Functional thyroid carcinoma is an unusual cause of thyrotoxicosis. We describe the clinical presentation and treatment of a patient with thyrotoxicosis due to functional thyroid carcinoma and Graves disease, and discuss potential mechanisms causing the thyrotoxicosis. A 79-year-old woman with a remote history of hemithyroidectomy and current hyperthyroidism came to the hospital with upper and lower extremity weakness. Hospital evaluation revealed a suppressed thyroid-stimulating hormone (TSH) level, positive test for thyroid-stimulating immunoglobulins, as well as a thyroid nodule, lung masses, and a 4.4-cm gluteal mass. Fine-needle aspiration of the gluteal mass revealed metastatic differentiated thyroid carcinoma. Even after completion thyroidectomy and excision of her gluteal mass, her hyperthyroid status continued when she was not receiving levothyroxine. A radioactive iodine uptake and scan revealed unusually high lung uptake of 40%, and she was successfully treated with radioactive iodine (RAI) despite complete TSH suppression. The patient developed hypothyroidism 2 months after RAI administration; 6 months after RAI administration, her thyroglobulin (Tg) levels had fallen from a peak of 1976 ng/mL to 1.4 ng/mL. She had no anti-Tg antibodies. Repeated positron emission tomography–computed tomography nearly 1 year after RAI treatment shows substantial regression in the lung nodules, and Tg measured by mass spectroscopy is undetectable. This case demonstrates that thyrotoxicosis in the setting of metastatic thyroid carcinoma may be the result of functional thyroid carcinoma and may be successfully treated with selective surgery and RAI administration.
1. Case Report

A 79-year-old woman with a history of a remote right hemithyroidectomy and current hyperthyroidism of several years was admitted to the hospital after developing upper and lower extremity weakness over several months. In-patient treatment with intravenous (IV) immunoglobulins for acute inflammatory demyelinating polyneuropathy was initiated. The patient had undergone a hemithyroidectomy 30 years ago for a thyroid nodule, with resultant hypothyroidism, but had recently developed hyperthyroidism. Unfortunately, histology from the hemithyroidectomy and laboratory results from before her hospitalization could not be obtained. Home medications included methimazole 10 mg daily. Laboratory studies revealed a TSH level <0.01 mIU/L, despite treatment with methimazole, and free T4 level of 1.92 ng/dL. A chest radiograph revealed bilateral pulmonary nodules and an enlarged left thyroid lobe and computed tomography of the abdomen and pelvis revealed a 4.4-cm, hypervascular left gluteal mass. Ultrasound of the neck showed a hyperemic left thyroid lobe with a 1.5-cm nodule. A fine-needle aspiration biopsy of the gluteal mass was performed, and cytology was consistent with metastatic differentiated thyroid carcinoma, follicular in type, based on immunostaining for thyroglobulin (Tg) and thyroid transcription factor-1 [Fig 1(a–d)]. Her serum Tg level was 1976 ng/mL, with negative thyroglobulin antibodies. TSI (Quest Diagnostics) was 484% of baseline (reference, <140%).

The patient was discharged after completing her IV immunoglobulin course and was prescribed an increased dose of methimazole 20 mg once daily. Thyroid uptake and scan could not be performed due to the recent IV contrast administration. Fine-needle aspiration of the thyroid was not performed because completion thyroidectomy was planned in anticipation of treatment with radioactive iodine (RAI).

Figure 1. Images of the gluteal mass cytology. (a) Diff-Quik stain (Polysciences, Inc.). (b) Papanicolaou stain. (c) Stain for thyroglobulin. (d) Micrograph of cell-block section.
One month after discharge, the patient had a completion thyroidectomy, showing a 1.8-cm papillary thyroid carcinoma, classical variant. She was originally treated with levothyroxine 100 μg/d, but her TSH level was <0.01 mIU/L despite cessation of levothyroxine. Positron emission tomography–computed tomography was performed and showed abnormal fluorodeoxyglucose (FDG)-avid regions in the thyroid bed, lung, adrenal glands, and the 4.4-cm left gluteal muscle [Fig 2(b)]. The left gluteal mass was excised and revealed poorly differentiated thyroid carcinoma. The patient’s TSH level remained <0.01 mIU/L after the gluteal surgery.

Five months after discharge, an I-123 thyroid whole-body scan showed bilateral metastatic lung disease with lung uptake of 40% despite continued TSH suppression and no levothyroxine treatment [Fig 2(a)]. The patient was administered 101 mCi of I-131 to the patient without recombinant thyrotropin. The patient developed hypothyroidism 2 months after RAI administration and levothyroxine was initiated with a target TSH level of <0.1 mIU/L. Six months after RAI administration, her Tg level had fallen to 1.4 ng/mL, with a TSH level of 0.15 mIU/L.

