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症　　例

A Case of Hyperfunctioning Primary Thyroid Carcinoma

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Introduction

Hyperthyroidism due to functioning adenocarcinoma of the thyroid is exceedingly rare. Since the first case was documented by LEITER and associates[15], other instances of this pathological condition have been reported[1-11,14,18,19,22-24,26-30]. In most of them the hyperthyroidism was due to hyperfunction developing in metastatic lesions after the original tumor and the normal thyroid gland had been ablated. Hyperthyroidism truely attributable to hyperfunctioning of the primary thyroid carcinoma per se is more exceedingly rare and has been reported only five times (eight cases) to our knowledge[1)7)14)23)29)]. Our case showed hyperthyroidism due to functioning primary thyroid carcinoma as evidenced by an elevated serum level of triiodothyronine (T3) and almost normal concentration of thyroxine (T4).

Case Report

K. I., a 53-year-old Japanese woman, was admitted to the Wakayama Medical College Hospital on April 17, 1978, because of general fatigue and an enlarging mass in the neck. She, with a history of treated tuberculosis in 1952 and no contributory family history, had noted palpitation, dyspnea, hoarseness, sweating, heat intolerance and an enlarging mass in the neck in 1965 and had been administred orally 1-methyl-2-mercaptoimidazole (Mercazole®). This mass was 10 cm in right length, 9 cm in left length and 11 cm broad. She had subsequently undergone subtotal thyroidectomy (right lobe resected, 66 g ; left lobe resected, 34 g) for toxic goiter in 1970. The histological diagnosis was Basedow's disease. She, however, had noted again general fatigue, emaciation and the enlarging mass in the neck in 1974.

Clinical and laboratory findings: The patient weighed 55 kg and was 157.5 cm tall. Her

Key words　Functioning thyroid carcinoma, Hyperthyroidism.
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blood pressure was 170/80 mmHg, and puls rate 104 (beats)/min, regular in rhythm. She had a fine tremor of her fingers, excessive sweating, heat intolerance, moist and warm skin, but no exophthalmos or opthalmoplegia. Two firm masses were palpable ; large one, partially knobby, 5 by 8 cm, was in the region of thyroid and small one, thumb's head-sized, was in the right submandibular area. There were no signs of heart failure.

Hematologic findings were normal except for 0% stab form. An erythrocyte sedimenta-tion rate was 4 mm/h; thymol turbidity test (T. T. T.), 6.8 U(normal, 0 to 5 U); alkaline phosphatase, 12 King-Armstrong U (K-A U) (normal, 2.7 to 10 K-A U). Other laboratory data were normal. Results of the initial routine urinalysis were normal. An electrocardiogram showed only sinus tachycardia.

Radiologic Findings: A thoracic roentgenogram was normal. A lateral cervical roentgenogram revealed trachea pressed by an anterior cervical non-calcified mass (Fig. 1).

Special investigations : The basal metabolic rate (BMR) was +46.5% ; microsome test, over 25, 600 (normal, <100); total serum T4, 9.0 μg/dl (normal, 4.5 to 13.0 μg/dl) ; serum T3, 4.5 ng/ml (normal, 0.8 to 1.8 ng/ml); and serum thyroid stimulating hormone (TSH) was 1.25 μU/ml (normal, <10 μU/ml). A scintigram of the thyroid showed 52% uptake of radioiodine in 24 hours in the region of the thyroid gland and a palpable right submandibular mass (Fig. 2). An echogram of the thyroid showed solid in type (Fig. 3).

Clinical course: On April 24, biopsy of the right submandibular nodule revealed follicular adenocarcinoma without any normal thyroid, Basedow's disease and lymphatic tissues. Therefore, we decided to treat our patient with radioiodine, but we were refused our plan

Fig. 1 Lateral cervical roentgenogram : Anterior cervical mass pressing trachea without calcification.

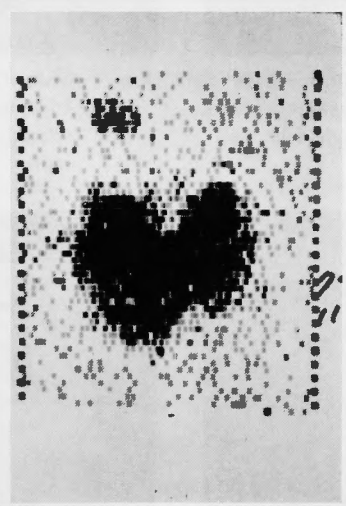

Fig. 2 Thyroid scintigram : Radioiodine is concentrated by the whole-thyroid and right submandibular mass. Uptake of the isotope after 24 hours is 52%.

