

CASE REPORT

THYROID ASSESSMENT AND PROSTATE CANCER - RELATED IATROGENIC ANDROGEN DEPRIVATION

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SUMMARY

Introduction: Androgen deprivation therapy in patients with prostate cancer improves the general prognosis but adverse effects like bone, metabolic anomalies, vasomotor symptoms are registered. Whether thyroid anomalies are among these it is still unclear. We present a male case diagnosed with prostate cancer and admitted for a thyroid mass and hyperthyroidism-like symptoms.

Case data: A 64-year male diagnosed with prostate carcinoma (based on biopsy) was treated with radiotherapy and injectable Gonadotropin Releasing Hormone analogues causing him hot flashes (thyreotoxicosis-like symptoms). Also, computed tomography detected a large thyroid nodule. An endocrine examination found clinical euthyroidism correlated with normal circulating levels of free levothyroxine. Ultrasound detected multiple nodules with a dominant one on the left lobe of 4.9 cm with a solid component (mixed echoic structure) and small cystic spaces insight with calcifications and right deviation of the trachea. Based on compression effects and suspected malignant behavior total thyroidectomy was performed. Pathological report revealed benign features: follicular adenoma underlying hyperplasia of the epithelial cells with interstitial hemorrhage, areas of colosteatoma, and sclerosis of the capsule; and reactive lymph nodes. Androgen deprivation was confirmed by low total serum testosterone and Follicle Stimulating Hormone and normochromic normocytic mild anaemia. Metabolic risk factors profile revealed obesity, arterial hypertension, hypercholesterolemia. Bone assessment found normal bone mineral density with low 25-hydroxyvitamin D.

Conclusions: The imagery profile necessary for cancer evaluation might incidentally discover a thyroid mass raising the suspicion of a second synchronous malignancy or a secondary site especially in large nodules with compressive effects or micro-calcifications or mixed structure at ultrasound. Menopause-like symptoms caused by iatrogenic hypogonadism may mimic hyperthyroidism both in males and females.

List of abbreviations: GnRH = Gonadotropin Releasing Hormone, ADT = androgen-deprivation therapy, DXA = Dual-Energy X-Ray Absorptiometry, BMD = Bone Mineral

RÉSUMÉ

L'évaluation de la thyroïde et le cancer de la prostate lié à la privation androgénique iatrogène

Introduction: L'hormonothérapie anti-androgénique chez les patients atteints de cancer de la prostate améliore le pronostic générale, mais des effets défavorables comme les anomalies osseuses, métaboliques, les symptômes vasomoteurs sont enregistrés. Si les anomalies thyroïdiennes se trouvent parmi ceux-ci, il n'est pas encore clair. Nous présentons le cas d'un homme diagnostiqué avec du cancer de la prostate qui a été hospitalisé pour un nodule thyroïdien et des symptômes d'hyperthyroïdisme.

Présentation de cas: Un homme de 64 ans diagnostiqué avec un cancer de la prostate (à base de la biopsie) a été traité par la radiothérapie et la libération des hormones analogues de la gonadotropine injectable lui causant des bouffées de chaleur (symptômes similaires à la thyrotoxicose). Également, la tomographie computerisée a détecté un grand nodule thyroïdien. Un examen du système endocrinien a trouvé de l'euthyroïdie clinique en corrélation avec les taux normaux de circulation de lévothyroxine libre. L'échographie a détecté plusieurs des nodules multiples avec un dominant le lobe gauche, de 4,9 cm avec un composant solide (structure échogène mixte) et de petits espaces kystiques aux calcifications et déviation à droite de la trachée. On a procédé à la thyroïdectomie totale en se basant sur les effets de compressifs et la suspicion d'un comportement malin. Le rapport pathologique a révélé des caractéristiques bénignes: adénome folliculaire soulignant l'hyperplasie des cellules épithéliales avec hémorragie interstitielle, zones de cholestéatome et la sclérose de la capsule; et les ganglions lymphatiques réactifs. La privation androgénique a été confirmée par une faible taux de testostérone sérique totale et l'hormone folliculo-stimulante et une légère anémie normochrome normocytaire. Le profil métaboliques des facteurs de risque ont montré l'obésité, l'hypertension artérielle, l'hypercholestérolémie. L'évaluation osseuse a trouvé une densité minérale osseuse normale avec l'hydroxyvitamine D faible.

