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# Appearance of TSH Receptor Antibody and Hyperthyroidism Associated with Metastatic Thyroid Cancer after Total Thyroidectomy

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**Abstract.** We report here on a patient who was diagnosed with follicular carcinoma in 1985, and who was treated with total thyroidectomy. Two years later, when metastasis was found in his neck lesion, lung, pelvis and right femur, the patient received $^{131}I$ treatment. Six years after receiving $^{131}I$ treatment, the patient presented with hyperthyroidism. Whole-body scan with $^{131}I$ revealed functioning metastasis in his right femur and pelvis. There was no hot spot in the neck region, confirming that no thyroid tissue remained. Blood panels revealed an increase in both TSH binding inhibitory immunoglobulin (TBII. 36.2%; normal. −10~10%) and thyroid stimulating antibody (TSAb, 176%; normal, less than 145%). Treatment with antithyroid drugs, dexamethasone and radioisotope therapy rapidly resolved his hyperthyroidism. Thyrotoxicosis and positive TRAb occurred in the absence of thyroid tissue, and many years after the completion of Rl therapy. The overproduction of thyroid hormone can therefore only be attributed to some mechanism of activity in the metastatic tumor tissue.

*Key words*: Follicular carcinoma, Hyperthyroidism, Thyrotoxicosis, TSH receptor antibody
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**NEARLY** 45 cases of thyrotoxicosis associated with thyroid carcinoma have been reported [1–20]. The occurrence of thyrotoxicosis is usually attributed to the overproduction of thyroid hormone in the thyroid tissue. In a few patients with metastatic disease, TSH binding inhibitory immunoglobulin (TBII) has been detected and resulted in thyrotoxicosis [6, 11, 20]. In all these patients, normal thyroid tissue remained, making it possible that the TSH receptor in this normal tissue served as an antigen. The RI therapy used to destroy the metastatic tissue might also have initiated an autoimmune response. This is the only case reported in which no normal thyroid tissue remained as a site for TSH receptors, and in which RI treatment had occurred so many years in the past that it was unlikely to have contributed to the disease.

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## Case Report

In November, 1985 a 53-year-old man was admitted to Ito hospital with nodular goiter (Table 1). He was diagnosed with thyroid carcinoma and underwent total thyroidectomy and neck resection. The histologic diagnosis was follicular carcinoma of the thyroid. He was treated with 150 mg daily of L-thyroxine for a year. A year later he developed right femur pain, and x-ray revealed an osteolytic region of bone. The anterior view of a $^{131}I$ whole-body scan showed a concentration of $^{131}I$ in the neck (probably thyroid bed), right lung, left pelvis, head of right femur and right femur (Fig. 1). He received 3.7 GBq of $^{131}I$ in January, 1987.

**Table 1.** Clinical course and laboratory findings

| | $T_4$ (nmol/L) | $FT_4$ (pmol/L) | $T_3$ (nmol/L) | $FT_3$ (pmol/L) | TSH (mU/L) | Tg (μg/L) | anti-Tg | anti-M | TBII (%) | TSAb (%) | Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 85.10.16 | | 12.4 | 2.76 | | 2.0 | | <100 × | <100 × | | | |
| 85.11. 7 | | | | | | | | | | | L-$T_4$ 100 μg/day |
| 85.11.20 | 157.0 | | 2.76 | | 0.2 | 860 | | | | | |
| 85.12.6 | | | | | | | | | | | total thyroid-ectomy |
| 85.12.14 | | | | | | | | | | | L-$T_4$ 150 μg/day |
| 86. 3. 7 | | 19.7 | 2.15 | | 1.0 | | | | | | |
| 86. 12.29 | | | | | | | | | | | L-$T_4$ discontinued |
| 87. 1.12 | | 7.6 | | | 21.7 | 208205 | <100 × | <100 × | | | $^{131}I$ therapy |
| 87. 1.17 | | | | | | | | | | | L-$T_4$ 150 μg/day |
| 87. 9.11 | | 18.7 | | 5.4 | 3.9 | | | | | | |
| 93. 8.30 | | 105.3 | | >46.1 | <0.05 | 329 | <100 × | <100 × | | | L-$T_4$ discontinued |
| 93. 9. 2 | | 96.7 | | >46.1 | <0.05 | | | | 36.2 | 176 | |
| 93. 9.13 | | 76.0 | | >46.1 | <0.05 | 311 | | | | | $^{131}I$ therapy |
| 93. 9.17 | | | | | | | | | | | MMI 30 mg/day, dexamethasone |
| 93.10.15 | | 18.7 | | 11.1 | 0.14 | | | | 2.1 | | |
| 93.12. 3 | | 2.6 | | 4.3 | <0.05 | | | | 0.2 | 90 | MMI 5 mg/day |
| 93.12.28 | 14.2 | | 1.46 | | 23.9 | | | | | | MMI discontinued |
| 94. 6.10 | | 5.5 | | 5.7 | 2.99 | 236000 | | | −6.4 | | |
| 95. 2.21 | | 2.6 | | 3.4 | 0.1 | | | | 5.5 | | |

