CASE REPORT

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Familial Clinical Heterogeneity of Medullary Thyroid Cancer with Germline RET S891A Protooncogene Mutation: 7-year Follow-up with Successful Sorafenib Treatment

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What is already known on this topic?

Different mutations in the *RET* gene are associated with varying age-dependent penetrance and disease manifestations in medullary thyroid carcinoma (MTC). The American Thyroid Association (ATA) has classified hereditary MTC into three risk categories ("moderate", "high", and "highest") based on the type of *RET* mutation. The S891A mutation in *RET* is a rare germline mutation associated with a moderate risk of MTC. The use of sorafenib and other RET-targeting tyrosine kinase inhibitors (TKIs) in childhood thyroid cancers MTC and disseminated thyroid cancer have rarely been reported.

What this study adds?

Despite the well-defined genotype-phenotype correlation of moderate risk *RET* p.S891A germline mutation, we report an early-onset, inoperable case of MTC. We also found an additional *SDHA* somatic mutation, p.S408L, in the same patient, which may have triggered the severity of the presentation. This co-occurrence has not been reported before. *RET* p.S891A may cause mixed MTC and papillary thyroid carcinoma. The patient experienced growth retardation possibly due to the side effects of sorafenib.

Abstract

Hereditary forms of medullary thyroid carcinoma (MTC) are rare. Different phenotypes with the same mutation may be due to differences in the timing of *RET* activation steps, additional mutations in other regions of the gene, or the co-occurrence of germline and somatic mutations, which is an infrequent possibility. Here, we present the different features and challenges during the follow-up of three family members with the same germline mutation. A 4-year-old male patient with respiratory distress was diagnosed with MTC and found to have a heterozygous germline mutation C.2671T > G(S891A) in the *RET* gene (classified as intermediate risk by the American Thyroid Association. As the tumor was inoperable, treatment with a tyrosine kinase inhibitor (sorafenib) was initiated. This treatment with sorafenib prevented tumor progression for seven years. Whole exome sequencing did not identify additional mutations. Segregation analysis showed the same mutation in the asymptomatic mother and sister. In the proband, thyroid tissues were examined for somatic mutations, and *SDHA* c.1223C > T (p.S408L) was found. The clinical presentation of rare mutations such as *RET* p.S891A differed among family members carrying the same germline mutation. Our index case's more severe clinical presentation may be due to an additional somatic mutation. Sorafenib treatment can be an option for advanced MTC and may prevent disease progression.

Keywords: Medullary thyroid carcinoma, *RET,* sorafenib

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Introduction

Medullary thyroid carcinoma (MTC) is a rare tumor that develops from parafollicular C cells of the thyroid gland, accounting for 1-5% of thyroid malignancies (1,2). It can occur sporadically or as part of a genetic syndrome, such as multiple endocrine neoplasia type 2 (MEN2). The pathogenesis of MTC involves activation of the "Rearranged during Transfection" (*RET*) protooncogene through germline mutations, somatic mutations, or gene fusions (2). *RET* encodes a receptor tyrosine kinase that plays a significant role in developing the enteric nervous system and the thyroid gland. Germline mutations in *RET* are important in the clinical progression and prognosis of hereditary MTC (MEN2A, MEN2B, and familial MTC), which are autosomal dominant disorders. Different mutations in *RET* are associated with varying age-dependent penetrance and disease manifestations. The American Thyroid Association (ATA) has classified hereditary MTC into three risk categories, "moderate", "high", and "highest", based on the type of *RET* mutation (2,3).

Genetic testing is therefore crucial in identifying patients at risk of familial MTC, as early diagnosis and prophylactic surgery may improve patient outcomes. Treatment of MTC typically involves surgical resection of the tumor (2). Systemic chemotherapy, such as cis-platinum, doxorubicin, vincristine, and 5-fluorouracil, has demonstrated limited effectiveness for metastatic MTCs (4). Fortunately, new targeted therapies with tyrosine kinase inhibitors (TKIs), such as vandetanib, cabozantinib, and sorafenib, provide hope for metastatic MTC treatment (4). The Food and Drug Administration recently approved Sorafenib for radioactive iodine-refractory thyroid cancer in adults, which inhibits RET and vascular endothelial growth factor (VEGF) receptor. It is approved for use in children aged 12 and above. For the patient we are sharing, the treatment was initiated after an international request was made under humanitarian aid provisions, and the medication was brought in based on expert committee reports (5). A meta-analysis by Vuong et al. (4) assessed data from eight trials involving 101 metastatic MTC cases. The results showed that sorafenib was a therapeutic option for patients with metastatic MTCs, particularly in cases where other treatment regimens have proven ineffective.

The S891A mutation in *RET* is a rare germline mutation associated with a moderate risk of MTC (2). Despite a well-defined correlation between genotype and phenotype, we present an inoperable case of a 4.2-year-old boy with a germline S891A mutation. To the best of our knowledge, there are no reported cases of individuals who carry both RET p.S891A germline mutation and a succinate dehydrogenase subunit A (*SDHA)* somatic mutation [p.S408L (c.1223C > T), which this patient was also found to harbor. This report also describes our experience with the treatment success and potential side effects of sorafenib.

