Int J Clin Exp Pathol 2016;9(1):367-372
www.ijcep.com /ISSN:1936-2625/IJCEP0018163

Case Report

Parathyroid carcinoma: a clinical and pathologic analysis of 8 patients in China

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Received October 19, 2015; Accepted November 28, 2015; Epub January 1, 2016; Published January 15, 2016

Abstract: Background: The aim of this study is to summarize the clinical and pathological characteristics of parathyroid carcinoma. Methods: A retrospective review of 8 patients with parathyroid carcinoma treated in China was conducted to describe clinical and pathological features. Results: A palpable mass in the central neck was found in 3 patients. 2 patients presented anorexia, fatigue and weight loss beyond 10 kg as their main complaints. 2 patients manifested frequency renal calculus and pancreatitis while another 1 patient presented mainly progressive elevation of ALP and deterioration of the ache on her back and heels. The mean and median intact PTH levels at initial presentation were 1088.3 and 954.2 pg/ml, respectively (range, 159.2~2500.0 pg/ml). The mean and median total blood calcium levels were 3.56 and 3.75 mmol/L, respectively (range, 2.65~4.09 mmol/L). The mean and median diameters of parathyroid specimens were 34.1 and 36.0 mm, respectively (range, 20.0~58.0 mm). Capsular invasion was observed in all these 8 patients; invasion into the adjacent soft tissues was observed in 62.5% of the specimens (n=5). Invasion into vascular, ipsilateral thyroid and lymph positive was observed in 25.0% of the specimens, respectively (n=2). Nerve invasion was observed only in 12.5% (n=1). Conclusion: Parathyroid carcinoma should be suspected when a patient presents severe elevation of total blood calcium and serum PTH, a palpable mass in the central neck area, nephropathy or osteopathy. The most prominent pathological features in this cohort include invasion into capsule, adjacent soft tissues, vessels, nerve and local lymph nodes.

Keywords: Parathyroid carcinoma, diagnosis, pathology, mainland China

Introduction

Parathyroid carcinoma (PC) is a rare endocrine malignant originating from parenchymal cells in parathyroid glands. The estimated incidence is 4-6 per 10,000,000 person-year [1] and it accounts for 0.5%-5.0% of all cases of primary hyperparathyroidism [2]. Most of PC are hyperfunctional with signs and symptoms mainly associated with severe hypercalcemia. Preoperative diagnosis of PC is often difficult since its presentations are clinically and biochemically similar to parathyroid adenoma. Malignancy may be suspended when both of serum PTH and calcium levels are significantly elevated. The most effective treatment for PC is radical surgery with en bloc removal of the lesion together with the ipsilateral thyroid, thyroid isthmus and lymph nodes. Distinguishing PC grossly from a benign parathyroid adenoma is also not that easy intraoperatively and the intraoperative findings of a firm, gray, large mass that is adherent to the surrounding tissues should arouse the suspicion of malignancy [3]. According to the data of SEER, 78.6% PC patients received only limited resection of enlarged parathyroid gland at the time of initial surgery, which may account for the high recurrence rate for PC (40-82% within 5 years) [4], but the benefit of prophylactic radical surgery and central lymph nodes dissection is still being debated [5, 6].

Although the natural course of the disease is generally slow and not that progressive with a 5-year overall survival (OS) 76-85% and a 10-year OS 49-77% [7], it's associated with a relatively high incidence of local recurrence and distal metastasis. PC patients usually die of systemic failure caused by severe hypercalcemia. Currently there is a limited amount of literature on clinicopathologic outcome predictors

Table 1. Demographic and clinical features of 8 patients with parathyroid carcinoma

Characteristics	Value (%)
Patients	8
Gender	
Female	6 (75)
Male	2 (25)
Age (y)	
Mean	47
Median	47
Range	33-67
PTH (pg/ml)	
Mean	1088.3
Median	954.2
Range	159.2-2500.0
Calcium (mM)	
Mean	3.56
Median	3.75
Range	2.65-4.09
Size (mm)	
Mean	34.1
Median	36.0
Range	20.0-58.0

