

Coexistence of resistance to thyroid hormone and papillary thyroid carcinoma

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Summary

Resistance to thyroid hormone (RTH) is a syndrome of reduced tissue responsiveness to thyroid hormones. RTH is majorly caused by mutations in the thyroid hormone receptor beta (*THRB*) gene. Recent studies indicated a close association of *THRB* mutations with human cancers, but the role of *THRB* mutation in carcinogenesis is still unclear. Here, we report a rare case of RTH with a papillary thyroid carcinoma (PTC). A 26-year-old woman was referred to our hospital due to a thyroid tumor and hormonal abnormality. She had elevated serum thyroid hormones and non-suppressed TSH levels. Genetic analysis of *THRB* identified a missense mutation, P452L, leading to a diagnosis of RTH. Ultrasound-guided fine-needle aspiration biopsy of the tumor and lymph nodes enabled the cytological diagnosis of PTC with lymph node metastases. Total thyroidectomy and neck lymph nodes dissection were performed. Following surgery, thyroxine replacement ($\geq 500 \mu\text{g}$) was necessary to avoid the symptoms of hypothyroidism and to maintain her TSH levels within the same range as before the operation. During the follow-up, basal thyroglobulin (Tg) levels were around 6 ng/ml and TSH-stimulated Tg levels were between 12 and 20 ng/ml. Up to present, the patient has had no recurrence of PTC. This indicates that these Tg values are consistent with a biochemical incomplete response or an indeterminate response. There is no consensus regarding the management of thyroid carcinoma in patients with RTH, but aggressive treatments such as total thyroidectomy followed by radioiodine (RAI) and TSH suppression therapy are recommended.

Learning points:

- There are only a few cases reporting the coexistence of RTH and thyroid carcinoma. Moreover, our case would be the first case presenting one with lymph node metastases.
- Recent studies indicated a close association of *THRB* mutations with human cancers, but the role of *THRB* mutation in carcinogenesis is still unclear.
- When total thyroidectomy is performed in patients with RTH, a large amount of thyroxine is needed to maintain their thyroid function.
- There is no consensus regarding the management of thyroid carcinoma in patient with RTH, but effective treatments such as total thyroidectomy followed by RAI and TSH suppression therapy are recommended.

Background

Resistance to thyroid hormone (RTH), a syndrome of reduced tissue responsiveness to thyroid hormones that was first reported in 1967 by Refetoff *et al.* (1), is

characterized by high levels of serum thyroid hormones and poor suppression of serum thyroid-stimulating hormone (TSH) levels. Some patients may be misdiagnosed with hyperthyroidism or hypothyroidism, if only

the serum thyroid hormone levels or the serum TSH levels are considered. In most patients, reduced sensitivity to thyroid hormones in peripheral organs is at least partially compensated with elevated serum thyroid hormone concentrations caused by elevated serum TSH concentrations or enhanced bioactivity of TSH.

Most cases of RTH have mutations in the thyroid hormone receptor beta (*THRB*) gene (2). To date, at least 171 different *THRB* mutations were reported in more than 459 RTH families. Mutations in the thyroid hormone receptor alpha (*THRA*) gene have also been recently identified (3). Hence, Refetoff *et al.* (4) proposed to use the terms 'RTH α ' or 'RTH β ' to distinguish RTH phenotypes. Several studies have demonstrated a close association of *THRB* mutations with human cancers, but the role of *THRB* mutation in carcinogenesis is still unclear (5).

Here, we describe a 26-year-old woman with RTH β and papillary thyroid carcinoma (PTC), with a dominant negative mutation of P452L in exon 10 of *THRB*. We surmise that sharing our experiences is important because coexistence of RTH and thyroid carcinoma is rare (6). Furthermore, we discuss the management of differentiated thyroid cancer in patient with RTH with respect to TSH suppression therapy.

Case presentation

The patient was a 26-year-old Japanese female who presented with persistent goiter since her teenage years. One year prior, she noticed hyperthyroidism symptoms, such as fatigue, finger tremors and palpitations, because of which she visited a regional hospital and was diagnosed with thyroid dysfunction and thyroid tumor. She was subsequently referred to our hospital for further examination. She was 165.5 cm tall with a weight of 59.3 kg; her BMI was 21.6 kg/m². Blood pressure was 94/42 mmHg, pulse rate was regular at 74 beats/min, and body temperature was 36.8 °C. She had diffuse goiter and hard mass in the right thyroid lobe.

