



Case Report

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Parathyroid Carcinoma Coincident With Neurofibromatosis Type 1

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Abstract

Neurofibromatosis type 1 is a genetic disorder resulting from a mutation in the NF1 gene, and is known to have an association with hyperparathyroidism that is caused by parathyroid adenoma in almost all cases. Parathyroid carcinoma in neurofibromatosis type 1 is extremely rare. Among the reports of neurofibromatosis type 1 with comorbid hyperparathyroidism have been a patient with coincident pheochromocytoma and medullary thyroid cancer, and a patient with a mutation of the RET gene, the causative gene of multiple endocrine neoplasia (MEN). These cases suggest an association between neurofibromatosis type 1 and multiple endocrine tumors, but the detailed mechanism is still unknown. Moreover, a mutation in the HRPT2 gene has been noted as a genetic cause of parathyroid carcinoma, but at presents no genetic link between neurofibromatosis type 1 and a mutation in the HRPT2 gene has been demonstrated, and the association between neurofibromatosis type 1 and parathyroid cancer remains unclear. We have reported an extremely rare case of neurofibromatosis type 1 with coincident hyperparathyroidism that is caused by parathyroid carcinoma.

Keywords:

Hyperparathyroidism; Parathyroid carcinoma; Neurofibromatosis type 1

Introduction

Neurofibromatosis type 1 is a disease caused by a mutation in the NF1 gene and is characterized by neurofibroma and café au lait macules, as well as pheochromocytoma, which are endocrine tumors. In addition to pheochromocytoma, hyperparathyroidism is a recognized complication of neurofibromatosis type 1 and is an endocrine disorder most frequently caused by parathyroid adenoma. Parathyroid carcinoma, on the other hand, accounts for only 0.5 to 5% of primary hyperthyroidism and is considered an extremely rare endocrine malignancy. Here we report an extremely rare case of hyperparathyroidism caused by parathyroid carcinoma that was coincident in neurofibromatosis type 1.

Materials and Methods

Case report

The patient was a 48-year-old female who presented at our

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facility complaining of nausea, loss of appetite, and back pain. Her previous medical history included fractures of both femurs, and neurofibromatosis type 1 was found as comorbidity. The patient did not use alcohol or tobacco. Physical examination findings were: BP 137/82, pulse 57, temperature 35.4°C, SpO₂ 96%, and a palpable 3 cm mass on the anterior right side of the neck, and café au lait macules and neurofibroma over the entire body (Figure 1).

Laboratory tests showed a serum calcium concentration of 13.4 mg/dL, serum phosphate concentration of 1.9 mg/dl serum alkaline phosphatase level of 739 U/L, and intact-PTH concentration of 845 pg/mL. The serum calcium, serum ALP and intact-PTH values were high, and serum phosphorus was low. CT imaging revealed a nodular lesion on the right posterior lobe of the thyroid (Figure 2), decreased trabeculae in the vertebral bodies and ilium, and a calculus in the left ureter (Figure 3). Ultrasonography of the neck revealed a 3 cm low-echo mass on the right posterior lobe of the thyroid (Figure 4). However, no enlargement of the cervical lymph nodes was found. In technetium-99m sestamibi scintigraphy (MIBI), localized accumulations in the right neck could be seen in both the early and delayed phase images (Figure 5). From these findings primary hyperparathyroidism resulting from glandular enlargement was diagnosed, and we decided to perform a parathyroidectomy. Surgical findings show an enlarged gland and slightly to the right of the front of the trachea, and although there were adhesions to the thyroid, trachea, esophagus, and carotid artery, no invasion was observed. The right recurrent laryngeal nerve was running between the ventral side of the enlarged gland and the dorsal side of the thyroid. The thyroid and the



Figure 1: Physical examination findings: Café au lait macules and neurofibroma over the body.

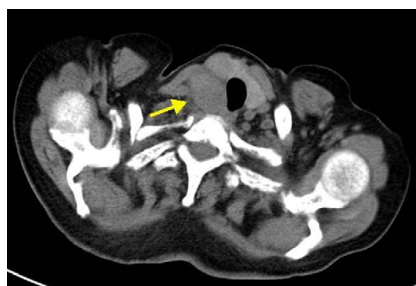


Figure 2: Neck CT: Nodular lesion on the right posterior lobe of the thyroid.



Figure 3: Abdominal CT. A calculus in the left ureter.

