

A case report of hyperfunctioning metastatic thyroid cancer and rare I-131 avid liver metastasis

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ABSTRACT

Thyroid cancer is usually, relatively hypofunctional; most patients with thyroid cancer are clinically euthyroid. The combination of thyroid cancer and thyrotoxicosis is not common. We herein, report a case of follicular thyroid cancer with hyperfunctioning metastasis in a 43-year-old woman who presented with thyrotoxicosis, a cold right thyroid nodule, and low I-131 uptake at the thyroid bed. An additional total body scan with I-131 revealed a large radioiodine avid osteolytic bone metastasis with soft tissue masses and liver metastasis. The patient received treatment with total thyroidectomy, methimazole, and I-131 at a cumulative dose of 600 mCi along with recombinant human thyroid-stimulating hormone before the first I-131 treatment and palliative radiation. The patient had normal liver function test and experienced a mild degree of bone marrow suppression after I-131. At the 2-year follow-up, the patient was still alive with the progression of bone metastases but was doing well with less severe thyrotoxicosis, good ambulation, and an Eastern Cooperative Oncology Group performance status of 2. Clinicians should be aware of the unusual concurrent presentation of thyrotoxicosis and thyroid cancer, a differential diagnosis in patients with thyrotoxicosis and low or normal radioiodine uptake over the neck and also potential pitfalls during radionuclide treatment.

Keywords: Bone metastasis, hyperfunctioning metastasis, liver metastasis, thyroid cancer, thyrotoxicosis

INTRODUCTION

Almost all the patients with thyroid cancer are clinically euthyroid, and cancer itself is relatively hypofunctional in relation to the normal thyroid tissue. Therefore, thyroid cancer nodules usually present as cold nodules on thyroid scintigraphy. Thyroid carcinoma concomitant with thyrotoxicosis is a rare condition and has been reported in only a small number of cases. Apart from the simultaneous occurrence of thyroid cancer with hyperthyroidism^[1] secondary to Graves' disease, toxic multinodular goiter, or toxic adenoma, only a few cases of hyperfunctioning, well-differentiated thyroid cancer with metastasis have been reported.

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CASE REPORT

A 43-year-old woman presented with thyrotoxicosis and a palpable right thyroid nodule. Her thyroid function test results were as follows: Free triiodothyronine (FT3) level of >32.55 pg/mL (reference range, 2.50–4.30 pg/mL), free thyroxine (FT4) level of 6.34 ng/dL (reference range, 0.90–1.70 ng/dL), and thyroid stimulating hormone (TSH) level of 0.026 μ IU/mL (reference range, 0.270–4.200 μ IU/mL).

Clinical findings, investigation, and diagnosis assessment

The patient was referred to nuclear medicine clinic for I-131 evaluation of thyroid uptake and performance of thyroid scintigraphy. I-131 100 μ Ci was administered orally for the I-131 thyroid uptake and then thyroid scan. The I-131 thyroid uptake

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at 4 and 24 h was 57% and 47%, respectively (normal thyroid uptake in Thai patient is about 30% and 50%, respectively). Planar thyroid scintigraphy with I-131 showed a cold nodule at the right thyroid lobe corresponding to the palpable nodule [Figure 1]. However, the discordance between very high FT3 level and slightly-above-normal-limits thyroid uptake prompted a nuclear medicine physician to further pursue an I-131 total body scan (TBS) to identify other endogenous extrathyroidal sources of thyroid hormone. The TBS with single photon emission computed tomography (CT)/CT revealed an 11.1 cm × 12.6 cm × 10.0 cm expansile focus of osteolytic bone metastasis in the right scapula and a 9.1 cm × 11.3 cm × 10.3 cm soft tissue mass at the right iliac bone. There was also a focus of radioiodine avid liver metastasis at hepatic segment VII [Figure 2].

