ORIGINAL ARTICLE

Parathyroid Carcinoma, a Rare Entity with Varying Presentation and Treatment

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Abstract

Background: Parathyroid carcinoma is a rare entity that has diverse presentation and diverse treatments. This case-series highlights the atypical and diverse presentation of parathyroid carcinoma and stresses the importance of the diagnostic approach and intraoperative strategy.

Methods: We report three patients with parathyroid cancer.

Results: In one patient, a parathyroid lesion was found to be a parathyroid carcinoma intraoperatively, resulting in a change of operative strategy. In another, parathyroid carcinoma was suspected preoperatively and was treated accordingly. A third patient presented with an already a metastasized parathyroid carcinoma.

Conclusion: The diagnostic approach and intraoperative strategy are instrumental to determining the best treatment and yielding the best outcome.

Keywords: Parathyroid, carcinoma, bilateral neck exploration.

INTRODUCTION

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. Less than 1% of patients with primary hyperparathyroidism have a parathyroid carcinoma, whereas in 80 to 90% hyperparathyroidism is caused by a parathyroid adenoma.[1-3] Parathyroid carcinoma is generally a solitary lesion, but multiple lesions have been described.[4] Both anamnesis, clinical features and serum levels of calcium and parathyroid hormone can be different in patients with parathyroid carcinoma. Distinguishing between benign and malignant lesions can be difficult, even when examined histopathologically. Here we describe three recent cases that illustrate the diverse clinical presentation and treatment approach and discuss the diagnostic strategy and treatment of this rare entity.

CASE DESCRIPTIONS

Patient 1

A 55-year-old-man presented with tremor in both hands and pain in both sides of his abdomen due to nephrolithiasis. He previously suffered from gout and hypertension, with no loss of any organ function. He was moderately obese, had a blood pressure of 160/95 mm Hg, was taking antihypertensive medication (atenolol and chlorthalidone). His PTH level was 11.2 pmol/l (normal range: 0.9 to 5.4 pmol/l) and his ionized calcium level was 1.52 mmol/l (normal values: 1.15 to 1.32 mmol/l). Scintigraphy suggested a solitary parathyroid adenoma on the posterior side of the right thyroid lobe. The patient underwent minimally invasive parathyroidectomy with intraoperative PTH-measurement. During the operation, the presumptive adenoma was quickly found at the typical anatomical location—dorsocaudal to the inferior thyroid artery. The adenoma was firm and tenaciously adherent to adjacent tissue, especially to the right thyroid lobe. Since a malignancy was suspected, the minimally invasive adenomectomy was converted to a conventional neck exploration and the parathyroid and right thyroid lobe were resected *en bloc*, preserving the recurrent laryngeal nerve and the cranial parathyroid gland. Intraoperative frozen section investigation was not done. One hour postoperative PTH serum level was normalized to 2.4 pmol/l, suggesting an adequate resection. The patient

had an uneventful recovery and was discharged the next day. Two weeks later, the patient's voice and serum calcium level were normal. The histological report described a radically excised parathyroid carcinoma, with thick fibrous bands, high mitotic activity, trabecular growth pattern and adjacent soft tissue invasion. The current survival is 39 months.

Patient 2

A 45-year-old woman presented with fatigue and pain in the extremities, especially in the upper legs, thirst with polydipsia, polyuria and nocturia, cold intolerance, and mood changes. During the previous six months she lost four kilograms but had a normal appetite. Physical examination showed no abnormalities. Her PTH level was 263 pmol/l and her ionized calcium level was 1.85 mmol/l, suspicious for parathyroid carcinoma. Ultrasound examination showed an enlarged lower left parathyroid gland with a diameter of 2 × 5 cm (Figs 1 and 2). The diagnosis was presumed to be primary hyperparathyroidism caused by a parathyroid carcinoma. During a conventional neck exploration the parathyroid gland was removed completely, preserving the recurrent laryngeal nerve, without rupturing the capsule and without a hemithyroidectomy. The postoperative recovery was uneventful and she returned home the next day. At a follow-up visit, five months after the operation, her ionized calcium level was 1.16 mmol/l. The histological report described a parathyroid carcinoma, completely excised, without capsular invasion. The current survival is 47 months.