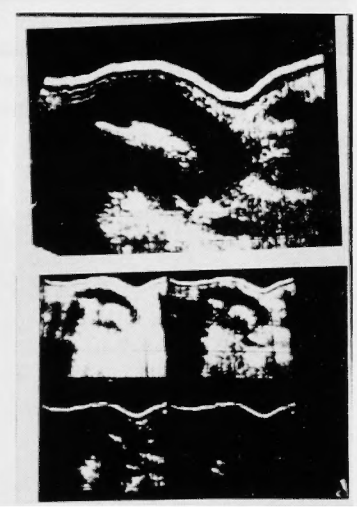

Fig. 3 An echogram of the thyroid, showing solid type.

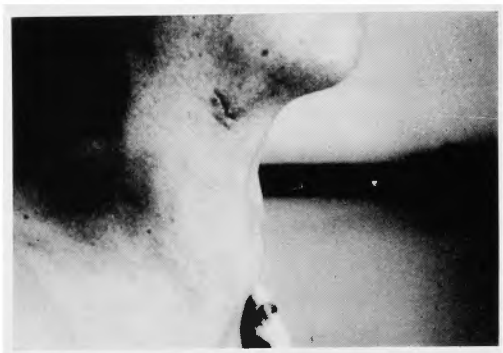

Fig. 4 The patient with an operative scar of biopsy for a functioning nodule in the right submandibular area, showing nodules at the lower part of isthmus and the upper left lobe.

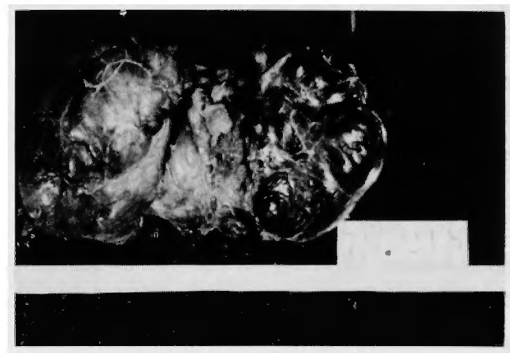

Fig. 5 Thyroid tumor mass, showing knobby surface, is 145g in weight.

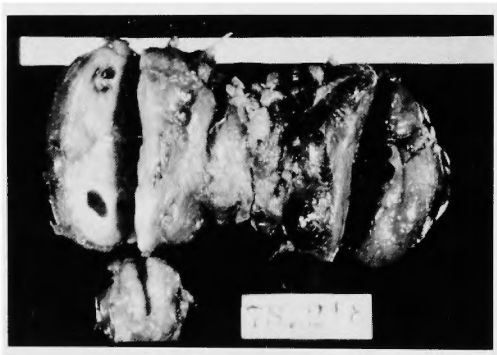

Fig. 6 A vertical section of tumor masses, showing the parenchymatous tissue with two cysts in the right lobe and one in the left.

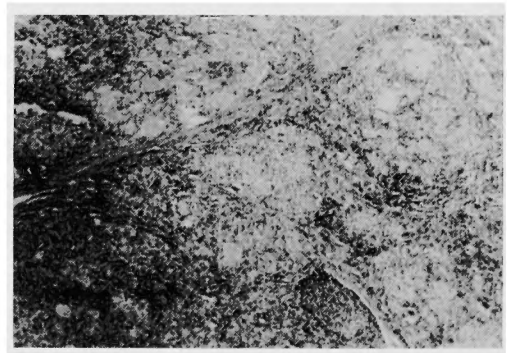

Fig. 7 Section from the excised thyroid showing follicular adenocarcinoma. Original magnification ×70. Hematoxylin and eosin stain.

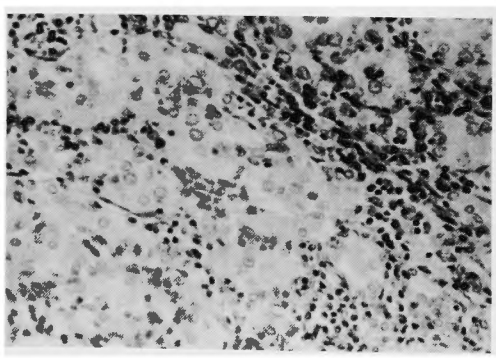

Fig. 8 Higher magnification of the Fig. 7. Original magnification ×140. Hematoxylin and eosin stain.