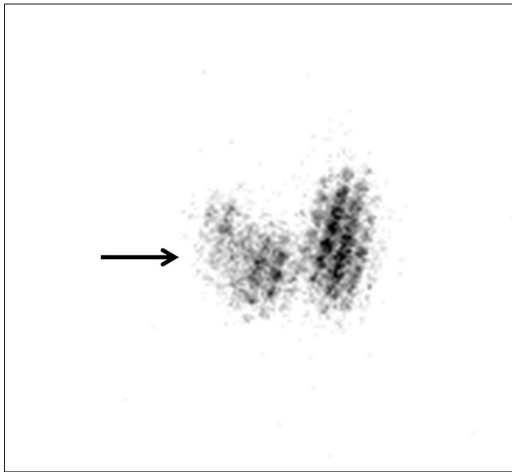


Figure 1: A thyroid scan revealed a cold nodule at the right thyroid lobe (arrow)

Additional history taking and physical examination revealed that the patient had had the right shoulder and right hip masses for 1.5 years, but she thought that they developed secondary to her car accident that occurred during the same period. She was able to ambulate well and had experienced no pain.

Treatment

The patient underwent a total thyroidectomy with the right modified lateral neck dissection, which revealed a 2.5 cm moderate to poorly-differentiated follicular thyroid carcinoma involving the right lobe with minimal extrathyroidal extension and angiolymphatic invasion. There were also metastatic carcinomas in four to six regional lymph nodes at the right cervical levels II, III, and IV. The presence of tumor invasion in the jugular vein was noted in the pathological report. The tumor cells were immunoreactive to thyroglobulin (TG), thyroid transcription factor-1, AE1/AE3, Ki-67 (30%), cyclin D1 (60%), and B-cell lymphoma 2, but negative for calcitonin.

After surgery, the patient still had thyrotoxicosis (FT3 level of 3.4 pg/mL, the FT4 level of 0.1 ng/dL, and TSH level of 0.01 μ IU/mL), which was controlled by the antithyroid drug methimazole (10 mg daily, continuously administered until after I-131 treatment). The patient's TG level was >5000 ng/mL and her TG antibody level were 1 IU/mL.

Two-dose regimens of recombinant human TSH (rhTSH) 0.9 mg intramuscular injections were given at 24 and 48 h before administration of I-131 to increase the TSH level which was 0.01 μ IU/mL at 3 weeks after surgery. The TSH level was >100 μ IU/mL on the day of I-131 treatment, and TG

