**Papillary Carcinoma of the Thyroid in Patients with Primary Hyperparathyroidism: Is there a link?**

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**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, 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 thi sgene 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- dihydroxycholecalciferol(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.

Figure: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

5. Egg shell type calcification around the periphery of a nodule with a broken calcified rim

All patients had parathyroid adenomas with an equal number of inferior and superior parathyroid gland involvement. One patient had two parathyroid adenomas. We had 2 patients under the age of 30 years and they were MEN 1 mutation negative. All patients had papillary thyroid carcinoma . One of the cases had a combination of Hurthle and PTC. The majority of the PTCs were small PT1 (1cm) to PT2 (2cm). Level VI lymph node metastasis was present in one case and one patient had Multifocal PTC. None of our patients had a history of head or neck radiation. There was no significant preoperative correlation between thyroid cancer and age, size of parathyroid adenoma and diameter of thyroid nodule.

Clinical information, investigations and results of the patients are presented in Table 1.

**Discussion**

PHPT associated with PTC has been reported frequently with rates varying between 2.7- 17.6% in patients who had neck surgery for PHPT. The rate of benign thyroid pathologies in patients with PHPT is higher between 17-40%. The majority of patients with coexistent PHPT and PTC are women, possibly due to the increased incidence of both these conditions in women but this coexistence has also been reported in men [16]. Overall thyroid and parathyroid pathologies are more frequently detected in patients with MEN syndromes. Medullary thyroid carcinoma (MTC) associated with PHPT due to genetic relationship is well documented in patients with multiple endocrine neoplasia (MEN) type 2. The pathogenic relationship between PHPT and PTC is not clearly understood. Carcinogenic and goitrogenic factors have been suggested to play a part in pathology, but no conclusive evidence is available. A common gene or growth factor has also been suggested. None of our patients had a history of radiation exposure to the head and neck area. Some authors have suggested possible etiological links between invasive papillary carcinoma and secondary HPT in anecdotal case reports [17] . In our series no patient had secondary or tertiary HPT. As coexistence of HPT with thyroid disease is high, so a thorough preoperative examination and imaging should be done particularly in male patients where the probability of malignancy is high in cases with single nodules. Any suspicious looking thyroid nodule should be evaluated with fine needle aspiration (FNA). Most reported cases of thyroid cancer are the classical variant of PTC usually less than 1 cm. Multifocality with lymph node involvement is reported to be rare. In our 12 cases, 4 cases had a single focus of PTC 2cm, 4 had Multifocal PTC and 3 patients had lymph node involvement. One patient had a Follicular variant of PTC and one had a combination of Hurthle cell and PTC. 7 patients had parathyroid adenoma involving inferior parathyroid glands and 5 had a superior parathyroid gland adenoma. One patient had both right sided superior and inferior adenoma.

There are no guidelines for management of coexisting PHPT and PTC. PTC in such patients is managed like cases of single PTC, according to recent BTA guidelines with parathyroidectomy. Minimally invasive parathyroid surgery is becoming popular, but the risk of coexistence thyroid pathology should be considered. In order to avoid this pitfall ultrasonogarphy of the thyroid should be done in patients with PHPT to exclude nodular thyroid disease.

**Summary and implications**

The coexistence of PHPT and PTC is frequently and more common in women, but has been reported in men.

Patients with PHPT can have bilateral, Multifocal and metastatic PTC.

Ultrasonography of both thyroid and parathyroid glands should be considered in patients with PHPT.

 Any suspicious looking thyroid nodule on an ultrasound scan should have FNA before surgery.

 If malignancy is detected, then imaging should be carried out for staging of PTC to avoid a second surgery that increases the morbidity.

Younger patients< 30 years of age and those with a family history of thyroid pathology requiring surgery should be offered genetic screening for MEN syndromes.

 In case of coexistent PHPT and PTC, the patient should be managed according to recent guidelines for management of PTC.

Our Hypothesis suggests that a primary parathyroid abnormality with a secondary effect on the thyroid gland is the causative factor. PHPT and PTC have different, but shared embryologic origin. A possible common responsible gene and/or growth factors may also play a role. The majority of patients with concurrent PHPT and NMTC are women and the reason could be due to the increased incidence of both PHPT and PTC in women.

**Conflict of interest statement**

None declared.

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