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Diagnosis and Treatment of Parathyroid Carcinoma: Report of Seven Cases and Review of Literature

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Abstract

Objective: To discuss the clinical features, diagnosis and treatment of parathyroid carcinoma.

Methods: From January 2005 to December 2014, a total of 7 patients were recruited. Their clinical data, clinical manifestation, examinations and surgical modes were analyzed retrospectively.

Results: One 70-year old patient died after operation because of severe hypocalcaemia. The remaining 6 patients were followed up for 37 ± 20.0 months (16-72) months. 2 patients underwent *En bloc* resection and 1 patients underwent parathyroidectomy were followed up until now without recurrence or metastasis. 3 patients underwent parathyroidectomy appeared metastasis or recurrence in the follow-up.

Conclusion: Our experience with small numbers indicated that *En bloc* resection in initial operation can reduce recurrence and metastasis rate. Aggressive treatment should be considered in initial operation. It can improve the cure rate.

ABBREVIATIONS

PTH: Parathyrin; Syn: Synaptophysin; CHG: Chromogranin; CK: Cytokeratin; CT: Calcitonin; TTF-1: Thyroid Transcription Factor-1; TG: Thyroid Epithelial Source; EMA: Epithelial Membrane Antigen.

INTRODUCTION

Parathyroid carcinoma (PC) is a rare endocrine malignancy, accounting for less than 1% of cases of primary hyperparathyroidism. It was first described by De Quervain in 1904, but there have since been fewer than 1000 cases of this pathology described in the English literature [1].

Preoperatively, it is often difficult to diagnose this type of cancer, because its clinical symptoms are not characteristic. Intraoperatively, it may also be difficult to determine whether a parathyroid gland is malignant because frozen sections often don't make a clear diagnosis.

Except the operation there are no other effective adjuvant systemic therapies that aid in halting progression of the disease. The cause of death is uncontrolled hypercalcemia. Follow up mainly depends on blood calcium and parathyroid hormone level.

The clinical manifestations, treatment and prognosis of 7 cases of PC are summarized in our hospital. And discuss the method of diagnosis and treatment of the disease. The overall survival at 5-year and 10-year was 85%-100% and 49-80% in reports. Despite the high survival rate, close to 50% of the rate of recurrences were observed [2,3].

MATERIALS AND METHODS

General data

From January 2005 to December 2014, a total of 7 patients who treated in our institution were recruited. 7 cases in 3 male, 4 female. When seeing a doctor with an average age of 49.6 ± 13.4 30-69 years. The average duration of 10.7 ± 16.9 (1~48) months.

Patients with symptoms including: recurrent nausea and vomiting, renal calculus, osteodynia, fractura, cervical mass. They were all found hypercalcemia and had different degrees of osteoporosis after treatment. Serum calcium concentration was average of 3.9 + 0.6 mmol/L (3.2-4.8) mmol/L (reference range: 2.3-2.8 mmol/L). Except for one patient was moderate hypercalcemia, the rest were severe hypercalcemia (Severe: more than 3.4mmol/L. Parathyroid hormone (PTH) increased significantly, an average of 2104.7 ± 942.0 pg/L (1147-3235) pg/L, (reference range: 13-53pg/ml). All the patients were diagnosed with primary hyperparathyroidism. Three patients could feel a palpable hard neck mass. All patients underwent imaging examinations in order to locate lesions, but no mass determined the nature preoperation (Figure 1).

