Case History

Amiodarone-Induced Hyperthyroidism in a Patient with Functioning Papillary Carcinoma of the Thyroid and Extensive Hepatic Metastases

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Thyroid hormone producing thyroid carcinoma is an uncommon cause of thyrotoxicosis. A patient with extensive hepatic metastases from well-differentiated carcinoma is presented. Administration of amiodarone for atrial fibrillation led to the development of hyperthyroidism. Precipitation of thyrotoxicosis by iodine-containing compounds in patients with thyroid carcinoma is rare. The relatively high iodine load and the slow elimination of amiodarone complicate the clinical management of such patients.

Introduction

THYROTOXICOSIS IN PATIENTS with thyroid cancer is uncommon. It may be the result of a variety of causes, especially excess thyroid hormone intake. Occasionally, well-differentiated thyroid carcinoma may produce thyroid hormone in response to a variety of stimuli, including antithyroidal antibodies or iodine. We describe a patient with extensive hepatic metastases who became thyrotoxic while receiving amiodarone therapy for atrial fibrillation.

Case Report

A 77-year-old man with a history of valvular and atherosclerotic heart disease presented with a right-sided thyroid mass for which he underwent a right thyroid lobectomy and partial left thyroid lobectomy. Histopathology revealed well-differentiated papillary cancer with follicular elements. The tumor was 6 cm in maximum dimension. There was capsular invasion but no evidence of nodal or other extrathyroidal involvement or distant spread. The MACIS (metastasis, age, completeness of resection, invasion, and size) score was 8.56 (1). Approximately 6 weeks postthyroidectomy, the patient underwent ablation of the thyroid remnant with 30 mCi of radioactive iodine (^{131}I). Posttherapy images showed uptake in the thyroid bed, more prominent on the left than the right. Follow-up ^{131}I scanning 3 months later showed residual radioactive iodine uptake in the neck and right upper quadrant of the abdomen. He was treated with 175 mCi of ^{131}I. Four months later, a left-sided neck mass was discovered. The patient underwent resection of residual thyroid tissue

and dissection of left jugular lymph nodes. Histopathology demonstrated postoperative and postradiation changes but no residual neoplasia. However, the thyroglobulin level was elevated at 420 ng/mL (normal, < 60 ng/mL). A whole-body ^{131}I scan 6 weeks postoperatively again demonstrated abnormal uptake in the neck and right upper quadrant of the abdomen. The patient received an additional 175 mCi ^{131}I for the residual uptake.

