Original paper

A Rare Encounter – Papillary Thyroid Cancer Meets Cushing's Disease

Case report and literature review

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Abstract

Glucocorticoids (GC) play major role in the physiologic stress response. However chronic exposure to glucocorticoids as seen in Cushing's disease (CD) has detrimental effects on multiple systems: cardiovascular, metabolic, immune, psychological. Papillary thyroid carcinoma is the most common type of thyroid cancer and the most common endocrine malignancy and its incidence has been increasing lately. However concomitant thyroid cancer with CD is uncommon.

We report a case of papillary thyroid microcarcinoma (PTMC) in a woman with metabolic syndrome and multinodular goiter, diagnosed with CD due to a corticotroph pituitary microadenoma. Both CD and thyroid cancer were cured after surgery.

A review of literature shown association between papillary thyroid carcinoma and Cushing's disease is very rare and so far there is no known genetic mutation to link the two neoplastic conditions. While this may be a random association, possible implications of chronic GC exposure in cancer progression are discussed.

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Introduction

Papillary thyroid carcinoma is the most common type of thyroid cancer (70-80% of all thyroid cancer). It is a differentiated type of carcinoma, it affects women between 30-60 years old, 3 times more often than males. Clinical outcome in patients with differentiated thyroid carcinoma is often favorable [1].

Glucocorticoids (GC) play major role in the physiologic stress response. However chronic exposure to glucocorticoids as seen in Cushing's disease (CD) has detrimental effects on multiple systems: cardiovascular, metabolic, immune, psychological. CD, caused by a pituitary adrenocorticotropic hormone (ACTH)-secreting tumor, is probably underestimated at 1.2-.2.4 per million per year and it affects mostly women (3-15:1) [2].

Association of Cushing's disease and papillary thyroid carcinoma is very rare and it appears that ACTH secretion is insufficient to cause typical cushingoid features in the described cases.

We report here a rare case of Cushing disease with concurrent papillary thyroid cancer, the course of the diseases and review of the literature.

Case report

A 56-year old Caucasian woman with metabolic syndrome (BMI of 51 kg/m^2) presented for recent discovered multinodular goiter and altered thyroid function tests, with suppressed TSH (<0.03 mUI/l). Thyroid ultrasound revealed multinodular goiter, while radioiodine uptake test- RAIU revealed low uptake in the thyroid.

Three weeks later she developed plethora, purpura on her breasts and bruised easily at venepuncture sites. Neutrophilia with lymphocytopenia, normal platelets and hyperglycemia were revealed.

Midnight plasma and salivary cortisol (2.59 µg/dL, NV <0.4 µg/dL) were high, morning plasma cortisol was borderline high, with increased ACTH. Urinary free cortisol (UFC) was 10 times over the upper limit of normal (1068.25 µg/24 h, NV 21-111 µg/24 h). Low dose dexamethasone suppression test revealed autonomous hypercortisolemia, suggesting CD. MRI of the pituitary revealed a microadenoma of 7.5/7 mm on the left side.

At this point the patient was diagnosed with CD and referred for transsphenoidal pituitary surgery that removed the tumor.

Serial 3 µm sections had been cut from paraffin blocks and stained with Hematoxylin and Eosin (HE). Histopathological evaluation showed that tumor tissue consisted of monomorphic basophilic and amphophilic round cells, with round nuclei, conspicuous nucleolus and with a sinusoidal pattern around the capillaries (Figure 1).
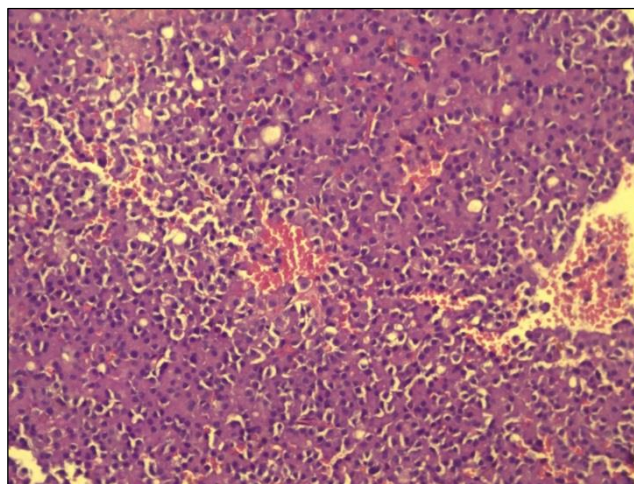