Investigation

Hematologic and blood chemistry tests were normal. Serum TSH level was 4.58 μ IU/ml (normal range, 0.6–4.6 μ IU/ml), free triiodothyronine (FT₃) level was 5.22 pg/ml (normal range, 1.71–3.71 pg/ml), and free thyroxine (FT₄) level was 2.17 ng/dl (normal range, 0.70–1.48 ng/dl); these indicated the presence of syndrome of inappropriate secretion of TSH (SITSH) from either RTH or a TSH-producing tumor (TSHoma). Thyroid

autoantibodies against thyroglobulin (Tg), thyroperoxidase, and TSH-receptor were all negative. Thyroid ultrasound (US) and computed tomography (CT) revealed enlargement and tumor measuring ~2 cm in the right lobe with features suggestive of malignancy (Fig. 1A). Furthermore, there were some enlarged lymph nodes, ranging from 0.8 to 1.5 cm in size, at the right side of the neck. US-guided fine-needle aspiration biopsy of the tumor and enlarged lymph nodes enabled the cytological

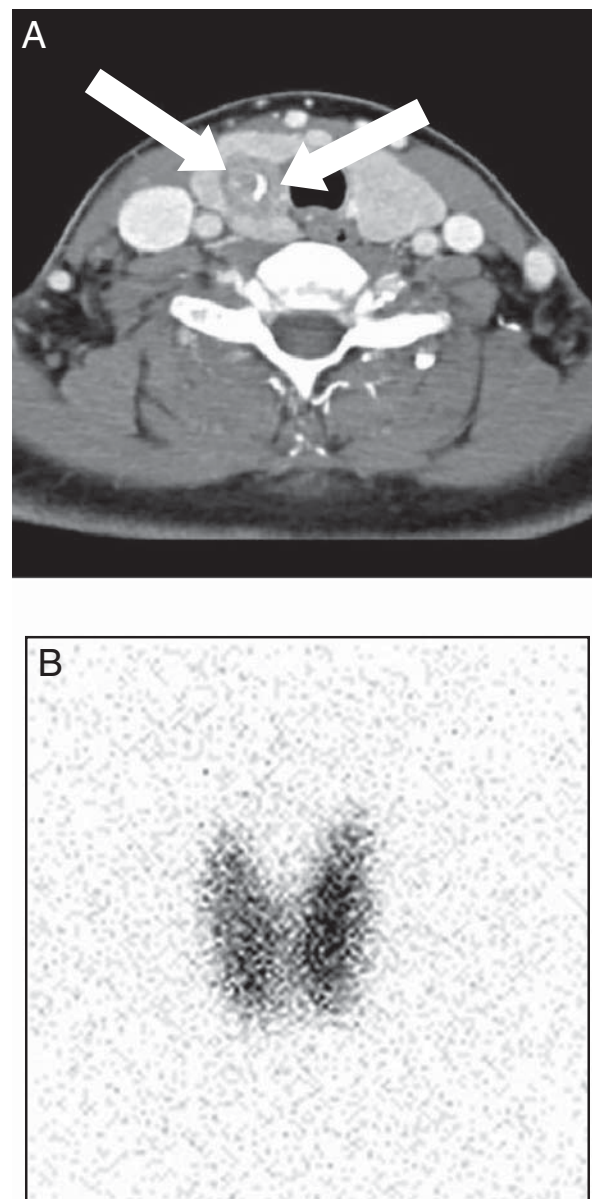


Figure 1
Radiologic imaging tests. (A) Enhanced CT showed diffuse enlargement of the thyroid gland and a tumor (arrows) in the right lobe of the thyroid. (B) Thyroidal uptake of radioiodine showed diffuse enlargement of both lobes of the thyroid with homogeneously increased uptake (52.74%).

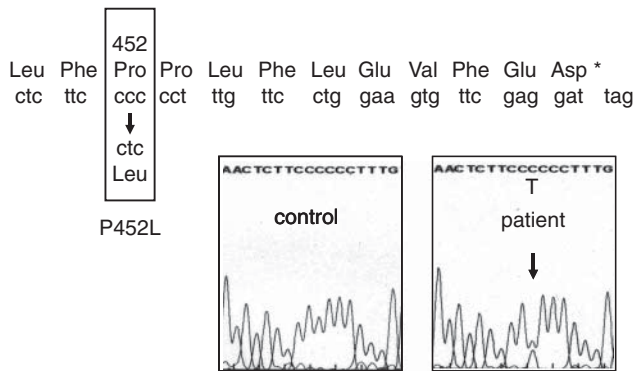


Figure 2
Direct sequencing of *THRβ* in the present case. Sequence analysis showed a heterozygous substitution of the proline (CCC) for leucine (CTC) at codon 452 (P452L). The asterisk indicates a stop codon.

diagnosis of PTC with lymph node metastases. Thyroidal uptake of radiolabeled iodine showed diffuse enlargement of the thyroid gland with increased uptake of 52.74% (Fig. 1B). Magnetic resonance imaging revealed no pituitary adenoma.