During the subsequent 3 years, the patient received 150 μg thyroxine daily. Two ^{131}I whole-body scans were reported to show no abnormal uptake in that period. The thyroglobulin rose to 2100 ng/mL. He was then referred to the University of Michigan. ^{131}I scintigraphy showed irregular mottled liver uptake suspicious for liver metastases (Fig. 1). Ultrasound-guided needle biopsy showed well-differentiated thyroid carcinoma within the liver. The patient was treated with 250 mCi ^{131}I. Two months later the thyroglobulin level was stable, measuring 2110 ng/mL with the patient taking 150 μg thyroxine. He remained relatively asymptomatic for the next 18 months, treated cautiously with 175 μg thyroxine to suppress thyrotropin (TSH) to barely detectable levels without aggravating his known coronary and valvular heart disease. The thyroglobulin level rose to 47,200 ng/mL. CT scan showed numerous hypervascular masses in the liver (Fig. 2). An FDG PET scan demonstrated increased uptake within the hepatic lesions. He remained asymptomatic from thyroid carcinoma. Two years later, the thyroglobulin rose further to 64,200 ng/ml while the patient was taking 175 mcg thyroxine daily. During a hospitalization elsewhere computed tomography (CT) scanning again
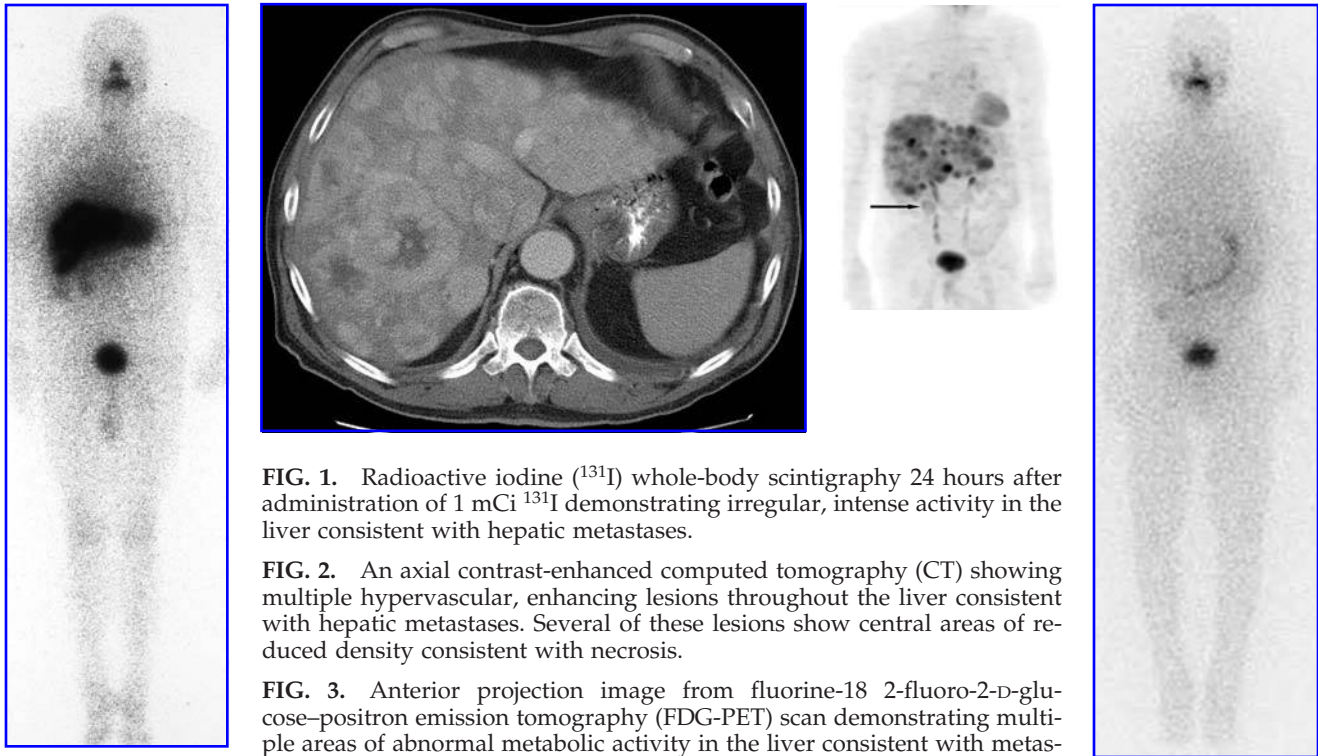
FIG. 1. Radioactive iodine (^{131}I) whole-body scintigraphy 24 hours after administration of 1 mCi ^{131}I demonstrating irregular, intense activity in the liver consistent with hepatic metastases.

FIG. 2. An axial contrast-enhanced computed tomography (CT) showing multiple hypervascular, enhancing lesions throughout the liver consistent with hepatic metastases. Several of these lesions show central areas of reduced density consistent with necrosis.

FIG. 3. Anterior projection image from fluorine-18 2-fluoro-2-D-glucose–positron emission tomography (FDG-PET) scan demonstrating multiple areas of abnormal metabolic activity in the liver consistent with metastases. Note also the abnormal activity in the mid-right abdomen (arrow).

FIG. 4. ^{123}I whole-body scintigraphy with 5 mCi ^{123}I performed about 3 weeks after cessation of amiodarone showed no radioactive iodine concentrating metastatic disease. Lack of uptake was attributed to amiodarone-related iodine overload.

showed multiple hepatic metastases and a new lesion initially thought to arise from the pancreas. Biopsy of this mass was initially interpreted as follicular carcinoma and later revised to well-differentiated thyroid carcinoma. The patient returned to the University of Michigan for follow-up of thyroid cancer.

The patient appeared cachetic but had no specific complaints. His weight had decreased from 164 to 127 pounds over the preceding 12 months. Medications included thyroxine, which had been decreased to 50 μg per day. Pulse rate was 88 beats per minute. There was a prominent systolic ejection murmur radiating to the carotid arteries. The liver was enlarged, measuring approximately 15 cm in length in the midclavicular line. There was marked lower extremity edema. At this point it was unclear whether his deteriorating status was the result of congestive heart failure, progressive tumor burden, or another etiology. A fluorine-18 2-fluoro-2-D-glucose–positron emission tomography (FDG-PET) scan was obtained to evaluate the extent of thyroid carcinoma and to search for other malignancies. FDG-PET scanning showed multiple areas of abnormal activity within the liver and an irregular, focal concentration in the right abdomen (Fig. 3), corresponding to the previously described mass. CT also showed multiple small pulmonary nodules consistent with metastases.

