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Parathyroid carcinoma: Report of 10 patients and literature review

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Abstract

OBJECTIVE: Parathyroid carcinoma (PC) is a rare disease with high rates of misdiagnosis and recurrence. This report summarized the clinical and pathological characteristics of 10 patients with PC at our hospital, to improve the early recognition and prognosis of PC.

METHODS: The clinical manifestations, imaging findings, pathological features, treatments, and prognostic data of 10 patients diagnosed with PC at the First Medical Center, Chinese PLA General Hospital from 2003 to 2021 were analyzed.

RESULTS: There were 7 male and 3 female patients with PC whose average age was 41.4 ± 9.4 years. All patients had bone involvement (bone pain and/or osteoporosis), meanwhile 6 patients had kidney stones and 7 patients had palpable neck masses. Five patients presented with tumor metastasis, invading lymph nodes, lung, liver, or bone. Laboratory examinations revealed elevated serum total calcium (4.15 ± 0.81 mmol/L), parathyroid hormone (PTH, 1236.1 ± 519.9 pg/mL) and alkaline phosphatase (405.8 ± 219.0 IU/L) levels. Especially, hypercalcemic crisis occurred in 9 patients. The diagnosis of PC depended on histopathological features of the parathyroid tumor, including capsular and/or vascular invasion. All patients underwent at least en bloc resection. In the follow-up, six patients with relatively high preoperative PTH levels (1519.5 ± 436.8 pg/mL) relapsed postoperatively. Two patients with the Ki-67 index ≥ 10% in parathyroid tumor tissue and distant metastasis died within 2 years after the operation.

CONCLUSION: Severe bone pain, kidney stones, hypercalcemic crisis, and markedly elevated PTH usually indicate PC. A markedly elevated PTH level, tumor metastasis, and the Ki-67 index ≥ 10% may be indicators of poor prognosis.

CASE REPORT

INTRODUCTION

Parathyroid carcinoma (PC) is an extremely rare type of malignant tumor, accounting for approximately 0.005% of all cancers (Cetani *et al.* 2019). The typically clinical manifestations are moderate to severe hypercalcemia with renal and skeletal involvement. However, in clinical practice, PC has often been misdiagnosed as parathyroid adenoma (PA), thyroid nodule/carcinoma, arthritis, or bone tumor. Patients are commonly diagnosed with PC months or years after onset, following relapse or metastases. Parathyroid surgery is the first choice for patients with PC, which has a high recurrence rate (approximately 50%) that is closely associated with delayed therapy (Cunha *et al.* 2022). Thus, early identification and complete resection of the lesion are important to improve the prognosis and reduce mortality among patients with PC (Xue *et al.* 2016). In this report, we summarized the clinical manifestations, imaging findings, pathological features, treatments, and prognostic data of 10 patients diagnosed with PC at our hospital from 2003 to 2021.

MATERIALS AND METHODS

Ethics

This study was approved by the Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from all patients for the publication of the case series and accompanying images.

Subjects

The medical data of patients diagnosed with PC at the First Medical Center, Chinese PLA General Hospital from 2003 to 2021 were collected retrospectively. The follow-up period was 1-10 years.

Diagnostic criteria

The diagnosis of PC was confirmed according to histopathological features of the parathyroid tumor. The pathological criteria included capsular and/or vascular invasion, invasion of surrounding structures, and the presence of metastases (Xue *et al.* 2016).

Clinical data and methods

The following clinical data were obtained from medical records: gender, age, history, symptoms, physical examination findings, laboratory results [serum levels of total calcium (normal range: 2.09-2.54 mmol/L), phosphorous (normal range: 0.89-1.60 mmol/L), intact parathyroid hormone (PTH; normal range: 15.0-65.0 pg/mL) and alkaline phosphatase (ALP; normal range: 0-130 IU/L), and imaging findings [ultrasound, computerized tomography (CT), dual-phase technetium-99 labeled sestamibi (^{99m}Tc-MIBI) scintigraphy, and technetium-99 conjugated with methylene diphosphonate (^{99m}Tc-MDP) whole-body bone imaging]. Postoperative pathological data [hematoxylin-eosin (H&E) and immunohistochemical staining of parathyroid lesions] were obtained from Department of Pathology, the First Medical Center, Chinese PLA General Hospital.

Statistical analysis

SPSS software (version 24.0) was used for the statistical analysis. Data are expressed as mean ± standard deviation. Comparisons of serum calcium and PTH levels before and after surgery were performed using paired *t*-tests. A p-value < 0.05 was considered significant.