Figure 1. Pituitary adenoma HE 20x. Monomorphic basophilic and amphophilic round cells, with round nuclei, conspicuous nucleolus and with a sinusoidal pattern around the capillaries.

The immunohistochemistry (IHC) was performed on 3 µm sections from 10% formalin-fixed paraffin-embedded tissues according to the IHC method, an indirect bistadial technique performed with a polymer-based detection system (EnVision™ Dual Link System-HRP, DAKO, Carpinteria, CA, USA). Tissue sections were spread on poly-L-lysine-coated slides immersed in three changes of xylene and rehydrated using a graded series of alcohol. Antigen retrieval was performed in microwave oven. In each section, endogenous peroxidase was blocked by 20 min incubation in 3% hydrogen peroxide. The sections were incubated with primary antibody: ACTH (DAKO, 1:2000, 02A3), LH (DAKO, 1:50, C93), GH (Leica, 1:50, Polyclonal), PRL (DAKO, 1:200, Polyclonal), FSH (Leica, 1:50, Polyclonal), TSH (Leica, 1:100, Polyclonal) and Ki67 (DAKO, 1:100, Mib-1) at room temperature for 1 hour. The DAKO EnVision Detection System-HRP was then applied for 30 min. Finally, the sections were incubated in 3'3-diaminobenzidine for 5 min, counterstained with Meyer's Hematoxylin and mounted. The slides were examined and photographed on Leica DM750 Microscope. Negative controls were obtained by replacing the primary antibody with non-immune serum. As a positive control a thyroid tissue section was used.

Immunohistochemically, the tumor cells presented zonal positive immunostaining for ACTH (Figure 2), negative for GH, PRL, TSH, FSH, LH and Ki67 was positive in about 1% in the tumor cells (Figure 3).
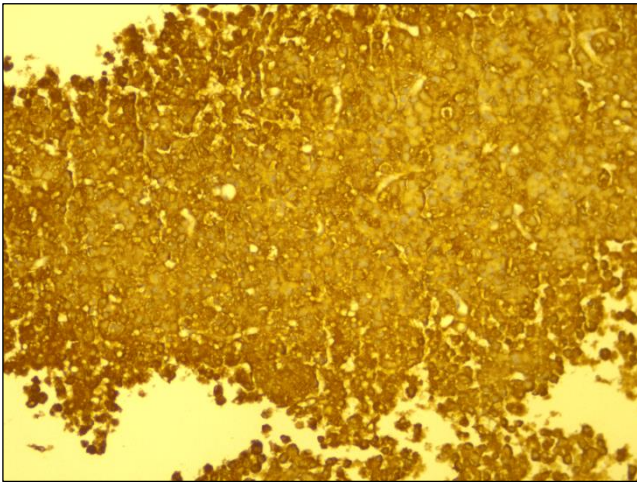
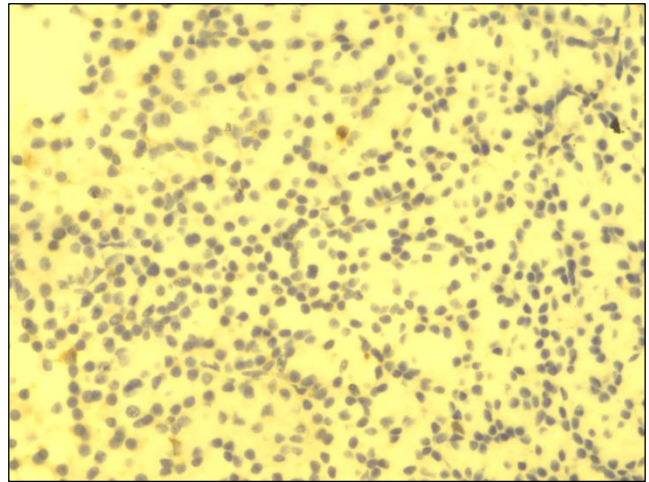**Figure 2.** Zonal ACTH positive immunostaining
of corticotroph adenoma.