MMI, methimazole. Reference ranges are as follows: $T_3$, 1.23 to 2.76 nmol/L; $T_4$, 64.4 to 167.3 nmol/L; $FT_3$, 3.8 to 8.4 pmol/L (from Jan., 1986 to March, 1993), 4.9 to 8.4 pmol/L (from April, 1993 to Sept., 1995); $FT_4$, 10.3 to 24.5 pmol/L (from Nov., 1986 to March, 1994), 11.6 to 23.2 pmol/L (April, 1994 to Dec., 1994), 12.9 to 23.2 pmol/L (from Jan., 1995); TSH, <5 mU/L (from April, 1985 to March, 1987), 0.3 to 3.5 mU/L (from April, 1988 to Feb., 1994), 0.3 to 4.0 mU/L (from March, 1994); Tg, <60 μg/L (from Oct., 1996 to May, 1991), <25 μg/L (from June, 1991); Anti-Tg, Anti-M, <100 ×; TBII, −10 to 10%; TSAb, <145%.

Subsequently the metastasis of head of right femur was resected, and total hip replacement was performed. After that he received replacement therapy with thyroid hormone.

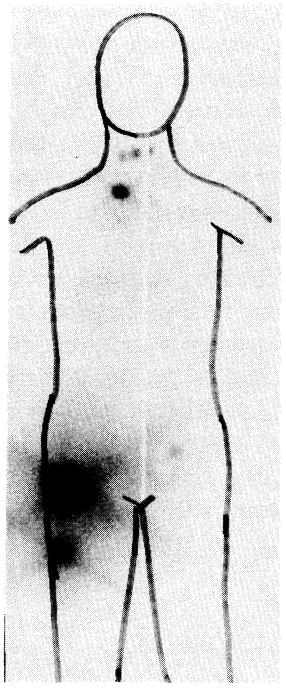
In August, 1993 he began to suffer from general fatigue, weight loss and heart palpitations. Diagnostic studies revealed a tumor of the right femur. Serum $FT_4$, $FT_3$ and TSH levels were 105.3 pmol/L, 0.46 pmol/L and 0.05 mU/L, respectively. TBII and TSAb values were high (36.2% and 176%, respectively). The chest x-ray revealed pleural effusion and cardiomegaly, and the patient was diagnosed as being in acute heart failure. The posterior view of $^{131}I$ whole-body scan revealed functioning metastasis in right femur and new metastatic lesions in the right pelvis, but hot spots in the neck, right lung and left pelvis seen in the previous scan had disappeared (Fig. 2).

He was treated with 3.7 GBq of $^{131}I$ in September, 1993 and also received methimazole, inorganic iodin and dexamethasone. The hyperthyroidism rapidly resolved, and TBII and TSAb values decreased to within the normal range. Antibodies to Tg (anti-Tg) and thyroid microsomal antigen (anti-M) were negative throughout the course of treatment. This patient had no signs of Graves ophthalmopathy and no family history of Graves disease.

## Methods

The following thyroid function tests were performed (in duplicate) with commercial assay kits: thyroxine ($T_4$, Dainabot Radioisotope Laboratory, Matsudo city, Chiba, Japan); free $T_4$ (Amerlex-M $FT_4$ kit, Amersham International plt, Buckinghamshire, U. K., from Nov. 1986 to March 1994.; Amerlex-MAB $FT_4$ kit, Kodak Clinical Diagnostics Ltd, Buckinghamshire, U. K., from April, 1994 to Dec., 1994.; IMx $FT_4$ kit, Abbott Diagnostics, U.S.A., from Jan., 1995.); triiodothyronine ($T_3$, Dainabot Radioisotope Laboratory, Matsudo city, Chiba, Japan); free $T_3$ (Amerlex $FT_3$

1



2

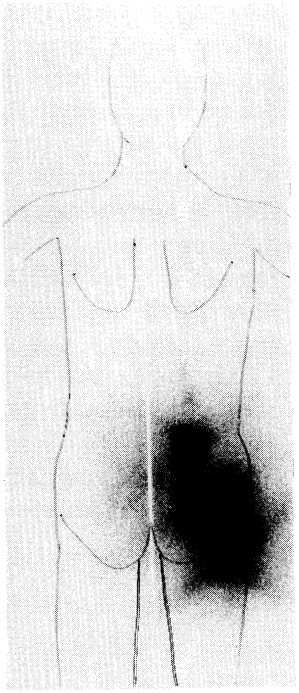


**Fig. 1.** Anterior view of whole-body scan showed concentration of $^{131}I$ in the neck (probably thyroid bed), right lung, left pelvis, head of right femur and right femur.

