

## CHALLENGES OF THYROID CANCER MANAGEMENT IN AMIODARONE-TREATED PATIENTS: A CASE REPORT

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### Abstract

*Thyroid carcinoma (TC) is the most common endocrine malignancy. Although the overall prognosis for patients with TC is good, up to 20-30% of patients have recurrent or persistent disease after conventional therapy by surgical resection and radioactive iodine (RAI). Amiodarone is a highly efficient anti-arrhythmic drug with a very long half-life, so it may interfere with RAI many months after the drug withdrawal. This case report mirrors the challenges of thyroid cancer management in an amiodarone-treated patient.*

**Keywords:** thyroid cancer, amiodarone, lymph nodes dissection, radioiodine

### Introduction

Thyroid carcinoma (TC) is the most common endocrine malignancy, with a rapidly rising incidence in recent years worldwide [1,2]. Thyroid malignancies mainly include four histological subtypes: papillary thyroid carcinoma (PTC), which is the most common TC subtype, and follicular thyroid carcinoma (FTC), which are summarized as differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma (MTC) and anaplastic thyroid carcinoma (ATC). Most of DTC have an excellent prognosis with a 5-year relative survival rate of 98% in localized disease [3]. Generally, DTC can be effectively managed by total thyroidectomy, ablative doses of radioiodine (RAI) and suppressive treatment. The follow-up is based on measuring serum thyroglobulin (TG) levels as a biomarker and imaging with radioiodine (RAI) therapeutic scans.

It has been estimated that about 20% of patients with PTC will present local or distant persistent or recurrent disease. In 75% of cases, the disease is located in the neck, most often in the lymph nodes. In 25% of cases, it is represented by distant metastases that can occur in the lungs

(50%), bones (25%), lungs and bones (20%) or other sites (5%) [4]. Loco-regional persistence/recurrence is generally treated with further surgery, RAI, and, occasionally, external beam radiation therapy. Complete biochemical remission has been reported in 25–75% of patients with recurrent disease in lymph nodes, but recurrences in the thyroid bed are often associated with a poorer prognosis [5]. Although, the majority of patients are being cured with standard therapy, older patients with metastatic disease at presentation, particularly if the disease is RAI-refractory, have poor prognosis [3], as do patients with anaplastic TC.

Amiodarone is a widely used drug for the prophylaxis and treatment of cardiac arrhythmias. Around 18% of patients treated with this drug develop thyroid dysfunction [6]. Most of the effects of amiodarone on thyroid function are thought to be due to the iodine load that is related to drug intake [7]. Every 200 mg dose of amiodarone contains 75 mg of organic iodine, an amount that exceeds the minimal daily needs of iodine. Moreover, it has a very long half-life of approximately 100 days, because it accumulates in the adipose tissue [8]. Consequently, effects associated to iodine load due to amiodarone ingestion may persist long after treatment discontinuation.

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### Case report

A 65 year-old man was admitted to the Endocrinology department of a tertiary academic medical center in October 2013 for the investigation of a left lobe thyroid macro-nodule that was accidentally discovered during a carotid Doppler ultrasonography exam. The patient's past medical history includes type 2 diabetes chronically treated with oral anti-diabetic drugs, therapeutically controlled hypertension, extrasystolic arrhythmia and a recent history of two syncopal episodes. In the past 2 years, the patient also received amiodarone, one tablet of 200 mg/d. He had no radiation exposure and his family history was negative for thyroid and neoplastic diseases. He did not consume alcohol and he had never smoked.

On physical examination, his blood pressure was 130/80 mmHg, with a heart rate of 82 beats/minute. Cardiac examination revealed extrasystolic arrhythmia and right bundle branch block; neurological examination established cardiogenic syncope and diabetic polyneuropathy. Physical exam was significant for a left-sided thyroid macro-nodule, of woody consistency, without spontaneous tenderness and on palpation measuring approximately 3cm. Thyroid ultrasound showed an asymmetric, isoechoic, homogeneous thyroid gland of normal volume. To the upper pole of the left lobe two, confluent solid nodular formations, of 4.22 ml (30.8/15.8/16.7 mm) were identified, which were described as hypo-echoic, confluent, inhomogeneous, vascularized and without halo.

