A Case of Parathyroid Carcinoma with a Highly Aggressive Clinical Course

Hiroko Mori, Yosuke Okada, Tadashi Arao and Yoshiya Tanaka*

First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan

Abstract : We describe a 59-year-old woman who presented with pathological osteoporosis, cerebral infarction, hypercalcemia, and markedly high parathyroid hormone levels. The diagnosis was primary hyperparathyroidism, and parathyroidectomy was performed. Histopathological examination showed parathyroid adenoma. Surgical exploration for recurrent parathyroid carcinoma was undertaken at 2 and 3 years after the initial neck resection. Pulmonary metastasis was diagnosed at 4 years after the initial surgery. Despite treatment with intravenous bisphosphonates, her calcium and parathyroid hormone (PTH) levels remained elevated, and leg amputation was performed following the development of arteriosclerosis obliterans at 6 years after the initial neck resection. The prognosis for parathyroid carcinoma is often difficult to predict due to recurrence.

Keywords : parathyroid carcinoma, pulmonary metastasis, arteriosclerosis.

Introduction

Although parathyroid neoplasms are common and often cause primary hyperparathyroidism, parathyroid carcinoma is a rare endocrine malignancy, accounting for less than 1% of cases of primary hyperparathyroidism [1]. Approximately 95% of parathyroid carcinomas are functional tumors. Patients with parathyroid tumors usually present with profound symptoms of hyperparathyroidism, with marked hypercalcemia, and high parathyroid hormone (PTH) levels. The single most effective therapy for parathyroid carcinoma is complete resection of the primary lesion at the time of the initial operation, when extensive local invasion and distant metastases are less likely [2]. The prognosis of patients with parathyroid carcinoma is variable; unfortunately, more than 50% have a persistent or recurrent disease due to a regional or distant disease [3]. The management of metastasis from parathyroid carcinoma is a clinical challenge. When parathyroid carcinoma is widely disseminated and surgical resection is no longer effective, the prognosis is poor.

Parathyroid carcinoma shares many clinical features with acute primary hyperparathyroidism. Here we report a rare case of a patient who underwent resection of multiple functional parathyroid carcinomas with pulmonary metastases and various complications, including bone disease, renal insufficiency and arteriosclerosis. We also discuss various aspects of the oncological management of advanced parathyroid carcinoma.

Case Report

In 2004, a 59-year-old woman was referred to the Department of Otolaryngology, University of Occupational

*Corresponding Author: Yoshiya Tanaka, MD, PhD. First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan. 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, 807-8555, Japan, Tel: +81-93-603-1611, ex: 2422, Fax: +81-93-691-9334, E-mail: tanaka@med.uoeh-u.ac.jp
and Environmental Health, complaining of backache and swelling in the left cervical area. The medical history included pathological fracture, gastric ulcer, and cerebral infarction. The cervical tumor was palpable, huge, hard, with a smooth surface, and fixed with poor movement. Blood tests demonstrated hypercalcemia (15.0 mg/dl), high alkaline phosphatase (6,032 IU/l), and high intact parathyroid hormone (iPTH) concentration (3,321 pg/ml). Serum phosphorus was 2.5 mg/dl and renal function was normal. Subsequent work-up included ultrasonography that showed a large inhomogeneous mass in the left lower thyroid lobe measuring 39×28×22 mm (Fig. 1A), and methoxyisobutylisonitrile (MIBI) scintigraphy demonstrated increased uptake on the left side (Fig. 1B). The provisional diagnosis was primary hyperparathyroidism or parathyroid carcinoma.

Parathyroidectomy was performed. Surgical exploration showed a large mass (40×33×26 mm in size, weight 16.1 g) adherent to the inferior pole of the left hemithyroid (Fig. 1C). The tumor had a grayish-white capsule and was lobulated. Histopathological examination showed parathyroid adenoma consisting mainly of chief cells without evidence of vascular invasion (Fig. 1D, E). Severe osteoporosis was also evident, with serum bone-specific alkaline phosphatase (BAP) of 1,060 U/l, urine N-telopeptide (NTX) 1,596 nmol BCE /nmol creatinine. Total and regional bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) was very low (lumbar spine: BMD 0.412 g/cm², t-scores – 5.4, 41%). Radiographic examination showed salt and pepper skull, rugger-jersey spin and subperiosteal resorption. She developed flail chest at the time of surgery. Although transient normocalcemia was recorded during the clinical course, she developed myocardial infarction and cerebral infarction.