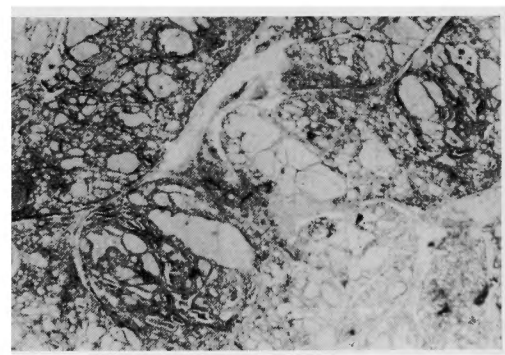

Fig. 9 Section from the specimen resected in 1970 showing Basedow's disease. Original magnification ×70. Hematoxylin and eosin stain.

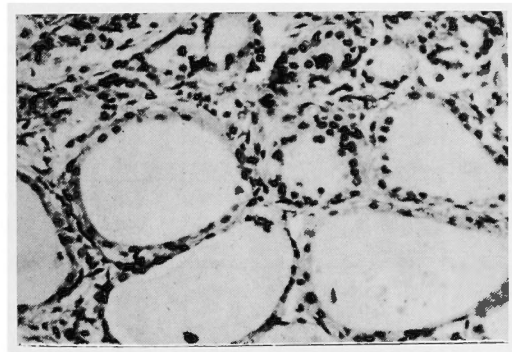

Fig. 10 Higher magnification of the Fig. 9. Original magnification ×140. Hematoxylin and eosin stain.

by the radiologists because of a law concerned with handling of radioisotope. Reluctantly we attempted to treat with telecobalt 60, total does of 4600 rad (200 rad by 23 times). Her hoarseness and symptoms of hyperthyroidism were improved and firm mass became softer and smaller as a result of radiation therapy. Soon after the radiation therapy, however, her symptoms and signs relapsed (Fig 4). On August 10, the patient underwent a total thyroidectomy with regional lymphnode cleaning.

Operative findings : The thyroid was attached to the thyroid cartilage, but there were no signs of invasion to the trachea. A daughter tumor mass beneath the right lobe of thyroid gland, spreading to the right supraclavicular fovea, was found. Regrettably, a left recurrent laryngeal nerve was cut off in process of tumor mass ablation.

The thyroid tumor mass removed weighed 145 g ; the right lobe was 7 by 4.5 by 3.8 cm; the left lobe, 6 by 4.5 by 3.4 cm; the isthmus, 5 by 2.8 by 2.5 cm; the daughter tumor mass, 2 by 2.8 by 2.7 cm in length, respectively (Fig. 5). The thyroid and daughter tumor masses were elastic firm.

On cut section, the tissue was parenchymatous except for three cysts (two cyst occurred in the right lobe, one cyst in the left lobe) containing thin yellowish and transparent fluid (Fig. 6).

Microscopical diagnosis of thyroid, daughter tumor masses and lymphnodes : Follicular adenocarcinoma, showing proliferation of anaplastic cells, very heavy infiltration with lymphocytes and plasma cells, scattered foreign body giant cells, and there were no normal thyroid and Basedow's disease tissue (Fig. 7, 8).

There were no metastatic findings in excised lymphnodes on histological examination.

Basedow's disease tissue (Fig. 9, 10) resected in 1970 was entirely different from this thyroid carcinoma tissue.

After total thyroidectomy, she had apparent hoarseness, but tetany and clinical signs of hyperthyroidism were not observed. She was discharged receiving desiccated thyroid (100mg daily).

A scintigram of the whole body with 99m-technetium showed no metastatic lesions.

Table 1 Serum hormone concentration

	T4	RT3U	T3	TSH	T7
befor biopsy (Feb. 1978)	9.0		4.5	1.25	
after biopsy (June 1, 1978)	13.3	28.7	3.5	1.25	3.81
after total thyroidectomy (May 5, 1979)	2.9	22.0	0.3	19.3	0.64
normal range	4.5–13.0 μg/dl	24–36%	0.8–1.8 ng/ml	<10 μU/ml	1.04–4.24

On May 5, 1979, laboratory data included: serum total T4, 2.9 μg/dl ; T3, 0.3 ng/ml; TSH, 19.3 μU/ml, when she received desiccated thyroid (50 mg daily) (Table 1).

