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Case Report

Primary Hyperparathyroidism and Thyroid Cancer: A Case Series

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Abstract

Primary hyperparathyroidism (PHTP) is the most common cause of outpatient hypercalcemia and has a prevalence of about one to seven cases per 1,000 adults. Concurrent thyroid disease and PHPT has been reported in 20% to 84% of the cases, although no causal relationship has been established. Malignant tumors of the thyroid are identified in approximately 2% to 20% of these cases. Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. Certain situations undoubtedly contribute to the development of both of these diseases, such as the use of therapeutic neck radiation for various clinical indications used in the past. Outside of these special situations with a clear etiology, the wide variation in reports of concomitant parathyroid and thyroid disease fuel debate as to the necessity and extent of thyroid evaluation prior to surgical treatment of PHPT. We report on 5 patients with thyroid cancer that was detected or suspected during work-up for surgical treatment of PHPT. In this case series, we aim to emphasize the need for preoperative evaluation of the thyroid gland in patients who will undergo surgical treatment for PHPT, as it is crucial to minimize reoperation rates and complications.

ABBREVIATIONS

PHPT: Primary Hyperparathyroidism; PTC: Papillary Thyroid Carcinoma; PTH: Parathyroid Hormone; FNA: Fine-Needle Aspiration; Ca: Calcium; US: Ultrasound; GERD: Gastroesophageal Reflux Disease; MEN: Multiple Endocrine Neoplasia; HPT-JT: Hyperparathyroidism – Jaw Tumor syndrome; NCCN: National Comprehensive Cancer Network; ATA: American Thyroid Association

INTRODUCTION

Primary hyperparathyroidism (PHTP) is defined as elevated levels of serum calcium or widely fluctuating serum calcium levels resulting from the inappropriate or autogenous secretion of parathyroid hormone (PTH) by one or more parathyroid glands in the absence of a known stimulus [1]. PHTP is the most common cause of outpatient hypercalcemia and has a prevalence of about one to seven cases per 1,000 adults [2,3]. The mean age at diagnosis is between 52 and 56 years [1,4].

PHPT is symptomatic in more than 95% of the cases if proper attention is paid to the subtle symptoms and signs that this disease can produce due to the fluctuating calcium levels [5]. The "classic" pentad of kidney stones, painful bones, abdominal groans, psychic moans, and fatigue overtones are rarely seen today since the advent and general use of automated blood analyzers in the early 1970s [1,6] Imaging studies are used to facilitate the surgical management of the disease. An example is the sestamibi scan which can be negative in patients with PHPT in up to 30% to 65% of the cases [7,8].

Concurrent thyroid disease and PHPT has been reported in 20% to 84% of the cases [9,10]. Malignant tumors [10] are identified in approximately 2% to 20% of the cases. In this case series, we aim to emphasize the need for preoperative evaluation of the thyroid gland in patients who will undergo surgical treatment for PHPT.

CASE SERIES

Case 1

A 60 y/o female presents to the office with a previous diagnosis of multi nodular goiter. She had a FNA biopsy of a prominent thyroid nodule which was reported as benign. She presented with symptoms characteristic of PHPT such as emotional lability, severe fatigue, irritability, episodes of depression and anxiety, insomnia, memory loss, loss of concentration, proximal muscle weakness, myalgia most prominent in the inferior extremities, bone pain, nicturia, asymptomatic nephrolithiasis, osteopenia, and hypertension. She also reported mild dysphagia. Work-up of the patient revealed the following: serum Ca: 10.6 mg/dl, urine Ca elimination: 251.1 mg/24 hrs, Vitamin D: 19.3 ng/mL,

Intact PTH: 40 pg/ml. Neck ultrasound identified three thyroid nodules, the largest measuring 22 mm x 10 mm, with irregularly defined borders. A FNA biopsy was taken from this nodule, which was compatible with colloid goiter, Bethesda II category. A diagnosis of PHPT and symptomatic bilateral multinodular goiter (more prominent on the right side) was established. A sestamibi scan was performed on the same day of the operative procedure based on our protocol as described by Dr. Norman [11]. Parathyroidectomy of enlarged right superior and right inferior glands and right hemithyroidectomy was performed. The procedure and immediate postoperative period where uneventful. Pathologic specimen of the resected parathyroid glands revealed bilateral adenomas. The right thyroid nodule was found to contain papillary carcinoma of the thyroid (PTC). A left hemithyroidectomy was performed one week after the first procedure. Pathologic specimen analysis revealed another focus PTC in the resected thyroid lobe. With a follow up of more than three years she is clinically and biochemically cured of her PHPT and no evidence of recurrent PTC.