Figure 3. Ki 67 1% immunostaining
of corticotroph adenoma.

Transitory adrenal insufficiency after cured Cushing's disease required substitutive hydrocortisone treatment. At 3 weeks postoperatively, patient had a BMI of 42 kg/m^2, no plethora and no purpura. Serum ACTH, midnight plasma cortisol were normal and urinary free cortisol was in the low-normal range. Thyroid function tests returned to normal. Hypothalamic-Pituitary-Adrenal (HPA) axis recovered after 2 months postoperatively, when hydrocortisone was stopped.

Three months later, after discussing management options with the patient, it was decided to undergo thyroidectomy for multinodular goiter.

Total thyroidectomy was performed with conservation of the parathyroid glands and recurrent laryngeal nerves. Histopathological examination showed papillary micro-carcinoma (PTMC) in the left lobe with the size of the tumor *focus* smaller than 1 cm (0.8/0.7 cm) (Figure 4, a.b) No vascular invasion was noted, however there was minimal extrathyroidal extension, pT1aNx, R1.
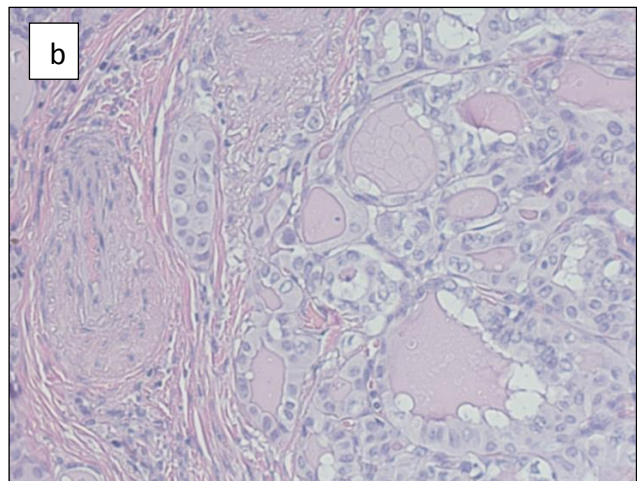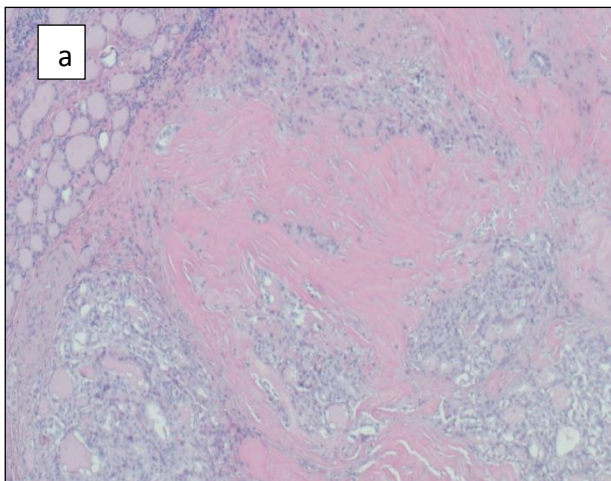

Figure 4. a. HEx4: Note in the center of the image the aspect of papillary thyroid cancer; **b.** HEx20: PTC cells with abnormal large nuclei display a series of abnormalities such as changes in size and shape, irregularities of the membrane and chromatin characteristics, marked remodeling of the nuclear envelope with irregular nuclear contours and nuclear inclusions.

IHC revealed that the tumor cells were chromo-granin negative, synaptophysin negative, PAX 8-positive, Thyroglobulin positive (Figure 5).