She has showed hypothyroidism, and continues to receive desiccated thyroid (80 mg daily).

Discussion

The vast majority of thyroid carcinoma exhibits hypofunction of the thyroid when compared with normal thyroid tissue. Hyperthyroidism attributable to functioning thyroid carcinoma is exceedingly rare, and has been reported rarely[1-11,14,15,18,19,22-24,26-30]. In most of these cases the cause of hyperthyroidism was hyperfunction caused by metastatic lesions after removal of the original tumor and/or the normal thyroid gland. Hyperthyroidism attributable to the primary thyroid carcinoma has been reported five times (eight cases) to our knowledge[1)7)14)23)29)].

Our patient represents another case in whom hyperthyroidism is due to primary thyroid carcinoma. However, hyperthyroidism of this form should be discriminated from that of accidental association of thyroid carcinoma complicated with Basedow's disease or autonomous adenoma.

That her hyperthyroidism was produced by her carcinoma and not by the other thyroid tissue is presumed by the following lines of evidence.

1. Her scintiscan clearly showed concentration of function in the entire thyroid gland.

2. The right submandibular mass also revealed radioactivity when the scanning agent was administered.

3. The microscopical finding of its biopsy and the specimens from the resected thyroid revealed no other tissue except for follicular adenocarcinoma.

4. Signs and symptoms of hyperthyroidism disappeared after total thyroidectomy, and on the contrary, the patient showed hypothyroidism.

We can not determine definitely whether the right submandibular mass is a metastic lesion or not, because of no lymphatic tissue in the mass. If this mass is not a metastatic

Table 2 Cases reported including our one

year of report	Authors	No.	Age at onset	Sex	histological Diagnosis	Metastasis
1946	Leiter, et al	1.	52y.	female	follicular-papillary carcinoma	+
		2.	45y.	male	follicular carcinoma	+
1953	Egmark, et al	3.	66y.	female	alveolar-follicular-solid carcinoma	+
	Rawson, et al	4.	59y.	female	alveolar-follicular carcinoma	+
1955	Hertz	5.	61y.	female	adenocarcinoma	+
		6.	57y.	female	adenocarcinoma	+
	Holsinger, et al	7.	46y.	female	papillary adenocarcinoma	+
1957	Sonenberg, et al	8.	51y.	female	follicular-alveolar carcinoma	+
1960	Hunt, et al	9.	61y.	female	unknown	+
1961	Studer, et al	10.	58y.	male	Struma Langhans	+
1963	Bloise, et al	11.	40y.	female	follicular carcinoma	+
	Ginsburg, et al	12.	62y.	female	papillary-follicular carcinoma	+
1964	Federman	13.	53y.	female	follicular carcinoma	+
		14.	38y.	female	unknown	+
		15.	59y.	female	adenocarcinoma	+
1968	Dorta, et al	16.	56y.	male	Struma Langhans	+
	Sussman, et al	17.	6y.	female	follicular-papillary carcinoma	−
1970	McLaughlin, et al	18.	70y.	female	unknown	+
		19.	56y.	female	follicular carcinoma	+
	Valenta, et al	20.	49y.	female	follicular carcinoma	+
		21.	58y.	female	follicular carcinoma	+
		22.	60y.	male	trabecular carcinoma	+
1971	Ghose, et al	23.	68y.	female	follicular carcinoma	+
	Nishikubo	24.	22y.	female	papillary adenocarcinoma	−
1972	Inoue, et al	25.	28y.	female	follicular adenocarcinoma	+
1973	Dunn, et al	26.	61y.	female	follicular carcinoma	+
	Sung, et al	27.	57y.	male	follicular carcinoma	+
1975	McConnon, et al	28.	45y.	male	follicular carcinoma	+
1976	Mornex, et al	29.	64y.	female	trabeculo-vesicular carcinoma	+
1979	Baumann, et al	30.	68y.	female	follicular carcinoma	+
		31.	61y.	female	follicular carcinoma	+
		32.	64y.	female	follicular carcinoma	−
		33.	52y.	female	follicular carcinoma	−
		34.	76y.	female	follicular carcinoma	−
		35.	86y.	female	follicular-trabecular carcinoma	−
1980	Authors	36.	49y.	female	ollicular adenocarcinoma	?

lesion, it is possible that the carcinoma of this case may be multiple carcinomatosa.