Table 2. Treatment and outcome of 8 patients with parathyroid carcinoma

	Value (%)
Patients	8
Surgery	
Local excision	2 (25)
En bloc excision	6 (75)
Radiotherapy	
Yes	2 (25)
No	6 (75)
Chemotherapy	
Yes	1 (12.5)
No	7 (82.5)
Follow-up (mo)	
Mean	44.6
Median	43.0
Range	12.0-76.0
Recurrence	
Yes	2 (25)
No	6 (75)
Metastasis	
Yes	2 (25)
No	6 (75)
Death	
Yes	1 (12.5)
No	7 (87.5)

of patients with PC, especially in China mainland. A multicenter review of 62 PC patients led by the Spanish Association of Surgery found that after a median 55-month follow up that 22.6% patients suffered recurrence and the most predictive independent variables on tumor recurrence were intraoperative tumor rupture, the presence of mitotic figures within tumor parenchymal cells and allocation in class III according to Schulte differentiated staging classification [8]. The study of Asare et al indicated that size of the tumor was more related to the outcome compared with lymph nodes status [9].

The literature on PC is limited and the large prospective study is still lack in China mainland. The aim of our study is to summarize the clinical and pathological characteristics and outcome predictors of 8 PC patients we collected from 2003 to 2014.

Patients and methods

Patients

This study involved a retrospective chart review of 8 patients (2 men and 6 women) with parathyroid carcinoma treated in Shanghai and Jiangsu Province. Demographic, clinical and pathological data were obtained from hospital records. The inclusion criteria were as follows: 1. Only patients with newly diagnosed, previously untreated parathyroid carcinoma were included; 2. Patients presented with hypercalcemia and elevated PTH level, and parathyroid mass was indicated by neck ultrasonography or CT or parathyroid ECT scanning; 3. All of the patients received parathyroidectomy and pathological examination confirmed the diagnosis of parathyroid carcinoma. A histopathologic diagnosis of parathyroid carcinoma was made only when there was unequivocal evidence of invasion into capsule or the surrounding tissues, vascular invasion, local lymph nodes positive and known distant metastasis [10].

Statistical analysis

All the statistics were analyzed using SPSS version 19.0. Demographic, clinical and pathological data were summarized using descriptive statistics. Therapeutic methods included surgery, chemotherapy and radiotherapy. Surgical intervention was grouped into 2 categories: local excision (LE) only, as a procedure which

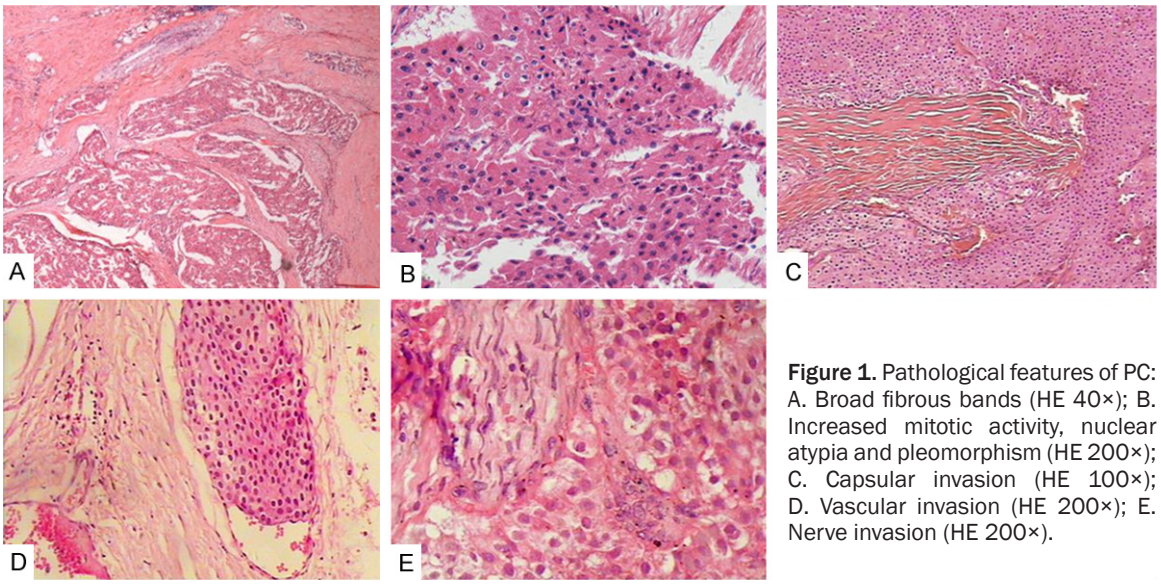

Figure 1. Pathological features of PC: A. Broad fibrous bands (HE 40×); B. Increased mitotic activity, nuclear atypia and pleomorphism (HE 200×); C. Capsular invasion (HE 100×); D. Vascular invasion (HE 200×); E. Nerve invasion (HE 200×).

comprised only pericapsular excision of the parathyroid lesion, and en bloc excision, which included en bloc and oncologic resection. En bloc excision describes excision of the parathyroid with circumferential soft tissues as the minimal criterion; oncologic resection additionally includes further surgery such as ipsilateral thyroid lobectomy, centrocervical lymphadenectomy, or further locoregional excision [11]. Prognosis was classified as recurrence, metastasis and death.