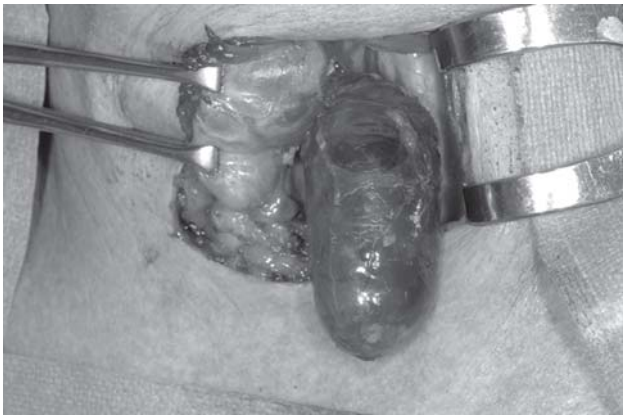

Fig. 1: Intraoperative photograph of patient 2 showing the thyroid gland being held on the right and the parathyroid carcinoma lifted outside of the wound

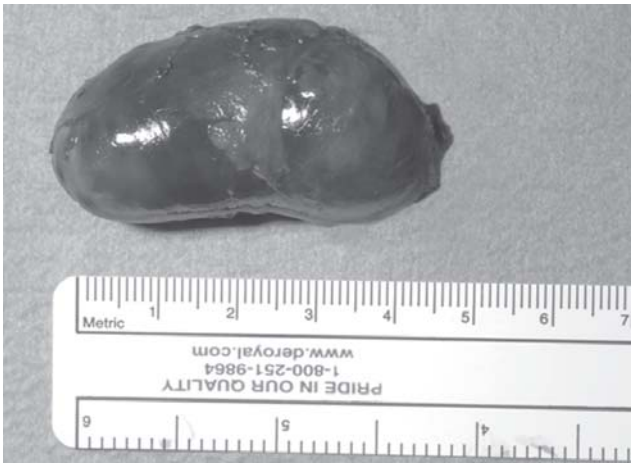

Fig. 2: The parathyroid carcinoma from patient 2: 5 cm long with an intact capsule

Patient 3

A 61-year-old woman initially visited her general practitioner because of general malaise, confusion, thirst and polyuria. In our institute, she had pain in her left upper arm and right knee, as well as loss of strength in both legs, causing instability. Physical examination revealed no abnormalities. She had a PTH level of 107 pmol/l and an ionized calcium level of 1.67 mmol/l. Computed tomography (CT) scanning and ultrasound examination showed a lesion suspicious for a parathyroid adenoma in the right thyroid gland. A CT can of the thorax showed three lesions in the right lung that were suspicious for metastases, and osteolytic lesions in 3rd and 6th rib on the right side. Radiographs of the proximal right humerus and right femur showed abnormal lesions that were suspicious for metastases. The presumed diagnosis was metastasized parathyroid carcinoma; therefore, conventional neck exploration was performed with the intent to perform an *en bloc* lobectomy and unilateral parathyroidectomy. The tumor was large, white, and granular, and extended retrosternally. Several lymph nodes were enlarged. We therefore decided to undertake an additional unilateral neck dissection (level II, III, IV en VI). Histological examination indicated surgical margins positive for tumor. Tumor cells were observed in some dissected local lymph nodes. More extensive surgery was indicated (resection of pulmonary metastases was considered), but the patient's poor condition made this impossible. Postoperatively, the patient's ionized calcium and PTH levels remained elevated (1.54 mmol/l and 30 pmol/l respectively). She continued to experience thirst and nycturia, without polyuria. She also had a pathological fracture of the left humerus, for which a palliative self-locking pin for osteosynthesis was placed because the patient's lung metastases progressed and she had lytic lesions in her bones, metastasectomy was not considered. Her serum ionized calcium and PTH levels increased to 1.68

mmol/l and 94 pmol/l respectively. Within 18 months after the diagnosis, the patient died of her disease.

CLINICAL FEATURES

The clinical features of parathyroid carcinoma are due primarily to the effects of excessive secretion of PTH, as illustrated in patient.[2] The characteristic symptoms of hyperparathyroidism include bone pain, fractures and renal colic.[1,2,4,5] Nephrolithiasis occurs in up to 56% of patients, and renal failure in 84%.[6] Most patients with parathyroid carcinoma die of metabolic complications due to primary hyperparathyroidism.[7]

In patients with parathyroid carcinoma, the ionized calcium level can be extremely elevated (>14 to 15 mg/dL).[8] Typical symptoms associated with severe hypercalcemia are fatigue, weight loss, anorexia, nausea, vomiting, pancreatitis, constipation, peptic ulcers, polydipsia and polyuria.[9,10] Pathological fractures and bone pain are also common, as in patient 3. Forty percent of patients with parathyroid carcinoma have radiological abnormalities that indicate skeletal diseases such as osteitis fibrosis cystica and subperiosteal bone resorption.[1,11-13] Simultaneous presentation of kidney and skeletal diseases is seen in 50% of patients, and hypercalcemic crisis in 10%.[8]