Conclusions: Le profil imagistique nécessaires à l'évaluation du cancer pourraient découvrir incidentellement une tumeur de la

Density, 25-OHD = 25-hydroxyvitamin D, CT = Computed Tomography, cm = centimeter, TPO = antithyroperoxidase antibodies, TSH = Thyroid Stimulating Hormone, Free T4 = free levothyroxine

Key words: thyroid nodule, hypogonadism, gonadotropin releasing hormone, androgen deprivation, prostate cancer, thyroidectomy

thyroïde soupçonnant une seconde malignité synchrone ou un site secondaire surtout dans les grands nodules aux effets de compression ou de micro-calcifications ou à structure mixte à l'échographie. Les symptômes de la ménopause provoqués par l'hypogonadisme iatrogène peuvent imiter ceux de l'hyperthyroïdie.

Mots clefs: nodule thyroïdien, hypogonadisme, hormone de libération de la gonadotropine, privation androgénique, cancer de la prostate, thyroïdectomie

INTRODUCTION

The introduction of therapy with Gonadotropin Releasing Hormone (GnRH) analogues greatly improved the hormone dependent cancers like breast neoplasia (especially in pre-menopause) in women or prostate carcinoma in men. (1, 2) It is regarded as neoadjuvant treatment to chemotherapy, surgery, radiotherapy. (3, 4) A complete estrogen/testosterone production blockade is necessary to achieve a maximal response to otherwise standard therapy. (5) Androgen deprivation therapy (ADT) seems as effective as surgical castration but more adverse effects are found based on some observations (especially related to fragility fractures and cardiovascular diseases). (6, 7) ADT induces multiple anomalies as metabolic syndrome including high blood pressure, diabetes mellitus, hyperlipemia, obesity (for instance SIMBOPROST cohort), osteoporosis, menopause-like vasomotor symptoms, sexual dysfunction, anemia, high fat mass, low muscle mass and strength. (8, 9, 10, 11, 12, 13) In some cases, the testosterone deprivation and associated hot flushes or chronic asthenia and/or anemia might suggest a thyroid dysfunction and require supplementary endocrine assays although some studies pointed out that ADT might impair the adequate interpretation of thyroid tests. (14, 15) In a study of 64 patients treated for prostate cancer 2% of subjects associated mild hypothyroidism. (14)

We introduce a male case previously diagnosed with prostate cancer who presented with an incidental large thyroid nodule which raised the suspicion of a malignant behavior.

CASE REPORT

This is a case report presentation. Thyroid, metabolic and bone evaluation is described. Thyroid profile is based on ultrasound, autoimmunity (circulating antithyroperoxidase antibodies or TPO), and function assessment (Thyroid Stimulating Hormone or TSH). Metabolic complications were reflected by biochemistry tests (lipidogram, glucose profile) and cardiologic examination. Skeleton was evaluated performing central Dual-Energy X-Ray Absorptiometry (DXA, GE Lunar Prodigy device). Bone Mineral Density (BMD) is expressed based on DXA providing T-score. The vitamin D status is reflected using the blood 25-hydroxyvitamin D (25-OHD). The informed written consent was obtained by the patient.

Medical history

A 64-year old smoking male was diagnosed and later on treated for prostate cancer. His medical family history is negative. He is known with mild blood pressure since the age of 50 years. At first, a prostate nodule of 1.3 centimeter (cm) was discovered and confirmed at Magnetic Resonance Imagery exam. A prostate biopsy was performed and an adenocarcinoma was confirmed (associating extra-capsular invasion and a Gleason grading of 7). No surgery was done but local radiotherapy was applied and the patient was offered injectable GnRH analogue therapy. Prostatic antigen level of 4.68 ng/mL was normalized within 4 months. He started to accuse hot flashes with a variable pattern and frequency. A thyroid function assay was recommended. A computed tomography (CT) scan at the level of thorax, mediastinum, abdomen, and pelvis was performed to check the potential disease spreading. A left thyroid nodule of 4.5 by 3.5 cm was found with micro-calcifications and extension up to the level of superior mediastinum.