Case Report

A 4.2-year-old male patient was admitted to the outpatient clinic due to difficulty in breathing, stridor, loss of appetite, and weight loss. His medical history was that he was born to non-consanguineous parents. Before his current hospitalization, he had been hospitalized three times and was misdiagnosed with bronchiolitis. On physical examination, he was 104 cm in length [-0.28 standard deviation (SD)] with a body mass index (BMI) of 13.87 kg/m^2 (-1.48 SD) and had a goiter. Chest X-ray showed an apple core lesion around the trachea (Figure 1A). Further radiologic examination with a thorax computed tomography scan revealed a hypoechoic lesion with punctate calcifications measuring 32x25x34 mm involving the right anterior cervical region, invading the thyroid parenchyma and encompassing the right internal carotid artery and the trachea. The scan also showed the presence of several lymph nodes with metastatic involvement (Figure 1B).

Laboratory evaluation reported normal thyroid function. Although the levels of thyroid stimulating hormone (TSH) at 3.24 mIU/mL [normal range (NR) 0.38-5.33 mIU/mL] and fT4 at 17.95 pmol/L (NR 11-22 pmol/L) were within the normal range, the levels of human thyroglobulin (hTg), calcitonin, and carcinoembryonic antigen (CEA) were significantly elevated [54.2 ng/dL for hTg, 1093 pg/mL for calcitonin (NR 0-10 ng/mL), and 22.74 ng/mL for CEA (NR < 0.3 ng/mL)]. Following the biopsy of the lesions, histopathological examination reported MTC. Molecular analysis revealed a heterogeneous pathogenic *RET* mutation [p.S891A (c.2671T > G) (rs75234356)]. According to ATA, this specific variant was in the moderate risk category (2). Due to the inoperable nature of the tumor, sorafenib was started at a daily dose of 200 mg and dosage titrated during close follow-up. He underwent annual thyroid and thorax magnetic resonance imaging (MRI). Although the tumor did not exhibit complete regression, there was a gradual reduction. In the second month of treatment, the tumor decreased to 24x16 mm. Furthermore, following sorafenib treatment, there was a decrease in calcitonin and CEA levels (Table 1).

Segregation analysis showed that the patient's asymptomatic mother and sister had the same *RET* mutation. The family received genetic counseling. Although

they had normal thyroid glands on imaging, the sister had a slightly elevated calcitonin level at 1.5 years of age (calcitonin 26.2 pg/mL, CEA 0.54 ng/mL), while the mother's serum calcitonin and CEA levels were normal. The younger sister and mother underwent prophylactic thyroidectomy at the age of 2 and 35 years, respectively. Pathological examination of thyroidectomy materials showed that the younger sister had C cell hyperplasia, while the mother had papillary thyroid cancer and accompanying medullary microcarcinoma (Figure 2). Whole exome sequencing (WES) was conducted on all family members to identify additional mutations, but none were found. The index case, who had the same *RET* mutation as the mother and sister in the moderate-risk category, had presented with a more severe clinical picture compared to them. When the pathological materials were molecularly evaluated for the possibility of a somatic mutation, *SDHA* somatic mutation [p.S408L (c.1223C > T)] was found in the index case's material, and no somatic mutation was found in the mother's. However, sister's pathological material was unsuitable for somatic mutation analysis.