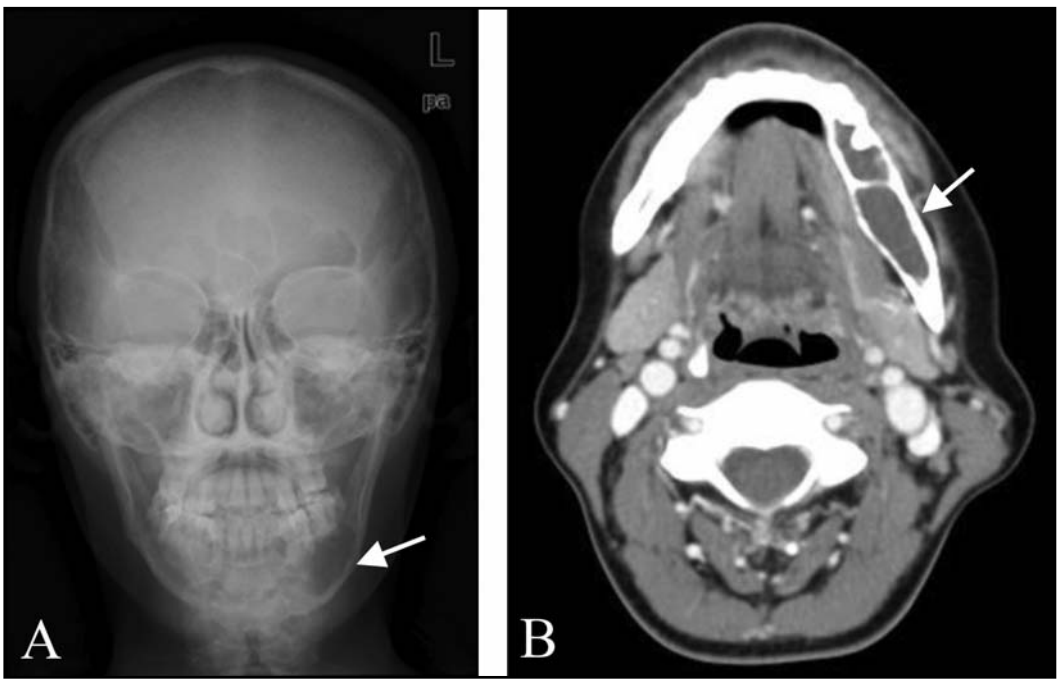

Fig. 1. Brown tumor of the jaw. (A) Skull X-ray image of patient 3 showing a brown tumor in the left mandible (white arrow). (B) Spiral CT scan of patient 3 showing a lytic expansile lesion in the left mandibular body (white arrow).

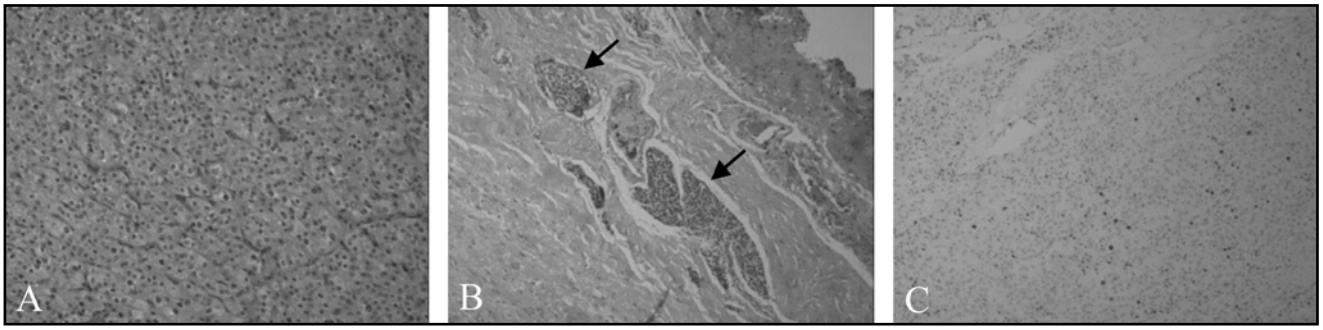

Fig. 2. Histopathological features. (A) Tumor cells of patient 1 were arranged in a cord-like pattern, and the nuclei were round and darkly stained (H&E staining, ×200). (B) Lymph-vessel cancer embolus of patient 1 (black arrow, ×100). (C) The Ki-67 index (patient 5) was 15% (×100).

