Synchronous papillary thyroid carcinoma and primary hyperparathyroidism : A rare association

R. Belaid, I. Oueslati, M. Chihaoui, M. Yazidi, F. Chaker, H. Slimane.
Department of Endocrinology, La Rabta hospital, University of Tunis El Manar- Faculty of Medecine of Tunis.

ABSTRACT

The coexistence of a papillary thyroid carcinoma and primary hyperparathyroidism is an uncommon phenomenon. Awareness of this condition will enable clinicians to evaluate for possible thyroid disease in patients with primary hyperparathyroidism.
Herein we report the cases of three adult women with synchronous primary hyperparathyroidism and papillary thyroid carcinoma which were confirmed surgically. 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 primary hyperparathyroidism, as it is important to minimize reoperation rates and complications.
Keywords: Parathyroid adenoma, Primary hyperparathyroidism, Papillary thyroid carcinoma.

INTRODUCTION

Primary hyperparathyroidism (PHPT), caused by parathyroid adenomas in 80% to 85% of clinical cases, represents the third most common endocrine disorder. Papillary thyroid carcinomas (PTC) represent up to 87% of all thyroid carcinomas with an incidence that has doubled over the past 30 years.
Concomitant thyroid and parathyroid pathologies have been reported in 15% to 70% of patients with primary hyperparathyroidism [1]. However, the reported incidence of non medullary thyroid carcinoma in patients with primary hyperparathyroidism is only approximately 3% (range, 2.4%–7%) [2]. It still remains controversial whether these two pathologies happen coincidental or are caused by specific risk factors or genetic changes [3]. Exposure to radiation especially in childhood, increased calcium, epithelial growth factors and insulin-like growth factor have been implicated in the pathogenesis of nodular thyroid and parathyroid disease, but have not been proven conclusively.
Although the probability of concomitant thyroid cancer is low, screening for thyroid lesions in patients with primary hyperparathyroidism is recommended. The identification of concomitant disease is important prior to primary operation in order to minimize surgical complications, patient discomfort, and costs [4].
Herein we report three cases of primary hyperparathyroidism associated with synchronous papillary thyroid carcinoma.

OBSERVATIONS

Case1:
A 65-year-old woman with no significant personal or family history of thyroid disease was referred to the department of endocrinology with incidental raised serum total calcium (116 mg/l; reference range 85–105); low-normal phosphate (25 mg/L; reference range 25-45 mg/ L) and increased parathyroid hormone levels (206 ng/L; reference range 10–65) which was consistent with primary hyperparathyroidism. She did not report any symptoms suggestive of hypercalcemia. Her clinical history was otherwise unremarkable. Physical examination was normal.
Serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were normal (2.3 mIU/L, 1.1 ng/dL respectively; reference ranges 0.35–4.5 mIU/L and 0.7-1.5 ng/dL respectively). Renal and liver function tests were normal.
Technetium (99mTc)-Sestamibi scintigraphy revealed an area of increased radioactivity at the inferior pole of the right thyroid lobe, which was suggestive of a parathyroid adenoma. The neck ultrasound revealed parathyroid adenoma at the inferior pole of the right thyroid lobe and bilateral thyroid nodules: a single 11 mm hypoechoic nodule within the right lobe and a single 15 mm nodule containing small calcifications within the left lobe of the thyroid gland.
The patient was subjected to uncomplicated right inferior parathyroidectomy and synchronous total thyroidectomy. No suspicious cervical lymph nodes were found during intraoperative exploration. Postoperative histopathological examination confirmed the diagnosis of parathyroid adenoma with coincidence of bifocal papillary thyroid carcinoma. After surgery, serum parathormone and calcium returned to their normal values and patient was referred to the department of Nuclear Medicine for a radioactive iodine ablation therapy.

Case 2:
A 65 year-old woman with a history of essential hypertension over 10 years, dyslipidemia and ischemic stroke was referred to our endocrinology department for an incidentally discovered hypercalcemia (115 mg/L; reference range 85–105)and low-normal phosphate (27 mg/L; reference range 25-45).
The patient was complaining of epigastralgia and bone pain since three years.
Physical examination revealed a nodule of two centimeter

Corresponding Author : Rym BELAID
E-mail adress: ouesibtissem@gmail.com

within the inferior pole of the right thyroid lobe. Neck examination was free from adenopathy.
Laboratory tests indicated an elevated parathyroid hormone value (84 ng/L; reference range 10–65) confirming the diagnosis of primary hyperparathyroidism. Thyroid function was normal (FT4 = 0.88ng/dl; reference ranges: 0.7-1.5 ng/dL and TSH=0.48 mIU/L; reference ranges: 0.35–4.5 mIU/L) .
The neck ultrasound displayed a multinodular goiter: a single 7 mm cystic nodule within the left thyroid lobe and four hypoechoic nodules of 10,19, 20 and 22 mm within the right thyroid lobe.
Cervical tomography revealed four hypodense thyroid nodules, the largest measuring 30 mm with irregular borders in the right lobe. No parathyroid adenoma or cervical adenopathy were found. Bone density by DXA revealed a distal radius T score of -3.2.
The patient underwent a parathyroidectomy of the right and left inferior parathyroid glands and right thyroid loboisthmectomy with lymph node dissection. The histological report diagnosed hyperplasia of the right inferior parathyroid gland and an adenoma of the inferior left one associated to a right encapsuled papillary thyroid carcinoma in its vesicular variant. Regional lymph nodes were not affected. A left hemi thyroidectomy was then performed. Postoperatively, the patient received an ablative dose of 100 mCi iodine- 131.
Post-radioactive iodine whole body scan showed an uptake in the thyroid bed, but no ectopic uptake suggestive of local or distant metastases was visualized.
The patient was followed-up on levothyroxine 150 mcg daily and was in a complete remission, with undetectable levels of serum thyroglobulin (Tg) and anti-thyroglobin antibodies. Serum parathormone and calcium returned to their normal values.

