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Annales d'Endocrinologie 76 (2015) 165–168
Annales d'Endocrinologie
Annals of Endocrinology

Journées Klotz 2015

Parathyroid carcinoma: Diagnostic criteria, classification, evaluation

Cancer parathyroïdien : critères diagnostiques, classification, évaluation

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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

Résumé

Le carcinome parathyroïdien est méconnu et difficile à diagnostiquer. Dans cette brève revue, nous nous focaliserons sur les critères diagnostiques, la classification et les méthodes d'évaluation de ce cancer à partir des dernières données de la littérature.

Mots clés : Carcinome parathyroïdien ; Présentation ; Diagnostic ; Classification ; Pathologie

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 *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

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http://dx.doi.org/10.1016/j.ando.2015.03.016
0003-4266/

Table 1
Clinical and biological characteristics of benign and malignant parathyroid tumors.

	Adenoma	Carcinoma
Clinical features		
F/M ratio	3–4/1	1/1
Median age (years)	55–65	45–55
Palpable mass	< 5%	30–60%
Median size (cm)	≤ 1.5	3
Concomitant bone and renal complications	Exceptional	40%
Biological features		
Median pre-op Ca++ (mg/L)	110	>140
PTH level	< 5 times UNL[a]	≥ 5–10 times UNL[a]
HCG	Normal	Elevated
N-PTH	Normal	Elevated

Modified from reference [8].
[a] Upper normal limit.

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 germinal 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 understage 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, alkalin 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 PRTC 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