A Case of Pulmonary Metastatic Thyroid Cancer Complicated with Graves' Disease.

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Abstract. We report a case of pulmonary metastatic thyroid carcinoma complicated with Graves' disease. A 56-year-old Japanese woman was referred to the Niigata Cancer Center Hospital for isotope therapy for pulmonary metastatic thyroid carcinoma. In 1993, she received a left-hemithyroidectomy. In 1999, the remnant thyroid was resected for isotope therapy of metastatic lesions in the lungs. Although she had been receiving suppressive therapy with levothyroxine, her general condition was good, and TRAb was positive before the operation. After a total thyroidectomy, the patient became thyrotoxic. For functioning metastatic lesions, the patient was treated with 5550 MBq of ^{131}I and methimazole. Thyroid function was normalized after the therapy but TRAb and TSAb levels remained high.

Keywords: Graves' disease, Thyroid cancer, Pulmonary metastasis, ^{131}I .

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Thyroid cancer occurs concomitantly in Graves' disease with a frequency of 5–10% [1–3]. However, there are few reports of metastatic cancer leading to thyrotoxicosis. We describe herein a patient with pulmonary metastatic thyroid follicular carcinoma complicated with hyperthyroidism showing a significant increase of TSH receptor antibodies (TRAb) and TSH receptor-stimulating antibodies (TSAb) despite total thyroidectomy.

Case report

A 56-year-old Japanese woman was diagnosed with a thyroid nodule in April 1991. She was in euthyroid state when she visited a local hospital. Needle aspiration of the thyroid nodule showed no malignancy but chest X-ray revealed bilateral nodu-

lar shadows. A left hemithyroidectomy was performed in April 1993 (histologic specifics and the reason why total thyroidectomy was not undertaken were not included in the letter of introduction) and she was placed on suppressive therapy with levothyroxine (150 $\mu\text{g}/\text{day}$). Her general condition was good when she was first referred to our hospital on Nov. 25, 1999, for isotope therapy of pulmonary metastatic lesions. At this time she did not manifest hyperthyroidism and was healthy.

Serum levels of TSH, free T_4 , and free T_3 under administration of 150 μg levothyroxine were 0.01 $\mu\text{IU}/\text{ml}$ (N: 0.35–4.94), 2.15 ng/ml (N: 0.71–1.48), and 5.72 pg/ml (N: 1.71–3.71), respectively. Thyroid echography revealed normal size and echogenicity of the remnant thyroid. Computed tomography (CT) of the neck-chest demonstrated only multiple pulmonary metastatic nodules (Fig. 1). For definite diagnosis, fine-needle aspiration of a pulmonary nodule guided by chest CT scan was done that revealed follicular thyroid carcinoma (Fig. 2). For isotope therapy, the remnant thyroid was resected at her previous hospital on Jan. 5, 2000 and was found to be normal thyroid tissue. Levothyroxine was dis-

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Fig. 1. Computed tomography (CT) of the chest. This demonstrated multiple pulmonary metastatic nodules. The mediastinal and other lymph nodes were not enlarged.

Fig. 2. Histological section of the pulmonary tumor (20×). The cells are cuboidal, with large nuclei, arranged around follicles that contain dense colloids.

Table 1. Laboratory data at admission

WBC	3400 / μ l	GOT	125 IU/l	TSH	<0.0 μ IU/ml
Seg	71.0 %	GPT	215 IU/l	F-T ₃	21.29 pg/ml
Lym	22.0 %	LDH	197 IU/l	F-T ₄	6.00 ng/dl
Mon	5.0 %	LAP	73 IU/l	Tg	1430 ng/ml
Eos	1.0 %	ALP	233 IU/l	TRAb	37.5 %
Bas	1.0 %	T-Bil	0.8 mg/dl	Tg-Ab	<0.3 mg/ml
RBC	380×10^4 / μ l	γ -GTP	64 IU/l	TPO-Ab	<0.3 mg/ml
Hb	11.4 g/dl	Ca	9.6 mg/dl	TSAb	333 %
Ht	35.1 %	P	4.1 mg/dl		
Plt	14.3×10^4 / μ l	TP	6.6 g/dl	BGA (3L nasal cannula)	
		Na	141 mEq/l	pH	7.415
CRP	0.1 mg/dl	K	3.9 mEq/l	PCO ₂	36.9 mmHg
ESR	14 mm 1h	Cl	107 mEq/l	PO ₂	80.1 mmHg
	34 mm 2h	Cr	0.3 mg/dl	HCO ₃	23.1 mmol/L
CEA	7.77 ng/ml	BUN	19 mg/dl	BE	-1.1 mmol/L
CA19-9	43.94 U/ml	UA	5.1 mg/dl	SaO ₂	98.1 %
Calcitonin	25.3 pg/ml	PBS	129 mg/dl		
		TC	130 mg/dl		
		TG	66 mg/dl		
		HDL-C	28 mg/dl		

continued after the operation, but her condition took a gradual change for the worse. She complained of dyspnea and presented symptoms suggesting thyroid hyperfunction (restlessness, insomnia, tremor, and 5 kg weight loss). She was transferred to our hospital

for isotope therapy on Jan. 25, 2000.

Physical examination on admission revealed that she was 149.2 cm in height and 52.5 Kg in weight (BMI=23.6 Kg/m²). Blood pressure was 94/54 mmHg, and pulse rate was 120 bpm and regular.