Postoperatively patient received 50 mCi^{131} I and levothyroxine aiming to suppress TSH as standard therapy for PTC. Follow up showed excellent response to therapy with serum thyroglobulin (Tg) 0.04 ng/mL (normal 0.9-54 / ng/mL), and no signs of local disease.

CD was still in remission at 2 years follow up, when patient returned with a BMI of 40 kg/m^2 and diabetes was controlled by nutritional therapy only.
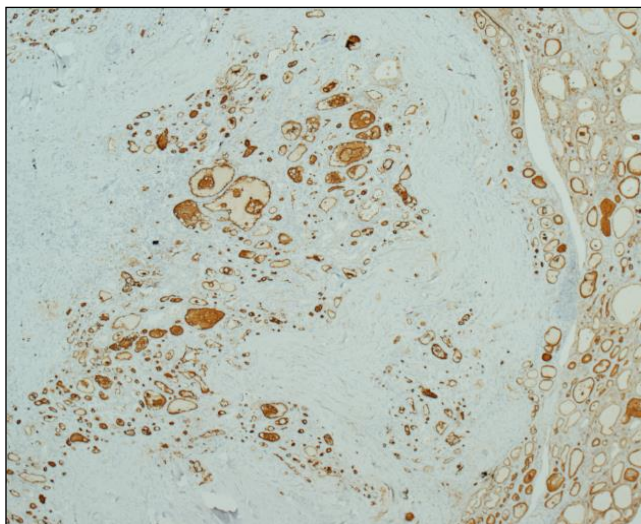
Figure 5. Positive ICH for Thyroglobulin in PTC.

Discussion

Papillary thyroid carcinoma (PTC) is the most frequent type of thyroid cancer and the most common endocrine malignancy. Most of the time is asymptomatic, incidentally discovered by neck ultrasonography. PTC incidence has been increasing lately, one of the many reasons being the extensive use of cervical echography and fine needle aspiration cytology examinations [3].

According to the World Health Organization classification system for thyroid tumors, papillary thyroid microcarcinoma (PTMC) is defined as PTC measuring ≤ 1 cm in greatest dimension [4]. The overall prognosis is excellent for patients with PTMC as it is associated with a 1.0% disease-related mortality rate [5]. A limited number of patients may develop locoregional recurrences or distant metastasis, mostly the ones harboring *BRAF* mutations [6]. It is well known that *BRAF* mutation is one of the most frequent molecular events in the pathogenesis of PTC in adults. Replacement of valine to glutamate at aminoacid 600 in the BRAF protein, results in exaggerated prolife-ration and differentiation of tumor cells, leading to a loss of control over the cellular cycle and hence drawing the progression of malignancy. LIU X. et al showed that BRAFV600E mutation in PTC is associated with extra thyroidal extension, lymph node recurrences and advanced TNM leading to increased mortality rates of the disease [6; 7]. In our case *BRAF* mutation screening was not available, but minimal extrathyroid extension was present, which counted for a possible risk of a more aggressive type of PTMC, moreover after chronic exposure to GC due to CD. In order to prevent the worse outcome, radioiodine adjuvant therapy was used after thyroidectomy.

HPA axis is critical for adaptation to stress and regulation of the circadian clock pulsation of gene expression [8]. Cortisol secreted by adrenal glands in response to pituitary ACTH is released with a characteristic circadian pattern with high levels just before awakening, followed by a ultradian pulsations throughout the day, declining down to nadir levels during the night sleep.

