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Follicular thyroid cancer associated with autoimmune polyglandular syndrome – A case report

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Abstract

Thyroid cancer is the most common malignancy of the endocrine system. We describe the clinical case of 53-years-old Caucasian woman with polyglandular autoimmune syndrome diagnosed subsequently with follicular thyroid carcinoma. The patient was diagnosed with type 1 diabetes mellitus in 1997 and Hashimoto thyroiditis in 2000. In 2019 cervical ultrasound highlighted a nodular goiter (left lobular node 29.9/19.9/32.3 mm and small thyroid isthmus nodule 4.5/5.1 mm). A fine needle puncture of the thyroid nodule was indicated but the patient did not perform the procedure. In 2020 a total thyroidectomy was performed. Histopathological examination revealed a micro-angio-invasive capsular follicular carcinoma with oxyphil cellularity on a background of chronic autoimmune thyroiditis. The association of the two endocrine conditions is controversial but increased insulin levels due to exogenous insulin administration were shown to stimulate (similar to insulin-like growth factor) the growth of follicular cells. In addition, chronic hyperglycemia exposure may be involved in the appearance of thyroid cancer by increasing oxidative stress and secondary to activation of the mitogenic pathway. This is the reason why we suggest the careful monitoring of thyroid function and morphology, especially in diabetic women.

Keywords: follicular thyroid carcinoma, diabetes mellitus, Hashimoto's thyroiditis.

Introduction

Thyroid cancer is the most common malignancy of the endocrine system. Thyroid cancer is categorized into four main subtypes: papillary thyroid carcinoma, follicular thyroid carcinoma (differentiated thyroid cancer), medullary thyroid carcinoma, and anaplastic thyroid carcinoma [1]. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer and its incidence is increasing [2]. Papillary thyroid carcinoma is the least aggressive type of cancer because it grows and metastasizes slowly and represents 70–80% of thyroid cancers. Follicular thyroid carcinoma is more aggressive than papillary thyroid carcinoma and represents 14% of thyroid cancers. Medullary thyroid carcinoma represents 3% of thyroid cancers and is often associated with multiple endocrine neoplasia while anaplastic thyroid carcinoma is the least frequent (2% of thyroid cancers) but the most aggressive form of thyroid cancer because it early metastasizes loco-regional and at distant sites [1]. Treatment of thyroid cancer varies depending on the type and stage of cancer and includes thyroidectomy with central neck lymph node dissection, radioactive iodine therapy, and molecular therapies with tyrosine inhibitors/chemotherapy [3].

The polyglandular autoimmune syndromes (PAS) are characterized by the coexistence of two or more endocrine autoimmune-mediated diseases in a single patient [4]. According to the

age of onset, characteristics of disease combinations and models of inheritance, two major subtypes of PAS have been described [5, 6]. Type I PAS usually manifests in infancy or in early adolescence and is defined by persistent mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (Addison disease). In the general population, type I PAS is a very uncommon disease with an incidence <1:100.000/year and the female to male ratio is 4/3 [6]. Type II PAS occurs mostly in adulthood (peak incidence during the third and fourth decades) and is diagnosed by two or more manifestations including Addison disease, autoimmune thyroid disease (Hashimoto's thyroiditis, **Graves' disease),** and type 1 diabetes mellitus (T1DM). Other manifestations of type II PAS are hypogonadism, hypophysitis, myasthenia gravis, celiac disease, serositis, and vitiligo. The incidence of type II PAS is 1–2:10.000/year and the female to male ratio is 3/1 [6, 7]. Treatment and management of type II PAS includes hormonal replacement therapy and evaluation of the risk for developing another organ-specific autoimmune disease [8].

Case report

A 53-year-old woman was admitted to the "N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest in December 2020 for clinical, metabolic, and endocrinological evaluation. The patient had a family history of thyroid carcinoma. At admission the patient was overweight (body mass index (BMI): 26.4 kg/m^2), with the good general condition, clinical examination highlighting the presence of areas of depigmented skin at the level on extremities (vitiligo), a postoperative scar in the anterior cervical region. The patient was diagnosed with the following conditions:

1. Primary amenorrhea treated with hormone replacement from the age of 16 years for 13 years;
2. Vitiligo;
3. T1DM diagnosed in 1997, treated with insulin in a basal-bolus regimen;
4. Hashimoto thyroiditis diagnosed in 2000 with euthyroidism (thyroid-stimulating hormone (TSH): 2.13 µU/ml, reference range: 0.55–4.78 µU/ml, free thyroxine (Free T4): 1.16 ng/dl, reference range: 0.89–1.76 ng/dl);
5. Type II PAS based on the association of T1DM and autoimmune thyroiditis;
6. Nodular goiter diagnosed in 2019 – the cervical ultrasound highlighted a left lobular node 29.9/19.9/32.3 mm and a small thyroid isthmus node 4.5/5.1 mm; fine needle puncture of the thyroid nodule has been recommended but the patient did not perform this procedure.
7. Dyslipidemia with statin treatment (atorvastatin) 20 mg QD;
8. Hypertension treated with angiotensin II receptor antagonist (candesartan 8 mg QD).

