

Case Report

Thyroid Follicular Carcinoma in a Fourteen-year-old Girl with Graves' Disease

Kanako Kojima-Ishii¹, Kenji Ihara¹, Kazuhiro Ohkubo¹, Terumichi Matsuo¹, Naoko Toda¹,
Hiroyuki Yamashita², Shinji Kono³, and Toshiro Hara¹

¹*Department of Pediatrics, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan*

²*Yamashita Thyroid and Parathyroid Clinic, Fukuoka, Japan*

³*Harasanshin Hospital, Fukuoka, Japan*

Abstract. Here we present the case of a 14-yr-old girl who developed thyroid follicular carcinoma accompanied by Graves' disease. She was diagnosed with Graves' disease at 10 yr of age and soon achieved a euthyroid state after starting treatment. When she was 13 yr of age, her hyperthyroidism and goiter worsened despite medical therapy. Multiple nodules were found in her enlarged thyroid gland by ultrasonography. Her serum Tg level seemed within the normal range. She underwent near-total thyroidectomy for control of thyroid function. Histopathological study demonstrated that multiple oxyphilic follicular neoplasms were surrounded by the thyroid tissue compatible with Graves' disease. Capsular invasion was identified in one of the nodules, and thus the histological diagnosis was minimally invasive follicular carcinoma. She did not have signs suggesting metastasis, and has had no relapse for 18 mo after the operation. Although some previous studies showed a high prevalence of thyroid cancer with an aggressive nature in adult patients with Graves' disease, few reports about thyroid cancer accompanied by Graves' disease are available in children. The present case, however, suggests that careful investigation is needed when we detect thyroid nodules or progressive thyroid enlargement, especially in children with Graves' disease.

Key words: Graves' disease, thyroid cancer

Introduction

Thyroid carcinoma is considered to be rare in childhood and adolescence (1). Histologically,

most thyroid carcinomas are of the papillary type, with the follicular type accounting for 5% of cases (2). Although there have been a number of reports about thyroid carcinoma with Graves' disease in adult populations (3), few reports are available in children or adolescents (4, 5). Here we describe a 14-yr-old girl with thyroid follicular carcinoma unexpectedly found during the treatment of Graves' disease. Through the clinical features of this case, we reconfirmed the importance of careful investigation of the thyroid gland, especially in patients with Graves' disease and even in childhood or adolescence.

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Corresponding Author: Dr. Kanako Kojima-Ishii, Department of Pediatrics, Graduate School of Medical Science, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 814-8582, Japan

E-mail: k-kanako@momo.so-net.ne.jp

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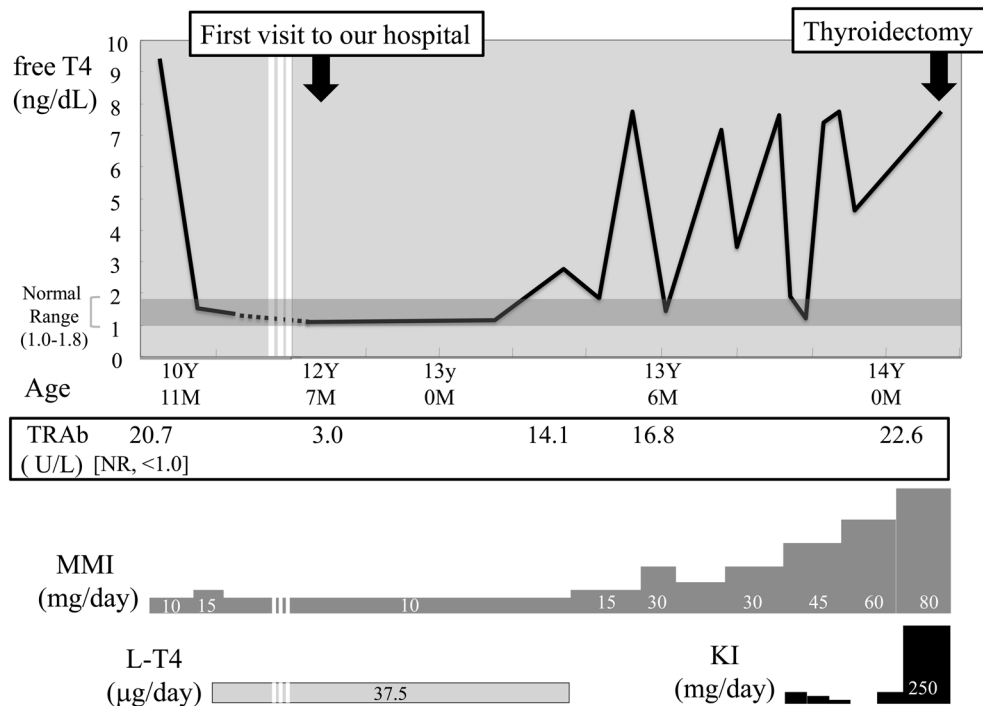


Fig. 1. Clinical course from onset until thyroidectomy. TRAb, TSH receptor antibody; MMI, thiamazole; L-T4, levothyroxine; KI, potassium iodine; NR, normal range.