The daily rhythm of HPA axis is regulated from the suprachiasmatic nucleus from which axonal projection to the paraventricular nucleus of the hypothalamus inhibit corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) release during the night sleep, thus switching off the pituitary ACTH and adrenal CG secretion. In order to induce appropriate reactivity to physical or psychological stressors, the brain stem and limbic system also modulate HPA activity. Axonal terminals in the median eminence release CRH and AVP into the hypophyseal portal system that stimulate pituitary corticotrophs to release ACTH. ACTH binds to melanocortin type 2 receptor (MCR2) at the adrenal cortex, thus stimulating the production of GC, mainly cortisol. Cortisol is responsible to produce its characteristic metabolic, cardiovascular, immunological and cognitive effects that ensures adaptation to stress. Cortisol also acts via an autoregulatory negative feedback loop to inhibit the HPA axis and limit the stress response from overshooting. GCs in excess exert a non-specific negative feedback on other types of anterior pituitary secreting cells. Thyroid-stimulating hormone (TSH) synthesis and release are inhibited and may be acutely low in patients treated with moderate to high dose glucocorticoids. Serum total thyroxine (T4), total and free triiodothyronine (T3) concentrations are usually low normal, but free T4 levels are normal. Despite these alterations, manifestations of hypothyroidism are not apparent.

Chronic excess levels of GC result in adverse effects: hypertension, increased thromboembolic risk, diabetes mellitus, immunosuppression, osteoporosis and depression. GCs exhibit powerful anti-inflammatory functions : induce apoptosis of T lymphocytes, neutrophils, basophils and eosinophils, downregulate proinflammatory genes encoding cytokines, chemokines and inflammatory enzymes, inhibit antigen presentation, major histocompatibility complex class II expression and antibodies, and favor T helper 1 versus T helper 2 responses [8].

Cushing's disease is a rare disorder, caused by prolonged exposure to excess glucocorticoids. It is associated with significant morbidity and mortality. Clinical presentation can be broad, and establishing the diagnosis can be difficult. Early recognition and rapid control of hypercortisolaemia is necessary to decrease morbidity and mortality in these patients. While the diagnosis can be straightforward in florid cases, establishing the diagnosis can be challenging in cases with mild hypercortisolism and subtle clinical features, especially given the overlap in symptoms in individuals with and without the syndrome [2].

Our patient had a supressed TSH with a low-normal T3, but had symptoms uncorrelated with hypothyroidism: weight loss, restlessness. She also had a metabolic syndrome (central obesity, hypertension and impaired fasting glucose), but not typical Cushingoid features. Recent onset plethora and purpura on her breasts led us to screen her for Cushing's syndrome (CS).

Although population-based studies demonstrate a low incidence of endogenous CS, more evaluations of patients with uncontrolled diabetes mellitus or hypertension suggest that this may be an underestimation [9].

Weight gain is the most common sign of CS, but it is also extremely common in patients without the syndrome. Leibowitz et al screened 90 obese subjects with uncontrolled diabetes mellitus (HbA1c >9%), and found three (3.3%) to have CS [10]. However, this reported prevalence of 2%-5% was not confirmed in other studies. Widespread screening for CS in overweight individuals or patients with type 2 diabetes mellitus is therefore not recommended [11]. Instead, a case-finding approach in patients with other features of CS or uncontrolled diabetes or hypertension despite appropriate treatment may be indicated. Our patient had a morbid obesity at presentation BMI 51 kg/m^2 which dropped to 40 kg/m^2 two years postoperatively.

Diagnosis of CS is based on proving autonomous hypercortisolism (cortisol non-suppressible at a low dose dexamethasone suppression test). If CS is confirmed, the next step is to determine the etiology. An inappropriately normal or elevated ACTH level (>20 pg/ml) is consistent with an ACTH-dependent form of CS, mostly due to CD, while ACTH<5 pg/ml suggest adrenal CS.

A new study suggests that measuring midnight-to-morning serum TSH ratio is a potential new way to diagnose CS with a higher sensitivity than the current diagnostic methods, as in CS patients the nocturnal serum TSH surge is abolished [12].

A pituitary MRI should be obtained in ACTH-dependent cases. A mass >6 mm strongly suggests CD. However, ACTH-secreting pituitary tumours are usually small and may not be detected, even with newer, more advanced MRI techniques in 20%-58% of patients with CD. Moreover, ~10% of "healthy" individuals can have incidental pituitary lesions up to 6 mm in size [13].