Two years after parathyroidectomy, she presented with persistently high serum calcium level (11.9 mg/dl), high alkaline phosphatase (468 IU/l), and iPTH (498 pg/ml), indicative of recurrent disease, despite successful resection of the parathyroid adenoma in the left lower gland. Cervical echo demonstrated two masses in the left upper (19×13×12 mm in size) and middle (10×8×6 mm in size) glands (Fig. 1F). MIBI scintigraphy demonstrated no uptake (Fig. 1G). She underwent a second and more extensive surgery in 2006, with removal of adjacent left thyroid tissue for recurrent parathyroid carcinoma. Tissue samples stained with hematoxylin and eosin (H&E) demonstrated evidence of capsular, thyroid and vascular invasion (Fig. 1H). The tumor contained chief cells (which were the predominant cell type) arranged in a trabecular, solid, or acinar pattern, with loss of the typical lobular pattern. It was composed of clear, partially oxyphil cells, showing atypia and nuclear pleomorphism with increased mitotic activity (Fig. 1I). Histopathology was suggestive of parathyroid carcinoma. However, she presented with a persistently high level of serum calcium (11.8 mg/dl), alkaline phosphatase (397 IU/l), and iPTH (197 pg/ml), indicating recurrence of disease. Cervical echo identified two masses in the left neck (each measuring 10×5 mm) (Fig. 1J). MIBI scintigraphy demonstrated uptake on the left and right side (Fig. 1K). Surgical exploration was conducted for recurrent parathyroid carcinoma in 2007, 3 years after the original neck resection, and pathology was suggestive of parathyroid carcinoma. Furthermore, she presented with pulmonary metastasis in 2008, 4 years after the original neck resection.

At that stage, she refused surgery and was treated with zoledronate and loop diuretics. Despite the administration of intravenous bisphosphonates, her serum calcium and PTH levels remained high, and amputation of the leg was performed due to arteriosclerosis oblitertans in 2009, 6 years after the original neck resection. The patient died because of infection in 2011.

**Discussion**

Parathyroid carcinoma is a rare tumor, and accounts for 0.4-5.2% of all reported cases of hyperparathyroidism, and approximately 0.2% to 0.5% of all malignant endocrine tumors [4], with about 800 cases reported worldwide [1, 5, 6]. Diagnosis of parathyroid carcinoma is difficult and includes histopathological diagnosis of capsular, vascular, or perineural invasion or metastasis [7]. The suspicion of malignancy should be high in the presence of hypercalcemia greater than 14 mg/dl, extremely high serum PTH level (five times the upper limit of normal), as well as the presence of large masses and unilateral vocal cord paralysis [8]. In our patient, although serum calcium level was 15.0 mg/dl, iPTH concentration was 3,321 pg/ml and tumor size was 4 cm. The diagnosis of the first parathyroid tumor was parathyroid adenoma, which was
confirmed by pathological examination. However, the tumors in the second and third resections were parathyroid carcinomas. The histopathological distinction between benign and malignant parathyroid tumors is often difficult, with up to 50% of patients presenting metastases after having been initially diagnosed with benign disease [5, 9].

The clinical features of parathyroid carcinoma are primarily related to the effects of excessive secretion of PTH by the functioning tumor rather than to infiltration of vital organs by tumor mass. Parathyroid carcinoma is an indolent, albeit tenacious, tumor with rather low malignant potential. It tends to recur locally at the operative site and spread to contiguous structures in the neck. Metastases occur late in the course of the disease, spreading via both lymphatic and hematogenous routes, and the lung (40%) is involved most commonly [1]. In the present case, the patient had recurrence with lung metastasis, together with a multitude of complications, including cardiovascular pathologies, cerebral infarction, arteriosclerosis obliterans, renal failure, and bone disease, that appeared during the long clinical course. We suggest that the control of PTH level is the most important factor for a good prognosis and quality of life in patients with parathyroid carcinoma.

