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Parathyroid Carcinoma: A Rare Endocrine Malignancy

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ABSTRACT

Introduction: Parathyroid carcinoma is a rare neoplasm that may present sporadically or in the context of a genetic syndrome. Diagnosis and management are challenging due to the lack of consensus on the optimal management strategy.

Case report: We report the case of a 51years old male, diagnosed initially with parathyroid carcinoma, and presented recurrence and lymph node involvement.

Conclusions: Parathyroid carcinoma is a very rare cancer, that continues to pose considerable challenges in terms of diagnosis and management. The aim of parathyroid carcinoma therapy is not only oncological, but also to achieve biochemical remission. Surgery is the gold standard treatment of this entity. Future prospective randomized studies are needed to assess the effects of different surgical approaches on morbidity, mortality and oncological outcomes.

Key words: Parathyroid - Carcinoma - Hyperparathyroidism - Management - Prognosis.

INTRODUCTION

Parathyroid carcinoma is an uncommon malignancy originated from parathyroid parenchymal cells which has been described as the rarest endocrine malignancy [1,2]. It is usually associated with more severe clinical manifestations than parathyroid adenoma [3]. Diagnosis is generally confirmed only after surgery by anatomopathological analysis unless there is preoperative evidence of local invasion, cervical lymph nodes, or distant metastases [4].

It's important to consider parathyroid carcinoma in the differential diagnosis of hypercalcemic disorders, as morbidity and mortality are significant and the best prognosis is associated with early detection and surgical resection [5]. Due to its rarity, there is currently no consensus on the optimal management strategy of this entity [2].

The aim of our case report is to highlight diagnosis and management challenges of parathyroid carcinoma.

CASE REPORT

A 51 years-old male patient, with a medical history, the observation 9 years before, of a left anterior cervical swelling. A cervical ultrasound was performed (no available documents), and the patient underwent a lobo-isthmectomy, and the histopathological study showed no signs of malignancy.

Five years after, due to lower back pain and irritability, a phosphocalcic assessment was requested, revealing hypercalcemia with elevated PTH levels. Further evaluation included a cervical ultrasound and a Sesta

MIBI scintigraphy that showed intense left fixation. The patient underwent a right parathyroidectomy (superior and inferior) and a left parathyroidectomy (inferior), along with total thyroidectomy. The histopathological study revealed:

- ✓ Left inferior parathyroid mass: initially suggestive of parathyroid carcinoma. Immunohistochemical confirmation compatible with parathyroid carcinoma with invasion of peritumoral soft tissues.
- ✓ Right superior parathyroid: Hyperplasia.
- ✓ Right inferior parathyroid: Hyperplasia.
- ✓ Total thyroid specimen: nodular dystrophic thyroid parenchyma.

Postoperative course was marked by acute hypocalcemia, and the patient was subsequently placed on Levothyroxine, Alfacalcidiol, and Calcium, which were discontinued later after one year due to reascension calcium levels. The patient was hospitalized in our department. Clinical examination was normal. Biological tests showed hypercalcemia to 148 mg/dL and elevated PTH to 330 pg/ml. Correction of hypercalcemia was administered (intravenous hydration + Furosemide + Methylprednisolone + Zoledronic acid), resulting in a control calcium level of 99 mg/dL. Further investigations included:

- ✓ Parathyroid scintigraphy (Tc99m-MIBI): Two nodular MIBI-Tc retention foci projecting towards the mediastinum and lateralization to the left suggesting ectopic parathyroid tissues (Figure1).
- ✓ FDG18 PET scan: Two hypermetabolic nodular foci retro and supra-sternal on the left suggesting ectopic mediastinal location, with no metabolic evidence of secondary involvement in the liver, lungs, adrenal glands, or bones (Figure 2).

Surgical management was planned, the patient underwent surgical removal of individualized lesions along with a large lymph node dissection. The pathological analysis revealed: Recurrence and cervical and mediastinal lymph node involvement of the previously diagnosed and treated parathyroid carcinoma.