Treatment and pathology

All of the patients underwent operation. They were all solitary

lesion, 4 cases located on the right side, 3 cases were on the left. The maximum diameter rang was 3.0 + 0.8cm (1.5-4.0) cm. 5 cases performed simple parathyroidectomy during initial surgery. Only 1 case performed a re-exploration of the neck. 2 cases in the initial surgery were underwent radical resection of parathyroid cancer (*En bloc* resection, including the parathyroid tumor, ipsilateral thyroid lobe, the surrounding soft tissue and associated lymph node). The texture of mass was mostly hard, dark red or dark brown. In 1 case, the mass invaded the recurrent laryngeal nerve. The operation peel the nerve from the tumor tissue carefully in the surgery and this patient showed no recurrent laryngeal nerve paralysis and hoarseness post operation. Intraoperative frozen section could not distinguish between benign and malignant. The postoperative pathological diagnosis of 6 cases were PC, 1 case was parathyroid adenoma (The malignant diagnosis was made after 3 years later). Histopathology revealed focal vascular, capsular, and soft tissue invasion, irregular nucleus and a few mitotic. Immunohistochemistry mostly showed PTH (+), Syn (+), CHG (+), CK (+), CT (-), TTF-1 (-), TG (-), P53 (-), Ki-67 (+), EMA (focal +) (Figure 2). 2 cases resect central lymph nodes and pathology showed no lymph node metastasis.

OUTCOMES

This article reviewed 7 patients. They were followed up for 37 ± 20.0 months (16-72) months. 2 patients underwent *En bloc* resection, their symptoms preoperative were relieved and their level of serum calcium and PTH were normal until now.5 patients underwent parathyroidectomy only. 1 patient had no recurrence or metastasis.3 patients had recurrence or metastasis.A-69-year-old senile female died of severe hypocalcemia postoperative. The following is the data of 3 cases of recurrence or metastasis.

Case 1

Seven months after operation, a-38-year-old male who underwent simple parathyroidectomy found thyroid nodule. He was followed up for 6 months, the nodule increased to 1.0cm in diameter, and the boundary was not clear. At the same time the level of PTH continued to increase. So fine needle aspiration was performed, cytologic diagnosis was papillary thyroid carcinoma. Reoperation was performed to resect the right thyroid lobe, isthmus, left subtotal lobe, surrounding soft tissue and VI lymph nodes. Postoperative pathology confirmed PC (Figure 2). Because of the left humerus metastases existed at the same time, the level of PTH did not decrease to normal. He took external radiotherapy treatment after operation.

Case 2

A-53-year-old male underwent simple parathyroidectomy. He was treated by reoperation in half a month after initial surgery because the postoperative serum calcium and PTH was still high. En bloc resection and the remaining parathyroid exploration were performed in the reoperation. Exploration found no abnormalities. Postoperative serum calcium and PTH were not decreased, patients with hypercalcemia performance complained anorexia, nausea, vomiting. Lumbar metastasis was found by PET-CT in 2 months after reoperation. And then spinal metastasis appearanced. Now the patient was treated by drugs (Calcitonin 40ug qd) and radiotherapy.

Case 3

The pathological diagnosis of a-30-year-old female was adenoma after primary operation. Three years later, she complained continued ostealgia. Laboratory examination showed that the levels of serum calcium and PTH were high. Further imaging studies revealed two pulmonary metastasis. Her calcium was greater than 4.0 mmol/L. Now she received treatment in the internal medicine to control serum calcium. (Calcitonin 40-80ug qd, metacortandracin 80mg/qd)

Hematoxylin and eosin, original magnification (a) ×10; (b) ×40

The immunohistochemical staining, CK positive, Ki-67 positive

DISCUSSION

Parathyroid carcinoma (PC) occurs equally in men and women, while benign parathyroid disease predominates in women by a ratio of 3-4:1.In our case, 4 female, 3 male, the ratio of 4:3. It is habitually a sporadic disease, but familial cases have been described. When diagnosed, this neoplasm is a solitary lesion but anecdotal cases of multiple lesions have been described, extremely rarely were bilateral parathyroid carcinomas reported [4]. In our case, 7 patients were all sporadic cases, with no family history, and were solitary lesion. While the etiology of PC remains unclear, it has been associated with certain clinical risk factors, including familial hyperparathyroidism, a history of neck irradiation, and end-stage renal disease [5]. There was report the overall survival at 5-year and 10-year was 85% and 49% [6].