RESULTS

Patient characteristics

There were 10 patients with PC (2.32%) among 431 patients with primary hyperparathyroidism (PHPT) admitted into our hospital from 2003 to 2021, including 7 male and 3 female patients (mean age, 41.4 ± 9.4 years). Six patients had palpable neck masses; bone involvement: five patients had bone pain, while hand X-rays or dual-energy X-ray bone scans revealed osteoporosis in all patients; kidney involvement: six of the 10 patients had kidney stones, and 1 patient presented with renal colic. Six patients had mild to moderate renal insufficiency [estimated glomerular filtration rate (eGFR), 37.4-88.3 mL/min/1.73 m^2). Notably, four patients (patients 4, 7, 9, and 10) were admitted to our hospital due to postoperative recurrence of PC. Five patients had tumor metastasis, invading lymph nodes, lung, liver, or bone. The detailed clinical characteristics of the patients were shown in Table 1.

Auxiliary examinations

Laboratory examinations revealed elevated serum PTH (1,236.1 ± 519.9 pg/mL) and calcium levels (4.15 ± 0.81 mmol/L). Nine patients suffered from hypercalcemic crisis (serum calcium = 3.52-5.56 mmol/L), along with reduced serum phosphorous (0.64 ± 0.22 mmol/L) and elevated serum ALP (405.8 ± 219.0 IU/L) levels.

Neck ultrasound showed parathyroid nodules in all patients. Ultrasonographic features of these patients included large irregularly shaped lesions, heterogeneous echogenicity, calcification, and infiltration. Skull X-ray and CT images detected a brown mandibular tumor, which is a characteristic finding of hyperparathyroidism (Patient 3, Figure 1). Seven patients had ^{99m}Tc-MIBI scintigraphy-positive imaging findings. Five patients (patients 1, 3, 5, 6, and 8) showed enhanced radionuclide uptake in multiple bones throughout the body in ^{99m}Tc-MDP bone scans, which indicated metabolic bone disease. Histopathological findings of parathyroid tumor included that tumor cells arranged in nests or cord-like pattern and the nuclei were round and deeply stained with capsular and/or vascular invasion, as well as lymph vessel invasion (Figure 2). Immunohistochemical analysis showed the Ki-67 index of 1-25%, and the presence of PTH (+) in 9 patients, CgA (+) in 6 patients and Syn (+) in 6 patients. Calcitonin, thyroglobulin, and TTF tests were negative (Table 1).

Diagnosis

Six patients had been misdiagnosed with thyroid nodule (patient 2), thyroid carcinoma (patient 6), PA (patient 3), rheumatoid arthritis (patient 1), gouty arthritis (patient 5), or bone tumor (patient 10) before admission to our hospital. The diagnosis of PC depended on histopathological features of the parathyroid tumor, including capsular and/or vascular invasion.

Treatment strategies

All patients with PC underwent en bloc resection. Seven patients had ipsilateral thyroidectomy and 3 patients had anterior cervical lymph node resection. Bisphosphonate (pamidronate or alendronate) and calcitonin were administrated to lower the serum calcium level in all patients. Chemotherapy (paclitaxel combined with cisplatin) and PD-1 monoclonal antibody (bevacizumab) were administered to patient 7 following postoperative parathyroid tumor relapse.

Clinical outcomes and follow-up

Serum calcium (2.36 ± 0.57 mmol/L) and PTH levels (157.3 ± 154.9 pg/mL) of all the patients significantly decreased at 1-3 days postoperatively ($p < 0.01$). Bone pain relieved after the operation and bisphosphonate treatment. Six patients (patients 3, 5, 6, 7, 9, and 10) relapsed postoperatively with relatively high preoperative PTH levels (1,519.5 ± 436.8 pg/mL, $p < 0.05$). Two patients (patients 3 and 7) died within 2 years postoperatively due to refractory hypercalcemia. Both presented with lung, lymph node, bone, and liver metastasis, and immunohistochemical analysis showed the Ki-67 index ≥ 10% in parathyroid lesions (Table 1).

Tab. 1. Characteristics and treatment of patients with PC.