Thyroid function tests revealed normal thyroid function, as shown by a basal TSH level of 2.84  $\mu$ IU/mL and a FT<sub>4</sub> concentration of 16.1 pmol/L with normal anti-thyroid peroxidase antibody (13 UI/mL) and anti-thyroglobulin antibody (16 UI/mL) titers and normal calcitoninemia, of 4.84 pg/mL. Radioisotope thyroid scan evidenced lack of <sup>99m</sup>Tc uptake on the left lobe ("cold" macro-nodule). Subsequently, the percutaneous fine needle aspiration (FNA) was performed and the result indicated category V in the Bethesda System for Reporting Thyroid Cytopathology, *i.e.* positive for malignant cells.

The patient was referred to the Surgery department and in December 2013 he underwent total thyroidectomy. The histopathology test revealed well-differentiated papillary cancer of the left lobe with thyroid capsule and peri- thyroidal lymph nodes invasion, T<sub>3</sub>N<sub>1a</sub>M<sub>x</sub>. Four weeks after thyroidectomy, the patient was referred to the Nuclear Medicine department and underwent adjuvant radioiodine therapy with 90.65 mCi of radioactive iodine (<sup>131</sup>I). The 72-hours <sup>131</sup>I-whole body scan (WBS) failed to indicate uptake, which was in discordance to high thyroglobulin (Tg) levels of 927.4 ng/mL (normal < 0.1 ng/ml in cured TC), low titers of anti-Tg antibodies of 26 IU/ml (normal  $\leq$ 115 IU/mL), high basal TSH of 72.8 mIU/L (normal 0.27-4.2 mIU/L) and presence of lateral cervical lymph nodes of below 10 mm diameter, which were noted at ultrasound examination performed by the endocrinologist. The

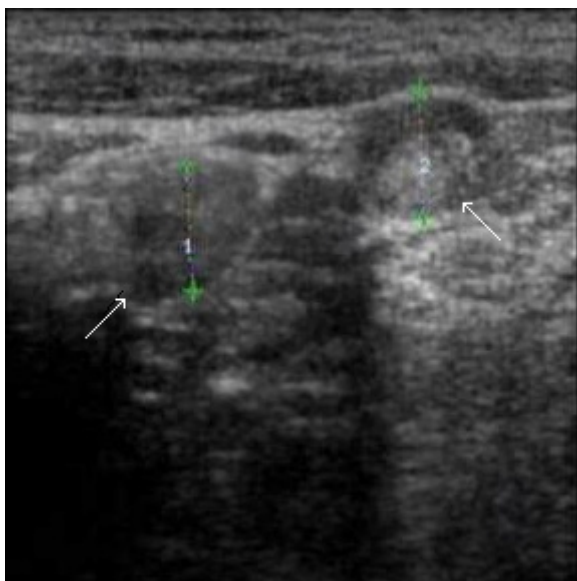
patient started hormone suppression therapy with 150 $\mu$ g levothyroxine daily, to maintain the TSH level  $\leq$ 0.1 mIU/L and FT<sub>4</sub> within normal limits.

In view of prior use of amiodarone for the past 2 years, which was interrupted 6 weeks before RAI therapy and negative WBS, in March 2014 the patient was evaluated for serum amiodarone concentration, which was <0.01 mg/L but associated with high serum (192  $\mu$ g/L, normal 46-70  $\mu$ g/L) and urinary iodine (782  $\mu$ g/L, normal 20-299  $\mu$ g/L) levels, which indicated excessive iodine body load. According to the patients' medical records, the Tg level decreased to 393.3 ng/mL. Thyroid and neck ultrasound were performed and pathological cervical and supraclavicular lymph nodes of below 13 mm diameter were described. Thorax computer-tomography (CT) scan was negative, and the patient was referred to Fluor-18FDG positron emission computer tomography (PET-CT) scan, which exclusively confirmed left latero-cervical and supraclavicular lymphadenopathy (Figure 1) as indicated by neck ultrasonography, and no distant metastases.



