A case of metastatic follicular thyroid carcinoma complicated with Graves’ disease after total thyroidec- tomy

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Abstract. Thyroid cancer and Graves’ disease may present simultaneously in one patient. The incidence of the development of hyperthyroidism from metastatic differentiated thyroid carcinoma is rare. We herein report a case of metastatic follicular carcinoma complicated with Graves’ disease after total thyroidec- tomy. A 57-year-old woman underwent right hemithyroidectomy for follicular carcinoma. Metastatic lesions appeared in the lungs and skull two years after the first surgery, and remnant thyroidec- tomy was performed for radioactive iodine-131 (RAI) therapy, during which the TSH receptor antibody (TRAb) was found to be negative. The patient was treated with RAI therapy four times for four years and was receiving levothyroxine suppressive therapy. Although radiiodine uptake was observed in the lesions after the fourth course of RAI therapy, metastatic lesions had progressed. Four years after the second surgery, she had heart palpitations and tremors. Laboratory data revealed hyperthyroidism and positive TRAb. She was diagnosed with Graves’ disease and received a fifth course of RAI therapy. 131I scintigraphy after RAI therapy showed strong radiiodine uptake in the metastatic lesions. As a result, the sizes and numbers of metastatic lesions decreased, and thyroid function improved. Metastatic lesions produced thyroid hormone and caused hyperthyroidism. RAI therapy was effective for Graves’ disease and thyroid carcinoma.

Key words: Thyroid carcinoma, Graves’ disease, Metastasis

BETWEEN 1.7 AND 2.5% of patients with Graves’ disease have thyroid cancer [1]. Limited information is currently available on the metastatic lesions of thyroid cancer that result in thyrotoxicosis. We herein report a patient with multiple metastases of follicular thyroid carcinoma who developed hyperthyroidism despite undergoing total thyroidec- tomy for radioactive iodine-131 (RAI) therapy.

Case presentation

A 57-year-old woman underwent right hemithyroidectomy at a local hospital. The diagnosis was follicular carcinoma (Fig. 1). Two years after surgery, she noted a mass in the frontal region, which was diagnosed as bone metastasis. Computed tomography (CT) revealed metastatic lesions in the lungs. She underwent remnant thyroid resection for RAI therapy. Resected thyroid tissue revealed no abnormal findings pathologically. She did not concurrently have hyperthyroidism and the TSH receptor antibody (TRAb) was negative. After the second surgery, she received replacement therapy with levothyroxine sodium hydrate (L-T4). She was also treated with 100 mCi of RAI therapy four times for four years. 131I scintigraphy after the fourth course of RAI therapy still showed strong radiiodine uptake in the metastatic lesions without decreases in their size or number. Soon after the fourth course of RAI therapy, she presented with heart palpitations and tremors. Laboratory data were as follows: TSH 0.01> μU/mL (normal 0.65–5.55 μU/mL), free T3 10.2 pg/mL (normal 2.30–3.70 pg/mL), and free T4 2.0 ng/dL (normal 0.95–1.75 ng/
dL) under the administration of L-T4. TRAb was 20.0 IU/L (normal 0.0–1.5 IU/L). Since she was diagnosed with Graves’ disease, replacement therapy with L-T4 was stopped and thiamazole (MMI) therapy was initiated. Brain metastasis was detected one month after the initiation of MMI therapy. Laboratory data at that time were as follows: TSH 0.01 μU/mL, FT3 13.2 pg/mL, and FT4 1.81 ng/dL under the administration of 100 mg MMI daily. TRAb was elevated to 25.4 IU/L and thyroglobulin (Tg) was 55,000 ng/mL (normal 0.0–32.7 ng/mL). A chest CT scan showed multiple metastatic nodules in the bilateral lungs. Head magnetic resonance imaging (MRI) revealed tumors in the skull and right occipital lobe (Fig. 2A). Stereotactic radiotherapy (SRT) was performed for the metastatic lesions in the brain. Thyroid function was not controlled by MMI therapy. Therefore, a fifth course of RAI therapy (100 mCi) was performed. In 131I scintigraphy after the fifth course of RAI therapy, massive radioiodine uptake was observed in the metastatic lesions (Fig. 3). After SRT and RAI therapy, the sizes and numbers of pulmonary metastases decreased, while bone and brain metastases were stable (Fig. 2). Thyroid functions and TRAb were reduced and MMI was gradually tapered. Five months after the fifth course of RAI therapy, MMI was stopped. Eighteen months after the fifth course of RAI therapy, she died of metastatic disease. The clinical course and results of blood examinations are shown in Fig. 4.

**Discussion**

Previous studies reported that thyroid cancer occurs concomitantly with Graves’ disease [2-7]. The incidence of thyroid carcinoma in patients with Graves’ disease is between 1.7 and 2.5%, which is higher than...
that in the general population (0.25%) [1]. Limited information is currently available on metastatic differentiated thyroid cancer leading to thyrotoxicosis after total thyroidectomy.

There have been six cases that showed hyperthyroidism and were diagnosed as Graves’ disease after total thyroidectomy for thyroid carcinoma (Table 1) [2-7]. All six cases had follicular carcinoma with large metastatic tumors. Information on TRAb before total thyroidectomy was not provided for all cases.

