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Review

Parathyroid carcinoma

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ABSTRACT

Parathyroid carcinoma is a rare form of endocrine malignancy accounting for only a small minority of cancer cases. Due to the rarity of this cancer, there are no generalized guidelines for its management; however, surgery remains to be the mainstay therapy. The purpose of this article is to review and summarize the available literature on parathyroid carcinoma, while discussing proposed staging systems and the role of available adjuvant therapies.

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Introduction

Parathyroid carcinoma is a rare endocrine malignancy, accounting for an estimated 0.005% of all cancers [1–6]. This entity was first described by the Swiss surgeon Fritz De Quervain in 1904 [7], and since, less than 1000 cases have been reported in the literature worldwide [1,5,8]. It is generally accepted that parathyroid carcinoma accounts for less than 1% of cases of primary

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hyperparathyroidism [5,9], however, this number has been reported to be higher in some publications, reaching up to 5% [10–13]. Due to its rarity and the paucity of large-scale published series of patients with parathyroid cancer, there still is a lack of understanding of the natural course and prognostic implications of this disease. In addition, there is still no clear consensus regarding its management and follow-up. The purpose of this review is to discuss and summarize the available literature on parathyroid carcinoma, and to explore the currently recommended modes of treatment of this rare malignancy.

Epidemiology

Unlike parathyroid adenoma, which is three times more common in females than in males, no gender preponderance has been demonstrated in parathyroid carcinoma [5,6,14,15]. The mean age of presentation is reported to be between 45 and 59 years, which is a decade younger than that in patients with parathyroid adenomas [5,6,15]. No disproportionate clustering by race, income level, or geographic region has been demonstrated in the literature. The SEER (Surveillance, Epidemiology, and End Results) cancer registry identified 224 patients with parathyroid carcinoma from 1988 to 2003. During this time period, the incidence of parathyroid cancer was found to be very low (<1 per million population per year), however, incidence was shown to increase from 3.58 to 5.73 per 10 million population when comparing the first three years to the last three years of the study. It was assumed that this increase may be secondary to routine serum calcium screening, which may have identified more patients with asymptomatic parathyroid carcinoma [4].

Etiology and pathogenesis

The etiology of parathyroid cancer is unknown, and to date, no established predisposing factors have been identified. However, history of neck radiation is a known risk factor of head and neck cancers, and cases of patients with parathyroid carcinoma who previously received radiation therapy to the neck have been described [11,16–19]. Other associated factors previously described include secondary and tertiary hyperparathyroidism caused by chronic renal failure [20]. Currently, there is no evidence that parathyroid carcinoma arises from malignant transformation of preexisting parathyroid or thyroid lesions. However, an association between parathyroid cancer and hyper-functioning parathyroid glands or thyroid cancer has previously been observed [15,21,22].

Parathyroid carcinoma may occur sporadically or as part of a genetic syndrome. These syndromes include MEN1, MEN2A, and isolated familial hyperparathyroidism [3,23–26]. In addition, 15% of patients with hyperparathyroidism jaw tumor syndrome (HPT-JT), an autosomal dominant type of familial hyperparathyroidism, develop parathyroid carcinoma [5,24,25,27,28]. Advances in molecular biology increased our understanding of the pathogenesis of this malignancy. A mutation in HRPT2 (also known as CDC73), a tumor suppressor gene, has been recognized to play a fundamental role in the molecular pathogenesis of parathyroid carcinoma [24]. This gene, which is located on chromosome 1, encodes the protein parafibromin, whose function involves regulation of gene expression and inhibition of cell proliferation. Inactivating germline mutations of this gene are responsible for the development of HPT-JT [27,29]. In addition to the increased risk of parathyroid malignancy, these patients are predisposed to develop ossifying fibromas of the jaw, cystic and neoplastic renal lesions, and uterine tumors [30].

It should be noted that sporadic cases of parathyroid carcinoma have also frequently been shown to be associated with HRPT2 mutations, with a reported rate of 25% [31–33]. In a study attempting to evaluate the value of parafibromin immunostaining in parathyroid carcinoma diagnosis, tumor specimens were obtained from 16 patients with parathyroid adenomas and 8 with parathyroid carcinoma [34]. All were immune-stained with a parafibromin antibody and the expression of parafibromin was analyzed. Parafibromin stained strongly positive in 17 of 18 adenomas (94.4%) (indicating normal expression of parafibromin) and in only 2 of the 8 carcinomas (25%). Negative staining was noted in 3 of 8 carcinomas, and weak positivity was found in 3 of 8 carcinomas. It was concluded by the authors that the loss of parafibromin expression (negative or weak positivity) demonstrated 94.4% specificity in the diagnosis of parathyroid carcinomas. However, clinical application of this finding is yet to be established.

Other somatic gene mutations have been implicated in the development of parathyroid carcinoma, including abnormal expression of the retinoblastoma and p53 proteins. Also, the presence of an additional tumor suppressor gene on chromosome 13 in the vicinity of retinoblastoma gene has been proposed [35-37]. However, no clinically significant conclusions have been reached, and further investigation is still required.

Clinical presentation

Patients with parathyroid adenomas typically present with mild symptoms of hypercalcemia, or are discovered incidentally upon routine blood tests that demonstrate elevated serum calcium levels. In contrast, in patients with parathyroid cancer, signs and symptoms of severe hypercalcemia often dominate the clinical presentation. These include polydipsia or polyuria, myalgia or arthralgia, nephrolithiasis, weakness, fatigue, nervousness, depression, renal insufficiency, pancreatitis, peptic ulcer disease, or weight loss [11,13,38–40]. Skeletal involvement is also common at the time of presentation, and may manifest as bone pain, osteopenia, osteofibrosis, or pathological fractures [15,41]. Renal and skeletal involvement in particular are a prominent manifestations of parathyroid carcinoma, and are reported to occur in some series in up to 80 and 90% of patients, respectively [38,42]. Two to seven percent of patients are asymptomatic [11,38,42,43].

Some patients with parathyroid carcinoma may present with hypercalcemic crisis, also referred to as parathyroxicosis [44]. This life-threatening condition is characterized by azotemia, oliguria and anuria, as well as neurological manifestations such as profound weakness, somnolence and coma. This emergency is usually associated with severe hypercalcemia (>16 mg/dl), and requires urgent medical attention. Parathyroid crisis is reported to be the presenting manifestation in 7–12% of patients with parathyroid carcinoma [11,14,19,45]. However, it should be noted that patients with primary hyperparathyroidism due to benign causes may also present with hypercalcemic crisis.

As many as 10% of the patients with parathyroid carcinoma have a nonfunctioning tumor [46,47]. Unlike functioning tumors, patients usually present late, with symptoms related to “mass effect”, including a palpable neck mass, hoarseness (due to recurrent laryngeal nerve involvement), dysphagia or dyspnea [46,48–50]. Rare cases of incidental nonfunctional parathyroid carcinoma have also been described [51].

On physical examination, unlike benign parathyroid tumors which are almost never palpable, a neck mass can be palpable in 40–70% of cases of parathyroid carcinoma [2,8,11,14,38,52]. This finding, in the presence of hyperparathyroidism, should immediately trigger the clinician’s suspicion of a malignant parathyroid tumor. The presence of a paralyzed recurrent laryngeal nerve (as demonstrated by a paralyzed vocal cord on laryngoscopic