Differential diagnosis of ACTH-dependent CS can therefore be very challenging. In our case, the MRI revealed a left sided pituitary microadenoma of 7.5/7 mm. If there is a lesion less than 6 mm on the pituitary MRI, further invasive techniques are required to differentiate from ectopic ACTH syndrome.

The complications of CS are influenced by age and sex and the severity and duration of the disease. Decreased bone mineral density, osteoporosis and fractures are present in 50%-80% of patients with CD. After cure, bone mineral density improves, but additional specific treatment for fractures and related pain may be needed. Bone loss can be more severe in primary adrenal disease compared to CD. This may be related to a protective effect of the higher adrenal androgen levels in CD. Our patient was diagnosed with osteoporosis (lumbar T score -3.7SD) at initial presentation and treatment with bisphosphonate was initiated (Risendronate), resulting in a bone mineral density rise of 5.5% 2 years after treatment.

Glucose intolerance occurs in 45%-70% of patients with CS. This reported prevalence of glucose intolerance is likely an underestimate, as many patients with normal fasting glucose have underlying glucose intolerance, and not all patients with CS undergo glucose-tolerance testing [14]. Our patient had an impaired fasting glucose at initial presentation, which remitted after surgery and weight loss.

Hypertension (due to mineralocorticoid effects of excess cortisol and cortisol-mediated enhancement of vascular reactivity to vasoconstrictors) is frequently seen in patients with CS, with a prevalence of approximately 80% [15]. Our patient presented with controlled hypertension, which persisted after CD remission.

Non-alcoholic fatty liver disease and increased visceral adipose tissue are common in patients with CS. These features of metabolic syndrome, along with a hypercoagulable state leads to an increased cardiovascular risk that may not return to baseline after successful treatment [16].

Recently Obradovic and colleagues have unveiled that dexamethasone precipitates breast cancer metastasis (17). These results suggest not only that the widespread clinical use of GC is detrimental to patients with cancer, but also that chronic exposure to GC as seen in CD or high degree of social stress, have an unsuspected negative impact on disease outcome at least in some patients.

Concerning the relation between chronic exposure to GC in CD and papillary thyroid carcinoma, there are no published studies. The association between the two diseases is rare, with just 5 isolated cases described so far in the medical English written literature.

The first report by Ringel MD describes a patient with substernal metastatic thyroid carcinoma and hypopituitarism due to hypophysectomy for CD, emphasizing the importance of recombinant TSH for the PTC metastasis imaging on radioiodine scan [18].

Kageyama presented a case of subclinical CS, PTC and non-functioning adrenal tumor that had a polymorphism of the menin gene, unlikely to cause the association [19].

Kuo reported a metastatic PTC followed by CD in 2 yrs from diagnostic [20].

Wang reported a cyclical CS due to ectopic ACTH production from pulmonary carcinoma and bilateral nodular hyperplasia concurrent with PTC. This case harbored a novel mutation in PDE11A: c.2032 (exon 12) G > A, which is associated with primary pigmented nodular adreno-cortical disease (PPNAD) [21].

Mazeh reported a case of concurrent papillary, medullary, follicular thyroid carcinoma with adrenal Cushing's syndrome which was tested for RET mutations which were not found [22].

Tumoral corticotrophic cells of CD secrete increased interleukin 6 levels which could lead to increased proliferation of thyrocytes [23], however hypercortisolemia inhibits IL6 production. Invitti et all demonstrated a significantly higher prevalence of multinodular goiter in patients with CD, assuming that a growth factor stimulating both corticotroph and thyrocyte proliferation might be involved [24], but this was not confirmed by later studies

[25]. Immunosuppression due to hypercortisolemia could be a factor that triggers tumorigenesis and there are several other cases with CS associated with non-papillary type of thyroid carcinomas or other non-endocrine neoplasms [26].

In conclusion association between PTMC and CD is very rare and so far there is no known genetic mutation to link the two neoplastic conditions, and no clear relationship between neoplastic thyroid and hypercortisolemia has been established in the current endocrine literature.

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