The patient experienced postoperative hypocalcemia, for which he received intravenous correction, and started after oral alfacalcidiol-calcium supplementation. Calcemia and PTH levels remained normal under supplementation. No further or adjuvant treatment was indicated, a close follow-up is planned.

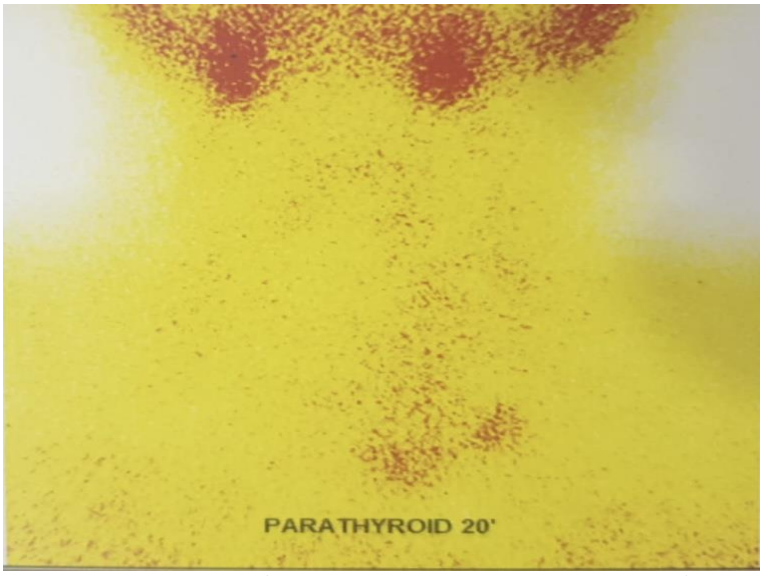

Figure 1 : Parathyroid scintigraphy (Tc99m-MIBI) of our patients showing Two nodular retention foci projecting towards the mediastinum and lateralization to the left.

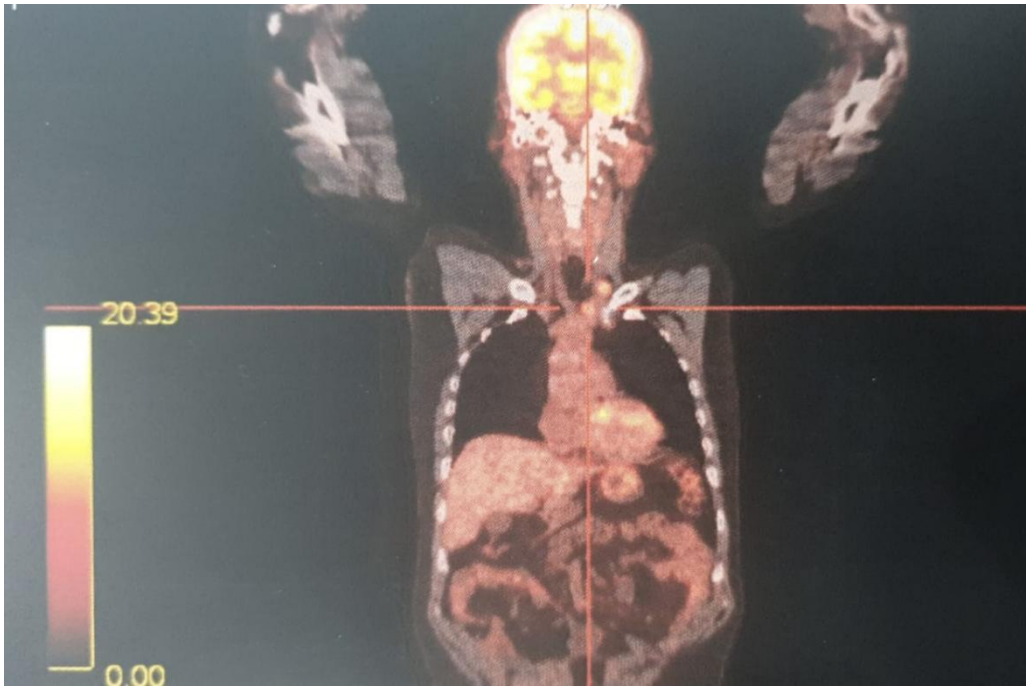

Figure 2: 18-FDG PET scan of our patient showing two hypermetabolic nodular retro and supra-sternal left foci.