In February 2020, a total thyroidectomy has been performed for the nodular goiter. Histopathological examination revealed a micro-angio-invasive capsular follicular carcinoma with oxyphil cellularity on a background of chronic autoimmune thyroiditis. Levothyroxine 100 µg QD was recommended postoperatively. In July, the assessment of TSH and Free T4 indicated values within normal limits (TSH: 0.6 µU/ml and Free T4 16.9 ng/dl).

In September 2020, the patient discontinued treatment with levothyroxine and followed the hypo-iodate diet; in October 2020 after clinical and paraclinical evaluation, the patient was given radioactive iodine – 100 mCi I-131, well-tolerated without immediate or acute adverse effects. Prior to administration of radioactive iodine, the paraclinical evaluation highlighted TSH: 30.2 µU/ml, thyroglobulin: 1.49 ng/ml (reference range: 1.4–78 ng/ml), anti-thyroglobulin antibodies undetectable, *glycated hemoglobin* (HbA_{1c}): 9%. The anterior cervical ultrasound revealed post-thyroidectomy status, non-homogeneous thyroid lodges, right lodge with hypo-ecogenic thyroid rest 6.3/2.1 mm, bilateral latero-cervical poly-micro-adenopathy with fusiform appearance, most without Doppler signal inside.

A single-proton emission computerized tomography (SPECT) scan performed post-radioiodine therapy with I-131 revealed post-thyroidectomy status, intense iodine-uptake

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areas projected at the level of both thyroid lodges, more evident in the left lodge (iodo-fixing thyroid remnants). No other pathological-looking iodine-uptake images were observed in the rest of the body, accumulations of radioactive iodine on the physiological routes of elimination: salivary glands, nasal corneas, stomach, intestine, and bladder. Imaging of SPECT scan is shown in Figure 1.

At discharge it was recommended to limit radiation exposure for other people, resume treatment with Levothyroxine at a dose of 100 µg/day and determine TSH, free T4, thyroglobulin, and antibodies anti-thyroglobulin over two months. In December 2020 biochemical determinations have highlighted: TSH: 1.91 µU/ml, Free T4: 1.37 ng/dl, thyroglobulin: 0.08 ng/ml (reference range: <0.04 in patients without thyroid), antibodies anti-thyroglobulin undetectable, blood glucose: 183 mg/dl, HbA_{1c}: 9.21%.

Discussion

Information on the association between diabetes mellitus (particularly type 1 diabetes) and thyroid cancer risk is controversial. A prospective cohort of 200.566 women and 295.992 men aged between 50 years and 71 years were included in the National Institutes of Health American Association of Retired Persons (AARS) Diet and Health Study performed in the United States. Subjects completed a questionnaire regarding the relationship between lifestyle factors and cancer. The results showed that among diabetic women the risk of thyroid cancer was significantly increased but not among men. Authors mention that "*diabetic women with differentiated thyroid cancer were at somewhat higher risk of follicular thyroid cancer* (HR = 1.92; 95% CI: 0.86–4.27) *than papillary thyroid cancer* (HR = 1.25; 95% CI: 0.80–1.97)" and concluded that diabetes can increase the risk of differentiated thyroid cancer [9].

In another study, the prevalence of diabetes mellitus was evaluated by Paulus Y. M. et al. in 1313 patients with newly diagnosed papillary thyroid carcinoma. In this population, the prevalence of diabetes was 8% of which 92% had T2DM and 24% were treated with insulin. The study revealed an increased prevalence of diabetes in subjects with papillary thyroid cancer who were under the age of 44 years [10].