A palpable mass in the neck is found in 30 to 76% of the patients with a parathyroid carcinoma.[1,5] This clinical symptom can help to differentiate between a benign or a malignant process because fewer than 5% of patients with benign hyperparathyroidism have a palpable mass in the neck.[2] Parathyroid carcinoma should be suspected if a patient has pareses of the recurrent laryngeal nerve and no prior surgery in that region. Age and gender are not risk factors for parathyroid cancer.[1,9]

MOLECULAR PATHOGENESIS

The involvement of oncogenes and tumor suppressor genes in the development of parathyroid carcinoma has become clear recently. Four genes, involved in the control of the cell cycle, are associated with the development of parathyroid carcinoma: Cycline D1(/parathyroid adenomatosis gene 1), tumor suppressor gene RB (retinoblastoma), BRCA2-gen, and hyperparathyroidism 2 tumor suppressor gene.[1,2,7] Labeling of cyclin D1 is increased in parathyroid carcinoma, but utility of this approach is limited as it is also seen in adenomas.The best evididence has been provided by mutations of the HRPT2 gene, responsible for the hyperparathyroidism with jaw-tumor (HPT-JT) syndrome, a rare autosomal disorder. 10-15% of patients will have malignant parathyroid disease.[14,15]

LOCALIZATION

Parathyroid carcinoma can be suspected if a patient has high PTH levels and a large palpable lesion.[4,9] Parathyroid carcinoma cannot be diagnosed with radiological imaging alone; histological examination is essential. Preoperative imaging can help determine whether the surgical strategy should be minimally invasive adenomectomy or conventional neck exploration. Ultrasound examination can localize up to 80% of adenomas, but is not very sensitive in localizing ectopic lymph nodes. To detect ectopic lymph nodes, CT and T2-weighted magnetic resonance images are more useful.[5,16] The accuracy of thallium-technetium subtraction scintigraphy depends on the size of the adenoma.[17] Pre-operative Tc99m sestamibi-scanning detects up to 90% of adenomas.[5,18] If findings from ultrasonography and Tc99m sestamibi-scanning are concordant, the localization of the parathyroid gland is accurate in more than 95% of patients.[18-20]

Since MIBI is taken up by both parathyroid adenoma and carcinoma, sestamibi-scanning can be used for detecting malignant tumors, however no strong evidence is available.[21]

TREATMENT

Conventional neck exploration is indicated in patients suspected of having parathyroid carcinoma. Intraoperative findings are important to distinguish between an adenoma and a carcinoma. Parathyroid carcinoma has a fibrous capsule and grayish color, and is often tenaciously adherent to the adjacent tissues (thyroid, trachea, esophagus, recurrent laryngeal nerve and overlying muscles). Parathyroid carcinomas are usually localized in the inferior glands.[1,2,5,8] Sometimes, the surgical strategy must be changed during the operation. When there are no preoperative signs of parathyroid carcinoma, minimally invasive adenomectomy is the procedure of choice. If possible, only the involved parathyroid gland should be removed, without rupturing the capsule, but if, during surgery, invasive growth is suspected, *en bloc* resection of the ipsilateral thyroid lobe is mandatory, as is the segmented removal of the overlying muscles of the paratracheal fibrolymphatic compartments and the remaining tissue around the involved parathyroid gland.[7]

Incomplete surgery should be avoided, as it may influence the risk of locoregional recurrence.[2, 5] The recurrent laryngeal nerve may be left *in situ* if no tumor involvement is suspected. However, if a radical resection is required, sometimes the nerve must be removed.

A bilateral neck exploration to view all four parathyroid glands is recommended to exclude hyperplasia because it

is associated with parathyroid carcinoma. Standard lymphadenectomy is seldom necessary since lymphogenic metastasis occurs in less than 5% of patients. *En bloc* resection yields long-term survival rates of 90% with 10% local recurrence.[8] Incomplete resection of the primary lesion, as in patient 3, results in 50% local recurrence and a 46% mortality rate, mostly from hypercalcemia or systemic metastasis.[13] When resection is not possible, chemotherapy and radiotherapy may be used. Bifosfonatos may normalize calcium levels and therefore reduce clinical symptoms of hyperparathyroidism.

Recent advances in immunohistochemistry, especially the evaluation of HRPT2 gene abnormalities, will improve the accuracy of the diagnosis of parathyroid carcinoma. An aggressive surgical approach will improve the long-term survival. Also to lengthen survival and palliate hypercalcemia-associated metabolic complications, surgical decreasing of tumor mass is important.[4,8] To establish valid evidence for patient management in the future, a collaboration of endocrine specialists is essential to conduct well-designed clinical studies for this rare disease.[22]

In conclusion, parathyroid carcinoma is a rare entity that has a diverse presentation and treatment strategy, as illustrated by our three cases. The diagnostic approach and intraoperative strategy are instrumental to determining the best treatment and yielding the best outcome.

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