**Figure 1.** F18-FDG-PET-CT showing high glucose uptake in the neck, suggesting tumor persistence/recurrence.

At 6-months follow-up, at reevaluation in the Nuclear Medicine department, in July 2014, serum Tg increased to 863 ng/mL and therefore, the patient received an additional dose of 76.4 mCi  $^{131}\text{I}$  radioiodine and thyroid hormone suppressive dose was increased to 200  $\mu\text{g/d}$  L-thyroxin to maintain full suppression. The post-therapeutic WBS showed RAI uptake in the neck. In October 2014 the Tg level was still elevated at 1105 ng/mL, so the patient was treated with another completion dose of 118.8 mCi  $^{131}\text{I}$ , followed in March 2015 by another dose of 100 mCi  $^{131}\text{I}$ , at a Tg level of 766 ng/mL. Pathological lymph node uptake was confirmed at WBS and no uptake in the thyroid bed or distant secondary disease was evidenced. Neck ultrasonography (Figure 2) confirmed multiple left latero-cervical and supraclavicular round, hypo-echoic, intensely, vascularized lymph adenopathies with increased stiffness at thyroid elastography and with a diameter of up to 18 mm. In view of lack of adequate response of the disease to radioiodine treatment, and no organic metastases, the patient was proposed for therapeutic lymph node dissection.



**Figure 2.** Neck ultrasonography showing left latero-cervical hypo-echoic, lymph adenopathies with a diameter of up to 18 mm.

### Discussion

Amiodarone is a widely used, highly efficient anti-arrhythmic drug; however, treatment puts the patient at risk for a broad thyroid pathology, either hypothyroidism or thyrotoxicosis and, possibly, thyroid malignancy [9,10]. Complex mechanisms are involved in amiodarone-induced thyroid disorders such as autoimmunity, inflammation and unveiling of latent hyperthyroidism by excessive iodine intake [11,12]. Amiodarone therapy was motivated by cardiac disease in our patient, which developed no thyroid dysfunction, and was stopped at the moment the suspicion for thyroid malignancy was set.

In recent years, several case reports raised the possibility of an association between amiodarone and cancer [13,14]. To be mentioned that in rats exposed to amiodarone, the prevalence of TC is increased [15]. In the first large population-based cohort study in that the overall malignancy risk was evaluated in 6418 patients treated with amiodarone, Su et al. [16] demonstrated a higher risk of total malignancies in patients, particularly males, treated with amiodarone in comparison to the general population. Amiodarone and cancer occurrence were associated in a dose-dependent manner. The use of amiodarone was not found to be associated with TC, but the case number was too small to draw a definite conclusion.

Previous case reports [17,18] of cancers developing after regular amiodarone use, for a period of 2 to 5 years suggest that a latency period and high cumulative doses might be prerequisites for the development of amiodarone-associated malignancies.

In high amounts, iodine saturates the thyroid gland, blocking further absorption of both non-radioactive and radioactive iodine, thus, a 1-3 weeks low-iodine diet time interval is recommended in TC patients prior to radioactive iodine treatment [19]. As in the presented case, iodine uptake blockade is prolonged for several months after high iodine exposure by amiodarone intake and may explain lack of RAI image on WBS in our patient in spite of biochemical and ultrasonography data. Approximately 6 months after discontinuing amiodarone (as demonstrated by the low serum drug levels), both the serum and urinary iodine concentrations were still elevated.

Although in most thyroid cancer patients treated conventionally by surgery with or without RAI, a good disease control is achieved, up to 20-30% may present persistent disease or develop recurrences [3]. Prognosis of thyroid cancer may largely vary with the histological type with a 10-year mortality rate of 5-10% for papillary TC and 15-20% for follicular TC, whereas the one-year mortality rate for anaplastic TC approaches 100% [20].

Papillary TC is more frequent in women (3:1), but mortality rates are two times higher among men than women. Age at diagnosis is a critical predictor of patient outcome as patients aged > 60 years commonly present with more aggressive disease, meaning a higher prevalence of lymph nodes and distant metastases, and have an increased mortality rate compared to younger patients (31% vs. 1.2%) [21]. Moreover, differentiated TC in older patients is less iodine-avid [22].

Lymph node involvement is very common in patients with papillary and follicular TC, ranging from 20 to 90% during primary surgery, nonetheless the prognostic significance of lymph node metastasis remains controversial. Still, the recently published SEER (Surveillance, Epidemiology and End Results Program) National Cancer Institute data, assessing patient outcomes, have shown that lymphatic metastases are a poor prognostic

indicator in older (>45 years) PTC patients [23].

Routine or prophylactic lymphadenectomy is defined as the removal of lymph nodes in the absence of lymph node metastasis evidenced by preoperative imaging studies or intraoperative inspection. While elective or therapeutic lymphadenectomy involves the removal of regional lymph nodes which are detected pre- or intra-operatively and are suspected to harbor metastases, routine or prophylactic neck dissection defines the removal of lymph nodes in the absence of lymph node metastasis evidenced by preoperative imaging studies or intraoperative inspection.

