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Parathyroid carcinoma: Challenges in diagnosis and treatment

Le carcinome parathyroïdien : défis dans le diagnostic et traitement

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Abstract

Parathyroid carcinoma is a malignant neoplasm affecting 0.5 to 5.0% of all patients suffering from primary hyperparathyroidism. This cancer continues to cause challenges for diagnosis and treatment because of its rarity, overlapping features with benign parathyroid disease, and lack of distinct characteristics. The third/second generation PTH assay ratio provides valuable information to distinguish between benign parathyroid disease and parathyroid carcinoma. An abnormal ratio (> 1) could indicate a high suspicion regarding carcinoma and metastatic disease. Early *en bloc* surgical resection of the primary tumour with clear margins remains the best curative treatment. Although prolonged survival is possible with recurrent or metastatic disease, cure is rarely achievable. The efficacy of classical adjuvant therapies, such as radiotherapy and chemotherapy, in management of persistent, recurrent, or metastatic disease has been disappointing. In metastatic disease the goal of therapeutic support is to control the PTH-driven hypercalcemia that represents the primary cause of mortality. Calcimimetics, which are allosteric modulators of the calcium sensing receptor, have a sustained effect in lowering serum calcium levels. Bone anti-resorptive therapy, like intravenous bisphosphonates (pamidronate and zolendronate), or more recently denosumab (fully human monoclonal antibody with high affinity to bind RANK ligand) might be temporarily useful. In a small number of cases treated with anti-PTH immunotherapy, inducing anti-PTH antibodies, promising results have been seen with clinical improvements and decrease of calcemia. In one case metastasis shrinkage has been observed.

Keywords: Parathyroid carcinoma; Hypercalcemia; PTH ratio; Surgery; Immunotherapy

Résumé

Néoplasie endocrinien rarissime, le carcinome parathyroïdien affecte 0,5 à 5 % des patients souffrant d'hyperparathyroïdie primaire. Ce cancer énigmatique pose une grande difficulté diagnostique et thérapeutique du fait de sa rareté, de l'absence de signes cliniques et paracliniques caractéristiques, qui miment ceux de l'hyperparathyroïdie primaire bénigne. Le ratio entre les valeurs de la PTH dosées avec les kits de troisième/deuxième génération, fournit actuellement des informations très précieuses dans le diagnostic différentiel de l'hyperparathyroïdie primaire bénigne et le carcinome parathyroïdien. Un ratio anormal (> 1) soulève une grande suspicion de carcinome et de maladie métastatique. Le meilleur traitement, à visée curative, demeure la chirurgie avec résection « en bloc » de la tumeur primitive avec marges de sécurité oncologique. Dans le cas de la maladie métastatique, une survie assez prolongée est possible, aux prix des multiples interventions, la guérison n'étant que très rarement acquise. L'efficacité des thérapies adjuvantes classiques, comme la radiothérapie ou la chimiothérapie, dans le contrôle d'une maladie évolutive, récurrente ou métastatique, est très décevante. Dans la maladie métastatique, le but du traitement est de maîtriser l'hypercalcémie maligne PTH-induite, qui représente la première cause de mortalité. Les calcimimétiques, modulateurs allostériques du récepteur sensible au calcium, ont un effet significatif dans la réduction des taux de calcium sériques. La thérapie antiresorbtive, avec puissants bisphosponates en intraveineux (pamidronate et zolendronate), ou plus récemment le dénosumab (anticorps monoclonal humanisé, avec grande affinité pour le RANK-ligand) peut se montrer d'une utilité temporaire. Dans quelques cas, l'immunothérapie anti-PTH a montré des résultats encourageants, avec induction d'anticorps anti-PTH, suivie d'amélioration clinique et réduction de la calcémie. Dans un cas, une régression des métastases a été observée.

Mots clés : Carcinome parathyroïdien ; Hypercalcémie ; PTH ratio ; Chirurgie ; Immunothérapie

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1. Introduction

A very rare malignancy, parathyroid carcinoma represents less than 0.005% of all cancers. It is also a very rare endocrine cancer (<1% of all cases of primary hyperparathyroidism) with a reported incidence ranging from 0.5 to 5% with some geographic variation (1% in Europe and USA and about 5% in Japan) [1–4].

Since the first description of a parathyroid carcinoma by De Quervain in 1904 [5], nearly 1000 cases have been reported around the world [1,2,4,6].

The great majority of parathyroid carcinomas are secreting tumors, presenting as primary hyperparathyroidism (which is the third most frequent endocrine disorder [7]). This apparently benign presentation is responsible in part for the great diagnostic difficulty.