Patient No.	Sex	Age (years)	Skeletal disease	Kidney stones	Thyroid carcinoma	Palpable neck mass	Tumor metastasis	Ca	P	PTH	ALP	eGFR (CKD-EPI)	US	CT	^{99m}Tc MIBI	Surgery	Pathology	Relapse
1	Male	40	+	-	-	+	-	3.9	0.66	1211	477	141.2	+	NA	+	En bloc resection in the parathyroid	4´3´1.5 cm tumor with capsular, vascular and lymph-vessel invasion; Ki-67 (+5%), PTH (+), CgA (+), Syn (+)	-
2	Male	53	+	-	+	-	Lymph nodes	3.52	0.61	626.9	412	117.5	+	NA	+	En bloc resection with ipsilateral thyroidectomy and lymph node resection in the central neck region.	2.5´1.5´1.5 cm tumor with capsular and vascular invasion; Ki-67 (+5%), PTH (+), CgA (-), Syn (+)	-
3	Female	37	+	+	-	-	Lung	5.12	1.03	1649	347	39.0	+	+	-	En bloc resection with ipsilateral thyroidectomy	4´2´2 cm tumor with capsular and vascular invasion; Ki-67 (+10%), PTH (+), CgA (+), Syn (+)	2 years, died
4	Male	38	+	-	-	-	Bone	2.9	0.65	534.7	431	88.3	+	NA	NA	En bloc resection with ipsilateral thyroidectomy	NA	-
5	Male	40	+	+	-	+	-	5.56	0.34	1829	857	37.4	+	-	+	En bloc resection in the parathyroid	4´3.5´2.8 cm tumor with capsular invasion; Ki-67 (+15%), PTH (+), CgA (+), Syn (-)	3 months
6	Female	44	+	+	-	+	-	3.52	0.72	2177	259	136.8	+	NA	+	En bloc resection with ipsilateral thyroidectomy and lymph node resection in the central neck region.	3´2.5´2 cm tumor with capsular invasion; Ki-67 (+5%), PTH (+), CgA (-), Syn (-)	1 year
7	Female	39	+	+	+	+	Lymph nodes, bone, and liver	4.71	0.61	1083	302	74.6	+	NA	+	En bloc resection with ipsilateral thyroidectomy and lymph node resection in the left neck region.	4´2.5´2.2 cm tumor with capsular and vascular invasion; Ki-67 (+15–25%), PTH (+), CgA (+), Syn (+)	5 months, died

Patient No.	Sex	Age (years)	Skeletal disease	Kidney stones	Thyroid carcinoma	Palpable neck mass	Tumor metastasis	Ca	P	PTH	ALP	eGFR (CKD-EPI)	US	CT	^{99m}Tc MIBI	Surgery	Pathology	Relapse
8	Male	33	+	+	+	+	-	4.49	0.59	871.1	642	43.7	+	-	+	En bloc resection with total thyroidectomy	2′1′1 cm tumor with capsular invasion; Ki-67 (+1%), PTH (+), CgA (-), Syn (-)	-
9	Male	35	+	-	-	+	-	3.75	0.3	1208	78	120.4	+	NA	NA	En bloc resection with ipsilateral thyroidectomy	2′1.8′1.3 cm tumor with capsular invasion; Ki-67 (+5%), PTH (+), CgA (+), Syn (+)	6 years
10	Male	62	+	+	+	-	Lymph nodes	3.99	0.91	1171	253	50.8	+	NA	+	En bloc resection with ipsilateral thyroidectomy	3′2′1 cm tumor with capsular invasion; Ki-67 (+5%), PTH (+), CgA (+), Syn (+)	1.5 years

Ca: total serum calcium; P: serum phosphorous; PTH: serum parathyroid hormone; ALP: serum alkaline phosphatase; eGFR: estimated glomerular filtration rate; CKD-EPI: chronic kidney disease epidemiology collaboration; US: ultrasound; 99mTc-MIBI: Technetium-99 labeled sestamibi; NA: not available.

DISCUSSION

PC is a rare disease present in 0.5-5.0% of patients with PHPT (Rodrigo *et al.* 2020). In most studies involving American and European populations, this entity reportedly affects less than 1.0% of patients with PHPT (Ferraro *et al.* 2019). But the incidence of PC seems to be higher in China (up to above 5.0%), and has increased in recent years (Zhao *et al.* 2013; Hu *et al.* 2020). In this series, ten patients accounted for 2.32% of patients with PHPT were diagnosed with PC at our hospital between 2003 and 2021.

The etiology of PC is unclear. PC is usually sporadic, but also form part of a genetic syndrome such as multiple endocrine neoplasia syndrome or hyperparathyroidism-jaw tumor (Pawlak *et al.* 2013; Singh Ospina *et al.* 2016). CDC73 mutation and PI3K/AKT/mTOR pathway were reported to be involved in the occurrence of PC (Singh Ospina *et al.* 2016). Pancreatic/pituitary tumors, pheochromocytoma, and other neuroendocrine neoplasms were not detected in our PC patients. X-ray and CT imaging examinations of patient 3 showed a brown tumor in the left jaw which may be a hyperparathyroidism-jaw tumor patient.