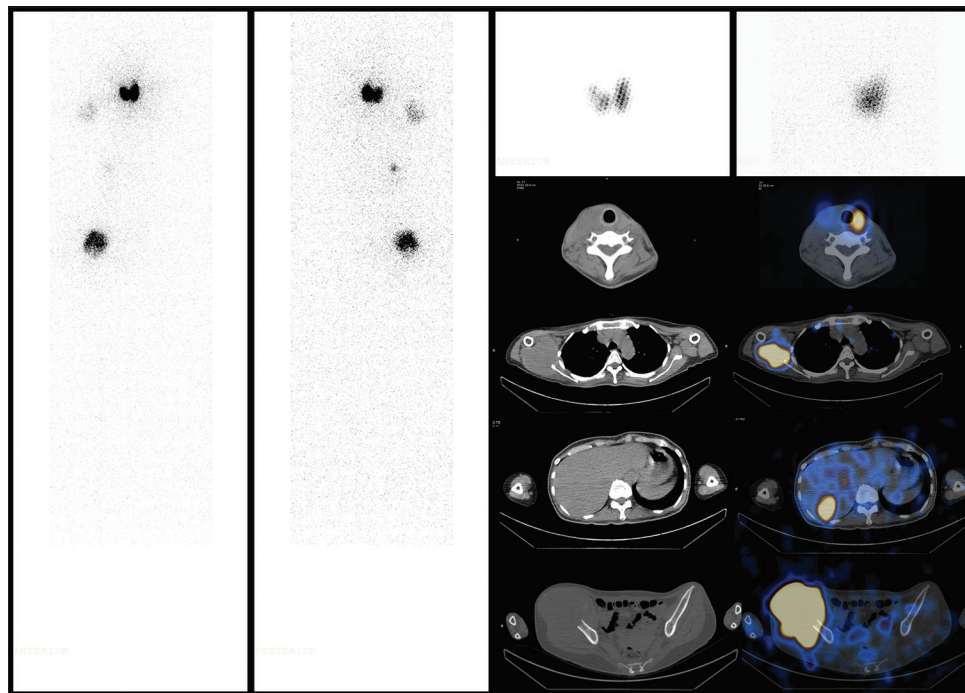


Figure 2: Planar total body scan and single photon emission computed tomography-computed tomography images revealed a radioiodine uptake at the thyroid bed (with a cold nodule at the right thyroid lobe) and masses at the right shoulder, liver, and right hip

level was >5000 ng/mL. The patient was admitted for the treatment of 200 mCi of I-131, orally 30 days after surgery and 56 days after the first I-131 scan. Methimazole was also given during the I-131 treatment. After the I-131 treatment, the patient had hypothyroidism for 2 months, and her thyrotoxicosis subsequently decreased in severity with continued administration of methimazole (2.5 mg daily). Bone marrow suppression (pancytopenia) occurred 2 months after I-131 treatment and spontaneously recovered during the next 2 months.

After this treatment, the patient still had the persistent metastatic disease of the bone and liver [Figure 3] as well as thyrotoxicosis. Therefore, she received the second and third I-131 treatments at 200 mCi each and palliative external-beam radiation therapy (3 Gy \times 13 fractions) at the right shoulder and right hip. The patient's degree of marrow suppression (pancytopenia) increased after each I-131 treatment, and she required a blood transfusion and treatment with recombinant methionyl human granulocyte colony-stimulating factor after the third I-131 treatment without life-threatening event. The liver function test was normal during the course of treatment and follow-up.

Despite the intense radioiodine avidity at the metastatic tumor sites and the additional radiation treatment, the metastatic masses did not significantly change in size. The patient's thyrotoxicosis transiently improved within a short period after the I-131 treatment, then relapsed.

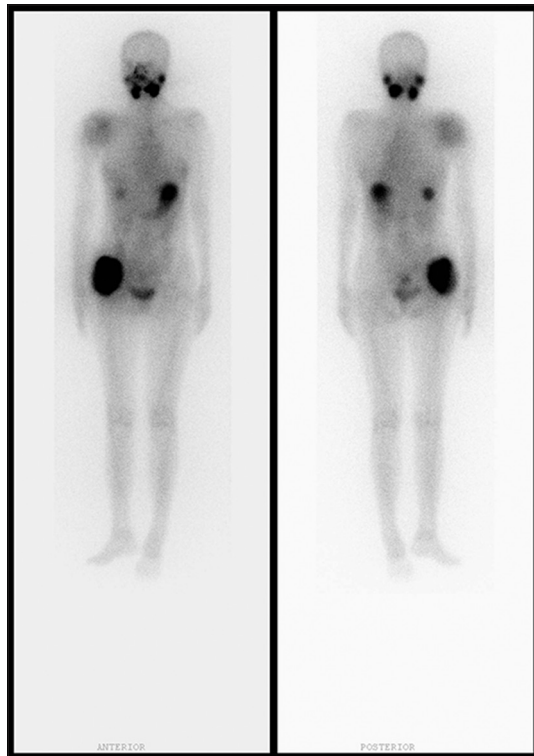


Figure 3: Planar follow-up total body scan after the first I-131 treatment revealed no radioiodine uptake at the thyroid bed. There were foci of radioiodine uptake at the right shoulder, liver, and right hip

Follow-up and outcomes

At the 2-year follow-up, the patient exhibited progression of the bone metastases to the skull and L3 vertebra on ^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP) bone scan [Figure 4] which were not shown on the last I-131 TBS posttreatment 6 months ago. The patient had developed bone pain that could be controlled with tramadol at 100–150 mg/day. Methimazole at 2.5 mg/day had been given to the patient to treat the thyrotoxicosis and maintain her TSH level at <0.1 $\mu\text{IU/mL}$. The patient remains alive, can ambulate well, and has an Eastern Cooperative Oncology Group performance status of 2. The timeline of treatment, investigation, and key clinical symptoms is shown in Figure 5.