There are no specific guidelines for the management and treatment of parathyroid carcinoma. The only curative treatment for parathyroid cancer is surgical resection. *En bloc* resection with avoidance of capsular violation or tumor spillage should be the initial surgery if carcinoma is suspected. The optimal surgical treatment is *en bloc* tumor resection combined with ipsilateral thyroid lobectomy when the diagnosis is suspected and until it is proven otherwise. Long-term survival is largely dependent on the extent of the pri-

---

**Fig. 2. Summary of the clinical course, including changes in serum levels of Ca, ALP, and intact PTH from 2004 to 2010.** The patient underwent resection of multiple functional parathyroid tumors. She was later diagnosed with pulmonary metastases and had various complications, such as bone disease, renal insufficiency, and arteriosclerosis. •: serum calcium (Ca), ▲: alkaline phosphatase (ALP), —: intact parathyroid hormone (intact PTH).
mary surgical resection. However, all too commonly the diagnosis is made intraoperatively, and occasionally, postoperatively [10]. Lee et al. [11] reported that most parathyroid cancers (78.6%) were resected by simple parathyroidectomy, whereas only 12.5% of patients underwent en bloc resection. In the present case, parathyroidectomy was performed during the first presentation. The case was diagnosed after surgery the second time. It is possible that aggressive surgery with ipsilateral thyroid lobectomy performed during the initial presentation could have improved the outcome in our patient.

Reoperation in patients with localized parathyroid carcinoma is recommended because it relieves symptoms of hypercalcemia, and it normalizes serum calcium and PTH levels in most patients. When parathyroid carcinoma becomes widely disseminated and surgical resection is no longer effective, the prognosis is poor. For patients with unresectable parathyroid carcinoma, a protocol-based treatment with chemotherapy and external radiotherapy should be considered [3]. When metastasis is extensive and surgical options are exhausted, clinical management should focus on the control of hypercalcemia [5]. Saline infusion and loop diuretics are often used, but in the majority of cases, drugs that inhibit bone resorption are needed. Potent intravenous bisphosphonates may transiently control hypercalcemia, but patients frequently become refractory to them [5]. In our case, zoledronate effectively controlled serum calcium initially, but failed to do so subsequently. Cinacalcet has been shown to be effective in controlling hypercalcemia in patients with inoperable parathyroid cancer [12]. Cinacalcet is an important adjunct for the control of hypercalcemia associated with recurrent and metastatic disease. Moreover, denosumab offers long-term calcium control with less frequent administration. Bowyer et al. [13] advised the use of denosumab in the treatment algorithm for patients with hypercalcemia secondary to parathyroid cancer. Treatment with cinacalcet or denosumab could have resulted in a more efficient control of hypercalcemia.

In conclusion, the diagnosis and treatment of parathyroid carcinoma is often difficult. This is associated with delayed diagnosis when the tumor is already palpable. In addition, prognosis is often difficult to predict because recurrence occurs in most cases after the malignancy is confirmed. The most important aspect of management of patients with metastatic parathyroid carcinoma is the control of serum calcium level.

We described a rare case of parathyroid carcinoma with pulmonary metastasis and various complications, including atherosclerosis. More cases and analyses are needed to select the best outcome for patients with parathyroid carcinoma.

Conflict of Interest

The authors state that they have no Conflict of Interest (COI).

References


重度な進行性の臨床経過をたどった副甲状腺がんの1例

森 博子, 岡田 洋右, 新生 忠司, 田中 良哉
産業医科大学 医学部 第1内科学講座

要　旨：骨粗鬆症, 脳梗塞, 高カルシウム血症, そして高parathyroid hormone (PTH) 血症を呈した59歳女性について報告する。原発性副甲状腺機能亢進症と診断され, 副甲状腺摘出術を施行された。病理学的所見では, 副甲状腺腫の結果であったが, 副甲状腺摘出2年後, 3年後に副甲状腺腫大を来し, 4年後には肺にも転移し, 臨床経過および再摘出病理より副甲状腺癌の再発と診断された。ビスホスホネート静注療法を施行するもカルシウムとPTHは高値のまま, 動脈硬化は進み, 副甲状腺摘出6年後には下肢閉塞性動脈硬化症により下腿切断となった。副甲状腺癌は有病率0.005%と非常に稀であるが, 再発など病気の進行をコントロールすることは非常に難しいと考えられた症例であった。

キーワード：副甲状腺癌, 肺転移, 動脈硬化症。