Results

Demographics and clinical features

This study included 8 PC patients (2 men and 6 women). As shown in **Table 1**, the mean and median age at the time of diagnosis was both 47 years (range, 33~67 years). A palpable mass in the central neck area was found in 3 patients at their first visit, among whom 1 was 4 months after receiving left thyroidectomy and had no other symptoms and signs, 1 was suffering from an ache on both of her knees meanwhile and another 1 had had a pathological fracture on her left clavicle. 2 patients presented anorexia, fatigue and weight loss beyond 10 kg as their main complaints. 2 patients manifested frequency renal calculus and pancreatitis while another 1 patient presented mainly with progressive elevation of ALP and deterioration of the ache on her back and heels. The mean and median intact PTH levels at initial presentation were 1088.3 and 954.2 pg/ml, respectively (range, 159.2~2500.0 pg/ml). The mean and median total blood calcium levels were 3.56 and 3.75 mmol/L, respectively (range, 2.65~4.09 mmol/L). 1 patient received timely comprehensive therapy including a large quantity of fluid replacement, diuretic, calcitonin and glucocorticoid because of hypercalcemia crisis. Preoperative imaging included neck B-ultrasound in 5 patients, neck CT in 4 patients, parathyroid ECT in 5 patients, and all these imaging procedures did find parathyroid mass. 1 patient underwent fine-needle aspiration biopsy and pathological examination showed thyroid papillary carcinoma could not exclude. The mean and median diameters of parathyroid specimens were 34.1 and 36.0 mm, respectively (range, 20.0~58.0 mm).

Therapy

All of 8 patients received surgery intervention, among whom 2 patients received LE, 5 patients received parathyroidectomy and ipsilateral total or subtotal thyroidectomy, 1 patient received ipsilateral centrocervical lymphadenectomy and recurrent laryngeal nerve exploration besides. Radiotherapy was performed in 2 patients and chemotherapy in 1 patient after surgery, as shown in **Table 2**.

Pathological analysis

Pathological pictures of 8 patients were re-evaluated and confirmed the diagnosis of PC by 2 pathologists in our hospital. Differing from

Table 3. Histopathological data of patients with parathyroid carcinoma

	Value (%)
Patients	8
Capsule invasion	
Yes	8 (100)
No	0(0)
Invasion to adjacent soft tissue	
Yes	5 (62.5)
No	3 (37.5)
Invasion to ipsilateral thyroid	
Yes	2 (25)
No	6 (75)
Vascular invasion	
Yes	2 (25)
No	6 (75)
Lymph node	
Positive	2 (25)
Negative	6 (75)
Nerve invasion	
Yes	1 (12.5)
No	7 (87.5)

that of parathyroid adenoma, PC is usually larger in size without apparent capsule and adjacent to surrounding soft issues widely. Under light microscope, PC is characterized by rich trabeculated parenchymatous cells, increased mitotic activity, nuclear atypia, pleomorphism and broad fibrous bands [12] (**Figure 1A** and **1B**). As shown in **Table 3**, Capsular invasion was observed in all these 8 patients (**Figure 1C**); invasion into the adjacent soft tissues was observed in 62.5% of the specimens (n=5). Invasion into vascular (**Figure 1D**), ipsilateral thyroid and lymph positive were observed in 25.0% of the specimens, respectively (n=2). Nerve invasion was observed only in 12.5% (n=1) (**Figure 1E**).

Prognosis

The mean and median follow-up in this cohort were 44.6 and 43.0 months, respectively (range, 12.0~76.0 months). During our follow-up, 25% patients (n=2) developed recurrence, one of whom received LE only while the other received radical surgery intervention. 25% patients (n=2) developed metastasis, which was featured with multiple metastases in both of lungs. One of these 2 patients also suffered from multiple metastases in double tibiofibula meanwhile, and then died of systemic failure caused by severe hypercalcemia.