DISCUSSION

We have reported an uncommon case of a hyperfunctioning metastatic thyroid carcinoma in the setting of thyrotoxicosis and inappropriate I-131 thyroid uptake. This case emphasizes that clinicians should keep this uncommon entity in mind as a differential diagnosis in patients with thyrotoxicosis and low or normal radioiodine uptake over the neck. Other differential diagnoses in such patients include thyroiditis (painless, acute, subacute, or drug-induced), iatrogenic thyrotoxicosis, thyrotoxicosis factitia, struma ovarii, and metastases from thyroid cancer (mostly from the follicular cell type).^[2,3] A radioiodine TBS can help to diagnose struma ovarii and metastatic thyroid cancer.

Patients with thyroid cancer usually present with euthyroidism. Thyrotoxicosis with thyroid cancer is an unusual condition. One study showed a 2.8% incidence of hyperthyroidism among patients with thyroid malignancy in an iodine-deficient area.^[4] The reported sites of autonomous hyperfunctioning thyroid cancer are either at the primary site at the thyroid bed, which is seen as a hot nodule on thyroid scintigraphy,^[1,5-9] or at a metastatic site.^[10-15] Some reported the mechanism of activated receptors on the cancer cells with high level of TSH-binding inhibitory immunoglobulin and thyroid stimulating antibody in the absence of thyroid tissue, occurred in metastatic site after the completion of radioiodine treatment for many years.^[16]

In this case, the pretreatment radioiodine TBS revealed tumor heterogeneity, which was seen as a cold nodule at the primary site but hyperfunction at the metastatic site. This was confirmed by the presence of persistent thyrotoxicosis after radioiodine treatment and the lack of evidence of a thyroid remnant at the thyroid bed but functional metastasis on the follow-up TBS. Furthermore, during follow-up, there were additional metastatic sites from the posttreatment TBS detected by ^{99m}Tc -MDP bone scan at 6 months later which could be due to progression of bone metastasis and/or discordant findings between both tracers. The discordant findings between bone scan, TBS and even fluorodeoxyglucose positron emission tomography are not uncommon. It depends on the aggressiveness of the tumor and proportion of osteoblastic and osteolytic activity.