Case 2

A 48 y/o female patient with a history of osteopenia presented with symptoms compatible with hyperthyroidism, prominent thyroid nodules, and a serum calcium of 10.7 mg/dl. Four weeks prior to her office visit she presented with heat intolerance, intermittent diaphoresis, inability to gain weight, and hand tremor. She had non-specific symptoms of PHPT which included irritability, diminished social interaction, generalized headaches, polyuria, polydipsia, nicturia, palpitations, and osteopenia with a possible L4 pathologic vertebral fracture. Thyroid function tests revealed an elevated T4 of 14.20 ng/dL, elevated total T3 of 2.54 ng/dL, and a low TSH of 0.0001 uUI/ml. Anti-thyroglobulin antibodies: 53.23, anti-thyroid peroxidase: 10.33. Serum calcium was elevated at 10.9 mg/dl, 25-hydroxi Vitamin D was low at 21.2 ng/mg, and intact PTH was 62.6. Neck ultrasound revealed two prominent thyroid nodules, one on the right measuring 7 mm and one on the left measuring 11 mm, both with irregular borders, micro calcifications and with central hyper vascularity. Thyroid scintigraphy revealed a diffusely hyper functioning thyroid. FNA biopsies of both thyroid nodules were negative for malignant neoplastic cells. A diagnosis of PHPT, Hashimoto disease in a hyperthyroid stage, and two prominent thyroid nodules with suspicious sonographic features for malignancy was made. She underwent radioactive iodine ablation per the indication of her endocrinologist. Laboratory work up was repeated six months after ablation and confirmed the diagnosis of PHPT. A sestamibi scan was performed on the day of the operative procedure based on our protocol, as proposed by Dr. Norman [11]. Parathyroidectomyof a left inferior adenoma and total thyroidectomy was performed. Pathological specimen analysis of the left inferior parathyroid revealed a parathyroid adenoma. Thyroidectomy specimen revealed two foci of PTC, one was a classical variant, the other was a follicular variant.

With a follow up of more than two years she is clinically and biochemically cured of her PHPT and no evidence of recurrent PTC.

Case 3

A 48 y/o female presented to the office with serum calcium of 11 mg/dl and a previous diagnosis of multinodular goiter. Signs and symptoms related to PHPT included emotional lability, depression, irritability, general malaise, fatigue, intermitent pain in the lower extremities, headaches, memory loss, proximal muscle weakness, polydipsia, polyuria, nocturia, nausea, pruritus, insomnia, diminished concentration and reaction time, decreased libido, hair thinning and intermittent palpitations. Further laboratory testing revealed intact PTH of 40.2 pg/mland urine calcium of 161.1 mg/24 hours. Total Vitamin D 25-OH was at 37. Neck US showed multinodular goiter with two prominent nodules, both of which were biopsied by FNA with benign results. A diagnosis of PHPT was established. A sestamibi scan was performed on the day of the operation, based on our protocol as pioneered by Dr. Norman [11] Parathyroidectomy was performed with excision of the four parathyroid glands and auto transplantation of half a gland in the left forearm. There were no perioperative or postoperative complications and recovery was uneventful. Calcium and vitamin D supplementation were started the evening of the operation.

With a follow up of more than two years she is clinically and biochemically cured of her PHPT.

She was undergoing ultrasonographic surveillance for her thyroid nodules and 29 months later, due to changes in the characteristics of the nodule a repeat FNA was performed and it was positive for PTC (Bethesda V category). A total thyroidectomy was then performed. In account of the previous neck operation, intraoperative recurrent laryngeal nerve monitoring was used. Pathological analysis confirmed the presence of PTC. Six months after the operation she has no clinical, laboratory, or radiographic evidence of recurrent PTC.

Case 4

65 y/o female patients were referred to the office for evaluation of a periareolar breast lump about the size of a bean, along with an axillar lymphadenopathy measuring 2 cm x2 cm. A prominent, left sided, thyroid nodule was palpated during examination. Work up laboratory studies revealed serum calcium of 10.3 mg/dl, and the patient reported a history of osteopenia in the past and intermittent headaches. Further blood tests revealed and intact PTH of 120.9. Neck US revealed a left thyroid nodule with sonographic suspicion for malignancy. FNA of the thyroid nodule revealed cytology suspicious of PTC. A mammogram was performed and the breast nodule was classified as BIRADS 4B. A core needle biopsy revealed ductal ectasia. An FNA biopsy of the axillary lymph node was non-diagnostic. A sestamibi scan, which was performed on the day of the operation based on our protocol that was pioneered by Dr. Norman [11], detected increased uptake in all 4 parathyroid glands. The patient was subjected to open excisional breast biopsy, open excisional biopsy of the axillary node, parathyroidectomy of the three and a half glands, leaving half of the right superior gland in situ, and left hemithyroidectomy. Pathologic analysis of the breast biopsy was compatible with ductal ectasia. The axillary node was positive for a moderately differentiated adenocarcinoma likely of breast origin. The left thyroid nodule was positive for PTC. With a follow up of more than three years she is clinically and biochemically

cured of her PHPT and no evidence of recurrent PTC. Her occult breast cancer was managed per NCCN guidelines [12] and currently has no evidence of recurrent disease.