DISCUSSION

Parathyroid carcinoma is a rare cancer. The first known case, documented by the Swiss surgeon, De Quervain in 1909, was a non-functioning tumor whose malignancy was revealed only by the macroscopic features of the lesion. In 1929, Wilder reported a case in a patient with primary hyperparathyroidism. In 1938, Armstrong described another case of metastatic parathyroid carcinoma with primary hyperparathyroidism [5,6].

Parathyroid carcinoma accounts for 1% of parathyroid gland tumors and less than 1 % of primary hyperparathyroidism [7], its prevalence is 0.005% of all cancers [1,8]. Parathyroid carcinoma occurs equally in men and women with no significant gender difference in the incidence, and the average patient is in the fourth or fifth decade of life [1,5,9].

The Pathogenesis and etiology of parathyroid cancer are unknown. It may be sporadic or occur in the context of a genetic endocrine syndrome (increased risk) as in hyperparathyroidism/jaw tumour syndrome, multiple endocrine neoplasia type 1 (MEN1), type 2A (MEN2A), and familial isolated hyperparathyroidism [1,5,10,11].

Most specialists believe that there is no evidence of parathyroid carcinoma resulting from the transformation of a parathyroid adenoma, which could be due to different genetic changes between those two entities [1].

Several different mutations have been implicated in parathyroid cancer pathogenesis. Some oncogenes and tumor suppressor genes have been associated with parathyroid carcinomas, particularly those involved in cell cycle control, including the retinoblastoma (Rb), p53, breast carcinoma susceptibility (BRCA2) and cyclin Dl/parathyroid adenomatosis gene 1 (PRAD1) genes. No single one of these genes has been attributed a primary role in pathogenesis [3,5].

The vast majority of parathyroid cancers are functioning tumours. The main signs and symptoms of parathyroid carcinoma are due to high calcium and PTH levels. As a result, patients most often present with symptoms and signs of hypercalcemia, such as fatigue, malaise, weakness, weight loss and anorexia; psychiatric manifestations (depression) and digestive symptoms (nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis and constipation). 50% of patients show renal and bone

manifestations, with different degrees of severity, osteopenia, osteoporosis, osteofibrosis, osteitis fibrosa cystica, and pathologic fractures, they also often complain of polyuria, renal colic and nephrolithiasis [4,5,6,12]. These signs are typical of primary hyperparathyroidism not only in patients with parathyroid carcinoma. They should not be considered cancer-specific signs [6].

About 10% of cases of parathyroid carcinoma are not functioning, because of the absence of PTH secretion. Diagnosis is more problematic in these cases and the prognosis is worse. Patients usually present at a more advanced stage, with symptoms of local and adjacent structure invasion, hoarseness and/or dyspnea and/or neck mass [4,6].

Up to 25% of all patients might present with metastatic disease, the common sites of metastases include the lung (40%), cervical nodes (30%), and liver (10%). Rarely, distant metastases to bone, pericardium, pleura, and pancreas can also occur [11,13].

The course of parathyroid carcinoma is typically indolent but usually progressive [11]. As a result of its rarity, there is no standardized diagnostic, prognostic and therapeutic approach, and the TNM staging algorithm is not universally accepted [14].

While imaging studies are not definitive in the differential diagnosis between parathyroid adenoma and carcinoma, when malignancy is suspected, higher-resolution anatomical studies are of considerable value [5].