Because of his comorbidities, Thyrogen-stimulated thyroid cancer scanning was performed to determine whether the new mass concentrated radioiodine and could be treated

with ^{131}I. ^{123}I scintigraphy after human thyrotropin (hTSH) stimulation showed no focal abnormal areas of uptake within the liver or within other sites of known thyroid cancer metastases (Fig. 4). At this time the free thyroxine (T$_4$) had risen to 3.56 ng/dL (normal, 0.73–1.79 ng/dL). TSH remained suppressed (< 0.01 μU/mL). The patient and his daughter denied thyroid hormone ingestion other than the prescribed 0.50 mg daily, and the possibility of autoimmune induced hyperfunction of thyroid metastases was raised. Thyroid-stimulating immunoglobulins (TSI) were less than 1 (negative if ≤ 1.3). Careful review of the patient's medication with his daughter showed that he had had amiodarone prescribed several months previously for an episode of atrial fibrillation; the amiodarone had been stopped 3 weeks prior to evaluation. Thyroid hormone was stopped and the patient was treated with methimazole. One week later the free T$_4$ declined to 2.99 ng/dL. The hyperthyroidism was thus attributed to endogenous thyroid hormone production by the well-differentiated hepatic metastases in response to the iodine load from amiodarone. The patient was referred for chemotherapy but declined. Four-month follow-up showed that the patient had gained 6 pounds and his thyroid hormone had been restarted at 0.1 mg daily. The patient's free T$_4$ level fell to be below normal limits (0.4 ng/dL) despite the presence of progressive metastatic disease. The patient died about 6 months later from congestive heart failure. Laboratory values and the clinical course are summarized in Table 1 and Figure 5.

TABLE 1. SUMMARY OF THE THYROXINE DOSE, THYROGLOBULIN, THYROID-STIMULATING HORMONE,
AND FREE THYROXINE LEVELS OVER THE COURSE OF THE PATIENT'S TREATMENT

Date/ diagnosis	Thyroxine dose (μg)	Tg (ng/mL)	TSH (mlu/L)	FT_4 (ng/dL)	Weight (lbs)	Comment
1 month	0	200	2.4	0.7		Right lobectomy and partial left lobectomy
5 months	125	420	16.2	0.5		Microsomal and thyroglobulin antibodies absent; 30 mCi [131]I
9 months	125	120	4.1	1.6		5 mCi ^{131}I scan: large focus uptake left thyroid lobe; treatment with 175 mCi [131]I
1 year	125	420				Tg antibodies absent
2 years	125	1100	0	1.9		5 mCi ^{131}I scan: uptake right neck and RUQ; Left lobectomy followed by 175 mCi [131]I
4 years	150					5 mCi ^{131}I scan: no uptake in neck
5 years	150	2100	0.12	1.4	201	3 mCi ^{131}I scan: no uptake in neck
6 years	175	2080	0.01	1.65	199	4 mCi ^{131}I scan: liver metastases; treated with 250 mCi [131]I
7 years	125	47200	0.01	0.76	171	Clinically doing well
8 years	125	38100	0.01	0.05	164	Clinically doing well
8 years, 10 months	125					CT and PET scanning showed liver and lung metastases Amiodarone begun for supraventricular tachycardia
9 years, 4 months	0	64200	< 0.01	2.99	127	Amiodarone stopped; 5 mCi ^{123}I scan: no uptake in liver or other metastases
9 years, 8 months	100				133	Died 6 weeks later from complications of metastases

T_4, thyroxine; Thyroxine dose = Prescribed daily dose of thyroxine (μg); TG = thyroglobulin (ng/mL); TSH = thyroid stimulating hormone (normal 0.3–5.5 mlu/L); FT_4, = free thyroxine (normal 0.73–1.79 ng/dL); CT, computed tomography; PET, positron emission tomography

Discussion

Thyroid carcinoma rarely produces clinically substantial amounts of thyroid hormone, and thyrotoxicosis due to functioning thyroid carcinoma metastases is uncommon. In a review of the literature in 1990, Paul and Sisson (2) found only 48 cases of hyperthyroidism associated with well-differentiated thyroid carcinoma. In most cases in which thyroid carcinoma and thyrotoxicosis coexist, thyrotoxicosis is usually caused by Grave's disease with the thyroid carcinoma being an incidental finding (3). In the patient described, there was no detectable radioiodine uptake by the thyroid metastases at the time the patient was hyperthyroid, although iodine-avid metastases in the liver had been previously documented. The absence of radioactive iodine uptake was due to the high iodine load from amiodarone. Thus the hepatic metastases were almost certainly the source of the excess T_4 given the absence of residual normal thyroid tissue after surgery and multiple ^{131}I therapies.

Thyrotoxicosis in patients with metastatic thyroid carcinoma usually results from a large bulk of tumor functioning either autonomously, or in a patient with coexisting Grave's disease caused by stimulation of TSH receptors on the metastatic cells by TSI (4,5). The latter mechanism may occur in more than half of cases with functioning metastases (2). We were able to identify only one other reported case in which excess iodine was a precipitating factor; in that patient the excess iodine was due to iodinated radiographic contrast (6).

