VARIABILITY OF CLINICAL PRESENTATIONS IN THREE CASES OF PARATHYROID CARCINOMA

Horng-Yih Ou, Chung-Jye Hung, Wei-Hsin Hsu, Eugene Hsin Yu, and Ta-Jen Wu

Abstract: Parathyroid carcinoma accounts for 0.5 to 4.0% of cases of primary hyperparathyroidism. The prognosis depends largely on the extent of successful resection at the time of initial operation. Therefore, early diagnosis before surgery is important. We report 3 cases of primary hyperparathyroidism. The first patient, a 20-year-old uremic female, had refractory hypercalcemia after 5 years of hemodialysis treatment. Hypercalcemia persisted despite repeated parathyroidectomy. Pathology revealed diffuse hyperplasia of the parathyroid glands with focal adenomatous changes. Multiple pulmonary metastases were found later. The second patient, a 45-year-old female with history of nephrolithiasis, presented with severe osteoporosis. She underwent repeated parathyroidectomy for local recurrence. Pathology disclosed typical features of parathyroid carcinoma with adjacent lymph node metastasis. The third patient, a 34-year-old male, had recurrent episodes of extremity fracture and hypercalcemia with palpable neck mass. He underwent resection of the parathyroid tumor. Vascular and capsular invasions were noted microscopically. All three patients were relatively young and had extremely high intact parathyroid hormone (iPTH) level (15 to 31 times the upper limit of normal). The first patient died of hypercalcemia and respiratory failure and the other 2 were treated successfully with surgical excision and, in case 2, combined chemotherapy and radiotherapy. The latter 2 patients had no recurrence during 18 months and 14 months of follow-up, respectively. Our experience with these cases suggests that the combination of the following characteristics are highly suggestive of parathyroid carcinoma: young age, palpable neck mass, concomitant renal and skeletal disease, and extremely high iPTH level in patients with PTH-dependent hypercalcemia.

Key words: Hypercalcemia; Hyperparathyroidism; Parathyroid neoplasms


Parathyroid carcinoma is an uncommon endocrine malignancy. Only 0.5 to 4.0% of cases among patients with primary hyperparathyroidism are caused by parathyroid carcinoma. Parathyroid carcinoma should be considered in the differential diagnosis of hypercalcemic disorders because the morbidity and mortality are substantial and improved prognosis is associated with early recognition and surgical resection. Here we report 3 cases treated in our hospital during the past 14 years.

Case Reports

Case 1
A 20-year-old female patient suffered from intermittent hematuria and progressive deterioration of renal function since childhood. She began hemodialysis therapy at the age of 15 years. Over the next 5 years she complained of bone and joint pain. Due to hypercalcemia, intravenous vitamin D₃ was administered thrice weekly for 5 months. She was then referred to our hospital for treatment of refractory hypercalcemia. At initial examination, her serum calcium was 3.6 mmol/L, phosphate 2 mmol/L, alkaline phosphatase 586 U/L, and intact parathyroid hormone (iPTH) 1968 ng/L. X-ray of the skull and fingers revealed ‘salt and pepper’ appearance and subperiosteal resorption of phalanx, respectively. Thallium (TI-201) and technetium (Tc-99m) subtraction parathyroid scan disclosed hot spots in the upper poles of both parathyroid lobes. Subtotal parathyroidectomy was performed. The right upper, right lower, and left upper parathyroid glands weighed 6.22 g, 1.06 g, and 4.8 g, respectively. Only the left lower gland was biopsied. Pathology revealed diffuse hyperplasia of the parathyroid glands with focal adenomatous changes. Total parathyroidectomy of the remaining gland,
which was hyperplastic on histology, was performed 6 months later, due to persistent hypercalcemia (serum calcium, 3.3 mmol/L and iPTH, 2155 ng/L). There was no evidence of ectopic parathyroid gland. However, there was no response to the second operation and chronic hypercalcemia was unchanged.

Chronic cough and intermittent hemoptysis developed thereafter. Chest X-ray and computed tomography scan showed multiple pulmonary nodules with progression that were shown to be metastatic parathyroid carcinoma by open lung biopsy. She died of hypercalcemia and respiratory failure 1 year after diagnosis of parathyroid carcinoma.

**Case 2**
A 45-year-old female patient suffered from generalized bone pain for 4 months. She had nephrolithiasis and was treated with extracorporeal shock wave lithotripsy 7 years ago. On this examination, severe osteoporosis of the lumbar spine (by dual energy X-ray absorptiometry) and hypercalcemia (serum calcium, 3.4 mmol/L; phosphate, 0.7 mmol/L) with elevated iPTH (> 1000 ng/L) were found. Hyperparathyroidism was suspected. Imaging studies including ultrasonography and Tc-99m sestamibi scanning revealed right upper parathyroid tumor and 2 lymph node metastases. Resection of the tumor and metastases was performed. Examination of a frozen section of the parathyroid gland obtained during this operation revealed parathyroid carcinoma. Parathyroidectomy and right subtotal thyroidectomy were then performed. Pathology disclosed typical features of parathyroid carcinoma with adjacent lymph node metastasis. Three months later, she underwent a second operation for local recurrence. Concurrent chemotherapy and radiotherapy followed. There was no further recurrence during 18 months of follow-up.

