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Review Article

Parathyroid carcinoma an unusual endocrine neoplasm: current review

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ABSTRACT

Parathyroid carcinoma is an unusual endocrine neoplasm, in practice, diagnosis and clinical approach is challenging, it could be suspected during pre-surgical approach or in the same surgical procedure, however most of the cases get the diagnosis with histopathology time after surgery, radical surgical approach is the first line treatment of choice, with bloc resection of parathyroid tumor, with the excision of ipsilateral thyroid lobe, cause is unknown, it generally arises as a sporadic disease, although familial cases have been described, most have a painless course, and the most frequent clinical manifestations are due to hypercalcemia secondary to excessive parathyroid hormone secretion by the tumor, on physical examination there is usually nothing evident, mortality is generally due to intractable hypercalcemia rather than to tumor, survival at 5 and 10 years has been reported between 70 to 100% and 50 to 90% respectively.

Keywords: Parathyroid, Carcinoma, Endocrine, Neoplasm, Hypercalcemia

INTRODUCTION

Parathyroid carcinoma is an unusual endocrine neoplasm, represents the 0.005% of all neoplasms in America and great part of western countries, and less than 1% of sporadic primary hyperparathyroidism cases, most frequently a functional neoplasm, with indolent course and progression to local invasion, the main characteristics of presentation are related with parathyroid hormone and the clinical features related to hypercalcemia, as bone disease, renal alterations, cardiac arrythmias and neurological disorders, while clinical manifestations due to tumor size occur lately in course.[1]

Nonfunctional parathyroid carcinoma variant, which is characterized with normal levels of serum calcium and normal levels of parathyroid hormone is extremely rare, it accounts only the 2% of total parathyroid neoplasms, manifests mainly with signs and symptoms of tumor growth and tumoral invasion of adjacent structures.[2]

In practice, diagnosis and clinical approach is challenging, it could be suspected during pre-surgical approach or in the same surgical procedure, however most of the cases get the diagnosis with histopathology time after surgery, few cases can confirm diagnosis while long follow up when presenting local recurrence or distant metastases.[3]

A radical surgical approach is the first line treatment of choice, with bloc resection of parathyroid tumor, with the excision of ipsilateral thyroid lobe,[4] to obtain disease free margins of tumor resection.[5]

EPIDEMIOLOGICAL FEATURES

Estimated annual prevalence is 0.005% in America, with an incidence of 0.015 per 100,000 persons in general population.[6] An increase in incidence has been reported in some countries, probably due to the greater use of screening tools, changes in diagnostic criteria and true increase in incidence, literature describes both genders men and women are affected in same proportion, in comparison with primary hyperparathyroidism which has greater predilection for females, as well as the age of presentation, which is usually in fourth and fifth decade of

life, ten years earlier compared with primary hyperparathyroidism.[7]

ETIOLOGY

The cause is unknown, it generally arises as a sporadic disease, although familial cases have been described in literature, particularly the hyperparathyroidism – jaw tumor syndrome, which is a rare autosomal dominant disease, where 15% of sick individuals develop this carcinoma, some fewer common associations have been described, such as multiple endocrine neoplasia type 1 and multiple endocrine neoplasia type 2A.[6]

Mutations in the CDC73 tumor suppressor gene have been described in familial forms, as well as in some sporadic cases, this gene codes for a protein named parafibromin which functions as a tumor suppressor, it is involved in regulation of cell proliferation, apoptosis and chromosome stability, loss of parafibromin expression has been found in most of parathyroid carcinomas, but rarely found in parathyroid adenomas.[8]

CLINICAL FEATURES

Most parathyroid carcinomas have a painless course, and the most frequent clinical manifestations are due to hypercalcemia secondary to excessive parathyroid hormone secretion by the tumor, rather than local or distant organ spread; they are similar, although more serious than those related to benign pathologies.[6]

At the time of presentation, renal involvement with nephrolithiasis, nephrocalcinosis, decreased renal function and bone manifestations such as diffuse osteopenia, pathological fractures and bone pain are present in 80 to 90% of the patients, as well as salt and pepper subperiosteal resorption in the skull and osteitis fibrosa cystica in more than 40% of the X-rays.[7]

Other symptoms described include fatigue, malaise, weakness, polydipsia and polyuria, gastrointestinal symptoms such as nausea, vomiting, abdominal pain, peptic ulcer, recurrent severe pancreatitis, and constipation may also occur, none of the previously mentioned symptoms are pathognomonic, hence the challenge in the diagnosis and recognition between primary hyperparathyroidism and parathyroid carcinoma.[6]

The non–functioning variant of parathyroid neoplasm, very unusual and mostly present only manifestations due to local increase in size of tumor and invasion to adjacent structures, such as cervical mass, hoarseness, and dysphagia, with few exceptions, it generally occurs in patients between the sixth and seventh decade of life with ranges described between the ages of 20 and 70 years.[2]

On physical examination there is usually nothing evident, but the presence of a palpable neck mass and hoarseness strongly suggest parathyroid neoplasm, at initial presentation lymph node metastases occur in approximately 15–30% of patients, and one third have distant metastases, most commonly in lungs, liver, and bone.[1]

Most tend to recur locally, with extension to contiguous structures in the neck, recurrent disease is characterized by marked hypercalcemia and other metabolic complications, metastatic spread tends to occur lately in the course of the disease, with involvement of structures previously commented.[7]

Asynchronous parathyroid multiglandular involvement can occur in patients carrying the CDC73 germline mutation, so hypercalcemia after initial surgery may be due to recurrence and/or metastasis of the primary tumor or involvement of an additional parathyroid gland.[7]