Several physio-pathological mechanisms have been proposed regarding the link between thyroid cancer and diabetes:

- Increased insulin levels due to exogenous insulin administration stimulates follicular cells

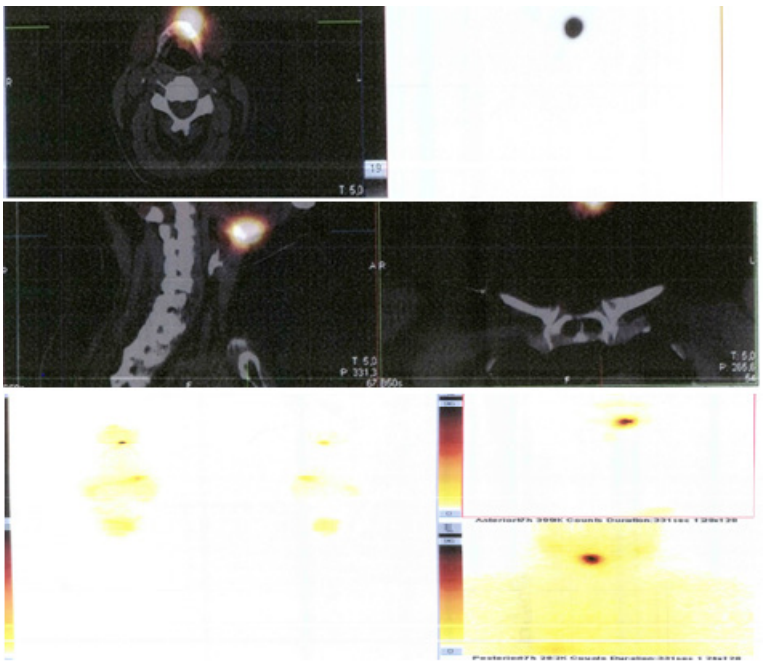

Figure 1: Imaging of SPECT scan.

due to insulin structural similarity to insulin-like growth factor (IGF-1). Follicular cells synthesize IGF-1 and have IGF-1 receptors [11] and IGF-1 has been involved in tumor transformation, invasion and metastasis as well as in tumor cell apoptosis [12].

- The relation between increased BMI and thyroid cancer is not completely elucidated. Shih SR and collaborators mention in a review published in 2012 that "*Some studies showed that BMI and TSH levels were positively correlated, but others did not. TSH and insulin influence the growth and differentiation of follicular cells. Adipokines such as adiponectin, leptin, and hepatocyte growth factor may regulate cancer cell proliferation and may be related to cancer progression*" [11].
- Chronic exposure to hyperglycemia and hypertriglyceridemia may be involved in the appearance of thyroid cancer by increasing oxidative stress. The increased levels of free fatty acids and glucose-stimulated nuclear factor-kB, which increases the production of nitric oxide, a substrate for reactive oxygen species. Increased reactive oxygen species is observed in cancer cells [13, 14].

In contrast, other studies have not highlighted an association between diabetes mellitus and thyroid cancer. In 2012, Tseng C. H. published a study on thyroid cancer risk in patients with diabetes. The study included 999.730 subjects; logistic regression estimated the odds ratio and their 95% confidence intervals for variables including age, sex, diabetes status, duration of the disease, anti-diabetic drugs, comorbidities, and examinations that might potentially lead to the diagnosis of thyroid cancer in various models. The results of the study revealed that "*There is a lack of an overall association between diabetes and thyroid cancer, but patients with diabetes duration <5 years have a significantly lower risk. Sulfonylurea may increase the risk of thyroid cancer*" [15]. Another analysis of five prospective studies reported no evidence of an association between a history of diabetes and thyroid cancer risk [16].

In 2011, Almquist M. and coworkers published in *Cancer Causes & Control* a prospective cohort study about the impact of metabolic factors (BMI, blood pressure, blood levels of glucose, cholesterol, triglycerides) on the risk of thyroid cancer. The study included 578.700 adults with a mean age of 44.0 years at baseline who have been followed up for a period of 12 years. During the follow-up, 133 men and 255 women were diagnosed with thyroid cancer. In women, the study revealed an inverse association between glucose and thyroid cancer risk and a positive association between BMI and thyroid cancer risk [17].

The association between thyroid cancer and chronic autoimmune thyroiditis remains unclear. The most frequent association is noted between Hashimoto's thyroiditis with papillary thyroid cancer while population-based studies using fine-needle aspiration biopsy data reported no linkage between the two endocrine conditions [18].

Conclusion

The association of thyroid cancer with PAS is controversial but increased insulin levels due to exogenous insulin administration in T1D stimulates follicular cells due to insulin structural similarity to insulin-like growth factor. In addition, chronic hyperglycemia exposure may be involved in the appearance of thyroid cancer by increasing oxidative stress and secondary to activation of the mitogenic pathway. This is the reason why we suggest the careful monitoring of thyroid function and morphology, especially in diabetic women.

Conflict of Interest

The authors declare no conflict of interest.

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