Endocrine panel

The subject was referred for a complete endocrine evaluation (at age of 65). He had no major complaints related to breathing problems, neither cervical constriction symptoms. Thyroid function and autoimmunity were tested. (Table 1) Clinical euthyroidism was correlated with normal circulating levels of freeT4 although a mild decrease of TSH was registered. (Table 1) Also, a mild increase of TPO was detected. Thyroid ultrasound showed: right thyroid lobe of 2.9 by 2.3 by 6.4 cm, with lightly hypo-echoic pattern and two nodules of 1.7 by 1.8 cm, respectively of 0.9 by 0.9 cm, isthmus of 0.9 cm with several hypo-echogenic small nodules of maximum 0.5 cm, a left thyroid nodule of 4.9 by 3.7 cm with a solid component (of both hypo and isoechoic structure) and small cystic spaces insight with calcifications. (Fig. 1) The large nodule descends posteriorly to sternum and causes a small trachea deviation to the right side. Neuroendocrine markers as calcitonin and chromogranin A were normal (serum chromogranin A of 66 ng/mL, normal limits between 20 and 125 ng/mL). (Table 1)

Androgen deprivation was confirmed by low total serum testosterone levels of 0.45 ng/mL (normal between 1.75 and 7.81 ng/mL), decreased Follicle Stimulating Hormone of 5.24 mUI/mL (consistent for a central hypogonadism mechanism) and associated normochromic

Table 1 - The endocrine parameters of a male patient previously diagnosed and treated for prostate cancer, currently presenting with a large thyroid nodule

Parameter	Patient's value	Normal limits	Units
Method of detection			
Thyroid stimulating hormone (TSH) Chemiluminescence	0.17	0.5 – 4.5	μ UI/mL
Free Levothyroxine (FreeT4) Chemiluminescence	12.73	9 – 19	pmol/L
Anti-thyroperoxidase antibodies (TPO) Chemiluminescence	43	0 – 35	UI/mL
Calcitonin Chemiluminescence	1	1 – 11.8	pg/mL

normocytic anaemia (based on haemoglobin levels of 12.4 g/dL (normal: 14-17%), and a hematocrit of 37.3% (normal: 41-53%).

Metabolic risk factors profile revealed obesity (body mass index of 30 kg/sqm), arterial hypertension (controlled under low doses of anti-hypotensors), hypercholesterolemia (total cholesterol level of 241 mg/dL, with normal ranges less than 200 mg/dL) and normal fasting glucose (of 92 mg/dL, with normal levels between 70 and 110 mg/dL). (Fig. 2)

Bone assessment was required noting the patient's age and induced hypogonadism. Vitamin D deficiency was found (25-OH D of 12.6 ng/mL, with optimal levels above 30 ng/mL. DXA results were within patient's age as following: lumbar DXA BMD was 1.297 g/sqcm, T-score = -0.6SD, T-score = -0.8SD, femoral neck BMD was 0.963 g/sqcm, T-score = -0.8SD, Z-score = 0.1SD), total hip BMD was 1.142 g/sqcm, T-score of 0.3 SD, Z-score of 0.7 SD.