DIAGNOSTIC APPROACH

Diagnosis is very complicated due to the lack of reliable clinical diagnostic criteria and in the vast majority of cases this is done after surgery in histological examination, presence of distant metastases is the only unequivocal criterion of malignancy, but this develops in the last stages during follow-up, suspicion during the preoperative approach is extremely relevant, since the best chance for a definitive cure depends on the initial surgery, which is recommended to be more extensive.[6,7]

Clinical characteristics that should lead us to suspect parathyroid carcinoma are male sex, mean age 50 years, evidence of renal and skeletal manifestations, neurological signs, palpable neck mass and/or laryngeal nerve palsy, elevated levels of parathyroid hormone 3 to 10 times the normal value, the combination of elevated serum calcium levels greater than 14 mg/dl, and patients with presence of primary hyperparathyroidism with serum ionized calcium levels >1.77 mmol/l.[4,9]

It can be suspected if large, whitish – gray, irregular, firm, hard and lobulated lesions greater than 3 centimeters are observed during the surgery, strongly adherent to contiguous structures, or when lymph node metastases are found in neck.[7]

There are standard imaging techniques such as neck ultrasound, Technetium 99 m sestamibi and in some cases computed tomography and magnetic resonance imaging, although sensitive, they have limited specificity since they cannot preoperatively distinguish between parathyroid carcinoma from a benign parathyroid gland tumor, unless local signs of invasion are evident.[10]

When at least three diagnostic imaging tools are used, sensitivity can reach up to 95%, fine needle aspiration biopsy should not be performed as it cannot distinguish between benign from malignant lesions and may be associated with risk of tumor seeding.[7]

The main challenge in the histopathological study is to be able to distinguish parathyroid carcinoma from atypical adenomas, since these share similar histological characteristics such as diffuse growth pattern, fibrous septa, and high mitotic activity; however unequivocal signs of malignancy are capsular, vascular, and perineural invasion.[11]

THERAPEUTIC MANAGEMENT

Surgery is the first line of treatment, preoperative suspicion, intraoperative recognition, and surgeon's experience are of great importance for an adequate surgical approach, standard approach is radical surgery, with bloc resection of the primary lesion and excision of the ipsilateral thyroid lobe and adjacent structures involved, with free margins in the initial surgery, any capsular rupture of the tumor and spillage of neoplastic cells should be avoided, since their seeding can lead to recurrence, the recurrent laryngeal nerve in the absence of signs of infiltration should be preserved, otherwise it should be removed, cervical lymph node dissection should be recommended in cases of evident metastasis, prophylactic dissection of the central compartment is still controversial, since it does not improve patient prognosis and may otherwise increase morbidity, successful surgery is usually followed by severe hypocalcemia and hypophosphatemia, called hungry bone syndrome requiring calcium and active D vitamin therapy.[4-7]

When diagnosis is made after surgical intervention with histological examination, management plan is more complicated, in this situation clinical judgment and a prompt decision should be made for cervical exploration versus continue follow-up, if there are histological signs of vascular or capsular invasion or if persistence of hypercalcemia exist, reoperation must be foreseen, if serum calcium levels and parathyroid hormone are normal, follow-up can be chosen.[7]

Postoperative adjuvant radiation has not been widely accepted in the treatment strategies, since parathyroid carcinoma is considered radioresistant, however some studies have shown lower recurrence rates, requiring further investigation, chemotherapy use is infrequent due to its low efficacy, tyrosine kinase inhibitors still require further evaluation.[12,13]

When there is metastatic disease and there is no possibility of surgical treatment, clinical management turns towards control of hypercalcemia, saline infusions and loop diuretics are generally used, but in most cases other medications are needed, as calcium receptor modulators, as well as bisphosphonates and denosumab can be used to reduce serum calcium levels.[6]

PROGNOSIS

Despite previously described management, recurrence occurs in more than 50% of patients, more often after 2 to 4 years, although disease-free intervals up to 20 years have also been reported in literature, appropriate localization studies should be performed before a reoperation, local recurrences and metastases to lymph nodes in the neck and mediastinum should be removed with wide margins if possible, reoperations may be required as they offer palliative options, although their morbidity must be taken into account, distant metastases should be resected if possible, although surgery is rarely curative, palliative volume reduction of tumor can increase efficacy of medical treatment to hypercalcemia control.[7,14]

Negative prognostic factors for survival are initial surgery limited only to parathyroidectomy, elevated serum calcium at time of recurrence, recurrent disease, presence of distant metastases, need to use medication to control serum calcium levels, and non-functioning parathyroid carcinoma variant.[5]

Mortality is generally due to intractable hypercalcemia rather than to tumor, survival at 5 and 10 years has been reported between 70 to 100% and 50 to 90% respectively.[15]

CONCLUSION

Parathyroid carcinoma is an endocrine neoplasm with an indolent tendency towards local invasion, therefore classic manifestations are related to hypercalcemia due to parathyroid hormone levels, with manifestations due to tumor size that occur lately in history.

Diagnosis is difficult and challenging, preoperative clinical suspicion should be continued with a more aggressive immediate surgical approach compared to benign disease, the surgical approach continues to be the first line of treatment and strict surveillance is mandatory for early identification of recurrence or metastasis.

If necessary, reoperations should be performed, even if they are palliative options, although their morbidity must be considered, if the tumor is not a candidate for surgical treatment for resection, medical treatment for hypercalcemia becomes essential in these patients.

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