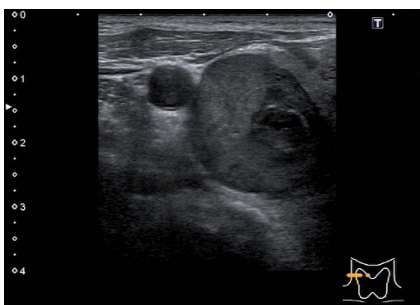


Figure 4: Neck Ultrasonography: A low-echo mass on the right posterior lobe of the thyroid.

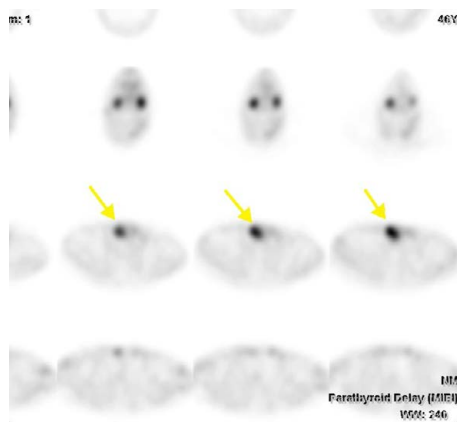


Figure 5: Technetium-99m sestamibi scintigraphy: Accumulations in the right neck seen in the delayed phase image.

enlarged gland were detached, and the right recurrent laryngeal nerve was identified and preserved. No clear invasion from the enlarged gland into the right recurrent laryngeal nerve was observed. Then the enlarged gland was detached around the margin and resected. Pathological examination found a tumorous lesion coated with a fibrous capsule of irregular thickness, partial necrosis within the tumor, and venous infiltration that led to a diagnosis of parathyroid carcinoma (Figure 6). No extracapsular invasion was found. In the postoperative course, the intact-PTH value normalized at 18 pg/mL starting on postoperative day 1, but serum calcium was still low at 6.9 mg/dL on postoperative day 7 and was treated with 12 mg per day of calcium lactate and 1 µg/day of oral alfacalcidol. By postoperative day 14 the serum calcium had recovered to 8.5 mg/dL and the patient was discharged on postoperative day 22.

Discussion

Parathyroid carcinoma is an extremely rare endocrine malignancy and accounts for only 0.5 to 5% of primary hyperthyroidism. Damage to the capsule in parathyroid carcinoma carries a risk of dissemination. Therefore, cytology from a needle or fine-needle aspiration biopsy is generally prohibited, and a definitive pathological diagnosis prior to surgery cannot be performed. Moreover, in parathyroid carcinoma it is important to perform an en bloc resection of the tumor and surrounding tissue during the initial procedure [1] to achieve local cure, so the ability to detect parathyroid carcinoma from clinical laboratory findings is extremely important. Serious hypercalcemia is a known laboratory test result in parathyroid carcinoma, and dramatic gastrointestinal symptoms such as nausea, vomiting, and weight loss, as well as bone symptoms such as diffuse osteitis fibrosa, osteoporosis, bone pain, and pathologic fracture have been reported [2]. However, these signs and symptoms are also found in benign adenoma, and cannot be considered specific for parathyroid carcinoma. Typically, characteristic clinical laboratory findings for parathyroid carcinoma are a serum calcium level of >14 mg/dL and intact-PTH that is at least double the normal value. Moreover, in many cases the bone symptom of diffuse osteitis fibrosa is present, and palpation often reveals an anterior neck mass. Parathyroid carcinoma is considered a likely diagnosis when all of the above signs and symptoms are present [3]. Characteristic findings for parathyroid carcinoma during surgery include a 3 cm or larger white or somewhat gray irregular tumor coated by a thick fibrous capsule, and in many cases adhesions and invasion of the surrounding tissues. However, due to the difficulty in diagnosing parathyroid carcinoma before and during surgery, the opportunity for en bloc resection during the initial procedure is often lost. Although en bloc resection is considered important for local therapy, in reality it has been said only 12% to 52% of patients are treated by en bloc resection from the start [4]. In this particular case, ureter calculus, osteoporosis and bone pain were present, and in the surgical findings as well, the tumor had adhesions to surrounding tissue, so the possibility of parathyroid carcinoma was taken into account. In the surgical findings, however, no overt invasion from the parathyroid tumor into the thyroid was found, and the recurrent laryngeal nerve was present between the ventral side of the parathyroid tumor and the posterior side of the thyroid. Therefore, separating the parathyroid tumor from the thyroid was important for identifying and conserving the recurrent laryngeal nerve, and to accomplish en bloc resection it was necessary to remove the recurrent laryngeal nerve together with the right lobe of the thyroid and the parathyroid tumor. The general indication for combined resection of the recurrent laryngeal nerve is a case in which a tumor has invaded the nerve with subsequent loss