After obtaining written permission from the patient and her family and the approval by the ethics committee in Kumamoto University, gene analysis of *THRβ* was performed. Genomic DNA was isolated from peripheral blood leukocytes. Seven genomic DNA fragments (spanning exons 4–10 of *THRβ*) were amplified using specific primers. Direct sequencing was performed using automated sequencing system (Beckman CEQ 2000 XL; Beckman Coulter, Brea, CA, USA). Genetic analysis revealed a heterozygous point mutation of *THRβ*, CCC to CTC, resulting in substitution of proline to leucine at codon 452 (P452L) (Fig. 2). Finally, the patient was diagnosed with RTH β and PTC. The patient's mother, older sister, and three children also underwent genetic analysis, but only her mother had the same genetic mutation and was diagnosed with RTH β . She also did not have any thyroid autoantibodies.

Treatment

She underwent total thyroidectomy with neck lymph node dissection (right, levels I–VI and left, levels III). Histological examination showed that the thyroid tumor measuring 2 cm was classical PTC without extrathyroidal extension. We confirmed metastatic lymph nodes in 7 of 46 dissected lymph node specimens (T2N1bM0). She did not receive radioiodine (RAI) ablation for the reasons that the resection of the tumor and lymph nodes was

considered complete and her mental status was unstable at that time. After surgery, $\geq 500 \mu\text{g}$ of thyroxine was administered in the attempt to maintain TSH levels within preoperative levels and to avoid symptoms of hypothyroidism.

Outcome and follow-up

More than 10 years have passed since total thyroidectomy was performed and the patient has now been followed up at 3-month intervals. Neck-US, X-rays, and CT scan were performed every year for the first 5 years, and then every 2 years. Large amount of thyroxine was continued and recurrence of thyroid carcinoma has not been found so far. Fig. 3 shows the changes of TSH and Tg after thyroidectomy. Basal Tg levels were about 6 ng/ml and TSH-stimulated Tg levels were between 12 and 20 ng/ml. These Tg values were consistent with a biochemical incomplete response or an indeterminate response.

Discussion

Here we describe a rare case of RTH β with PTC, presenting with lymph node metastases for the first time. Moreover, we identified a missense mutation, P452L, in the *THRβ* gene. This mutation was reported by Izabel in 2005 for the first time (Cited 2015 Aug 19 <http://www.lats.org/PremiosLats/JovensPesquisadores.aspx?jp=12>). However, it has not been reported in officially published theses and

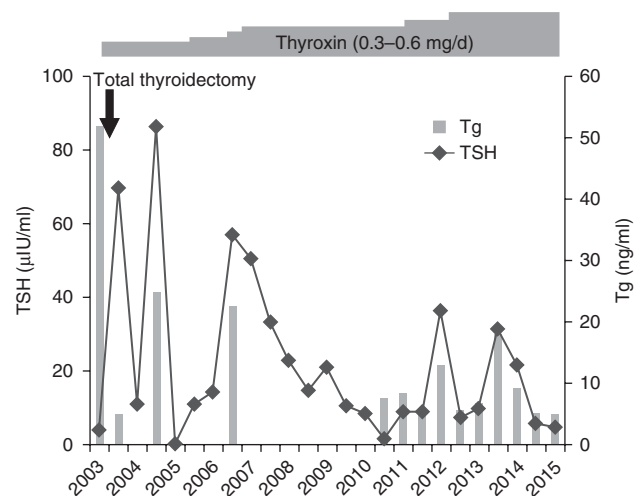


Figure 3
Changes in TSH and thyroglobulin (Tg). Tg levels were measured by the RIA before 2010. Since 2010, they have been measured by the electrochemiluminescence immunoassay (ECLIA).

also has not been registered in the Human Gene Mutation Database (HGMD).