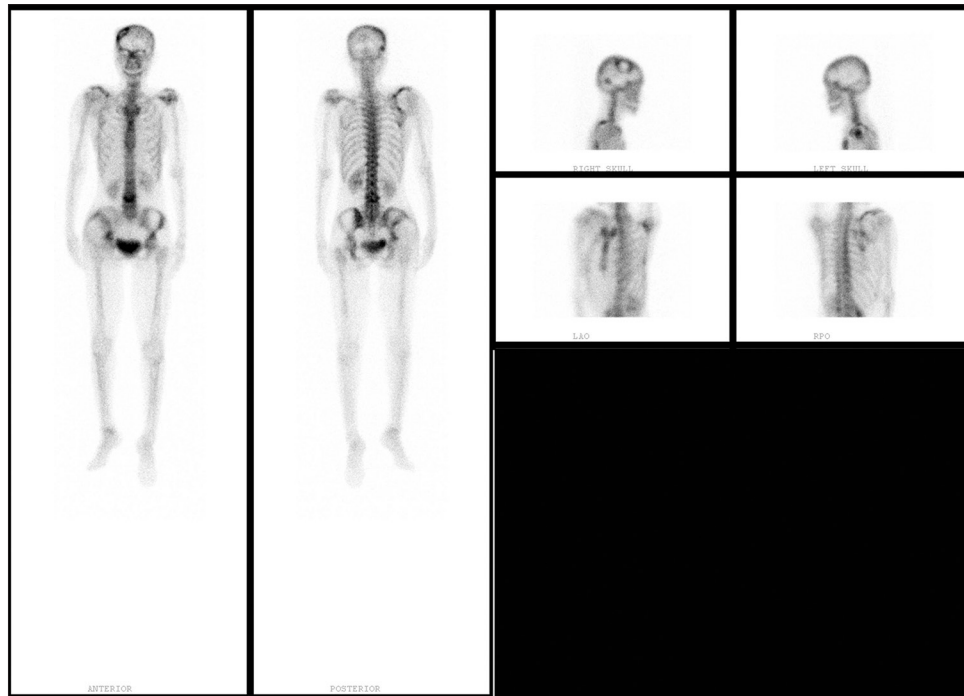


Figure 4: ^{99m}Tc -methylene diphosphonate bone scan performed 2 years after the initial treatment (6 months after the last radioiodine treatment) showed bone metastases at the right parietal and temporal bones, right shoulder, L3 vertebra, and right hip

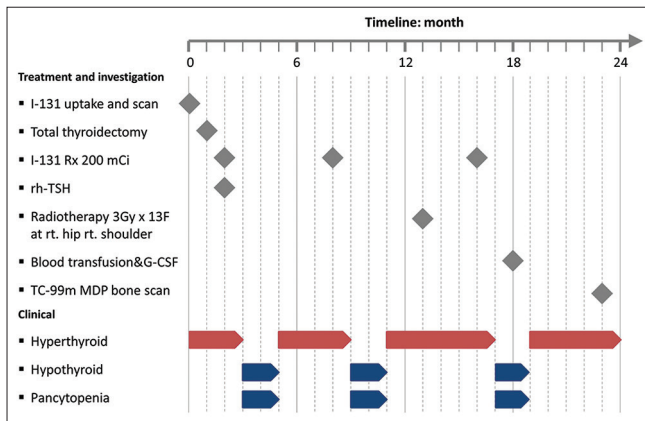


Figure 5: The timeline of treatment, investigation and key clinical symptoms

The major sites of distant metastasis in patients with thyroid cancer are the lymph nodes, lung, and bone. Metastasis to the liver is rare with a reported incidence of only 0.5%; in addition, it is not usually radioiodine avid.^[17,18] The present patient had an unusual site of thyroid cancer metastasis in the liver. This soft tissue lesion showed persistent focal radioiodine avidity in all TBSs.

The American Thyroid Association guideline for the treatment of hyperthyroidism mentioned the potential for thyrotoxicosis in patients with metastatic thyroid cancer who have received multiple rhTSH injections before imaging.^[3] In our patient, she received rhTSH only before the first I-131 treatment to increase the TSH level. The severity of her thyrotoxicosis was stable during treatment and declined after treatment. The usage of

rhTSH, in this case, is controversial because the pre-TBS already showed good I-131 avidity at thyroid bed and metastatic sites. Therefore, increasing TSH level is not necessarily and might be harmful because of the potential cause of more thyrotoxicosis.

Radioiodine treatment with antithyroid medication is the treatment of choice for hyperfunctioning metastatic thyroid cancer. Some authors have reported the use of dexamethasone. Clinicians who perform I-131 treatment should be aware of bone marrow suppression and whole-body radiation exposure due to a large amount of radiolabeled thyroid hormones produced by the functioning tumor. We experienced this clinical situation in our patient, but without life-threatening events. Calculation of the I-131 dose using radiation dosimetry is recommended, and the antithyroid drug should be given before I-131 treatment to decrease the chance of a thyroid storm.^[2]

Learning points

- Clinician should be aware of an unusual concurrent presentation of thyrotoxicosis and thyroid cancer
- A differential diagnosis in patients with thyrotoxicosis and low or normal radioiodine uptake over the neck
- Careful clinical history taking and physical examination is of paramount important
- Potential of more thyrotoxicosis during I-131 and rhTSH treatment in thyroid cancer patient with thyrotoxicosis and the role of antithyroid drugs
- The high potential of bone marrow suppression after I-131 treatment in patient with thyroid cancer and thyrotoxicosis from hyperfunctioning metastasis.

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Conflicts of interest

There are no conflicts of interest.

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