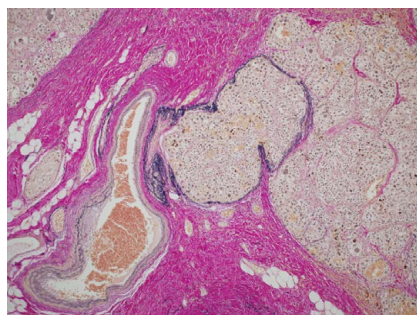


Figure 6: Pathological examination: Venous infiltration was noted.

of function [5], but because the function of the recurrent laryngeal nerve was intact in this particular case, conservation of the nerve was prioritized, and parathyroidectomy without en bloc resection was performed.

Neurofibromatosis type 1 is an autosomal dominant disease that presents peripheral nervous system tumors caused by a mutation in the NF1 gene, and the incidence is said to be 1 in 3,000 persons. As diagnostic criteria, neurofibromatosis type 1 is diagnosed when 2 or more of the following clinical findings are present [6]: 1. Six or more 'cafe au lait' macules of significant size, 2. Two or more neurofibromas and/or one plexiform neurofibroma, 3. Auxiliary or inguinal freckling, 4. Optic glioma, 5. Two or more retinal Lisch nodules, and 6. Osseous lesions such as sphenoidal dysplasia or pseudarthrosis. Moreover, it is known that pheochromocytoma is found at a frequency of 1% to 2%, and roughly half of those patients are symptomatic.

The NF1 gene is located on chromosome 17 (17q11.2), and codes for neurofibromin. Neurofibromin is thought to be a negative regulator of the ras signal transduction pathway, but neurofibromin expression is deficient in neurofibromatosis type 1, and a variety of signs and symptoms develop [7]. Several cases of hyperparathyroidism coincident with neurofibromatosis type 1 have been reported. Most, however, have been accounts of parathyroid adenoma as a complication of neurofibromatosis type 1, and there is only one documented case of parathyroid carcinoma in neurofibromatosis type 1 [8]. In these reports bone lesions accompany both hyperparathyroidism and neurofibromatosis type 1, so the existence of a genetic link between the two has been suggested. Moreover, recently among the cases of thyroid gland C-cell hyperplasia coincident with neurofibromatosis type 1 was a patient with mutations in both the NF1 gene and the RET gene, which is the causative gene of multiple endocrine neoplasia (MEN), thus suggesting an association between neurofibromatosis type 1 and MEN 2A [9]. In addition, a neurofibromatosis type 1 patient has been reported with coincident pheochromocytoma and hyperparathyroidism [10], and a neurofibromatosis type 1 patient has been reported with coincident pheochromocytoma, hyperparathyroidism, and medullary thyroid cancer, which is similar to the MEN 2A patient but with no mutation in the RET gene [11]. These reports suggest an association between NF1 gene mutations and multiple endocrine tumors, but no detailed mechanism has been discovered.

Much is unclear about the mechanism in the development of parathyroid carcinoma, but the HRPT2 gene has been identified in hyperparathyroidism-jaw tumor syndrome (HPT-JT syndrome), which is a form of genetic hyperparathyroidism. HRPT2 is a cancer suppressor gene that codes for a protein called parafibromin. A mutation in the HRPT2 gene has been found not only in HPT-JT syndrome, but also in sporadic parathyroid carcinoma [12], and the gene has been noted as an important cancer suppressor gene relevant to the oncogenesis of parathyroid carcinoma. At present, however, no genetic link has been shown between the mutation in the HRPT2 gene believed to cause HPT-JT syndrome, familial parathyroid carcinoma, and neurofibromatosis type 1, and any association between neurofibromatosis type 1 and parathyroid cancer remains unclear.

We have reported an extremely rare case of neurofibromatosis type 1 with comorbid parathyroid carcinoma. We believe it is useful to screen for hyperparathyroidism in neurofibromatosis type 1 patients. Not only will this reveal conditions such as ureter calculus and bone

problems such as pain and fractures caused by hyperparathyroidism to enable treatment before they become more severe, but it also will enable earlier treatment of parathyroid cancer, however rare it may be.

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