Usually the disease has an indolent but slowly progressive course. Most of the patients will die due to uncontrollable hypercalcemia, causing complications such as renal failure, cardiac arrhythmias or pancreatitis, rather than direct tumor invasion or metastases [7]. In our case, all patients have symptoms of hypercalcemia. In contrast, postoperative hypocalcemia should also be attention ded to 1. Senile female patient with severe postoperative hypocalcemia, lead to respiratory failure and death. Therefore, both hypercalcemia and hypocalcemia could lead to serious consequences.

PC is most functional, and as such, symptoms and signs are related with the metabolic consequence of hypercalcaemia. The most frequent complaints are fatigue, weakness, anxiety, anorexia, nausea, vomiting, and loss of weight, dyspepsia, constipation, headaches, polydipsia and polyuria. Bone, joint, muscular pain, pathological fractures, and renal colic are frequent when hyper parathyroid state is severe [8]. Similarly, in our 7 patients mainly manifested as pain, backache, anorexia and vomiting. Prevalent in patients accompanied with osteoporosis, renal calculi, and pathological fracture. There are no significant differences between PC and the benign disease in terms of clinical symptoms. All those clinical signs are unspecific and often lead to a delayed diagnosis.

Imaging techniques such as neck ultrasound, computer tomography scanning (CT) and 99mTc sestamibi scan can help localize disease, but they are not useful in the assessment of malignancy potential. In our case, patients preoperative

Table 1: The clinical data of 7 patients with parathyroid carcinoma.

Gender	Age	Symptom	Bone and kidney disease	Tumor Size(cm)	Serum calcium (mmol/L)	PTH (pg/L)	Operation mode	Follow up time (month)	Result
Female	44	Backache	Renal calculus	1.5	3.7	1147	parathyroidectomy	72	No recurrence
Female	70	Fracture	Osteoporosis	3.5	3.6	1204	parathyroidectomy	/	Death
Female	61	Ostealgia	Osteoporosis Renal failure	3.0	3.2	3043	En bloc	16	No recurrence
Female	30	Ostealgia	Osteoporosis Renal calculus	3.0	4.3	2918	parathyroidectomy	48	Metastasis
Male	38	Ostealgia	Osteoporosis Renal calculus	2.5	3.4	1238	parathyroidectomy	26	Recurrence
Male	53	Vomit	Osteoporosis	3.5	4.4	3235	parathyroidectomy	30	Metastasis
Male	52	None	None	4.0	4.7	1948	En bloc	30	No recurrence

Note: Serum calcium normal value: 2.0-2.6mmol/L; PTH normal value: 13-53pg/ml.

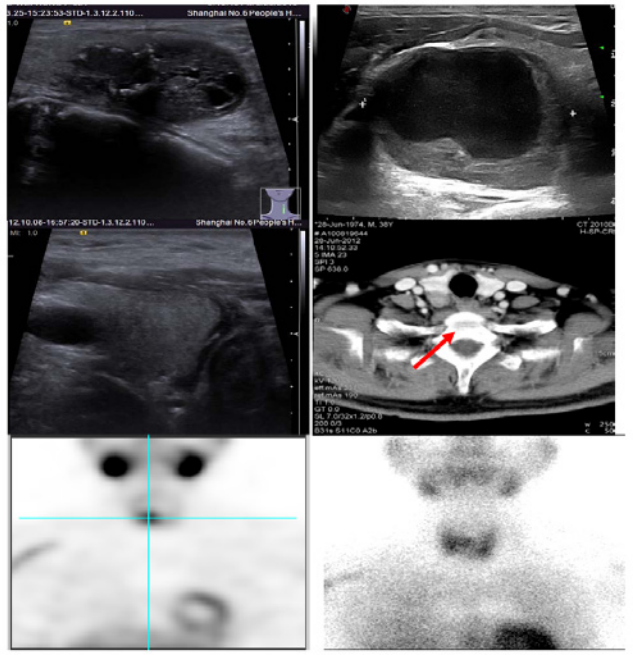

Figure 1 Imaging findings
A: Neck ultrasonography, demonstrating cystic and solid mixtured nodule of 30 mm in maximum diameter in the thyroid lobe, punctuate calcification, obscure boundary. B: Neck ultrasonography, demonstrating multiple inhomogeneous hypoechoic nodules in the thyroid lobe, the maximum diameter was 34mm. C: Neck ultrasonography, appearance of a heterogenous thyroid mass, measuring 15 mm in maximum diameter, obscure boundary. D: Computed tomography (CT) manifestation of PC, a hypodense lesion was visible in the posterior thyroid. E, F: Tc99m sestamibi scan of PC, there was focal retention of tracer over the right lower pole of the thyroid.