Discussion

Due to the very low incidence and limited efficient diagnostic methods, there are no well-accepted diagnostic standards and therapeutic procedures for PC. A palpable mass in the central neck area was found in 37.5% patients at their first visit in our study, making it a main manifestation of PC. 30%~60% of PC patients develop severe hypercalcemia (total blood calcium >3.5 mmol/L), which may cause frequent occurrences of renal calculus and pancreatitis, so some patients may manifest symptoms or signs related to renal calculus or pancreatitis as their first presentation, leading to the delayed diagnosis of PC. The excessive secretion of PTH will increase bone turnover, thus ostealgia or pathological fracture may be the main complaints of some patients. In addition, patients with hyperparathyroidism recurrence after parathyroidectomy should be highly suspected of PC.

Preoperative imaging is needed for lesion location and analysis. Combination of at least two imaging procedures is recommended to improve the sensitivity and specificity. Neck B ultrasound, as a convenient and noninvasive procedure, is supposed to be a regular examination for PC with a 69% detection rate. A retrospective study found the mean diameter of PC is about 38 mm compared with 23 mm of benign adenoma [13], which is similar to our study. But limited by the small sample number, we did not find a correlation between tumor size and prognosis as Asare's study. Thin-layer CT scanning is conducive to find local invasion of PC with a detection rate of nearly 93% [14]. Fine-needle aspiration of cervical masses should be avoided in patients with suspected PC because of the documented risk of cutaneous or subcutaneous seeding along the needle track.

It is still difficult to distinguish PC from benign parathyroid adenoma based on clinical manifestations, biochemical markers and imaging. Pathology is yet the golden standard. Another challenging aspect of PC is its histopathologic examination. Diagnosis should not be based on single features like broad fibrous bands,

increased mitosis activity, nuclear atypia and pleomorphism [15]. Like other endocrine malignancies, biological behaviors are what determine benign or malignant. The most reliable features for the diagnosis include invasion into capsule and the surrounding tissues, unequivocal vascular invasion, positive lymph nodes and known distant metastasis. In our study, one of the 2 patients whose pathological examination showed vascular and ipsilateral thyroid invasion developed recurrence and the other developed metastasis, and 2 patients with positive lymph nodes both developed metastasis. We recognize that our study included a very small number of patients; nevertheless, vascular invasion, ipsilateral thyroid invasion and local lymph node metastasis seem to be the predictors of worse clinical outcome.

The extent of initial surgery has previously been shown to be predictive of disease-free survival [16]. The results of several studies provide evidence indicating that initial en bloc resection of the tumor and adjacent soft tissues, which involves procedures like ipsilateral thyroid lobectomy, thymectomy, and central neck dissection, provides the best outcomes for disease-free survival. Limited by our small number of patients, we did not find an obvious relationship between surgery intervention and prognosis. Whether postoperative radiotherapy is effective in reducing disease recurrence in patients with high risks or not is still controversial. Erovic et al [17] included the largest series with respect to the use of adjuvant radiotherapy in treating PC in their study where 11 patients was given radiotherapy after surgery. Of these 11 patients, 7 developed recurrence. Because of the very small number of patients and a selection bias toward patients who had more advanced disease that were receiving radiation therapy, the benefits of this treatment cannot be determined.

In conclusion, the diagnosis of PC should be suspected when a patient present with severe elevation of both total blood calcium (>3.5 mmol/L) and serum PTH (>3 upper normal limit) [18, 19], a palpable mass in the central neck area, nephropathy or osteopathy, especially when a middle-aged patient combines with systemic involvements such as anorexia, fatigue and fast weight loss. Combination of at least two imaging procedures is recommended. B ultrasound is supposed to be a regular examination and thin-layer CT scanning has a detection rate of nearly 93%. Pathological diagnosis is yet the golden standard. The most prominent pathological features for the diagnosis of parathyroid carcinoma in this cohort include invasion into capsule, adjacent soft tissues, vascular, nerve and local lymph nodes. Vascular invasion, ipsilateral thyroid invasion and local lymph node metastasis seem to be the predictors of worse clinical outcome. To reduce the risk of recurrence and metastasis, the extent of initial surgery should be large enough. Benefits of postoperative radiotherapy still remain to be elucidated and validated in multiple-institution collaborative studies that involve an adequate number of patients.

Acknowledgements

This study was supported by Key Discipline Fund of Tongji Hospital Affiliated to Tongji University.

Disclosure of conflict of interest

None.

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