Case Report

A 10-yr-old girl was brought to a hospital because of neck swelling. She was diagnosed with Graves' disease based on the findings of diffuse thyroid gland enlargement, hyperthyroidism and positive results for TSH receptor antibodies (free T3, >30 pg/mL [normal range (NR), 2.20–4.40]; free T4, 9.42 ng/dL [NR, 1.00–1.80]; TSH, <0.1 µU/mL [NR, 0.27–4.20]; TSH receptor antibody, 20.7 U/L [NR, <1.0]; thyroid stimulating antibody, 404% [NR, <180]). She had no history of appreciable diseases and no family history of thyroid diseases or early-onset cancers. Treatment with thiamazole (MMI) was started, and levothyroxine (L-T4) replacement was added subsequently. Her thyroid function was normalized within 2 mo, and the drug therapy was continued. When she was 12 yr old, she was referred to our hospital owing to a move with her family. At the first visit, we did not find swelling of her neck, and her thyroid hormone levels were

within normal ranges, whereas she still showed positive antibody results (free T4 1.10 ng/dL, TSH 1.20 µU/mL, TSH receptor antibody 3.0 U/L). Her clinical course is shown in Fig. 1. We continued the therapy with MMI and L-T4, and then her clinical condition remained stable for 8 mo. At the age of 13 yr and 3 mo, her hyperthyroidism worsened and neck swelling began again. We stopped the L-T4, increased the dose of MMI up to 80 mg/d and added treatment with potassium iodine (KI), the final dose of which reached 250 mg/d. Despite the intensive medical therapy, her thyroid hormone levels remained above normal ranges. Laboratory findings at 13 yr and 11 mo of age are shown in Table 1. Her level of Tg seemed within the normal range, although the accuracy could not be evaluated because of a high level of serum TgAb. Her consciousness was clear and physical examination showed anterior neck swelling without a palpable tumor, finger tremor at rest and no heart murmur or arrhythmia by auscultation. Her blood pressure was 112/50

Table 1 Laboratory findings at 13 yr and 11 mo of age

WBC	4.33×10 ³	μL	ALP	620	U/L	free T4	>7.77	ng/dL
Hb	12.2	g/dL	TC	111	mg/dL	free T3	>32.55	pg/mL
Plt	275×10 ³	/μL	TG	73	mg/dL	TSH	<0.01	μU/mL
TP	6.2	g/dL	BS	105	mg/dL	TgAb	1273.5	U/mL
Alb	3.9	g/dL	CPK	66	U/L	TPOAb	1404	U/mL
BUN	13	mg/dL	CRP	0.01	mg/dL	TRAb	22.6	U/L
Cr	0.31	mg/dL	BNP	6.9	pg/mL	TSAb	800	%
AST	23	U/L				Tg	8.1	ng/mL
ALT	30	U/L						

TgAb, Tg antibody; TPOAb, thyroid peroxidase antibody; TRAb, TSH receptor antibody; TSAb, thyroid stimulating antibody.

mmHg and heart rate was 118/min. While she presented with severe hyperthyroidism with a high level of TSH receptor antibody, no symptoms suggestive of thyroid crisis were observed. Thyroid ultrasonography showed diffuse goiter and increased blood flow by Doppler analysis, and these findings were consistent with an active state of Graves' disease. In addition, we detected multiple nodules in both lobes, the diameters of which were 10–17 mm. One nodule in the right lobe had heterogeneous internal echogenicity and others showed homogeneous internal echogenicity. All of these nodules appeared to have regular margins without microcalcifications (Fig. 2). When she was 14 yr and 1 mo of age, she underwent near-total thyroidectomy to control thyroid function. The weight of the isolated thyroid gland was 105 g (right lobe 55 g, left lobe 50 g), and multiple nodules were seen in both lobes as detected by ultrasonography. Histopathological study showed multiple oxyphilic follicular neoplasms. Capsular invasion with full-thickness interruption of the capsule was detected in one of the nodules in the left lobe (Fig. 3). The tissue surrounding the nodules showed typical finding of Graves' disease. The histological diagnosis of the nodule was minimally invasive follicular carcinoma. Other nodules were not histologically qualified for carcinoma. Vascular invasion, or lymph node or distal metastases of tumor cells were not observed. At present, 18 mo after the surgery, she has no sign of relapse and maintains a euthyroid state with L-T4 replacement therapy.

