

## Parathyroid carcinoma: a 16-year experience in a single institution

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**Abstract.** Introduction: This study aims to describe our experiences of parathyroid carcinoma. Materials and Methods: The data of clinicopathological features, surgical treatment and outcomes of seven cases of parathyroid carcinoma among 171 patients who underwent surgery for primary hyperparathyroidism over a 16-year period were analyzed. Results: The major symptoms at the diagnosis included a neck mass in three cases and multiple bone pain in five. Two patients were asymptomatic. No remarkable increases of serum calcium levels were noted in the patients, but serum parathyroid hormone (PTH) concentrations were high in most of the patients (4 of 5 in available). A variety of imaging studies including ultrasonography, sestamibi scan, and computed tomography scan were helpful in identifying the abnormal parathyroid glands, but not specific for the diagnosis of parathyroid carcinoma. In most patients, the parathyroid carcinomas were suspected at the time of neck exploration, and confirmed by final histopathologic examinations. All patients underwent complete surgical excision with curative intent. During the follow-up period, one patient developed lung metastases 6 years later and the other one died of unrelated cause. Conclusion: Preoperative diagnosis of parathyroid carcinoma is difficult, but operative findings are helpful in the diagnosis. The optimal surgical treatment is en block radical resection including adjacent structures when parathyroid carcinoma is suspected. Unusually, although our patients presented with high serum PTH concentrations, they had normal or mild elevated serum calcium concentrations. The reason of why should be investigated in future studies.

**Key words:** Parathyroid carcinoma, Hypercalcemia, Radical resection, Primary hyperparathyroidism, Parathyroid hormone

**PARATHYROID** carcinoma is a rare neoplasm, accounting for less than 1% of patients with primary hyperparathyroidism [1]. It was first described as a nonfunctioning lesion in 1904, and functioning lesion in 1933 [1-3].

Although several clinical and biochemical features differentiate parathyroid carcinoma from benign forms of hyperparathyroidism, accurate pre- or intra-operative diagnosis is not easy. The diagnosis of parathyroid carcinoma is usually established by pathologic examination of surgical specimens, characteristically by vascular or capsular invasion [4]. Optimal surgical

resection is mandatory for the treatment of parathyroid carcinoma [5].

We describe here our clinical experiences of parathyroid carcinoma treated in our institution during the past 16 years.

### Materials and Methods

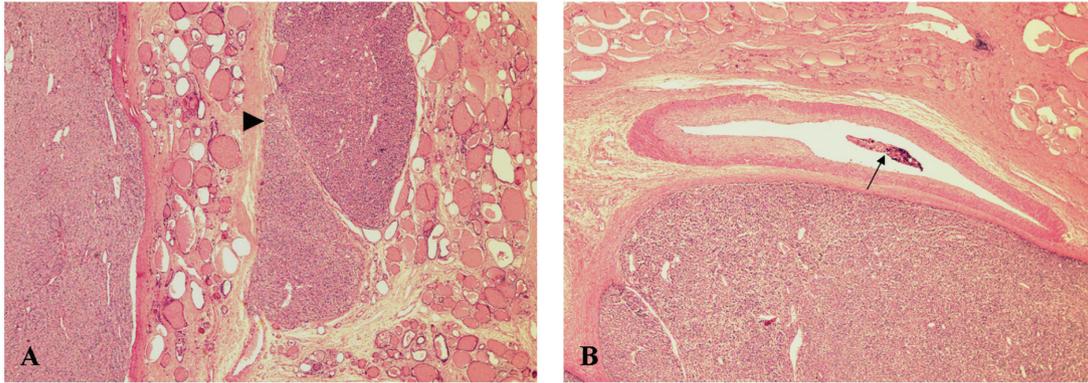
Between January 1992 and December 2007, 171 patients with primary hyperparathyroidism were treated in the Yonsei University College of Medicine; of these, eight patients (4.7%) were treated for parathyroid carcinoma. One patient was lost to follow-up, and the remaining seven patients were enrolled in this study. The mean follow-up period was 103.4 months (range, 36-254 months).

Pathological diagnosis of parathyroid carcinoma was confirmed by one pathologist who re-reviewed

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**Fig. 1** Histopathologic findings (H&E x40) showing (A) infiltrative growth into the thyroid gland (arrow head), and (B) vascular invasion and tumor emboli (arrow) in vascular spaces.