More frequently, the diagnosis is retrospective, either during surgery, or, most likely, consequent to histologic analysis. However, it is not rare to observe the relapse of hypercalcemia due to metastatic disease years after the initial surgery.

The only curative treatment is surgery. Due to the very low incidence of parathyroid carcinoma and the lack of specific clinical and paraclinical signs, surgery of primary hyperparathyroidism is rarely performed as a specific anti-cancer intervention.

Most experts recommend *en bloc* resection, which is the minimum requirement for obtaining the best survival rates. Despite these recommendations, most retrospective studies have shown that the commonest surgical technique is actually simple local excision, performed in over 50% of interventions [3,8,9]. This oncologically-incomplete technique leads to a significant increase of the recurrence and mortality risks to 60% and 35% of cases, respectively [3,8,9]. Most likely, this important discrepancy between expert recommendations and clinical practice is due to the lack of pre-surgical factors that could raise the clinical suspicion of a parathyroid carcinoma in regard to the numerous cases of benign primary hyperparathyroidism.

Therefore, it becomes of paramount importance to identify the very few patients at risk of having a parathyroid cancer among the large group of patients suffering from primary hyperparathyroidism.

In this brief overview we will present, in light of the latest research, the clinical, biological and imaging parameters that may raise suspicion of malignancy in patients with primary hyperparathyroidism prior to surgery. Also, we will focus on the novel therapeutic possibilities in the management of metastatic disease.

2. Epidemiology

The rarest cause of primary hyperparathyroidism (PHPT), parathyroid carcinoma (PC) has an incidence of less than 1% of PHPT patients reported in the USA and Europe. It accounted for 0.005% of all malignancies according to the National Cancer Data Base from 1985–1995 and Surveillance, Epidemiology, and End Results (SEER) Cancer Registry from 1988 through 2003 [1,3,4,6]. The incidence was 5.1% of cases of PHPT in a national survey in Japan from 1980 to 1989, suggesting that there may be significant regional variations [2]. Parathyroid carcinoma occurs with equal frequency in men and women. There is a slight male predominance in some series, in contrast with benign PHPT where females predominate. Classically, the disease is described to occur one decade earlier than primary benign HPT, but the largest registry studies do not seem to confirm these data, as the mean age at diagnosis was found between 54–56 years [3,4,10–12], similar to benign HPT.

3. Etiology and risk factors

The etiology of parathyroid cancer, like that of other malignancies, is unknown. It is obvious that multiple environmental and genetic factors interact in a very complex manner. Exposure to radiation therapy, especially at a young age, increases the risk of benign parathyroid disease [13,14], as well as of thyroid and parathyroid neoplasia [15–18]. Nonetheless, whether such exposure represents a potential etiologic factor in parathyroid cancer is still unclear.

Parathyroid cancer usually occurs sporadically, but it has also been reported as part of genetic syndromes. These syndromes include the rare autosomal-dominant disorder familial hyperparathyroidism [11,19–21], as well as multiple endocrine neoplasia types 1 (MEN1) and 2A (MEN 2A) [22–25]. The most recent advances in the understanding of parathyroid cancer genetics have come from clinical and genetic studies of patients with hyperparathyroidism-jaw tumor syndrome (HPT-JT), a rare autosomal dominant familial disorder. In this syndrome the affected individuals develop primary hyperparathyroidism, mandibular and maxillary fibro-osseous lesions and renal and/or uterine tumors. Up to 15% of patients with HPT-JT develop parathyroid cancer. The gene responsible for this syndrome is known as *HRPT2/CDC73*, located at 1q13 and coding for a nuclear protein named parafibromin [26], which acts as a regulator of transcription. Mutations in *HRPT2/CDC73* gene were found in around 25% of cases with apparently sporadic parathyroid carcinoma [27–30]. Genetic DNA analysis for germline mutation in *HRPT2/CDC73* gene is recommended in all patients with parathyroid cancer, due to the potential benefit for offspring and their surveillance.

Immunohistochemical analysis of parathyroid tumors for loss of parafibromin expression offers new promise as a diagnostic tool that could facilitate the histologic diagnosis of parathyroid carcinoma, which is often far from obvious [31].

Other somatic gene mutations have been involved in the development of parathyroid carcinoma, including aberrant expression of retinoblastoma (RB) and p53 protein, but no clinically significant conclusions have been reached [29].

4. Clinical features

When evaluating a patient with primary hyperparathyroidism, the most important goal is to differentiate between benign and malignant disease prior to surgery. This can be difficult as there are no specific clinical characteristics that allow differentiation of parathyroid cancer from benign disease. As the majority of parathyroid cancers are functioning tumors, many clinical symptoms are similar to those of benign