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Two case reports of parathyroid carcinoma and review of the literature

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ABSTRACT

Parathyroid carcinoma is an infrequent endocrine malignant neoplasm with an aggressive behavior. Two cases of parathyroid carcinoma are described, one with a late diagnosis after previous surgeries for parathyroid hyperplasia, and the other diagnosed after pathologic fracture. The aim of this article is to make a review on recent parathyroid carcinoma literature and discuss these two illustrating cases. There has not been established any etiology for parathyroid carcinoma and no predisposing factors were identified. Parathyroid carcinoma may occur sporadically or as part of a genetic syndrome. The clinical features of parathyroid carcinoma are similar to benign cases of hyperparathyroidism and the pathologic diagnose is difficult. In the absence of metastatic disease in addition to a similar clinical setting, it can be difficult to distinguish benign and malignant hyperparathyroidism. Parathyroid carcinoma is a rare disease which diagnose can be challenging. Recent advances in immunohistochemical analysis may have helped in histopathologic evaluation, but pre-operative detection relies on imaging exams that may not differentiate malignant from benign hyperparathyroidism. The first surgical approach is paramount for disease control. There is still few effective therapeutic options for recurrent and metastatic disease, and these patients' prognostic status remain poor. Promising results were observed with denosumab and PTH immunization, and they may be a useful therapy for advanced cases in the future, but further investigation is required.
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1. Introduction

Parathyroid carcinoma is an endocrine malignant neoplasm with an aggressive behavior. It was first described in 1904 by Fritz De Quervain, when he reported a case of non-functioning neoplasm, and then, 26 years later, Sainton and Millot described the first functioning parathyroid carcinoma.[1,2] It is an infrequent neoplasm, with a prevalence of 0,005% of all cancers and accounting for 0,4–5% of all cases of primary hyperparathyroidism.[3] There is no gender dominance in parathyroid carcinoma and its onset is usually a decade earlier than parathyroid adenomas, with a mean age of 45–59 years.[4,5,6] It has not been described any preponderance concerning race, income level or geographic region in the literature.[5]

2. Objective

The aim of this article is to make a review on recent parathyroid carcinoma literature and discuss two illustrating cases.

2.1. Etiology

There has not been established any etiology for parathyroid carcinoma and no predisposing factors were identified, it seems to be a result of a complex intereaction of environmental factors and inherited genetic predispositions. There have not been established a definite progression sequence of benign to malignant lesions. The absence of conclusive data is attributed to the rarity of this tumor.[7] Neck radiation, adenoma, secondary and tertiary hyperparathyroidism have been reported in patients with parathyroid

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carcinoma.[8]

Parathyroid carcinoma may occur sporadically or as part of a genetic syndrome. Multiple endocrine neoplasia type 1, 2A and isolated familial hyperparathyroidism are syndrome describes to be associated with parathyroid carcinoma. Additionally, 15% of patients with hyperparathyroidism jaw tumor syndrome may develop parathyroid carcinoma.[9] Somatic genes mutations have been associated with parathyroid carcinoma, such as HRPT2 (CDC73, or Parafibromin) gene mutation, abnormal expression of the retinoblastoma and p53 proteins, and tumor suppressor gene on chromosome 13 on the surroundings of retinoblastoma gene. Sporadic cases have also been associated with HRPT2 mutations in up to 25%. Albeit these discoveries, these molecular changes have been identified in studies with small cohort of tumor samples and further investigations is required.[10–12]

2.2. Clinical and laboratory features

The clinical features of parathyroid carcinoma are similar to benign cases of hyperparathyroidism and the pathologic diagnose is difficult. These factors make parathyroid carcinoma a challenge. Aside from that, less than 10% of parathyroid carcinoma cases are nonfunctional. The majority presents as functioning tumors with hypercalcemia and its symptoms, such as depression, anxiety, weight loss, weakness, bone disease, renal involvement, abdominal pain, and peptic ulcer disease. Skeletal involvement includes osteopenia, bone pain, osteoporosis, osteofibrosis and pathologic fractures (found in up to 90%) of patients. Renal disease manifest as nephrolithiasis and renal insufficiency (seen in up to 80%).[3,13–16] Other clinical signs that may help are palpable neck mass and hoarseness.[7] Serum calcium levels are frequently higher than 14mg/dL and PTH serum levels are commonly 3 to 10 times higher than the upper limit of normal.[6,17,18] It has been described recently the method which third to second generation parathormone (PTH) ratio is calculated and a result higher than one can predict whether the tumor is malignant with a sensitivity of 75–82% and a specificity of 97–98%. This result relies on the tendency of the parathyroid carcinoma in producing more amino-PTH, which is identified by third generation assays.[19–22] Levels of alkaline phosphatase and alfa and beta subunits of human chorionic gonadotropin may be higher in malignant primary hyperthyroidism than in benign cases.[23,24]