**Table 1** Clinicopathologic features of patients

Sex/Age	Past history	Symptoms	Preoperative Ca/P/PTH	Postoperative Ca/P/PTH	Extent of thyroidectomy	Extracapsular invasion	Outcome
F/47	Hypertension	Neck mass, bone pain	12/2/-	9.7/2.5/24.4	Lobectomy	Yes	AWOD
F/31	Renal stone	Bone pain	10.9/1.7/1340	8.4/2.9/56.9	Lobectomy	Yes	AWOD
F/50	-	Neck mass, bone pain	10.5/2.1/-	8.5/3.7/51.3	†Total thyroidectomy	No	AWOD
M/59	-	Incidental finding	10.3/2.0/130	9.4/2.2/26.3	Lobectomy	No	AWOD
M/23	-	Bone pain	12.3/2.2/162.8	9.2/2.6/25.1	Lobectomy	No	Recurrence
F/33	Breast cancer	Incidental finding	12/2.4/50.6	9/3.3/32.3	Lobectomy	Yes	AWOD
F/60	-	Bone pain	11.8/2/1417	9/2.6/-	Lobectomy	Yes	AWOD

\*Abbreviation: Ca, calcium; P, phosphorus; PTH, parathyroid hormone; AWOD, alive without disease

†Case 3 underwent total thyroidectomy due to the concurrent invasive follicular carcinoma in thyroid.

all pathologic slides. Diagnosis was based on histopathologic characteristics, local invasiveness, and/or metastasis (Fig. 1) [4].

Clinicopathological features were reviewed retrospectively, and biochemical markers including serum calcium, phosphorus and parathyroid hormone concentrations were evaluated serially from the initial presentation and through a follow-up.

## Results

The clinicopathologic characteristics of the patients are listed in Table 1. Of the seven patients, two (28.6%) were men and five (71.4%) were women, with the mean age of 43.3 years (range, 23-60 years).

One patient had a history of hypertension and was treated with anti-hypertensive agents one had a history of renal stones, and one had undergone breast cancer surgery.

Five patients initially presented with constitutional symptoms, including bone pain and/or neck mass. Two patients were asymptomatic despite hypercalcemia.

In laboratory findings, all seven patients had mild hypercalcemia at the time of the initial presentation; the mean serum calcium concentration was 11.4 mg/dL (range, 10.3-12.3 mg/dL). Hypophosphatemia was present in all cases. The initial intact parathyroid hormone concentrations (iPTH) were available for five patients; four patients (80.0%) had elevated iPTH concentrations and one (20.0%) had a normal iPTH concentration despite the presence of hypercalcemia. The mean iPTH concentration was 620.08 pg/mL (range, 50.6-1417.0 pg/mL).

Laboratory values after surgery including serum calcium and phosphorus concentrations were within normal ranges in all patients.

Neck ultrasonography and computed tomography

were performed in all patients for preoperative imaging. One patient was examined by thallium-<sup>99m</sup>technetium subtraction scanning, and two by <sup>99m</sup>technetium-sestamibi scanning. These imaging modalities were helpful in identifying the abnormal parathyroid glands, but not specific for the diagnosis of parathyroid carcinoma. Ultrasonography-guided fine needle aspiration cytology was performed in four (57.1%) patients, but it was not useful in obtaining a definite diagnosis. Only one patient was suspected of having parathyroid carcinoma.

The diagnosis of parathyroid carcinoma was made by the peri-operative frozen section in all cases, and then all of the seven patients underwent complete surgical excision with curative intent (Fig. 2); seven underwent combined resection of the ipsilateral thyroid lobe, and one underwent total thyroidectomy because of coincident follicular thyroid carcinoma.

Of the seven patients, three (42.9%) were locally invasive parathyroid carcinoma; the sites of local invasion were the strap muscles in two patients and a recurrent laryngeal nerve in one patient. None of the seven patients received adjuvant treatment such as chemotherapy or radiation therapy.

There was no loco-regional recurrence, but one patient had a distant metastasis to the lung 6 years after surgery; this patient remains alive 30 months after the diagnosis of metastasis. Only one patient died of causes unrelated to parathyroid carcinoma.

## Discussion

Our results show a higher incidence rate (5.3%) than reported incidences of parathyroid carcinoma. It might not only be due to the referral center of our hospital in Korea but also in overlooking patients with mild primary hyperparathyroidism. Thus, all pathologic slides were re-reviewed by one pathologist.

Parathyroid carcinoma usually developed during the fourth decade of life as observed in our results (mean, 41.1 years), and has a sex distribution of approximately 1:1, although parathyroid adenoma has a female predominance (female:male ratio of 3:1) [6, 7]. In our series, however, there were slight female:male ratio bias (5:3) and such a difference might be due to the small number of patients.

Although the etiology of parathyroid carcinoma is unclear, parathyroid carcinoma is often associated with several clinical factors and hereditary disorders includ-



**Fig. 2** Surgical specimen showing enlarged parathyroid glands and a locally invasive solid mass in the left thyroid parenchyma (arrow) (RIP, right inferior parathyroid gland; RSP, right superior parathyroid gland; LIP, left inferior parathyroid gland; CN, central node)

ing a prior history of neck irradiation, end-stage renal disease, multiple endocrine neoplasia syndromes, hyperparathyroidism-jaw tumor syndrome, and ossifying fibromas of the maxilla and mandible [8-13]. Recently, a tumor suppressor gene, which encodes the protein parafibromin, has been reported to be implicated in the pathogenesis of parathyroid carcinoma [14]. In our series, one patient had a history of end-stage renal disease, and the others had no above-mentioned history.