underwent ultrasound or CT examination, were found and localization of the lesion, but could not determine the nature. But we recommend routine ultrasound and CT examination preoperative. Because they are usually helpful for localizing abnormal parathyroid glands and CT may reveal an infiltrating parathyroid tumor and suggest possible malignancy.

Fine needle aspiration (FNA) prior to initial operation is not recommended. It would not be able to distinguish adenoma from carcinoma, as the diagnosis requires histological morphology and criteria. An FNA biopsy of a potential parathyroid cancer might induce seeding of the parathyroid carcinoma along the tract of the needle [9].

In summary, the preoperative diagnosis of PC is difficult.

PC is often undiagnosed preoperatively, suspected intraoperatively, and confirmed postoperatively. So when the patients under the following circumstances, should be highly suspected PC.

The presence of a palpable neck mass

On physical examination, a mass in the parathyroid area of the neck is an important sign for distinguishing between adenoma and carcinoma of the parathyroid gland. The American national cancer data base [10], confirmed in a report of 286 PCA a median size of 3.3 cm. So a palpable mass in the neck has been suggested as a strong predictive factor for PC [11]. Particular attention should be paid to a hyperparathyroid patient with a parathyroid mass larger than 3.0 cm.

In our case, the diameter of mass range of 3.0 + 0.8cm (1.5-4.0) cm.

Renal involvement, skeletal involvement, concomitant renal and skeletal disease

The kidney and skeleton are the sites most affected by PC-associated hyperparathyroidism, and their involvement is more

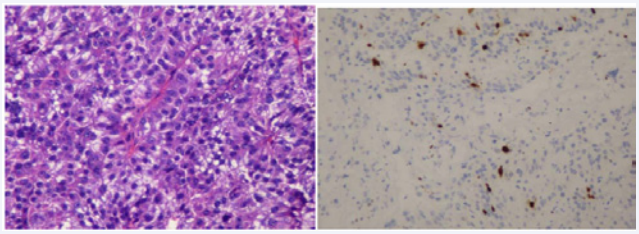

Figure 2 Pathology and immunohistochemistry
Hematoxylin and eosin, original magnification (a) ×10; (b) ×40.
a. The immunohistochemical staining, CK positive.
b. The immunohistochemical staining, Ki-67 positive.

frequent and more severe than in benign lesions,3 such as bone disease (brown tumors, subperiosteal bone resorption, lytic bone lesions, pathological fractures, salt and pepper appearance of skull), renal disease (nephrolithiasis, nephrocalcinosis). In our series all patients had at least renal or skeletal disease, and half of them had simultaneous symptoms.

A high degree of elevation of serum calcium and serum PTH

The serum calcium level of most patients with parathyroid carcinoma is higher compared to patients having benign lesions and are generally >14 mg/dl. The serum PTH levels are also elevated and are about 3 – 10 times above the limit of normal [12]. In our series, the serum PTH levels in the range of 2104.7 ± 942.0 pg/L (1147-3235) pg/L, elevated more than 10 times.