Exposure to increased quantities of iodine may induce hyperthyroidism in a patient who was previously euthyroid (Jod-Basedow phenomenon). This usually occurs in areas of endemic iodine deficiency, mainly in patients with nontoxic multinodular goiter. It may be associated with low radioiodine uptakes (7). Iodine-associated thyrotoxicosis in functioning thyroid metastases is a potentially fatal complication in patients with thyroid carcinoma who may have an abrupt increase in circulating thyroid hormone levels after ingestion of iodine-containing medications (6).

The treatment of amiodarone-induced hyperthyroidism includes the cessation of amiodarone if possible. Because of tissue storage of the amiodarone and its metabolites, and its slow release, thyrotoxicosis may persist for several months after cessation of the drug (8). Methimazole with potassium perchlorate has been advocated as the treatment of choice for most patients with amiodarone-induced thyrotoxicosis,
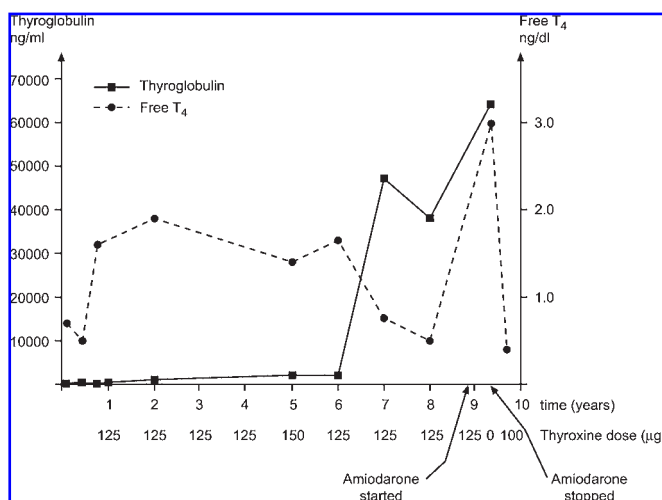

FIG. 5. Graphical description of thyroglobulin and free thyroxine (T_4) values over the clinical course with reference to prescribed T_4 doses.

and β-adrenergic antagonists may also be useful unless contraindicated. In patients with functioning thyroid carcinoma metastases, antithyroid drugs given alone may be useful in providing temporary control of the thyrotoxicosis, but ideally therapy should allow simultaneous treatment of the underlying malignancy and the thyrotoxicosis (3,9).

^{131}I has the potential to result in both improvement in the thyrotoxicosis and reduction of the thyroid carcinoma tumor bulk (10,11). Treatment of functioning thyroid carcinoma metastases with radioiodine requires consideration of several specific issues. Firstly, usual thyroid cancer therapy doses of ^{131}I may be deleterious if administered to patients with functioning metastases. Patients with functioning bulky metastases may secrete high amounts of radiothyroxine. This persists in the circulation with a half-life of 3–4 days, resulting in higher than usual radiation of normal tissues. Standard dosing of radioiodine assumes a low radioiodine uptake (often less than 1% of administered activity) by metastatic tissue. This is often not the case in patients with functioning tumor, which often accumulates considerably more ^{131}I (11). Although significant acute toxicity and bone marrow suppression are very uncommon after "routine" radioiodine therapy, patients with a large tumor burden and elevated serum T_4 levels are at higher risk for toxicity, with the potential for development of bone marrow suppression and radiation pneumonitis. Because of the prolonged retention of ^{131}I, dosimetry is recommended. (11). Body retention of ^{131}I should be measured and it has been suggested that if the patient is hyperthyroid, the maximum permissible dose should be reduced to 50%, because of the formation of circulating radiothyroxine, which has a longer biological half-life than radioiodine. When determining the therapy, careful consideration also needs to be paid to the general health of the patient, the extent of the tumor and the patient's tolerance of hyperthyroxinemia (12).

^{131}I therapy in patients with well-differentiated thyroid carcinoma producing thyroid hormone could exacerbate thyrotoxicosis, leading to thyroid storm and death. Because of this potential risk, some have recommended that the patient should be rendered euthyroid with antithyroid drugs if possible prior to radioiodine therapy (13). Pretreatment with antithyroid drugs likely lowers the risk of a thyroid storm by depleting the stored thyroid hormone within the metastatic disease.

In conclusion, amiodarone induced hyperthyroidism can occur not only in patients without previously known thyroid disease, but also in the uncommon patient with well differentiated metastatic thyroid cancer. Careful monitoring of such patients for thyrotoxicosis is in order if iodine containing medications are considered essential.

Acknowledgments

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