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Papillary carcinoma of the thyroid in patients with primary hyperparathyroidism: Is there a link?

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ABSTRACT

Primary hyperparathyroidism (PHPT) is present in up to 0.1% of the general population. The incidence is higher in women and increases with age. The majority of the cases is asymptomatic and up to 85% are due to single gland adenoma. Parathyroidectomy is the treatment of choice after localization of the hyperactive gland.

Papillary Thyroid Carcinoma (PTC) is the most common cancer of the thyroid and constitutes more than 70% of thyroid malignancies. PTC can present as a single nodule or can be Multifocal. The incidence is higher in women. Early treatment favors a good prognosis. PTC with PHPT has been reported in 2.3–4.3% of patients undergoing surgery for PHPT. The coexistence of parathyroid adenoma and incidental PTC is thought to be rare. The mechanisms underlying the relationship between PHPT and PTC have not been established. We suggest a possible hypothesis for the relationship based on shared embryological origin and genes, high parathyroid hormone (PTH), low 1,25 hydroxy vitamin D, hypercalcemia resulting in high levels of angiogenic growth factors. This promotes the formation of parathyroid adenomas and papillary thyroid carcinoma. Presence of these two diseases can complicate patient management due to untreated hypercalcemia, unrecognized thyroid cancer and need for second surgery if not screened for both diseases carefully.

Introduction

Primary hyperparathyroidism (PHPT) is present in up to 0.1% of the general population. It is characterized by hypercalcemia. The incidence of PHPT is 27–30 per 100,000 person-years. It is twice as high in women and increases with age. In majority of cases the condition is asymptomatic. A single gland adenoma accounts for 75%–85% of the cases. The treatment of choice for PHPT is surgical removal of the hyper-functioning gland after localization [1]. PHPT can also present as a part of multiple endocrine neoplasia (MEN) types I and IIa. Papillary Thyroid Carcinoma (PTC) is the most common cancer of the thyroid. PTC constitutes more than 70% of thyroid malignancies. There has been an increasing incidence of PTC worldwide over the past few decades. PTC can present as a single nodule or it can be Multifocal. The incidence is higher in women [2,3]. Early treatment favors a good prognosis. One-year survival rate compared to the other histological subtypes of thyroid cancers is good and has significantly increased from 97.7% to 99.5% over a period of 10 years in the UK. Non-medullary thyroid carcinoma (NMTC) with PHPT has been reported in 2.3–4.3% of patients undergoing surgery for PHPT. The majority of the cases were women and many of the cases were associated with previous head and neck irradiation [4]. The coexistence of parathyroid adenoma and incidental PTC is reported to be rare. In most Case reports discussing the coexistence of these two diseases, PHPT was usually the primary pathology and was diagnosed before the identification of the thyroid carcinoma that was usually diagnosed in a pathology specimens as an incidental finding. [5,6]. Presence of these two pathologies can complicate patient management due to untreated hypercalcemia, unrecognized thyroid cancer and the need for second surgery if not screened for both diseases carefully.

Hypothesis

The mechanisms underlying the relationship between PHPT and PTC have not been established. In most of the published studies,

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this relationship has been reported to be coincidental. Goitrogenic and carcinogenic factors have been implicated in the pathogenesis, but there is no conclusive evidence. The relationship appears to be multifactorial. We suggest a possible hypothesis for the relationship based on shared embryological origin, genes and transcription factors, high parathyroid hormone (PTH), low 1,25 hydroxy vitamin D, hypercalcemia resulting in high levels of angiogenic growth factors. This process promotes the growth of parathyroid adenoma and papillary thyroid carcinoma Thyroid development starts around the 4th week of gestation as an endodermal thickening in the midline floor of the pharynx between the first and second pharyngeal pouches. It reaches its final destination by the end of the seventh week of gestation. Part of the thyroid gland originates from the fourth and fifth pharyngeal pouches. The neural crest cells (ultimobranchial bodies) of these pouches contribute parafollicular C cells that produce calcitonin. The thyroid gland is able to function by the end of the third gestational month. The parathyroid glands start developing during 5th and 6th weeks of gestation from the third and fourth pharyngeal pouches. Usually 2 parathyroid glands develop on each side. The third pharyngeal pouch generates the inferior parathyroid glands and also the thymus. The superior parathyroid glands originate from the fourth pharyngeal pouch, along with part of the thyroid gland [7].

Several genes have been implicated in the development of the pharyngeal organs that include thyroid and parathyroids.