Case 3:
A 47-year old woman was referred to our endocrinology department for primary hyperparathyroidism.She had a history of hyperthyroidism secondary to a toxic thyroid nodule treated with radioactive iodine therapy and arterial hypertension over 4 months.
She had hypercalcemia of 106mg/L (reference range 85–105), hypophosphatemia of 21 mg/L (reference range 25-45) and elevated parathormone level of 393pg/ml (reference range :10–65). She did not report any symptoms suggestive of hypercalcemia.
Thyroid function was normal (TSH =2.3 mIU/L; reference ranges: 0.35–4.5 mIU/L).
The neck ultrasound revealed an hypoechoich mass of 6 x 6 x14 mm in the thyroid lower right pole suggestive of parathyroid adenoma and two isoechoic thyroid nodules of 9 mm and 11 mm with irregular borders and peripheral hypervascularity in the right thyroid lobe.
The 99mTc-sestamibi parathyroid scintigraphy revealed an area with increased uptake in the projection area of the nodule described at ultrasonography.

Parathyroidectomy of the right inferior gland and thyroidectomy were performed. Histopathological examination revealed a parathyroid adenoma and a papillary thyroidcarcinoma, respectively.
Postoperatively, PTH and calcium levels decreased to 8pg/mL and 91mg/L, respectively and the patient was referred to the department of Nuclear Medicine for a radioactive iodine ablation therapy.

DISCUSSION

A higher incidence of certain types of malignancy has been reported in patients with hyperparathyroidism. Specifically, an association between PHPT and PTC has been frequently reported [5].Various explanations have been proposed for the increased cancer incidence in hyperparathyroidism compared to general population. However, the pathogenetic mechanism of PHPT and PTC coexistence has not been completely established yet.
Some authors suggested this concurrence as a coincidental pathology, whereas most of them explain that by several predisposing factors such as increased goitrogenic and oncogenic effects induced by hypercalcemia [2, 6]. But until now, solid evidence is lacking and the relationship seems to be multifactorial. In fact, Taylor et al [7] theorized that calcium carbonate has a goitrogenic effect either by inhibiting the synthesis of thyroxine or by increasing iodine clearance by the kidney, and Ellenberg et al [8] reported that hypercalcemia also might be carcinogenic, increasing mitotic activity.
In addition, excessive production of parathyroid hormone was reported to have a tumor promoting effect by initiating a step in the cancer process in altering the DNA. Indeed, at the cellular level, PTH can increase the proliferation of the liver and bone marrow in vivo and in T lymphocytes in vitro [6].
Furthermore, previous neck or head irradiation, although not present in our patients ,can increase the risk for thyroid and parathyroid cancer and was found in the history of 15 to 30% of patients having an association of PHPT and well differentiated thyroid carcinoma [1,2].
On another hand, PHPT and PTC have different, but shared embryologic origin. Therefore, a possible common responsible gene and/or growth factors may also play a role in their pathogenesis [6].
In accordance to our patients, most reported cases of non-medullary thyroid cancer associated to PHPT have an unifocal, occult and right sided papillary thyroid carcinoma without cervical lymph node involvement [2].
Multifocality, bilaterality and metastasis were reported to be rare [9]. Patients having these concurrent pathologies were commonly middle-aged women probably because of the increased incidence of both these endocrine diseases in females [2, 6]. Nevertheless, this coexistence has also been reported in men [9].
In this association, the PHPT is usually the primary pathology while the PTC is commonly an incidental finding [9].
In spite of its rarety, the diagnosis of this concurrence should always be considered in PHPT in order to prevent the re-intervention like in our second case. Therefore, a careful palpation and inspection of the entire thyroid gland at the time of parathyroid resection is highly recommended to prevent the increased morbidity associated to the se-

cond neck exploration for completion thyroidectomy or neck dissection.

In term of localization, neck ultrasound exam is the most efficient tool to detect concomitant thyroid nodules that are not palpable or symptomatic in up to 25% to 45% of patients with PHPT. These incidental nodules are malignant in 5% of these patients.

Any suspicious looking thyroid nodule should be evaluated with fine needle aspiration (FNA) [10] which has high sensitivity (94%) and specificity (98%) for the diagnosis of malignant thyroid nodules [4]. Moreover, the 99mTc-MIBI scan is considered as a localization tool with the best sensitivity for the detection of eutopic and even ectopic parathyroid glands [11]. Thus, the combination of 99mTc-MIBI, US, and US-FNA (if needed) are recommended as the greatest diagnostic tool for parathyroid localization of PHPT and concomitant thyroid disease [1].

Finally, concurrence of the parathyroid and thyroid disorders makes their treatment more sophisticated. Given that there are no specific guidelines for the management of patients with synchronous PHPT and PTC, they should be managed like the cases of single PTC [12].

CONCLUSION

Our cases highlight the need for clinicians to be aware of synchronous PTC and PHPT. Coexistence of both pathologies may complicate patient management due to untreated hypercalcemia, unrecognized thyroid cancer and the need for second neck surgery in the absence of careful screening of both pathologies. Thus, plasma calcium and even PTH levels should be measured in all patients with known thyroid disease. On the other hand, preoperative thyroid ultrasound should be performed to patients with PHPT in order to detect thyroid nodules.

Conflict of interest statement: No conflicts of interest

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