

## Parathyroid Carcinoma on the Basis of Isolated Familial Hyperparathyroidism

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### Abstract

Parathyroid carcinoma is a very rare endocrine neoplasm which results high production of parathyroid hormone (PTH) responsible for pathologic high calcium levels resulting in bone pain/fractures, renal disease and other signs of hypercalcemia. Clinically the disease is detected in patients earlier important because the morbidity and mortality are significant and the best prognosis is associated with early diagnosis and surgical resection.

Here, we present a rare case of familial hyperparathyroidism in which he and his two sons were diagnosed. We report a case of a 59 year old male who presented to our hospital with persistent hyperparathyroidism and hypercalcemia 6 years after having undergone total of two parathyroidectomy operations in this hospital and another.

Development of parathyroid carcinoma in isolated familial primary hyperparathyroidism should be kept in mind. The primary treatment of parathyroid carcinoma on the basis of isolated familial hyperparathyroidism is surgery. When the tumor is no longer amenable to surgical intervention, treatment becomes focused on the control of hypercalcemia with medical therapy, which can include bisphosphonates, calcimimetic agents, or denosumab.

**Keywords:** Familial hyperparathyroidism, Parathyroid cancer.

### Introduction

Parathyroid carcinoma (PCA), a very rare endocrine neoplasm first described by de Quervain in 1904, occurs either sporadically or as a part of a genetic syndrome [1]. It accounts for less than 1% cases of sporadic primary hyperparathyroidism in the world with a higher incidence of 5 % in Japan and Italy. It affects men and women equally frequency during the fourth or fifth decade of life [2]. Parathyroid carcinomas are generally hormonally active, presented by very high serum levels of intact PTH (iPTH) and serum calcium levels but 10% of them are non-functional [3,4]. Patients with parathyroid carcinoma usually present with a severe form of hyperparathyroidism during the diagnosis including bone disease, renal failure, neurologic manifestations and gastrointestinal complaints, compared to the relatively asymptomatic presentation of benign parathyroid disease [5,6]. PHPT is observed in 80-90% of patients with the HPT-JT syndrome, parathyroid cancer is seen in 10-15%, and ossifying fibromas of the maxilla or mandible is seen in approximately 30%; furthermore, some patients have renal or uterine abnormalities [7]. We report a case of parathyroid carcinoma that developed 6 years after the first operation in a patient with familial hyperparathyroidism (Figure 1).

### Case Presentation

A 59-year-old male with a history of subtotal parathyroidectomy for parathyroid adenoma and nephrolithiasis admitted to the hospital with fatigue and resistant pain in the back and legs for a few months. He has a familial hyperparathyroidism history of his two sons. Both two sons of this patient developed parathyroid adenomas and jaw tumors. His boy was detected bilateral mandibula tumors with hyperparathyroidism. So this may be familial. Initial evaluation was notable for serum calcium concentration to 15,1 mg/dl (Reference range: 8,6-10,2 mg/dl), serum creatinine to 2.3 mg/dl (Reference range: 0,7-1,2 mg/dl) and parathyroid hormone level 420 pg/ml (Reference range: 15-65 pg/ml).

Neck ultrasound reported to show a 10x5 mm probable parathyroid lesion intimately related to the anterior pole of the left lobe of thyroid.

Computerized tomography (CT) scan of the neck viewed a 1.8x1.5 cm sized nodule located inferoposterior to the left thyroid lobe (Figure 2).

### Microscopically:

- A- In section stroma, parathyroid parenchymal cells and several fibrous bands are observed.
- B- In section fibrous bands and parathyroid cells are observed.
- C- In section oncocytic cells with eosinophilic cytoplasm and small ovoid round nucleus and chief cells with hyperchromatic nucleus and wide pale cytoplasmic are observed.
- D- In section fibrovascular stroma and cells with pale eosinophilic cytoplasm and large hyperchromatic nucleus and clear nucleolus are followed.

Postoperatively, patient's calcium levels started to decrease. PTH and serum calcium values had returned normal levels 25 pg/ml and 8,7mg/dl respectively.

