic difficulties. A proposal for a classification and TNM staging system of PRTC has been published only very recently. In the future, correct tumor staging performed ideally in a presurgical setting will be essential to guide resection and facilitate monitoring of the disease. Guidelines for work-up and management of PRTC are needed.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References