Case 5

A 44 y/o male presents to the office with hypercalcemia of 11.2 mg/dL. Medical history includes acne treated with head and neck radiation therapy, nephrolithiasis, hypertension, GERD and Helicobacter pylori infection treated with antibiotics. Repeat serum calcium was of 10.4 mg/dL. Intact PTH was at 84 pg/ml. Further questioning revealed symptoms consistent with pHPT including: emotional lability, depression, irritability, polyuria, polydipsia, nocturia, diffuse abdominal pain, insomnia and memory loss. Work up of the patient included 24-hour urinary calcium, vitamin D 25 OH, bone densitometry, and neck ultrasound. Urine calcium elimination was 283.2 mg/24 hrs. Vitamin D 25 OH levels were 24.8. Bone densitometry was normal. Neck US revealed bilateral thyroid nodules with suspicious sonographic features of malignancy. Both were biopsied by FNA. Pathology examination of both nodules revealed PTC. The patient was scheduled for a total thyroidectomy and parathyroidectomy. A sestamibi scan was performed on the day of the operation based on our protocol that was pioneered by Dr. Norman [11]. The right inferior and superior parathyroid glands were excised; the remaining two glands were macroscopically normal. Dissection was difficult during surgery due to the patient's history of neck radiation. The immediate postoperative period was remarkable for dysphonia and dysphagia, indicating a probable transient injury of the right recurrent laryngeal nerve. Both symptoms resolved gradually over the next months. Thyroid specimen analysis confirmed a well differentiated PTC. With a follow up of more than four years he is clinically and biochemically cured of her PHPT and no evidence of recurrent PTC.

DISCUSSION

Concomitant PHPT and PTC has been repeatedly reported in medical literature, but no causal relationship has been elucidated [13-19] Certain situations undoubtedly contribute to the development of both of these diseases, such as the use of therapeutic neck radiation for various clinical indications used in the past [20]. Outside of these special situations with a clear etiology, the wide variation in reports of concomitant parathyroid and thyroid disease fuel debate as to the necessity and extent of thyroid evaluation prior to surgical treatment of PHPT. Familial syndromes of PHPT and medullary thyroid carcinoma as part of the MEN2A construct has been extensively reported and studied, but no such relationship has been confirmed in the case of sporadic PHPT and PTC, although some would classify patients with PHTP as being at increased risk for PTC [16].

There currently appears to be no clear genetic link between PTC and PHPT. Most cases of PHPT are sporadic. About 2% to 5% of PHPT cases arise from familial disorders, which include MEN1, MEN2A, and hyperparathyroidism – jaw tumor syndrome (HPT-JT) [1,21] MEN1 is caused by a germline mutation (loss-of-function) in the MEN1 tumor suppressor gene that encodes Menin, a protein that is involved in transcriptional regulation, genome stability, cell division, and cellular proliferation [21]. These patients are at an increased risk of developing pancreatic neuroendocrine tumors and pituitary adenomas [1]. PHPT appears in 80% to 100% of these cases by age 40 [1] MEN2A is caused by a gain of-function germline mutation in the RET proto-oncogene, which encodes a receptor tyrosine kinase that binds glial-derived neutrophic factor (GDNF)-family ligands [1]. Patients are at an increased risk of developing PHPT, medullary thyroid cancer and pheocromocytoma [1]. The familial HPT-JT syndrome is characterized by an increased risk of parathyroid carcinoma and osseous jaw tumors [22]. It is caused by a mutation of HRPT2, which is a tumor suppressor gene that encodes the protein parafibromin, which plays a significant role in various essential cellular processes [21,1].

Sporadic forms of PHPT are associated with germline mutations involving MEN1, CDC73, CASR, CDKIs or PTH genes [23] Patients under 45 years of age presenting with parathyroid adenomas may have a de novo germline mutation in one of these genes [23]. In approximately 25% to 40% of sporadic parathyroid adenomas, there is a loss of heterozygosity at the site of the MEN1 gene [1]. A pericentromeric inversion involving the PTH promoter and the PRAD 1/CCND1 (cyclin D1) gene is found in approximately 8% to 18% of parathyroid adenomas, with overexpression of cyclin D1 found in 20% to 40% of adenomas and up to 90% of parathyroid carcinomas [24]. In transgenic mice, over expression of cyclin D1 caused abnormal parathyroid cell proliferation [25]. Loss of function of the retinoblastoma (RB) gene appears to be linked to the development of parathyroid carcinoma [26].