The clinical manifestations of PC are various, but excessive secretion of PTH leading to moderate to severe hypercalcemia (> 3.0 mmol/L), along with bone and renal involvement are typical features (Gao *et al.* 2017). Consistent with this, all 10 patients in our series exhibited bone destruction and pain due to osteoporosis. Most of these patients had nephrolithiasis with mild to moderate renal insufficiency. Biochemical indicators of patients with PC usually showed a markedly elevated PTH levels (more than 3 to 10-fold above the upper limit of normal), hypercalcemic crisis (serum calcium > 3.50 mmol/L), and serum ALP levels are higher than those in patients with PA (Liao Q & Liu 2019). In this report, nine of these patients had hypercalcemic crisis (90.0%); the serum PTH and ALP levels were markedly elevated. These biochemical findings are all consistent with PC. Neck ultrasound and parathyroid scintigraphy are the most common methods for detecting parathyroid lesions. Parathyroid masses were detected in all these patients via ultrasonography and ^{99m}Tc-MIBI-positive images. In addition, PC may be accompanied by papillary thyroid cancer, but only a few such patients have been described in the literature (Russo *et al.* 2019). In this series, four patients had papillary thyroid cancer, which was a relatively large proportion; the underlying mechanism was unclear and need to be further investigated.

Six patients in our series had been misdiagnosed with thyroid nodule/carcinoma, PA, arthritis, or bone tumor before admission to our hospital. Although typically clinical manifestations, hypercalcemic crisis and markedly elevated PTH levels can indicate PC, the final diagnosis depends on tumor metastasis status and histological characteristics, including parathyroid tumor

with capsular and/or vascular invasion, and invasion of surrounding neck structures. Immunohistochemical analysis is also necessary for the diagnosis of PC. The neuroendocrine tumor markers CgA and Syn are commonly expressed in parathyroid tumor issue, and a Ki-67 index > 5% should be considered indicative of possible malignant tumors (Erickson & Mete 2018). In the present report, the pathological characteristics showed that parathyroid tumors of all the patients had capsular and/or vascular invasion. Moreover, CgA (+) and Syn (+) presented in parathyroid tumors of 6 patients, and Ki-67 (index ≥ 5%) presented in parathyroid tumors of 8 patients.

Complete surgical resection of parathyroid lesions during the initial operation is the most effective therapy. The standard approach is en bloc resection in association with ipsilateral thyroidectomy (Quaglino *et al.* 2020). Medical treatment is mainly performed to relieve hypercalcemia. Bone antiresorptive drugs are appropriate treatments, especially bisphosphonates (e.g., pamidronate and zoledronate) can effectively reduce blood calcium levels. While in recent years, denosumab (a monoclonal antibody against the receptor activator of NF-kB ligand) has also been used to control hypercalcemia and may also be effective for refractory hypercalcemia (Çalapkulu *et al.* 2020). Calcitonin has a transient effect to reduce serum calcium. Calcimimetics (cinacalcet) which can reduce the serum PTH concentrations have emerged as another effective therapy (Takeuchi *et al.* 2017). The above-described medicines are commonly administrated for preoperative management or postoperative palliative treatment. Chemotherapeutic and radiotherapeutic treatments usually can not get good response. In this series, bisphosphonates and calcitonin were administrated to lower serum calcium effectively in all patients. Chemotherapy and PD-1 monoclonal antibody were administered to patient 7 during postoperative tumor recurrence, but the therapeutic effects were suboptimal.

PC has a high postoperative recurrence rate of approximately 40-60% (Storvall *et al.* 2019). In our series, serum calcium and PTH levels dramatically dropped postoperatively, but six patients with relatively high preoperative PTH levels relapsed postoperatively. Moreover, two patients with the Ki-67 index ≥ 10% and distant metastasis died within 2 years postoperatively. These findings implied that high PTH levels, tumor metastasis, and a high Ki-67 index may be indicators of poor prognosis.

CONCLUSION

PC is a rare disease with high rates of misdiagnosis and recurrence. Clinical diagnosis is difficult because of its complex manifestation. Severe bone pain, kidney stones, and markedly elevated levels of serum calcium (hypercalcemic crisis) and PTH usually indicate PC. Early recognition and complete resection of the lesion during the initial operation are pivotal to reduce mortality. A markedly elevated PTH level, tumor metastasis, and the Ki-67 index ≥ 10% are predictive of poor prognosis.

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