Discussion

There are a number of reports about the association between Graves' disease and thyroid cancer in adult populations. According to a recent review, the prevalence of thyroid carcinoma in Graves' disease is 0.5–15.0% (3). A study in Italy showed that the annual incidence of thyroid carcinoma in Graves' disease was 175/100,000 (6), which seemed higher than the recently reported incidence of 9.1/100,000 in the general population of Japan (7). However, due to differences in clinical or histological criteria, genetic background and iodine availability among the studies, it remains a matter of debate whether the prevalence of thyroid carcinoma is higher in patients with Graves' disease. Besides, there are reports that thyroid carcinoma accompanied by Graves' disease had an aggressive nature and association with high mortality (3, 6, 8–10). On the other hand, some studies did not show high-grade malignant characteristics of thyroid cancer in Graves' disease (11, 12). Therefore, the prognosis of thyroid cancer with Graves' disease has also been controversial. The mechanisms of the possible malignant potential of thyroid cancer in Graves' disease have not been elucidated. In previous reports, anti-thyroid drugs (13), stimulating TSH receptor antibody (14) or locally produced interleukins (15) were speculated to be factors that modify tumor characteristics.

Thyroid cancer is very rare in children and adolescents. It reportedly accounts for

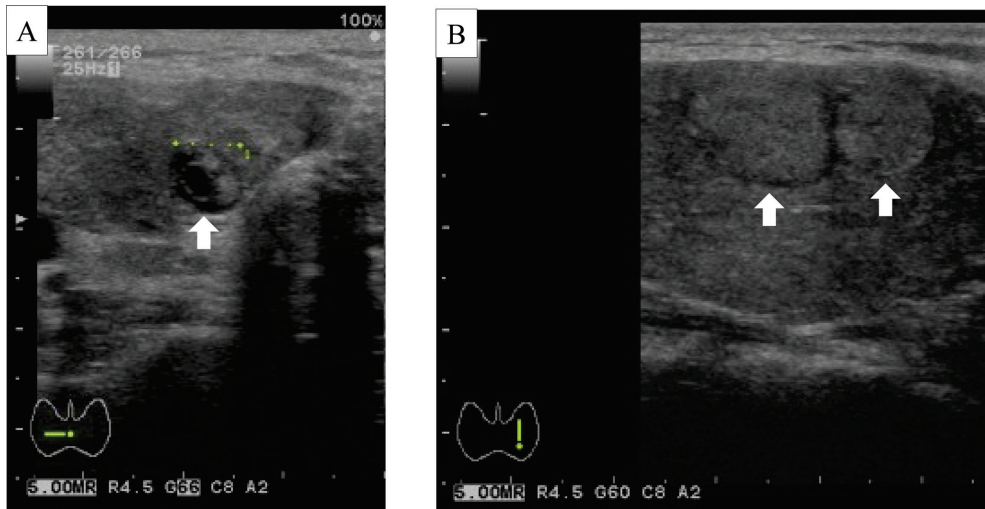


Fig. 2. Ultrasonographic thyroid images at 13 yr and 11 mo of age. Multiple nodules can be seen in both lobes. The diameters of the nodules range from 10 to 17 mm. The nodules did not have irregular margins or microcalcifications. A: Right lobe. B: Left lobe. The nodules are indicated by white arrows.

