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Surgical management of parathyroid carcinoma

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Cancer of the parathyroid glands is an exceedingly rare endocrine malignancy representing a very uncommon cause of primary hyperparathyroidism. It is characterized by markedly increased serum calcium and parathyroid hormone (PTH) levels far in excess of those exhibited by benign parathyroid disease. Diagnosis is made by histopathology, which may be problematic before initiating treatment for hyperparathyroidism. Because of its rarity, both staging classification and prognostic factors have been difficult to define and less useful in predicting the course of disease and treatment outcomes. Effective management involves comprehensive surgical resection, which offers the best opportunity for cure. Both radiotherapy and chemotherapy are largely ineffective modalities for treatment. Recurrent disease is generally incurable; however, repeat surgery and medical management of tumor-induced hypercalcemia may provide intermediate-term palliation.

Introduction and background

Parathyroid carcinoma is a very rare malignancy, representing less than 0.005% of all cancers. It represents less than 1% of all patients with primary hyperparathyroidism, with a reported incidence ranging from 0.525%-5% with some geographic variation (1% in Europe and the United States and approximately 5% in Japan).[1]

Since its first description in 1904 by de Quervain,[2] approximately 1,000 cases have been reported worldwide. Unlike many other endocrinopathies, parathyroid carcinoma may affect men and women equally and is noted for being more hormonally active than its benign counterpart. Despite the relative rarity of parathyroid carcinoma, it has been well characterized in the literature and has been extensively described both clinically and histopathologically.

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The etiology of parathyroid carcinoma, like that of most other malignancies, has not been characterized. Exposure to ionizing radiation, either diagnostic or therapeutic, especially at a young age, increases the risk of benign parathyroid disease, but this has not been described specifically for the development of parathyroid carcinoma. Parathyroid carcinoma generally occurs sporadically but may also occur as a component of genetic syndromes including familial hyperparathyroidism, a rare autosomal-dominant disorder, as well as multiple endocrine neoplasia types 1 and 2A.[3] A more contemporary understanding of parathyroid cancer genetics has been derived from both clinical and genetic studies of patients with hyperparathyroidism-jaw tumor syndrome, an autosomal-dominant familial disorder. Affected individuals with this syndrome may develop primary hyperparathyroidism, mandibular and maxillary fibro-osseous lesions, and renal or uterine tumors. Up to 15% of patients with this syndrome may develop parathyroid cancer (Figure 1). Development of the syndrome is linked to the gene known as HRPT2/CDC73 that is located at the locus 1q 13, and which codes for a nuclear protein named parafibromin, which acts as a

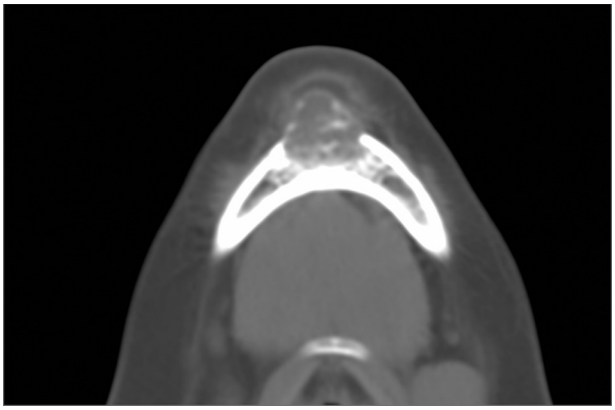

Figure 1 Radiograph demonstrating giant cell tumor of the jaw in a 13-years-old man with HPT-JT syndrome and parathyroid carcinoma. HPT-JT, hyperparathyroidism-jaw tumor syndrome.

regulator of transcription.[4] Mutations in this gene were noted in approximately 25% of cases with apparently sporadic parathyroid carcinoma. Immunohistochemical analysis of parathyroid tumors for loss of parafibromin expression may offer the possibility of a more definitive histologic diagnosis of parathyroid carcinoma, not otherwise readily evident.