### Discussion

Primary hyperparathyroidism (PHPT) is a general endocrine disease affecting up to 2% of individuals over the age of 55 years [8]. It is caused by

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solitary benign adenoma in 80–85%, hyperplasia in 10–15%, and parathyroid carcinoma in less than 1%. In up to 10% of cases PHPT is part of a familial syndrome like multiple endocrine neoplasia (MEN) types 1 or 2, hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP) or familial benign hypocalciuric hypercalcemia [9]. Our patient was investigated for MEN (pituitary, pancreas, stromal tumor) but no pathology was detected. A case of his boy whose bilateral brown tumors in the jaws spontaneously and totally improved after subtotal parathyroidectomy and endocrinological therapy who was closely followed up for 4 years even though the lesions were associated with impacted third molars [10]. Clinical findings of parathyroid malignancy include neck tumor, high serum parathormon values and associated hypercalcemia, and common fibrous osteitis [11, 12]. In addition, a report also states that findings such as depth/width ratio (D/W)  $\geq 1$  in the ultrasound image and a tumor growing into the thyroid gland could be useful evidences indicating malignancy [13]. From a genetic focus of view, the parathyroid carcinoma can consist of as a solitary finding in the isolated familial hyperparathyroidism or as a part of multiple endocrine neoplasia type I (MEN-1) [14]. Other genetic changes have been also found: the mutations of men1 gene (kr 11q13), loss of heterozygosity (LOH) in locus for retinoblastoma and overexpression of cyclin D1 [15]. Our patient has relatives parathyroidectomy due to parathyroid adenoma. Some patients had radiation therapy of the neck region in their medical history [16]. Our patient had no head and neck radioation story. The systemic oncological therapy of parathyroid carcinoma is not yet available. Some authors assume that radiotherapy could be useful against recurrent growth of the tumor. The post-operative follow of serum calcium value is significant. When taking operation decision, the value of intact parathormone as an initial parameter should be identified. Patients with parathyroid malignancy are repeatedly reoperated due to relapse. Persistent or relapsing disorder occurs in 50% of cases. When metastases are occurring, they are producing hormones and thus the aim is to remove metastatic focus in order to decrease the high parathormone serum levels. The surgical excision of local as well as distant metastatic lesions is the most effective process [17]. Significantly, with every reoperation, the frequency of perioperative complications increases (60%); the occurrence of recurrent laryngeal nerve paresis arrives up to 38 % [18]. FIHP is an autosomal-dominant disease characterized by the absence of a non-parathyroid clinical appearance of common syndromic PHPT [19].

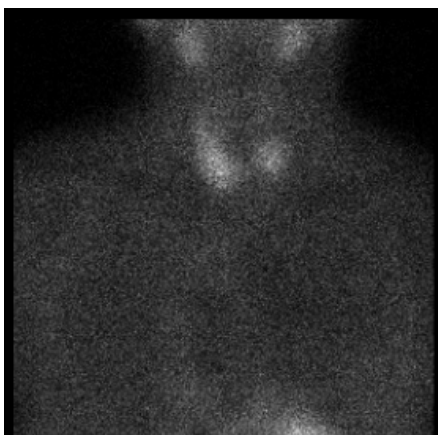


Figure1: 99mTc-sestamibi parathyroid scan

The cause of death of patients is mostly by uncontrolled hypercalcaemia, which leads to renal failure, heart dysrhythmias or pancreatitis [20]. Survivals rates vary from 90% at 5 years to 67% at 10 years in patients who

undergo complete en bloc tumor resection. Lymph node metastases during the diagnosis, distant metastases and non-functioning carcinomas are a few negative prognostic factors.

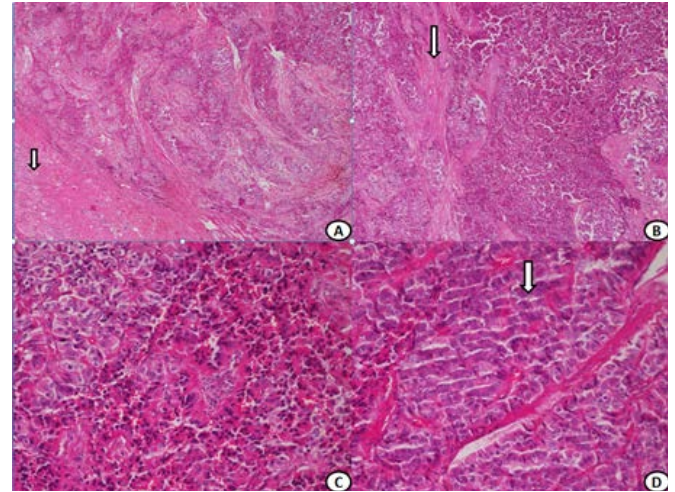


Figure 2: Histological appearance of surgical material

## Conclusion

In conclusion patients with familial hyperparathyroidism should be followed closely and should be alert for the development of parathyroid cancer.

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