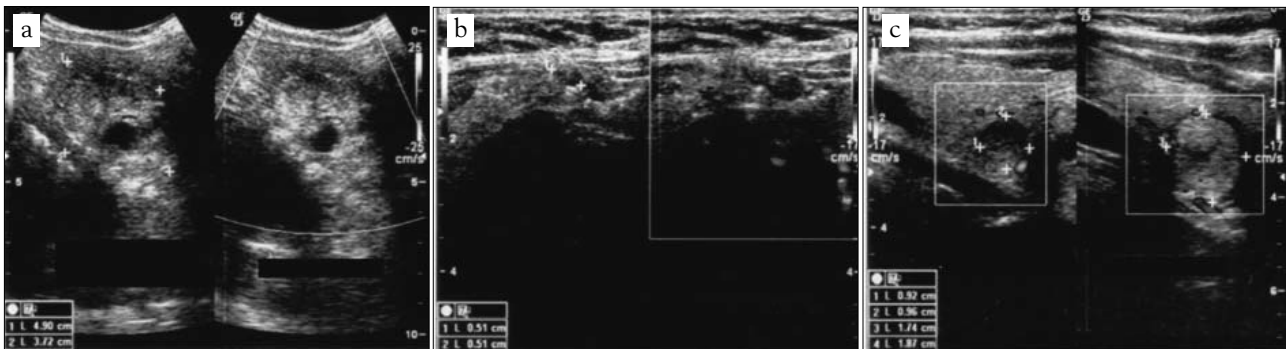


Figure 1 - Thyroid ultrasound on a 65-year old male patient with a prior diagnosis of prostate cancer
 a. Left thyroid lobe (longitudinal plane): a large nodule of 4.7 by 3.7 cm (conglomerate like lesion, with mixed structure: hypo and isoechoic); b. Isthmus of the thyroid gland (transversal plane): small nodules of 0.5 cm (hypoechoic and non-vascularised pattern); c. Right thyroid lobe (longitudinal plane): inhomogeneous font, two nodules of 0.9 by 0.9 cm, respectively of 1.7 by 1.8 cm (of hypoechoic, respectively isoechoic structure)

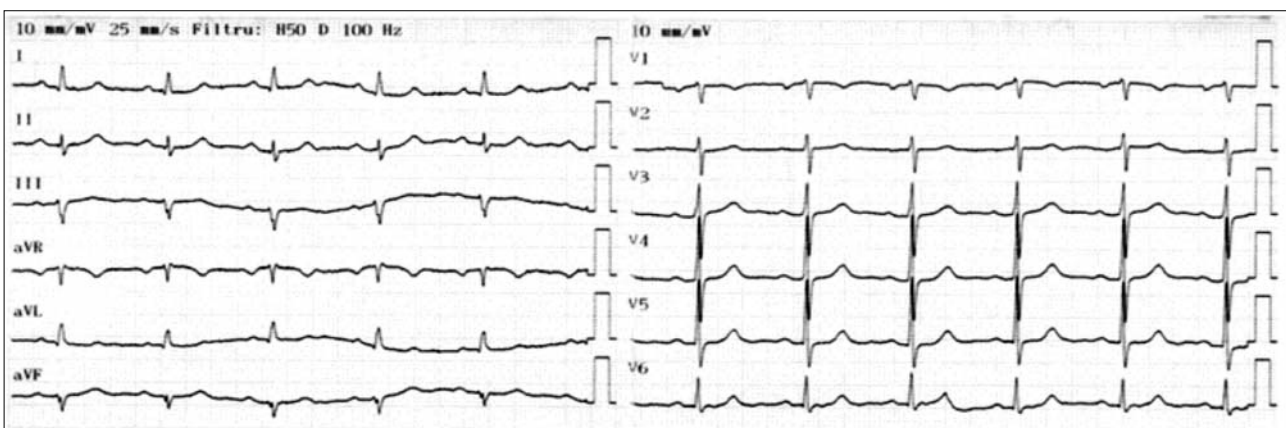


Figure 2 - Electrocardiography of a 65-year patient with androgen deprivation therapy for prostate cancer and nodular goiter: sinus rhythm of 71 beats per minute, QRS complex of 88 ms, mild left axial deviation