A repeated positron emission tomography–computed tomography scan 9 months after RAI treatment has shown near-complete resolution of FDG-avid areas [Fig 2(c)]. The patient has regained much of her strength and is in good spirits. Our long-term plan is to trend Tg levels maintain serum TSH levels between 0.1 and 0.5 mIU/L, and to consider another I 123 whole-body scan and RAI dose in the future, if uptake is seen. The investigators are also planning to send the gluteal and thyroid lesions for genotyping to identify any common mutations.

Figure 2. RAI scans and positron emission tomography-computed tomography (PET-CT) imaging. (a) Whole-body scan performed 1 week after RAI administration. (b) PET-CT images showing FDG-avid regions (arrow) before RAI treatment. (c) PET-CT images showing resolution of FDG-avid regions (arrow) 9 months after RAI treatment.
2. Discussion

Hyperthyroidism and thyroid carcinoma have been associated since the report from our institution describing the first therapeutic use of RAI in a hyperthyroid patient with widespread metastatic thyroid cancer despite total thyroidectomy [2]. Although differentiated thyroid carcinoma is a commonly diagnosed malignancy, the presence of a functional thyroid carcinoma causing thyrotoxicosis is rare, with ~70 cases reported in the literature [3, 4]. Certain features make the diagnosis of functional thyroid carcinoma more likely: (1) exclusion of hyperfunctioning goiter, (2) demonstration of RAI uptake by metastatic lesions, (3) low thyroid RAI uptake, and (4) unresolved hyperthyroidism after thyroidectomy [5].

Follicular thyroid carcinoma is most frequently associated with functional thyroid carcinoma, often in conjunction with widespread disease, but it has also been reported in association with papillary thyroid carcinoma and struma ovarii. Hyperthyroidism was originally considered as protective of thyroid cancer, but additional reports suggest GD is associated with more aggressive thyroid carcinoma, higher rates of multifocality and local invasion, and increased rates of metastases [6]. Furthermore, thyroid nodules found in a Graves gland may carry an increased risk of malignancy as compared with diffuse goiter [7].

Thyroid cancers are typically less efficient in concentrating iodine and producing thyroid hormone than normal thyroid tissue. Nonetheless, thyroid cancer can cause clinical hyperthyroidism in rare situations. One potential mechanism is that a large aggregate tumor mass can produce sufficient thyroid hormone to cause hyperthyroidism. Another possibility is that hyperthyroidism occurs because of the presence of thyroid-stimulating antibodies such as those that occur in GD, with in vitro studies suggesting that thyroid carcinoma cells respond to stimulation by thyroid-stimulating antibodies [8].

Treatment of functional thyroid carcinoma is similar to that of nonfunctioning thyroid cancer, with thyroidectomy, surgical debulking of any large accessible metastatic lesions, and RAI. Patients may require high-dose antithyroid treatment to control the hyperthyroidism. The ability of functional thyroid carcinoma to concentrate iodine may impart an improved response to treatment with RAI. One large series of functional thyroid carcinoma suggests that functional lung metastases may be particularly responsive to treatment, when compared with nonfunctional lung metastases [9].

The patient in this report had a functional thyroid carcinoma: She remained hyperthyroid even after thyroidectomy and removal of the large gluteal metastasis, and had extremely high uptake of RAI in the metastatic tissue. The origin of her metastatic disease remains unclear because the histopathological features of the thyroid cancer from the completion thyroidectomy (papillary thyroid cancer) were discordant with those of the gluteal mass (poorly differentiated thyroid cancer with features of follicular thyroid cancer). It is also possible that her current metastatic disease originated from the thyroid lobe resected 30 years ago. The pathophysiology of her hyperthyroidism may have been caused by the large tumor bulk, the stimulatory effects of the TSIs on the thyroid cancer cells, or a combination of both mechanisms.

Our treatment approach prioritized the removal of the large gluteal mass to allow concentration of subsequent RAI treatment in her remaining lung nodules. Post-RAI scans demonstrated extremely high uptake in the lung lesions. Based on the large and sustained decrease in Tg levels as well as the near-complete resolution of FDG activity on positron emission tomography scan 9 months after RAI administration, she has had a remarkable treatment response and we are hopeful that successful long-term control of her remaining disease can be achieved.

3. Conclusion

Functional thyroid carcinoma is a rare but well-described phenomenon and must be considered when evaluating thyroid carcinoma with concurrent hyperthyroidism. Most functional thyroid carcinoma is associated with follicular cancer but can exist with other subtypes.
as well. Despite the sporadic and usually inefficient iodine-concentrating ability of thyroid carcinoma, hyperthyroidism in the patient in this report may have resulted from a large aggregate tumor mass or the stimulating effects of the thyroid tumor cells by thyroid-stimulating antibodies. We cannot distinguish this cause from autonomous and excessive thyroid hormone production by the tumor. Treatment with RAI may be particularly beneficial in these patients in achieving long-term disease control.

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