Hypercalcemic crisis

Recurrent laryngeal nerve paralysis or hoarseness: Similarly, the intraoperative diagnosis of PC could also be not easy. PC may be distinguished from adenomas by their firm, stony hard consistency and lobulation [13]. Adenomas tend to be soft, round, or oval and of a reddish brown color [14]. The diagnosis of PC theoretically is made for the following: 1) sheets or lobules of tumor cells separated by tense fibrous bands; capsular or vascular invasion; mitotic figures within tumor parenchymal cells; capsular or vascular invasion, and/or lymph node invasion 2) patient with locally invasive tumor; and/or 3) patients with distant metastasis [15]. In the actual operation, diagnosis is not made easily even on histology. PC may have such bland cytological appearance that nothing but the invasiveness of the tumor can differentiate them from a benign lesion. Histologically, a definitive diagnosis of malignancy should be restricted to tumors displaying evidence of vascular invasion, capsular invasion with growth into adjacent tissues, or metastases. As criteria for malignancy are mostly architectural and require adequate sampling, frozen sections are of little value. For this reason, PC are often retrospectively diagnosed through surgery and histologically confirmed. In our case, all the patients were not diagnosed intraoperative. The pathology after operation made definite diagnosis.Occasionally a patient with a parathyroid carcinoma may remain undiagnosed until the tumor either recurs locally or develops distant metastasis. In our case, A middle-aged female patients, three years after resection of parathyroid adenoma, appeared extensive lung metastasis, then made the diagnosis of PC.

In recent years, the loss of retinoblastoma protein and parafibromin in immunohistochemistry could help in making a diagnosis [16,17].

The most effective treatment of PC is complete removal of the primary lesion during initial surgery. Additionally, caution must be taken to prevent rupture of the tumor capsule [3]. *En bloc* resection of the carcinoma and the adjacent structures in the neck, including ipsilateral thyroid lobe and isthmus, lymph nodes and soft tissues is recommended [18]. This is important because there are no other effective adjuvant systemic therapies that aid in halting progression of the disease [19]. Chemotherapy has been reported to be ineffective [20]. Radiotherapy is often used in the patient with unresectable neck disease or metastatic disease now. The efficiency of radiation therapy in parathyroid carcinoma remains controversial. A series from the mayo clinic reviewed 61 patients with PCA, 57 underwent en bloc surgery alone and 4 surgeries with adjuvant radiotherapy. The 4 patients who received adjuvant radiotherapy were alive with no recurrences at 60 months whereas 25 patients (44%) had locoregional recurrence at a median time of 27 months after surgery. It may be helpful as adjuvant therapy in preventing tumor regrowth after surgery [21,22]. Medical management, including calcitonin and bisphosphonates, may be used for patients with uncontrollable hypercalcemia with unresectable or widespread metastatic disease. However, these treatment have little efficacy in parathyroid carcinoma. There was report that *En bloc* resection resulted in an 8% local recurrence rate.In contrast, simple parathyroidectomy resulted in a 51% local recurrence rate [23]. In our case, 2 cases were treated with En bloc resection without recurrence (0/2,0%). 5 cases were treated with simple parathyroidectomy with 3 cases of recurrence (3/5,60%), 1 case died. Metastasis occurred in one patient post surgery three months later. He had got lumbar metastasis. Another patient appeared recurrence and humerus metastasis thirteen months later. One woman developed pulmonary metastasis 3 years after surgery.

Unfortunately, even by experienced surgeons, most of PC has been missed initially. The result is enucleation or piece meal resection, with the risk of tumor seeding in the operative field. In our series recurrent disease occurs in more than 50% (3/5, 60%) of patients with simple parathyroidectomy. The difficulty encountered by clinicians in diagnosing pre-operatively and intraoperatively this rare tumour may limit the effectiveness of the surgical treatment [24].

So if it is suspicious, aggressive treatment should be considered in initial operation. If a diagnosis is made in early postoperative period on the basis of histopathological examination, a re-exploration of the neck is warranted and a completion procedure be performed. Even if metastasis or recurrence is detected, aggressive resection of the metastatic parathyroid carcinoma is the most effective treatment to control hypocalcaemia and improve survival.

In summary, parathyroid neoplasms should be evaluated by experienced endocrine pathologists, *En bloc* resection with the adjacent structures at the first operation is the only curative treatment, and aggressive initial treatment is important to reduce local recurrence and improve the prognosis. In this paper, the number of patients was few, and the follow-up time was short. We need to observe more cases and observe the development of these patients, and then we can get better results.

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