**Case 3**
A 34-year-old male had 3 previous episodes of recurrent lower extremity fractures over a 10-year period beginning in 1992. He received autoimplantation of bone graft at a local hospital. As the healing was poor, a graft specimen was sent for pathological examination and the report revealed a giant cell tumor of bone and he was referred to our oncology clinic. Blood chemistry and endocrine examination revealed hypercalcemia (serum calcium, 3.9 mmol/L), elevated iPTH (2043 ng/L), high alkaline phosphatase (837 U/L) and renal insufficiency (serum creatinine, 168 µmol/L). A firm palpable parathyroid tumor with a diameter of 3 cm on ultrasonography was found at the posterior inferior aspect of the right thyroid lobe. Technetium-thallium subtraction scanning also disclosed a right parathyroid tumor.

The pathologic diagnosis of bone graft was revised as “hyperparathyroidism-related bone change”. He underwent resection of the parathyroid tumor. Vascular and capsular invasions were noted on microscopic examination of the tumor specimen. He had no recurrence during 14 months of follow-up at our hospital.

**Discussion**

Parathyroid carcinoma is an uncommon cause of PTH-dependent hypercalcemia. In most series, this entity accounts for less than 1% of cases of primary hyperparathyroidism. Clinical scenarios such as a history of neck irradiation, an adenoma or hyperplastic parathyroid gland, and end-stage renal disease may predispose patients to the development of parathyroid carcinoma. In addition, molecular mutations of both oncogenes (cyclin D1 of PRAD1) and tumor suppressor genes (RB gene and p53 gene) have postulated roles in the pathogenesis of parathyroid carcinoma.

Parathyroid carcinoma in chronically uremic patients, as in case 1 of this report, is a rare complication of secondary hyperparathyroidism. A report of such a case also reviewed 12 previous cases of parathyroid carcinoma in patients receiving maintenance hemodialysis. All demonstrated hyperplasia of other parathyroid glands. Nodular hyperplasia in patients with renal (secondary) hyperparathyroidism is associated with monoclonal growth. One would, therefore, anticipate that parathyroid carcinoma should occur, albeit the number of reported cases is low.

According to previous reports, the average age of patients with parathyroid carcinoma is usually in the fifth decade or middle fifties, approximately 10 years younger than those with typical primary hyperparathyroidism. Our patients, however, were much younger.

The presence of a palpable neck mass, a striking difference between benign and malignant parathyroid disease is an important clinical finding in parathyroid carcinoma. It has been reported in 30 to 76% of patients with parathyroid carcinoma.

Overt signs and symptoms of hypercalcemia often dominate the clinical picture of parathyroid carcinoma. There is a higher involvement rate of the classical target organs of PTH, kidney, and skeleton in parathyroid carcinoma, compared with benign hyperparathyroidism. Typical renal diseases include renal colic, nephrolithiasis, nephrocalcinosis, and renal insufficiency. Bone diseases include bone pain, pathological fracture and radiological signs of osteitis.
fibrosa cystica, subperiosteal bone resorption, ‘salt and pepper’ skull, and osteopenia. Concomitant renal and bone disease seem to be distinguishing features of parathyroid carcinoma. All of our patients had both renal and skeletal diseases.

Serum iPTH levels in parathyroid carcinoma usually range from 3 to 10 times the upper limit of normal and in primary hyperparathyroidism are usually less than twice the upper normal limit. In our experience of 24 cases of benign hyperparathyroidism patients at this center during the same period as the 3 cases of this report, mean iPTH levels were 3 times the upper normal limit (median, 212.5; range, 69 to 1447 ng/L; normal range, 10 to 65 ng/L). However, extremely high iPTH level, ranging from 15 to 31 times the upper limit of normal, were found only in these 3 parathyroid carcinoma patients (Fig.).

Making a pathological distinction between benign and malignant parathyroid carcinoma sometimes is difficult. The diagnosis could not be made until the detection of distant metastases in case 1. Two similar cases were reported in the review of Miki et al. Schantz and Castleman established criteria for the pathological diagnosis of malignancy based on histological features. These features are: 1) uniform sheets of chief cells arranged in a lobular pattern separated by dense fibrous trabeculae; 2) capsular or vascular invasion; and 3) mitotic features within tumor parenchymal cells that must be distinguished from endothelial cell mitosis. None of these features is pathognomonic of parathyroid carcinoma. An overall histological pattern is more useful than any single feature in the differentiation of parathyroid carcinoma from benign disease.

Complete resection of the primary lesion at the time of initial operation is the most effective therapy for parathyroid carcinoma. Surgical approach includes en bloc removal of the lesion together with the ipsilateral thyroid lobe and isthmus without rupture of the gland capsule. Parathyroid carcinoma tends to recur locally. Metastases occur via both lymphatic and hematogenous routes. The cervical nodes (30%) and lungs (40%) are most commonly involved, followed by the liver (10%). Once the tumor recurs, complete resection is unlikely. Significant palliation may result from resection of even small but accessible distant metastases.

Chemotherapy and radiotherapy have been disappointing in managing metastatic disease. Medical management of hypercalcemia could prolong survival in these patients. Novel therapies that show promise include calcimimetics, molecules with agonist action at the calcium-sensing receptor on parathyroid cells, used to lower serum PTH and calcium concentration, and immunization with human and bovine PTH.

In conclusion, parathyroid carcinoma is an uncommon cause of PTH-dependent hypercalcemia. The ultimate prognosis depends to a major extent upon successful resection of the tumor at the time of the initial operation. Features of parathyroid carcinoma that help to differentiate it from benign primary hyperparathyroidism deserve emphasis. Our experience suggests that characteristics that are highly suggestive of parathyroid carcinoma are young age, palpable neck mass, concomitant renal and skeletal disease, and extremely high iPTH level in patients with PTH-dependent hypercalcemia.

Fig. Plasma intact parathyroid hormone (iPTH) levels in patient groups with benign hyperparathyroidism and parathyroid carcinoma.

References