Removal of involved lymph nodes has not been systematically demonstrated to reduce local recurrence or to improve long-term survival [24] and central lymph nodes dissection (CLND) is recommended according to recent American Thyroid Association (ATA) guidelines to papillary TC patients with advanced disease [19]. Patients with smaller tumors may be treated by thyroidectomy alone. The European Thyroid Cancer Task Force indicates prophylactic CLND in patients with preoperatively suspected and/or intra-operatively proven lymph node metastases [25]. The term central compartment dissection describes removal of lymph nodes and soft tissues in level VI with preservation of the recurrent laryngeal nerves and at least the superior parathyroid glands. The term lateral compartment dissection refers to removal of all soft tissues and lymph nodes in levels IIA, III, IV and V. Drawbacks associated with the routine performance of CLND are an increased rate of morbidity, particularly permanent hypoparathyroidism [26].

In the present clinical case, therapeutic lymph node dissection is clearly recommended by persistent lymph node metastases with a diameter of  $\geq 10$  mm, in spite of repeated RAI therapy and the patients' age. Usually, patients with small lymph node metastases undergo  $^{131}\text{I}$  treatment, but abnormalities can still persist after two or three treatment courses. In addition, recurrent disease can develop after incomplete surgical resection of neoplastic tumors [26], and is not always prevented by postoperative radioiodine treatment [27]. In such cases, surgery should be considered. Treatment of disease that is limited to the neck can include extensive surgery and external beam radiotherapy [28]. However, patients over 40 years of age who have poorly differentiated tumors, no RAI uptake, a large tumor burden, rapidly progressive disease, soft tissue involvement, and high  $^{18}\text{F}$ -FDG uptake do not normally gain disease-free status after treatment of recurrent neck disease. Moreover, distant metastases are frequently detected in these patients during the subsequent follow-up period.

The most common early side effects of RAI treatment include radiation thyroiditis, neck pain and swelling, larynx edema, which may cause compressive symptoms, sialadenitis, and gastritis. Cumulative doses of RAI are associated with lacrimal and salivary gland dysfunction, pulmonary fibrosis, cancer, and leukemia.

These effects are dose-dependent and increase with cumulative activity. Over the last decade, a greater risk for secondary malignancies (leukemia and solid tumors) after high cumulative therapeutic activities (600 MCi, 22GBq) has been reported [29] but there is no international consensus on limiting the RAI dose to 600 mCi. In fact, the use of RAI should be individualized to balance the risks against therapeutic benefit.

Nearly all patients with distant metastases have high serum Tg concentrations and two-thirds of these patients have  $^{131}\text{I}$  uptake in the metastases [30]. Despite this, several series have demonstrated that patients with detectable serum Tg levels may have a negative whole-body scan [31]. Dealing with these patients is a real challenge. The first negative  $^{131}\text{I}$  WBS of our patient, despite increased Tg levels, could be explained, by the interference with the amiodarone treatment. Nevertheless, Tg was significantly lower at the 3 months post-RAI treatment evaluation. Occasionally, it is important to exclude false positive Tg levels and the presence of thyroid tissue that decreases the sensitivity to detect metastatic disease.

The most common cause of a negative iodine scan is tumor de-differentiation, which refers to a tumor, which fails to take up  $^{131}\text{I}$  and is therefore considered RAI-refractory. Many of these patients also have normal conventional imaging investigations (CT, MRI, neck ultrasonography). In these cases,  $^{18}\text{F}$ -FDG-PET/CT became a useful imaging study as it provides anatomical and prognostic information as patients with differentiated TC with evidence of RAI-refractory disease usually have higher glucose metabolism and positive FDG-PET scans [32]. Metastases may be observed on the post-therapeutic iodine scan [33] in patients with negative diagnostic WBS. In such patients, the higher dose of RAI has contributed to the detection of metastatic disease. RAI may still be of some advantage [34], however a therapeutic effect is not guaranteed and additional therapeutic methods should be considered. In the presented patient surgery was indicated in the view large lymph nodes and disease localized in the neck. Those patients with no uptake even with higher-dose RAI have true RAI refractory disease [35], requiring subsequent therapy and a more aggressive approach. For such patients, conventional chemotherapy with doxorubicin yields low response rates of short duration, is often associated with considerable toxicity, and does not prolong survival. In-progress trials investigating novel targeted molecular therapies open new perspectives in RAI-refractory TC.

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