1. *Hoxa*3gene; inactivation of this gene in mice results in absence of parathyroid, thymus and persistence of ultimobranchial bodies.
2. *Pax*1 and *Pax*9 are closely related members of the paired-box gene family, which play critical roles in the development of multiple organs [8]. Inactivation of *Pax*9 results in early failure of thymus, parathyroid and ultimobranchial body formation.
3. *Gene 1 Eyes absent (Eya1)* is involved in morphogenesis of organs derived from the pharyngeal region, including thymus, parathyroid and thyroid. Eya1 also regulates mature thyroid gland formation.
4. *Gcm2*, homologous to the Drosophila Glial cells missing gene encodes a transcription factor with a novel DNA binding domain. This plays a key role specifically for the organogenesis of parathyroid glands [9].
5. In addition to these transcription factors, retinoid signalling has been shown to be essential for the formation of the 3rd and 4th pharyngeal arches [10].

Studies have started to define specific genes controlling early pharyngeal organ development, but the identity of the regulatory pathways has not been defined as yet.

Thyroid malignancy was reported to be most prevalent cancer in patients diagnosed with PHPT. PTH was reported to have tumor-promoting effect with genetic predisposition to new malignancies. Interestingly parathyroidectomy was not found to be a risk-reducing, but only a delaying factor in cancer occurrence. This phenomenon may suggest that exposure to high parathyroid hormone levels may initiate a step in the cancer process in altering the DNA. PTH at the cellular level has shown to increase proliferation in the bone marrow and liver in vivo and in T-lymphocytes in vitro. In contrast to this the active form of vitamin D 1, 25- dihy droxycholecalciferol(1,25D3) appears to suppress cell proliferation and promote differentiation of immature or neoplastic cells. The tumourogenic action of excess PTH may act unopposed due to the deficiency of 1,25D3 in contributing to increased tumor formation as in chronic renal failure.

Hypercalcemia is also reported to be carcinogenic. The proposed goitrogenic effect of calcium carbonate is due to inhibition of thyroxine synthesis as a result of increased iodine clearance by the kidney. High level of calcium and excessive production of calcitonin in response to hypercalcemia has been proposed as a common pathogenic mechanism for the coexistence of thyroid carcinoma and PHPT [11,12].

Angiogenic growth factors like basic Fibroblast Growth Factor (bFGF) and Vascular EndothelialGrowth Factor (VEGF) ensures vascularisation and growth of tumor tissue. Higher production of bFGF has been documented in the follicular cells of thyroid gland carcinomas. bFGF is also produced by cells of parathyroid adenoma and stimulates follicular cell growth. It has mitogenic and differential effects. bFGF is a very strong activator of angiogenesis causing fibroblasts and endothelial cells proliferation and migration. bFGF production is minimal in the normal thyroid gland tissue but higher bFGF serum levels have been found in patients with thyroid adenoma and papillary carcinoma compared to the healthy population.

TSH activates the VEGF production in Thyreocytes resulting in initiation of angiogenesis. VEGF increases vascular permeability and has a role in the neovascularisation. It is a mitogenic factor for endothelial cells. VEGF also takes part in the lymphatic vessel formation and affects the tumor cells dissemination to the regional lymphatic nodes. The higher bFGF expression has also been reported in patients with MEN-1. bFGF has a mitogenic effect on the parathyroid tissue in vitro.

In patients with secondary hyperparathyroidism (SHPT) the parathyroids have a significantly higher number of vessels expressing CD105. CD105 preferentially labels activated endothelial cells that are associated with angiogenesis. SHPT glands have a significantly increased expression of b-FGF compared to the normal parathyroid gland. VEGF-A expression is also increased in the SHPT glands [13,14]. In summary, patients with PHPT have increased chances of developing PTC due to high PTH, hypercalcemia and low 1,25D3 resulting in mitogenesis and neovascularisation by stimulating angiogenic factors like b-FGF and VEGF because of shared embryological, genetic origin and transcription factors. Improved imaging techniques has also contributed to the detection of two pathologies (see Fig. 1).

Development: Shared embryological origin of thyroid and parathyroid. *Genes*: Shared genes and transcription factors during thyroid and parathyroid organogenesis. *Hormones and metabolic factors*: High PTH, hypercalcemia, low 1,25D3 and TSH. *Angiogenic factors*: Stimulation of b-FGF and VEGF are leading to the formation of parathyroid adenoma and PTC. *Improved imaging*: Better detection.

Summary of clinical observation

We report 12 cases of coexisting PHPT and PTC diagnosed and treated in last 3 years. Diagnosis was made prior to the surgical intervention. All patients were females with an age range of 26–74 years. The initial presentation of all these cases was PHPT. In our center we use dual imaging; Sestamibi Spect scan and high resolution ultrasound (USS) for the localization of parathyroid adenoma so thyroid nodules is frequently detected. In our series any thyroid nodule with suspicion of malignancy had a fine needle aspiration (FNA). The features suggestive of malignancy were, according to the British thyroid association (BTA) guidelines [15]:

1. Solid hypo-echoic nodule relative to the normal thyroid tissue that may contain micro-calcification
2. Irregular margin, intra nodular vascularity and absence of an associated halo
3. A "taller than wide" shape referring to Anterior/Posterior (AP) > Transverse (TR) diameter when imaged in the axial plane.
4. An irregular or spiculated margin