Fig. 3. The clinical course after admission: upper berth: change of transaminases; middle berth: change of TRAb and thyroglobulin; lower berth: change of TSH, FT₃ and FT₄. ¹³¹I: 131-iodine therapy. MMI: methimazole.

There were no palpable thyroid gland or neck lymph nodes. No ophthalmopathy was present. Areflexia of the Achilles tendon was noted. She complained of palpitation, dyspnea, and tremor.

Thyroid function test on admission showed elevated free T₄ and free T₃ and suppressed TSH. TRAb (N: 15%) and TSAb (N: 180%) were positive (Table 1). Other routine biochemical tests were normal except for mild elevations of GOT and GPT levels (Table 1). The first operative specimen from the previous hospital in 1993 was re-evaluated by two pathologists of our hospital. It showed typical collision of papillary carcinoma and invasive-follicular adenoma as evidenced by nuclear grooving and intranuclear inclusion.

Despite total thyroidectomy, the patient remained in a hyperthyroid state with elevated serum levels of free T₃ and T₄ and suppressed TSH (Fig. 3). The patient was then treated with 5550 MBq of ¹³¹I. Two

weeks later, radioiodine uptake was observed in the diffused pulmonary metastatic lesions (Fig. 4). Serum concentrations of free T₄ and free T₃ were elevated beyond the measurable range, and serum thyroglobulin level was 58,100 ng/ml (normally, 60 ng/ml). Serum levels of both GOT and GPT were more than 300 IU/L. There was no radioiodine uptake over the thyroid bed, but scans revealed massive uptake of diffuse pulmonary metastasis (Fig. 4). Whole-body scans were normal. She became sicker, and methimazole and propranolol were prescribed. Ten days later, her condition stabilized, and she was discharged from our hospital on March 4, 2000. Two weeks later, serum thyroglobulin concentration showed a marked decrease, and liver and thyroid functions returned to normal, while TRAb and TSAb remained positive at 33.1% and 962%, respectively. The pulmonary metastatic lesions demonstrated a marked reduction in size after isotope therapy.

Fig. 4. ^{131}I scintigraphy performed thirteen days after 5550 MBq sodium ^{131}I -iodine therapy. There was a massive uptake of the tracer in diffuse pulmonary metastases while none occurred over the thyroid bed.

Discussion

We have described herein a patient with pulmonary metastasis of thyroid cancer who showed hyperthyroidism despite total thyroidectomy. Thyroid tumors associated with hyperthyroidism occur under three conditions. The first is that of Graves' disease complicated with thyroid carcinoma, although the incidence of thyroid carcinoma in Graves' disease is still controversial [1–5]. The second is that in which hyperthyroidism is due to oversecretion of the thyroid hormone from thyroid carcinoma or metastatic lesions, wherein radioiodine uptake can be demonstrated in thyroid carcinoma or in metastatic lesions [5, 7]. Nevertheless, oversecretion of thyroid hormones from metastatic lesions has rarely been proven. The third is that in which primary thyroid carcinomas or other metastatic carcinomas rapidly and directly invade normal thyroid tissue. A large quantity of the thyroid hormone is released from normal thyroid tissue infiltrated by carcinoma and

manifest thyrotoxicosis. In these cases, patients eventually develop hypothyroidism. It is said that some patients manifest thyrotoxicosis in the case of a rapidly progressive malignant tumor. Cases of invasion by malignant lymphoma and pancreatic carcinoma have been reported to occur in hyperthyroidism [8–10].

Although the present patient belongs to the second type of hyperthyroidism, interestingly the stimulating antibodies were high. Since there is no previous report of thyrotoxicosis due to stimulation of pulmonary metastatic lesions by TSAb, this patient is the first such reported case.

In regard to the mechanism for the oversecretion of thyroid hormones in pulmonary metastatic carcinoma, one could hypothesize as follows. 1) TSAb may have stimulated the metastatic carcinoma to develop thyrotoxicosis in the patient. Development of Graves' disease has been described following parathyroidectomy [11], radioiodine therapy [12], acute and subacute thyroiditis [13] and in patients treated with a percutaneous ethanol injection (PEI) [14]. Before the remnant thyroidectomy at the previous hospital, TRAb was positive and remained stable after the operation. Although spontaneous development of Graves' disease cannot be excluded, the time sequence and the negative familial and personal history for autoimmune diseases suggest a possible connection between the two phenomena. The remnant thyroidectomy may have triggered an autoimmune response sensitizing the antibodies that would stimulate the cancer cells leading to thyrotoxicosis. This speculation is supported by the finding that the resected remnant thyroid was found to be of normal thyroid tissue and did not reveal histologic appearance of Graves disease. 2) The antibodies could have been functioning as bystanders while the carcinoma was producing the thyroid hormone itself. This hypothesis is supported by the finding that TRAb and TSAb did not show remarkable change. The exact mechanisms in the present case have not been elucidated and further study is required. Incidentally, exacerbation of thyrotoxicosis after administration of ^{131}I may be responsible for the destruction of thyroid cells in lung metastasis by radioiodine as previously reported [12].

We described here for the first time that hyperthyroidism induced by pulmonary metastatic carcinoma may occur after remnant thyroidectomy even

when no association with anti-thyroid antibodies is present.

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