Recent studies have suggested that *THRB* mutations may have oncogenic actions and may play a role in carcinogenesis, including liver, kidney, breast, colon, and pituitary tumors, in humans (5). It was also reported that knock-in mice harboring homozygous mutation in *THRB* (*Thrb^{PV/PV}* mice) had impaired T₃ binding and dominant negative activity and spontaneously developed thyroid cancer and pituitary tumors (7). Because TSH is the most important thyroid growth factor, elevated TSH levels may promote thyroid tumorigenesis in patients with RTH. Although these notions indicate that RTH has strong correlation with thyroid tumorigenesis and that patients with RTH are at an increased risk for thyroid carcinoma, there are only a few reports that describe coexistence of RTH and thyroid carcinoma (6). This could be because most patients with RTH have heterozygous *THRB* mutation, unlike the *Thrb^{PV/PV}* homozygous mouse model. Homozygous *Thrb^{PV/PV}* mice exhibited high levels of serum TSH (~400 times higher than WT mice) and developed thyroid cancers, whereas heterozygous *Thrb^{PV/+}* mice showed only slightly elevated serum TSH levels (~2 times higher than WT mice) and did not develop thyroid cancers (7).

In fact, although more than 3000 patients with RTH have been identified before, there were only a few cases reported that had both RTH and PTC. Since the incidence of PTC in patients with RTH does not appear to be high compared with that in the general population, it is conceivable that emergence of thyroid carcinoma in our patient may have been coincidental. In fact, the patient's mother, who carried the same *THRB* mutation, did not show any thyroid mass.

The patient underwent total thyroidectomy with neck lymph node dissection. To the best of our knowledge, this is the first case presenting with lymph node metastases. In order to discuss additional therapies, we stratified our patient according to the current guidelines although she was diagnosed in 2003. She was classified as T2N1bM0, stage I, by the version 7 of the UICC/AJCC TNM system (8). In accordance with the American Thyroid Association (ATA) risk of recurrence stratification system, she was stratified as intermediate risk (9). She did not receive RAI ablation because the resection of the tumor and lymph nodes was considered complete. Instability of her mental status after surgery was another reason adjuvant therapy was not administered. There have not been any studies specifically examining RAI treatment efficacy in the ATA intermediate risk group so far. Furthermore, RAI

therapeutic efficacy in patients <45 years of age with lymph node metastases is unclear. But the guideline of the ATA in 2015 states that RAI adjuvant therapy should be considered after total thyroidectomy in intermediate risk level differentiated thyroid cancer (DTC) patients, although it is a weak recommendation with low-quality evidence (9).

In general, TSH suppression therapy is considered useful to prevent recurrence of thyroid carcinoma. However, there is no agreed consensus regarding the management of DTC in patients with RTH. Unluturk *et al.* (10) showed four cases of DTC associated with SITSH including RTH. These patients received RAI treatment after total thyroidectomy and their outcomes were favorable despite the persistence of non-suppressed TSH levels. Unluturk *et al.* recommended effective treatment options such as the complete removal of the tumor followed by RAI and attempt to reduce the serum TSH to the lowest tolerable level. The other cases reported in the literature were classified as low-risk patients and most of them were not permitted RAI ablation (6). Vinagre *et al.* (11) reported a patient with RTH who had an incidentally discovered 4 mm PTC and high TSH levels after total thyroidectomy. According to the current guideline, the patient did not receive RAI. During the follow-up, the patient had disease progression, as suggested by the increased Tg levels. They speculated that the concurrence of *THRB* mutation, high TSH levels, and BRAF mutation may have acted toward the malignant transformation and the aggressiveness of the PTC in that case. They suggested that aggressive treatment can be an option to prevent tumor recurrence and persistence in the absence of an ideal TSH suppression. When large amount of thyroxine is administered to lower serum TSH level, there is a potential risk of causing hyperthyroidism. In that case, treatment with thyroid hormone analog, such as 3,5,3'-triiodo-L-thyronine may be useful in high-risk patients. In our case, ≥ 500 μ g of thyroxine had been continued, but the patient showed no symptoms of hyperthyroidism. As a matter of fact, it is very difficult to stabilize TSH values and they varied from 0.27 to 21.43 μ U/ml in the last 1 year without change in thyroxine dosage. Fortunately, there is no evidence of PTC recurrence even after 12 years. This indicates that serum Tg levels during the follow-up are consistent with a biochemical incomplete response or an indeterminate response.

In conclusion, we experienced a rare case of RTH β with thyroid carcinoma and this is the first case presenting with lymph node metastases. Further studies are of interest to elucidate the role of *THRB* mutation in

carcinogenesis and to achieve consensus regarding the management of thyroid carcinoma in patients with SITSH.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

Written informed consent was obtained from the patient.

Author contribution statement

All the authors have read the manuscript and have approved this article. M Igata is the author and E Araki is the corresponding author of this article. K Tsuruzoe, J Kawashima, D Kukidome, T Kondo, H Motoshima, S Shimoda, N Furukawa, T Nishikawa and N Miyamura are clinicians who contributed to the management of this case.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

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Received in final form 8 March 2016

Accepted 30 March 2016