TRAb was positive in the present case, and strong radioiodine uptake was observed in metastatic lesions in 131I scintigraphy after the fifth course of isotope therapy. Therefore, metastatic lesions were expected to have produced thyroid hormone and induced hyperthyroidism. We considered two mechanisms for the production of TRAb. Repeated RAI therapy may have triggered an autoimmune response and the production of TRAb. Stress may alter immunological homeostasis and trigger the production of TRAb. In previous studies, hyperthyroidism was observed after RAI therapy [2, 3] and surgery [5, 7]. The second proposed mechanism involves TSH receptors in progressive

Fig. 3 131I scintigraphy after the fifth course of RAI therapy
Strong radioiodine uptake was observed in metastatic lesions.

Fig. 4 Clinical course and results of blood examinations
RAI, radioactive iodine-131 therapy; Tg, thyroglobulin; TRAb, TSH receptor antibodies; MMI, thiamazole; L-T4, Levothyroxine Sodium Hydrate.
metastatic lesions stimulating the production of TRAb and inducing hyperthyroidism. Yoshimura et al. speculated that the TSH receptor in metastatic tumors functions as an antigen of TRAb, and TRAb stimulates the production of thyroid hormone, thereby producing hyperthyroidism [5].

RAI and MMI therapies were previously reported to be useful for the treatment of metastasis of thyroid cancer with Graves' disease [2-5, 7]. In our case, the fifth course of RAI therapy performed with 100 mCi was effective for hyperthyroidism and metastatic disease. RAI therapy has commonly been used in the treatment of Graves’ disease and differentiated thyroid carcinoma since the 1940s [8, 9]. Doses ranging between 5 mCi and 15 mCi of RAI are commonly administered to patients with Graves’ disease [8]. A higher dose, up to 20 mCi, may be required for patients with very large thyroid volumes. Doses ranging between 100 and 200 mCi of RAI are recommended for differentiated thyroid carcinoma based on the ATA guidelines [9]. The fifth course of RAI with 100 mCi for our patient decreased metastatic lesions, whereas the fourth course with the same dose had no therapeutic effect. The difference between the fourth and fifth courses of RAI was the absence or existence of TRAb. The existence of TRAb may be advantageous in treating the metastatic disease of differentiated thyroid cancer with RAI. We speculated that the expression of TSH receptors in pulmonary metastases was stronger than in other metastases. Therefore, after the fifth course of RAI therapy, the sizes and numbers of pulmonary metastases decreased, while bone and brain metastases were stable. As a result, only tumors with the weak or absent expression of TSH receptors, which were non-functional tumors, remained. The production of TRAb decreased, thyroid hormones were not produced, and the resumption of

MMI therapy was not necessary.

In previously reported cases, two patients were given 150 mCi RAI therapy [4, 7], three 100 mCi [2, 3, 5], and one additional RAI therapy (total 200 mCi) [3]. In most reported cases, thyroid function was controlled [2-5, 7], and metastases responded to therapy [2, 4, 5, 7]. In one case, metastases completely disappeared [2].

Anti-thyroid drug therapy is the most common treatment for Graves’ disease. It has a well-defined biochemical effect, reducing thyroid hormone by inhibiting the effects of thyroid peroxidase [10, 11]. It also exerts an immunosuppressive effect. MMI gradually reduces the number of circulating activated T helper/inducer cells and increases the number of circulating activated T suppressor/cytotoxic cells [11]. In addition to these slow effects, a rapid increase in the number of activated/suppressor T cells and T suppressor/cytotoxic cells in addition to decreases in the number of activated T helper and NK cells have been observed after only a few days of treatment [10]. TRAb may play a role in the initiation and progression of thyroid cancer [3, 4, 12, 13]. TRAb and TSH activate the same intracellular pathways, including the adenylate cyclase and phospholipase C cascades. These 2 cascades exert mitogenic and antiapoptotic effects on thyroid follicular cells. By up-regulating vascular endothelial growth and placental factors, TRAb stimulates angiogenesis in the thyroid, which has a critical role in the growth and development of tumors in the thyroid [14, 15]. Therefore, MMI therapy appears to be an effective therapy for controlling thyroid function and inhibiting the initiation and progression of thyroid cancer.

Although the fifth course of RAI therapy was effective, the patient died of metastatic disease 18 months

Table 1 Cases of thyroid carcinoma diagnosed as Graves’ disease after total thyroidectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>History of Graves’ disease</th>
<th>Type</th>
<th>Onset period (months)</th>
<th>Metastasis</th>
<th>Treatment for Graves’ disease</th>
<th>Effect of the treatment</th>
<th>TRAb after the treatment</th>
</tr>
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F, follicular carcinoma; RAI, radioactive iodine-131 therapy; MMI, thiamazole; ERBT, external beam radiotherapy.
after final RAI therapy. Tyrosine kinase inhibitors (TKIs) are now available for radioactive iodine-refractory differentiated thyroid cancer [9, 16]. If the patient attempted TKI therapies, her prognosis may have improved.

In summary, we herein described a case of hyperthyroidism induced by metastatic lesions of follicular thyroid carcinoma. In this case, the patient developed hyperthyroidism after total thyroidectomy and was diagnosed with Graves’ disease because TRAb was positive. In 131I scintigraphy, massive radioactive iodine uptake was observed in metastatic lesions only. Metastatic lesions may produce thyroid hormone and cause hyperthyroidism. RAI therapy was effective for Graves’ disease and thyroid cancer.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References