Computed tomography with contrast provides excellent details on the location of the tumor and its relation with other structures and can reveal as well invasion of surrounding structures and lymph nodes enlargement. Magnetic resonance imaging with gadolinium and fat suppression will give the best details on soft tissues of the neck, and can provide additional information, particularly as part of the preoperative assessment [5].

Surgery is the gold standard for the treatment of parathyroid carcinoma [4,6,7]. The aim of parathyroid carcinoma therapy is not only oncological, but also to achieve biochemical remission: normalization of blood calcium and PTH levels, arrest of bone calcium depletion, and regression of vascular, renal and neurological dysfunctions [5,6]. The majority of studies recommend *En bloc* dissection of the tumor with the thyroid lobe, the ipsilateral parathyroid and excision of any other affected tissue at the time of the initial surgery. It is the most suitable treatment and leads to the best prognosis with better local disease control and significantly improved long term-survival [5,6,7].

The radicalism of the initial surgery crucial, every effort should be made not to rupture the tumoral capsule and spill tumor cells in the field, as any residual or dispersed cells could lead to a fast recurrence [5,6]. It is considered the most effective therapy to control hypercalcemia and other clinical manifestations [14].

The postoperative management of the patients includes close monitoring of calcium levels and adequate replacement is necessary to avoid severe hypocalcemia due to 'hungry bone syndrome'[5,7]. Continued high postoperative calcium and PTH levels are a sign of the disease's persistence (metastasis or residual disease) [6].

Follow up involves periodic monitoring of calcium and PTH levels, markers for the disease's recurrence, the objective of this follow-up is early detection of potentially curable locoregional recurrence and/or secondary tumours [5,6]. The duration of follow up and surveillance has not been clarified [2].

Fernandes et al [5], proposed clinical examination with calcium levels and PTH monitored every 3 months for the first 3 years, 6/6 months until 5th year and yearly lifelong after that. If there is any suspicious findings it should be confirmed afterward with imaging tests [5].

Despite all technological and technical progress, recurrence is very common in parathyroid carcinoma. It is typically regional and frequently difficult to detect, as

it may be small, multifocal or develop in the scar from previous surgery [9,10].

Various case series report recurrence rates ranging from 40% to 100%. A significant proportion of patients remain undiagnosed at the time of initial surgery, and do not undergo complete resection. On average, recurrence occurs 2 to 3 years after the initial operation. Much longer delays, up to 23 years, have been reported previously [9].

The patients have a progressive increase in PTH and serum calcium levels, severe hypercalcemic crises are rare. The treatment approach includes hypercalcemia control, localization imaging and surgical excision of resectable disease [9]. Approximately one half of the patients with recurrence also present distant metastases [10].

The prognosis of parathyroid carcinoma is highly variable, and data on prognostic factors are different in the literature [3,8]. No single characteristic correlates with outcome. The best prognosis depends on early diagnosis and complete tumoral excision during initial surgery [3].

Long-term survival is reported as 40-86% at 5 years and around 49% at 10 years. In case of recurrence, survival at 5 years is 0% [6]. Tumor size > 4 cm, older age, Caucasian race, male sex, poorly differentiated carcinoma, and distant metastasis were linked to poor survival rates [15]. The most frequent causes of death are complications associated to hypercalcemia (renal failure, arrhythmias, pancreatitis) rather than tumour burden [9].

Tumor genomic profiling will contribute to the development of personalized therapeutic approaches for unresectable parathyroid carcinoma. Enrolling all patients diagnosed with parathyroid carcinoma in large-scale national and international registries will enhance our understanding of this disease [15].

CONCLUSION

To conclude, parathyroid carcinoma is a very rare cancer, that continues to pose considerable challenges in terms of diagnosis and management, which are frequently difficult. These include diagnosis delay, which diminishes the chances of performing a negative-margin histological resection, as this is the most important prognosis factor linked to prolonged disease-free survival. Future prospective randomized studies are needed to assess the effects of different surgical approaches on morbidity, mortality and oncological outcomes.

Declaration by Authors

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