In the 35 published cases (Table 2-1, 2-2) the majority (about 69%) of its histology were follicular type, the average age at onset was 54.7 years, the male: female ratio was 1: 4.8 and cases with metastatic lesions occupied 82.9%. Most of published cases had no endocrine ophthalmopathy except for the cases described by VALENTA et al[30] and LEITER et al[15], and hyperthyroidism due to functioning thyroid carcinoma as evidenced by an ele-

Table 3 T3 toxicosis criteria

1.	signs and symptoms of thyroid hyperfunction
2.	normal levels of total T4 as assessed by two or more of the following methods : column chromatography, competitive protein binding analysis, or PBI
3.	normal levels of free T4
4.	normal or raised radioactive-iodine uptake which could not be suppressed by 25 μg of liothyronine administered three times daily for 7-10 days
5.	a raised total T3 level

vated serum T3 level has been often described[18,22,28]. Our patient also had no signs and symptoms of endocrine ophthalmopathy, and high serum T3 level and almost normal T4. Therefore, in our patient, hyperthyroidism was most likely due to overproduction of T3 by thyroid carcinoma, that is, T3 toxicosis. But results of thyroid hormone examinations in our patient did not accept the criteria of T3 toxicosis completely (Table 3)[21]. Thus, our patient seems to come within the category of a common type that have been published up to the present.

STUDER et al[27] described that hormoneproduction of carcinoma was less per unit of weight than the normal thyroid. Each follicular carcinoma of the thyroid has different capacity of hormonesecretion, because large carcinoma masses do not always show more serious hyperthyroidism and higher hormoneproduction[1]. However according to the investigation of published cases, as to size, the thyroid tumor mass of our patient was large enough to bring about her hyperthyroidism.

The association of thyroid carcinoma with hyperthyroidism has been the subject of numerous reviews. The clinical analysis by SOKAL[25] indicated that carcinoma occurred in only 0.15% of 13,868 patients whose thyroid gland had been surgically removed because of diffuse toxic goiter. INAGAKI et al[13] also indicated, according to the clinical analysis after SOKAL, an extremely low incidence (0.19% of 15,077 patients).

However IIDA et al[12] reported that the association of thyroid carcinoma with hyperthroidism was about 20 times more frequent than that of other diseases except for carcinoam, for example thyroiditis, simple nodular goiter and so on. MATSUDA[17] reported that minimal thyroid carcinoma (less than 1 cm in diameter) was found infrequently (1.9%) in the thyroid gland tissue excised for hyperthyroidism, and all of these carcinoma were histologically diagnosed as papillary carcinoma. As to scintigram of the thyroid, MEADOWS[20] stated that carcinoma was found in 58% of "cold nodules", and 5% of "hot nodules". In addition, all thyroid carcinomas are said to be able to produce thyroid hormone[16].

In fact, the association of thyroid carcinoma with hyperthyroidism is infrequent. Hyperthyroidism due to carcinoma is much more infrequent. When hyperthyroidism is encountered, it must be always under the impression that there may be coexistence of carcinoma or functioning carcinoma. Autonomously functioning thyroid nodules, though benign in the vast majority of cases, should be observed periodically. If they continue to grow, they should be ablated as we have no correct criteria of operation or treatment with radioiodine concerning to the management of autonomous nodules of the thyroid.

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和文抄録

甲状腺機能亢進性原発性甲状腺癌の1例

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濾胞状甲状腺癌による甲状腺機能亢進症の珍しい症例（53才，女性）を経験したので報告する．血清 total-T_4 はほぼ正常で血清 T_3 が異常に高値であり，^{131}I による甲状腺シンチグラムでは，甲状腺と右顎下部の結節に集積を認めた．右顎下部の結節摘除と甲状腺全摘術を施行した．組織学的診断は両方ともに濾胞状腺癌で，正常甲状腺やの Basedow 病等の組織は発見されなかった．術後は血清甲状腺ホルモンは低値となり甲状腺機能低下症を呈した．それゆえ，この症例の甲状腺機能亢進症は甲状腺癌によるものと判断した．このような症例は極めてまれではあるが，一見良性の機能亢進性結節でも注意深い観察が必要である．