PTC, on the other hand, is the most common thyroid malignancy [27]. The RET proto-oncogene encodes a receptor tyrosine kinase which plays an important role in tumorigenesis by phosphorylation of the MAPK pathway. The fusion of the tyrosine kinase domain of RETS with other genes by rearrangement function as oncogenes and is implicated in the development of PTCs. This is especially true in PTCs appearing in young age and after radiation exposure [28]. The most common rearrangements found in these cases are RET/PCT1, RET/PCT3m, AGK-BRAF, and ETV6-NTRK3 [29,30]. In adults, the most common mutation comes in the form of the $BRAF^{V600E}$ on cogene, which also phosphorylates the MAPK pathway, and is present in about 45% of PTCs and is also correlated with poor clinical outcomes [27,31] Mutations in Ras (signal transduction protein), and TRK (a receptor with tyrosine kinase activity) are also commonly associated with PTC development. Tumor suppressor genes include p53, p16 and the recently identified CCDC67 [32].

The most useful application of preoperative neck ultrasound is the ability to detect concomitant thyroid nodules that are not palpable or symptomatic. Neck palpation can miss up to 94% of thyroid nodules that are less than 1 cm in diameter, and 42% of nodules measuring more than 2 cm [33]. Neck ultrasound detects non-palpable thyroid nodules in up to 25% to 45% of patients with PHPT[34]. Up to 5% of these incidental nodules detected by ultrasound are malignant [35,36]. FNA is the standard method of diagnosis due to its simplicity and high sensitivity (94%) and specificity (98%) [37]. It is our recommendation that all patients diagnosed with PHPT have a preoperative ultrasound for two reasons: 1) It may help localized an abnormal parathyroid gland in about 82% to 84% of the cases [38,39], 2) To evaluate the thyroid gland for suspicious thyroid nodules.

In our case series, all but one patient presented to the office with palpable thyroid nodules, which is usually not the norm. All five patients underwent neck US as part of the initial evaluation of both PHPT and the thyroid gland itself. Three patients had nodules with suspicious sonographic features (as defined by the NCCN and ATA guidelines: hypoechoic, microcalcifications, infiltrative margins, taller than wide transverse planes) [40], which were subsequently biopsied by FNA, detecting PTC in two cases. Indications for concomitant thyroidectomy at the time of parathyroidectomy in these patients included biopsy-proven thyroid cancer (two cases), symptomatic goiter (one case), and multiple nodules with sonographically suspicious features (one case), in which the patient requested the thyroidectomy to be performed at the operation because she did not want to deal with the follow up surveillance. Two patients required reoperation, one due to the development of PTC and another for completion thyroidectomy after a PTC was diagnosed from the lobectomy specimen. One patient also had a significant risk factor with previous neck irradiation. All five patients had normal renal function. No permanent complications resulted in all five patients. Their prognosis is deemed to be favorable, as the PTC was treated in a timely manner thanks to a thorough work-up of both pathologies.

In our practice, the routine operation performed is adherent to the technique described by Dr. James Norman, et al. [8], It is clearly seen here that although an FNA biopsy of suspicious thyroid nodules is mandatory, a negative result should be approached with caution and the surgeon should not hesitate to offer the patient a thyroidectomy if strong suspicion exists, due to the relatively high possibility of it harboring a cancerous tumor.

There appears to be no increased risk to the patient in terms of outcomes and complications when performing parathyroidectomy and thyroidectomy at the same operation [36,41]. Complication rates are similar when compared between patients receiving parathyroidectomy alone vs. with concomitant thyroidectomy [36,41]. Reoperationat a different time for thyroid resection, on the other hand, carries an added risk [42]. In patients undergoing thyroidectomy, inadvertent parathyroid gland removal can occur in as many as 20% to 28% of patients, especially if the parathyroid glands are in ectopic locations [42,43]. Recurrent laryngeal nerve palsy risk is higher in re-operated patients (5.5% vs 2.5%) than in first-time operations. There is also a higher incidence of hematoma formation (4.3% vs 1.7%) in re-operated patients. Risk of permanent laryngeal nerve injury, however, remains low (less than 2%) in expert hands [44].

The practice of neck radiation for the treatment of benign disorders such as acne vulgaris has been abandoned for several decades. However, patients who as children received this type of treatment are at increased risk of both PHPT and thyroid cancer [20,45,46]. A study by Woll et al., that included 1,428 patients compared people treated for PHPT who had a history of neck irradiation vs. patients who did not. They found no difference in recurrence rates, or in the incidence of multiglandular disease [47].

In conclusion, PHPT is an increasingly prevalent disease whose management is rapidly evolving to become an exclusively surgical disease. Current medical literature would suggest an increased risk of thyroid cancer in patients with PHPT. One must not neglect the timely and complete evaluation of the thyroid gland in order to prevent subsequent operations that could not only negate the initial benefits of a minimally invasive procedure, but leave an unsuspecting patient with a potentially cancerous lesion.

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