**Fig. 2.** Posterior view of $^{131}I$ whole-body scan revealed functioning metastasis in right femur and new metastatic lesions in right pelvis. Hot spots in the neck, right lung and left pelvis seen in the previous scan have disappeared .

kit, Amersham International plt, Buckinghamshire, U. K., from Nov., 1986 to March, 1993.; IMx $FT_3$ kit, Abbott Diagnostics, U. S. A., from April, 1993.); TSH (Daiichi Radioisotope laboratory, Tokyo, Japan, from Oct., 1985 to March, 1988; Delfia TSH kit, Farmacia AB, Wallac, Sweden, from April, 1988 to Feb., 1994.; Lumipulse TSH, Fuji Rebio Inc, Japan, from March, 1994.); and thyroglobulin (Human Thyroglobulin Immunoradiometric assay kit, Sorin Biomedica Diagnostics S.P.A., Salugoia, Italy, from Oct., 1996 to May 1991; ELSA-Thyroglobulin kit, CIS bio International, Saclay, France, from June 1991). Anti-Tg and Anti-M were determined by the haemagglutination technique with commercially available kits (Fujizoki, Inc., Tokyo, Japan). TSH binding inhibitory immunoglobulin (TBII) was assayed with a commercially available kit (R.S.R. Limited, Cardiff, U.K.). Thyroid stimulating antibody (TSAb) was assayed by measuring cAMP produced in porcine thyroid cells as an index of stimulation [21]. Reference ranges are shown in Table 1.

## Discussion

We considered two different mechanisms that might explain the hyperthyroidism in this patient. 1) The metastatic tumor functioned autonomously to produce thyroid hormone [6, 12–14, 17, 19, 22, 23]. 2) The TSH receptor in the metastatic tumor functioned as an antigen of TRAb, and the TRAb, in turn, stimulated the production of thyroid hormone and produced the condition. Although follicular carcinoma causes presenting of TSH receptor to the immune system as it invades healthy thyroid tissue, metastatic tissue has never before been demonstrated to be capable of presenting TSH receptor.

We know already that TSH can stimulate adenyl cyclase activity in follicular carcinoma [24]. In autoradiograms, follicular carcinoma and papillo-follicular carcinoma have been shown to concentrate iodine, proof of this TSH stimulation, so that follicular carcinoma is capable of producing thyroid hormone. But in cases of this kind previously reported, patients had large metastatic tumors, suggesting that a large mass of cancerous thyroid tissue was necessary to cause this overproduction of thyroid hormone, and that the ability of follicular carcinoma to produce thyroid hormone was not so great.

In this case, the patient had a large metastatic tumor in the right femur and pelvis, but no remaining thyroid tissue in the neck after total thyroidectomy and administration of 3.7 GBq of $^{131}I$. RI therapy had been given six years previously, ruling out its potential contribution as a producer of TRAb. We can therefore only assume that the metastatic tissue itself served either to directly secrete thyroid hormone or as the site for TSH receptors which acted as an antigen. We cannot rule out the possibility that the metastatic tumor autonomously produced the hormone because we have no way of determining when the TRAb appeared. It is also possible that both hypothesized mechanisms played a part in

producing the hyperthyroidism.

As far as we can determine from the published reports, there were 10 TRAb-positive cases [4, 6, 11, 16, 20, 26] out of the 45 cases of metastatic thyroid carcinoma reported in the literature in which TRAb was measured. Five out of these ten patients did not have any history of Graves' disease [6, 11, 20]. In two of the five patients, thyrotoxicosis and TRAb appeared after Rl therapy [11, 20]. In one, the condition occurred five months after Rl therapy [20], and in the other case, the time elapsed was unclear [11]. In the remaining three patients, thyrotoxicosis was diagnosed before total thyroidectomy was performed or Rl therapy begun. LATS appeared a month after RI therapy in one patient, and before RI therapy in the other two [6].

In our patient, Rl therapy was completed so long before the appearance of thyrotoxicosis that a relationship seems highly unlikely. Steffensen and Aunsholt speculated in their paper that differentiated, aggressive, metastatic thyroid tumors could initiate an autoimmune disorder. By destroying normal thyroid tissue, TBll can be produced, and the hyperplasia and hyperfunction of the thyroid gland can lead to hyperthyroidism [26]. In our patient, the mechanism appears to be different because no normal thyroid tissue remained, only metastatic tissue. Although we cannot delineate the mechanism of pathogenesis, this is the first report of thyrotoxicosis and positive TRAb that cannot be attributed to the activity of remaining thyroid tissue, or to Rl therapy. The origin of this condition must be attributed to some activity in the metastatic tumor tissue. We trust that further research will illuminate our findings further.

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