Presentation and diagnosis

Parathyroid carcinoma poses a formidable diagnostic challenge both clinically and histologically owing to a lack of definitive distinguishing features separating benign from malignant disease early in the course of disease development. Parathyroid carcinoma frequently presents with more severe levels of hypercalcemia than are usually associated with primary hyperparathyroidism caused by parathyroid adenoma or hyperplasia. Concurrent higher levels of intact PTH are usually found associated with these increased levels of hypercalcemia. The subtle symptoms associated with primary hyperparathyroidism occurring because of benign parathyroid disease may be noted within a constellation of additional symptoms, which should raise suspicion as to the presence of parathyroid carcinoma. These include osteitis fibrosis cystica, diffuse osteopenia, osteoporosis, bone pain and pathologic fracture, and renal calculi with progressive renal insufficiency. In general, there are no specific clinical characteristics that allow differentiation of parathyroid cancer from benign parathyroid disease. Certain characteristics are considered to represent high-risk indicators for the presence of parathyroid carcinoma. These include severe hypercalcemia, relatively young age, male sex, hypercalcemic crisis, synchronous renal and bone involvement, and the rare presence of a palpable neck mass, all of which should raise the suspicion of parathyroid carcinoma. Patients presenting with this combination of symptoms have a 4.5-fold increased risk of having parathyroid cancer when compared with minimally or asymptomatic patients.[5-7]

In patients suspected of potentially harboring parathyroid carcinoma based on clinical presentation, securing a definitive preoperative diagnosis of cancer is quite challenging. More often, the circumstances involve a suspicion that cancer is present in the setting of severe primary hyperparathyroidism, reserving tissue diagnosis until the operation is commenced or as revealed in a subsequent histologic diagnosis postoperatively. In general, intact PTH levels may be quite high in both malignant and benign parathyroid disease. When associated with severe levels of hypercalcemia (>12-13 mg/dL), the presence of malignant disease must be considered, especially when combined with the presence of clinical symptoms. A relatively recent diagnostic application, which uses both second- and third-generation PTH assays as a ratio, has been employed as a differentiating indicator for the presence of parathyroid carcinoma. Using this method, a ratio of PTH measurement is obtained by dividing third generation by second-generation assay results.[8] The mechanism applied in this measurement ratio is derived from the fact that the amino-PTH molecule, which has been shown to be overproduced in parathyroid carcinoma, is recognized by third-generation PTH assays but not by the antibodies used in the second-generation PTH kits.[9] In healthy individuals, a ratio of PTH levels (third or second) would generally not exceed 1:1 ratio. However, in patients with parathyroid carcinoma, this ratio may be found to be significantly greater than 1. A recent series of patients was described whereby a greater than 1:1 PTH ratio was noted in 83% of patients with advanced parathyroid carcinoma as compared to 0% in otherwise healthy control patients. This would indicate that a third generation to second-generation ratio exceeding 1:1 represents a tumor marker for parathyroid carcinoma with a sensitivity of approximately 79% and a specificity of approximately 99% among patients with primary hyperparathyroidism.[10,11]

Ultrasound evaluation of the neck in the setting of hyperparathyroidism may be used for both identification and localization of enlarged parathyroid glands. Although fine-needle aspiration biopsy technique using ultrasound guidance has been performed successfully in the identification of abnormal hyperfunctioning parathyroid glands in the setting of benign disease, it may be ill advised to use this technique for suspected malignant parathyroid glands owing to the potential for extraglandular seeding of tumor into the surrounding soft tissue. Moreover, cytology obtained using this technique may not be sufficient to differentiate between benign and malignant disease. Parathyroid carcinoma may appear on ultrasound evaluation to demonstrate large (>3 cm) hypoechoic lobulated lesions with irregular borders when compared with more clearly defined smooth parathyroid adenomas.[12] The presence of hypervascularity, calcifications, thick capsule, and soft tissue infiltration on ultrasound raises the suspicion for the presence of malignancy.[13]

In the absence of a definitive diagnosis of malignancy for patients with hyperparathyroidism, imaging techniques provide valuable information with respect to localization of diseased glands as well as demonstrating characteristics suggestive for malignancy. For patients in whom the diagnosis is established before surgery, localization techniques combining both anatomical and physiological modalities are necessary for