Management and follow-up

Considering the thyroid nodule's dimensions and associated effect on trachea surgery was considered. The large size and the presence of calcifications were suspected of a potential malignant feature. Total thyroidectomy was performed as well as local lymph nodes dissection. Histological findings were consistent with benign features: the large left lobe nodule was a follicular adenoma underlying hyperplasia of the epithelial cells with interstitial hemorrhage, areas of cholesteatoma, and sclerosis of the capsule; the other small nodules displayed adenomatosis and oxyphile areas; the lymph nodes were reactive. Therapy with levothyroxine daily was recommended to prevent iatrogenic hypothyroidism. Adequate levels of intact parathormon were found of 26.89 pg/mL with normal recommended ranges between 15 and 65 pg/mL but vitamin D and calcium supplements were offered to the patient because of prior 25-OHD levels. Cardiovascular medication will be continued to control cholesterol levels and arterial blood pressure. (Table 1) Thyroid function will be periodically tested (TSH, freeT4) as well as 25-OHD. Oncologic protocol for prostate cancer follow-up is necessary.

DISCUSSION

This is the case of a thyroid incidentaloma. Despite the general use of the term "incidentaloma" especially for adrenal and pituitary tumors a thyroid nodular mass in a previously diagnosed patient with a neoplasia may represent an accidental (incidental) finding. (16, 17) Most frequently, the imagery methods used to detect the thyroid anatomic anomalies in a cancer context are computed tomography or PET/CT (for instance, with 18F- fluorocholine). (18, 19) However, the most useful screening tool is thyroid ultrasound. (20, 21) Discrepancies between the thyroid nodules sizes between CT and echography might be seen, as in our case. (20, 21) The thyroid ultrasound, function, autoimmunity are recommended when a large thyroid nodule is found; calcitonin assay (which was normal in our case) is advisable in selected populations. (22, 23, 24) Fine needle aspiration has a great utility for lesions larger than 1 cm but in this particular case surgery was indicated anyway because of the thyroid nodule size on the left lobe. (25)

The differential diagnosis of thyroid mass includes metastasis from a prior cancer although thyroid is rarely involved as a secondary lesion; some reports refer to prostate or breast cancer and neuroendocrine tumors of different origins. (26, 27) This male case did not present any metastasis at diagnosis and during follow-up but the suspicion regarding the thyroid nodule (especially related to relatively high diameters and lack of suggestive medical history involving the thyroid) was presented. Thyroidectomy provided the pathological report and thus the confirmation of benign features.

The malignancy features which are highly suggestive before pathological report provided after thyroidectomy includes ultrasound characteristics (like size, shape, echogen

structure, margins of the nodule, micro-calcifications). (28) Overall, the thyroid echography represents the best method for current clinician to check up and follow-up thyroid nodules. Other methods as elastography or CT scan are not routinely recommended. (29) In our case, the scenario was quite the other way starting from CT examination into a general context of oncologic evaluation. A clinical clue for malign behavior is the presence of firm mass at clinical exam which was not relevant in this subject. (30)

This case presented normal central DXA exam with low levels of 25-OHD. New reports indicate some correlations between vitamin D deficiency and thyroid diseases but a well established cause-effect relationship is not clearly defined. (31, 32, 33)

The report of current case highlights the symptomatic androgen deficiency regarding well being and vasomotor flushes. (34) The patient's symptoms suggested a hyperthyroidism regardless the CT findings related to anatomic anomalies of the gland. Similar findings are described in vasomotor menopausal syndrome and carcinoid tumors, pheochromocytoma, etc. (35) On the other hand, hot flashes might bring the patient to a complete endocrine assay and incidentalomas may be found at different levels including thyroid. (36)

Overall, cost-efficiency studies showed that ADT brings a large economic burden related to adverse effects as metabolic or bone anomalies and careful risk-benefit evaluation is necessary on each patient. (37) Whether thyroid damage is included in this picture is still a matter of debate.

CONCLUSIONS

Androgen deprivation therapy, although beneficial for prostate cancer prognosis, may associate vasomotor symptoms which mimic hyperthyroidism in association with bone and metabolic disturbances as vitamin D deficiency, hypercholesterolemia, obesity, high blood pressure. The complete imagery profile in order to evaluate the neoplasia spreading might incidentally discover a thyroid mass raising the suspicion of a second synchronous malignancy or a secondary site especially in large nodules with compressive effects as seen on trachea or micro-calcifications at thyroid ultrasound.

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Conflict of interest: none

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