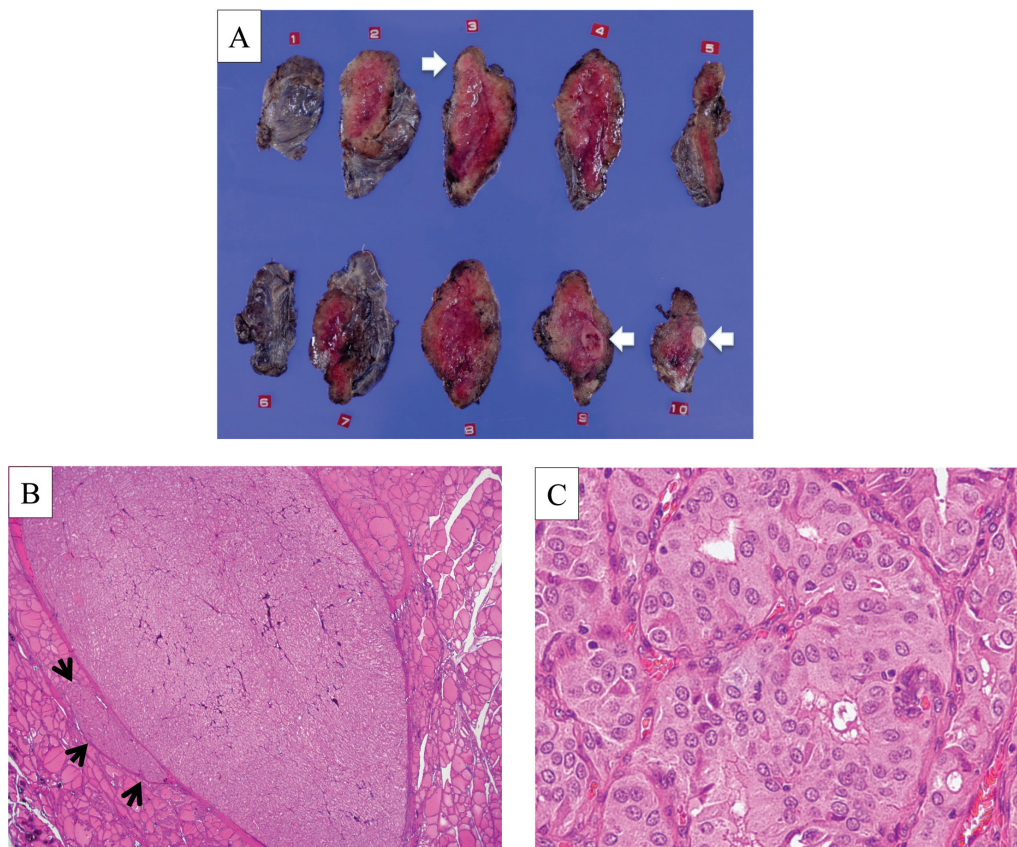


Fig. 3. Histological images of the thyroid gland. A: Macroscopic images of the isolated thyroid. Arrows indicate nodules in both lobes. B: Microscopic images (hematoxylin-eosin staining $\times 12.5$). C: Microscopic images (hematoxylin-eosin staining $\times 600$). Multiple oxyphilic follicular neoplasms can be seen. Capsular invasion is indicated by arrows in B. The thyroid tissue surrounding nodules is histologically normal with characteristic findings of Graves' disease.

approximately 0.5–3% of all carcinomas in their age groups (1), and its incidence under the age of 20 is about one in 100,000 in Japan (7). The prevalence of thyroid nodules in children was reported to be lower than that in adults (1, 16, 17). But some reports showed that the cancer risk of thyroid nodules is higher in children than in adults. In a review of 16 papers, the overall incidence of malignancy in thyroid nodules in children was 26.4% (18). On the other hand, a study of adults showed that the incidence of malignancy was 5.3% in cold thyroid nodules (19). In a recent study, the malignant risk of thyroid nodules was 22% in children, whereas it was 14% in adults (20). Thyroid cancer in pediatric populations has some specific characteristics, such as fast growing speed, high ratio of multifocal invasion and a tendency for metastasis and recurrence, although the overall survival rate of child patients was reported to be fairly high (2). Few children with thyroid cancer with Graves' disease have been reported. Niedziela *et al.* demonstrated a boy with thyroid papillary cancer accompanied by Graves' disease (4). Histologically, 90–95% of thyroid carcinomas are of the papillary type, and 5% are of the follicular type in all age groups (2). Therefore, the present case of thyroid follicular carcinoma with Graves' disease in a teenage girl was extraordinary rare. While no susceptibility genes have been identified for non-syndromic and non-medullary thyroid carcinoma, genetic alternations such as PAX8-PPAR gamma translocations or RAS mutations have been observed in thyroid follicular carcinoma (21). The present case had no familial history of any type of carcinoma; however, it might be possible that she had some genetic susceptibility to the onset of thyroid tumors and that a cancer-causing mutation, a so-called "second hit", occurred in a thyroid cell under stimulatory conditions through the TSH receptor as a result of organ-specific autoimmunity.

In this case, we did not think about the presence of thyroid cancer in the thyroid glands before thyroidectomy because clinical findings suggestive of coexisting malignancy

were not observed. In general, characteristic findings of a malignant thyroid nodule by ultrasonography include irregular shape, ill-defined edge, jagged border, heterogeneous nature or microcalcifications (18, 22), whereas minimally invasive follicular carcinoma often does not show any of these findings (22). In this case, although one nodule had heterogeneous internal echoes, we did not see other malignant findings. Consequently, we assumed that the progressing thyroid enlargement was simply a symptom of Graves' disease. However, we should have evaluated the thyroid much more intensively in consideration of the ultrasound features and substantial risk for carcinogenesis in Graves' disease, especially in adolescence.

In conclusion, we reported a case of thyroid follicular carcinoma accompanied by Graves' disease in a 14-yr-old girl. Although thyroid cancer rarely occurs in pediatric populations, careful investigation is needed if we observe progressive thyroid enlargement or detect thyroid nodules by ultrasonography, even in children with Graves' disease.

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