On a physical examination, whereas patients with parathyroid adenoma rarely presents with neck masses, up to 50% of patients with parathyroid carcinoma present with palpable neck masses because of locally advanced diseases [15].

The kidneys and skeletons are the classic target organs in parathyroid carcinoma. Renal involvement, including nephrolithiasis, nephrocalcinosis, and renal insufficiency presents in 30-84% of patients [16], and skeletal involvement, including osteofibrosis, osteoporosis, pathologic fractures, and bone pain occurs in more than 40% of patients [17]. Concomitant renal and skeleton involvement has been observed in up to 50% of patients with parathyroid carcinoma, but it is rare in patients with parathyroid adenoma [15]. Other symptoms of parathyroid carcinoma include fatigue, weakness, weight loss, anorexia, polyuria, and polydipsia; but those can be caused by other problems.

In laboratory findings, whereas patients with benign primary hyperparathyroidism usually present with mild hypercalcemia, within 1 mg/dL above the normal upper limit, patients with parathyroid carci-

noma usually have very high calcium levels, usually 3-4 mg/dL above the normal upper limit [18]. Our patients, however, presented with mild to moderate hypercalcemia, within 1-2 mg/dL above the normal upper limit. We cannot explain why our patients presented mild to moderate hypercalcemia. We speculate that the Korean patients with parathyroid carcinoma have unique clinical characteristics of hypercalcemia, but we did not find evidences to support the hypothesis.

Recent knowledge of whole PTH mentioned below would help the discussion of the possible explanation. Most commercial intact parathyroid hormone (intact PTH) assays cross-react with non-(1-84) PTH (likely 7-84 PTH). The 7-84 PTH showed inversed biological activity to 1-84 PTH resulting in hypocalcemia [19]. A higher ratio of 7-84 PTH to intact PTH or 1-84 PTH (whole PTH) may explain the results of high PTH levels with mild hypercalcemia in parathyroid cancer patients.

Preoperative imaging modalities including ultrasonography, computed tomography, magnetic resonance imaging, thallium-technetium subtraction scans and technetium-99m-sestamibi scans cannot differentiate between parathyroid adenoma and parathyroid carcinoma. In our series, we have performed preoperative imaging modalities including ultrasonography and computed tomography for the diagnosis of parathyroid carcinoma, but only one patient was suspected of parathyroid carcinoma preoperatively.

The use of fine-needle aspiration cytology in a suspected case of parathyroid carcinoma is not recommended for two reasons. First, the diagnosis of parathyroid carcinoma can be extremely difficult histologically and sampling error may lead to false-negatives, thus misleading the surgeon preoperatively. Second, by violating the capsule of the tumor there is a risk of seeding parathyroid cells [20, 21].

In our series, fine-needle aspiration cytology was performed in four patients for the suspected thyroid pathologies.

Macroscopically, parathyroid carcinomas tend to be large (often > 3 cm), firm in consistency, lobulated, and have a dense fibrous capsule, whereas parathyroid adenomas tend to be soft, oval, and brownish-red to tan in appearance (Fig. 2).

In histology, parathyroid carcinoma shows uniform sheets of cells arranged in a lobulated fashion with in-

tervening fibrous trabecular, capsular, and/or vascular invasion, and the presence of mitotic figures, which should be differentiated clearly from those observed in endothelial cells (Fig. 1) [4].

Intraoperative findings including lobulation, firmness, larger mass, enclosure by a dense, fibrous capsule, and adherence to adjacent tissues and structures may help to distinguish a benign adenoma from a carcinoma [15, 22].

Complete surgical resection is the treatment of choice for patients with parathyroid carcinoma. Appropriate surgical treatment consists of an en bloc resection of all involved tissues, which frequently includes the removal of the ipsilateral thyroid lobe, segmental excision of the overlying strap muscles, and removal of the paratracheal lymph nodes and other involved soft tissues along with the involved parathyroid gland [5]. A bilateral neck exploration with examination of all four parathyroid glands is routinely performed to exclude the presence of parathyroid hyperplasia. Lateral neck dissection is performed only in cases of clinically evident lateral lymph node metastases. Care should be taken during dissection to avoid rupture of the parathyroid gland capsule, as this increases the likelihood of tumor seeding [23].

Adjuvant treatment such as radiation therapy and chemotherapy has been ineffective as primary curative treatment [23]. However, adjuvant radiation therapy may effectively decrease the local recurrence rate in selected patients or after surgery [24].

Postoperative serum calcium concentrations should be monitored closely because patients may experience hungry bone syndrome which results in symptomatic hypocalcemia from calcium and phosphorous deposition into the bones, and calcium and calcitriol medication might be required [19].

## Conclusion

Parathyroid carcinoma is a rare disease which is difficult to diagnose pre- or intra-operatively. Understanding of the clinical features and biochemical findings in patients with parathyroid carcinoma may aid in diagnosis and treatment, as well as defining the extent of surgery. Unusually, although our patients presented with high serum PTH concentrations, they had normal or mildly elevated serum calcium concentrations. The reason of why should be investigated in future studies.

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