2.3. Imaging

The absence of metastatic disease in addition to a similar clinical setting, it can be difficult to distinguish benign and malignant hyperparathyroidism. Aside from that, all patients with hyperparathyroidism need to have their disease extension evaluated for treatment planning.[7] The diagnostic sensitivity and accuracy are increased when more than one imaging method is used.[4] The imaging modalities that have been used are ultrasonography, sestamibi scanning, computed tomography (CT), single-photon emission CT, magnetic resonance imaging (MRI), and positron emission tomography.[25–28]

Ultrasonography is a noninvasive and inexpensive method and for this reason is the most commonly used method.[9] Despite not being able to definitely discern malignant from benigns cases, some sonographic features may suggest carcinoma.[29] Parathyroid carcinoma usually presents as lobulated, hypoecoic and relatively large and ill-defined borders when compared to adenomas,[30,31] associated to local infiltration, calcification, suspicious vascularity and a thick capsule have been predictive of malignancy. Ultrasonography can also detect lymph node enlargement and invasion of the tumor to adjacent structures.[9]

Other imaging modality frequently used along with cervical ultrasonography is Technetium-99mm sestamibi scintigraphy.[32] Increased and prolonged uptake of this isotope is generally found in hyperfunctioning parathyroid tissue,[7] thus sestamibi scanning is a localization study that cannot differentiate benign from malignant cases, but it may be useful in diagnosis and localizing ectopic hyperfunctioning tissue and metastatic disease.[7,32,33]Nonetheless, this method is not completely specific for parathyroid tissue and thyroid nodules can have proeminent and delayed imaging.[33] Single photon emission computed tomography (SPECT) can simplify the localization of a parathyroid lesion, improving the sensitivity of 99mTc sestamibi scintigraphy.[34]

Computed tomography (CT) is an additional diagnostic method because it lacks sensitivity in detecting parathyroid carcinoma.[35] The same can be applied to MRI. These method may provide anatomical description of the lesion and its extent and also can detect other involved regions, making them useful for determining recurrence and metastatic spread.[9,4] When these modalities are used, it is useful to have an additional method such as ultrasonography and sestamibi scanning to determine the most likely site of abnormal glands and differentiate normal gland from lymph nodes and other unrelated structures.[36]

The sensitivity for localizing parathyroid carcinoma in the neck using ultrasonography, 99mTc sestamibi scan, CT and MRI were, respectively, 83%, 79%, 69% and 93%.[37]

Other diagnostic method that can localize functioning parathyroid tissue is selective venous catheterization with PTH measurement, and some studies have shown that it can demonstrate high sensitivity in localization.[38,39] Albeit its sensitivity, this is an invasive and not commonly available studies, being recommended only when other noninvasive studies fail to localize the disease or results are questionable.[40]

In the set of recurrence suspicion, when there is laboratory suggestion, imaging studies is essential. It is recommended two concordant studies, that may include ultrasound, CT, MRI, sestamibi scan, PET CT and/or highly selective venous sampling for PTH assay.[4]

2.4. Cytology and histopathology

Fine-needle aspiration cytology should be avoided,[41] because discerning between malignant and benign disease on cytology is challenging[4] and this procedure may cause tumor disruption and its seeding through the needle tract, leading to higher chances of recurrence.[4,35] However, it may be useful in distinguishing thyroid from parathyroid tissue or identifying metastatic parathyroid carcinoma.[42]

Intraoperative findings that suggest carcinoma are large grayish to white tumors, usually with 3cm or more. They are firm and can be adherent or invade surrounding structures, and it has been described a cystic component in 21% of the cases.[4] In the absence of preoperative or intraoperative clear signs of carcinoma, frozen section analysis may not help, since carcinoma and adenoma histopathological features are similar and sometimes indistinguishable.[43,7] It has been described morphologic features that may suggest parathyroid carcinoma,[4] which include fibrous band with a trabecular architecture (90%), capsular invasion (60%), vascular invasion (15%) and mitotic activity (80%).[4] Nonetheless, not all parathyroid carcinoma display these finding and they are not specific for malignancy.[44–48] In the absence of vascular invasion, perineural invasion, invasion to adjacent structures and metastasis, parathyroid carcinoma should not be yielded.[7]

Some borderline cases have been previously described as atypical parathyroid adenomas, but recent disclosures concerning biomarkers in molecular pathology have helped distinguishing

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