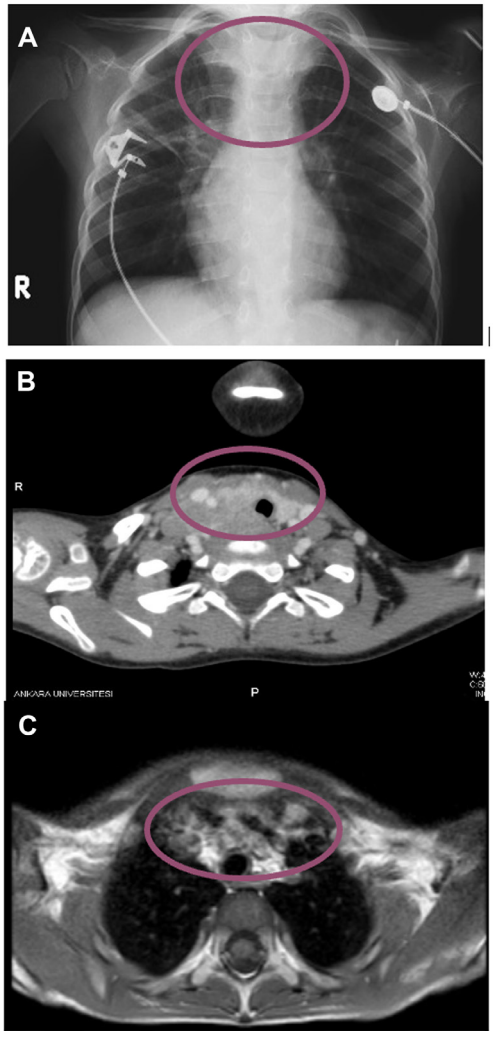

Figure 1. (A) An apple core lesion around the trachea. B) A heterogeneous hypoechoic lesion with punctate calcifications measuring 32x25x34 mm in size involving the right anterior cervical region adjacent to the thyroid gland, invading the thyroid parenchyma and encompassing the right internal carotid artery, causing circumferential stenosis, and displacing and compressing the trachea to the left of the midline. This lesion extended into the anterior mediastinum and was similar in contrast to the left lobe of the thyroid. The existence of several lymph nodes with metastatic involvement was shown (C)

Based on ATA guidelines, the index patient and his sister were evaluated for MEN2A. Calcitonin, CEA, and serum calcium levels were monitored (Table 1). On follow-up, he had no symptoms of hyperparathyroidism (HPTH) or pheochromocytoma (PHEO). At the age of 11 years, we began to screen 24-hour urine for metanephrines and catecholamines for PHEO. All were normal.

A notable slowing of growth velocity was observed under sorafenib treatment during follow-up (Figure 2). Hemogram and biochemical parameters were normal, including liver and kidney function, blood glucose, tissue transglutaminase autoantibody immunoglobulin A (IgA), and serum total IgA level. In addition, his urine analysis was normal. This phenomenon was considered a side effect of sorafenib. Somatamedin-C was 53.6 ng/mL (NR 76-499 ng/mL). At the age of 11 years a slight elevation of TSH (11 mIU/mL) with normal fT4 (14 pmol/L) was observed and thyroglobulin (69 pg/mL) was elevated. Thyroid peroxidase antibody and thyroglobulin antibody (TgAb) were negative, and urine iodine level was normal. He was on no other medication that could cause an elevation in TSH. It was concluded that this mild elevation of TSH was associated with tyrosine kinase

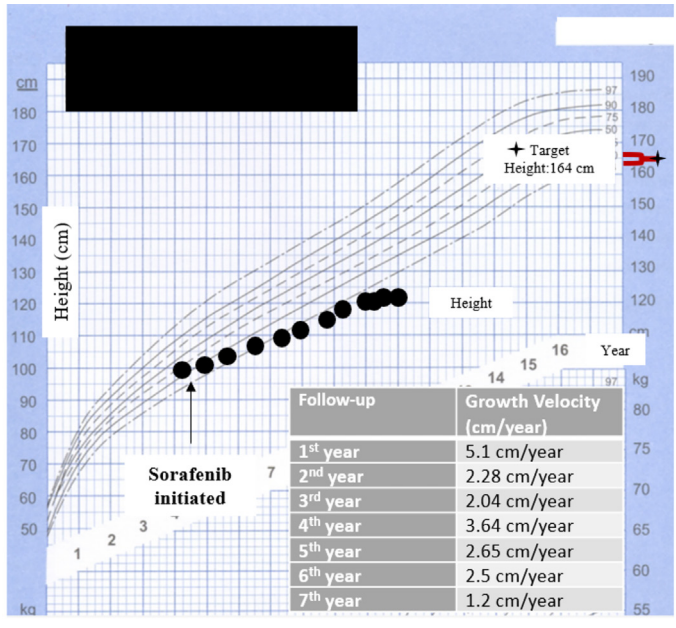

Figure 2. Height curves and the growth velocity of the patient

Table 1. Biochemical monitoring of the patient

Age	Calcitonin (pg/mL)	CEA (ng/mL)	Ca (mg/dL)	P (mg/dL)	ALP (U/L)	PTH (pg/mL)	TSH µIU/mL	FT4 pmol/L	Sorafenib (mg/day)
4.2	**1093**	**22.74**	9.7	4.3	219	14	3.24	17.95	100
4.9	**216**	**6.1**	10.4	4.6	236	15	3.64	21.5	100 + 100
5.6	**119**	**4.91**	9.6	3.17	135	43.5	6.2	21.6	200 + 100
5.9	**41.1**	**5.99**	9.8	3.43	155	32	5.31	10.57*	200 + 100
6.6	**67.6**	**3.76**	10	3.6	151	8.5	7.33	13.2*	200 + 100
6.9	**47**	**4.33**	10	5.4	165	92	5.74	14.04*	200 + 100
7.2	**39**	**3.5**	9.2	3.8	137	33.5	6.1	11.06*	200 + 100
8.8	11	2.9	9.4	3.8	152	62.4	6.12	13.61*	200 + 200
9.6	6.9	2.6	8.9	4.9	167	43	5.18	18.8	200 + 200
10.1	10	3.14	9	3.9	122	80	3.31	14	200 + 200
10.5	10.7	1.99	9.4	3.6	175	35	3.62	18	200 + 200
11.2	9.1	2.54	9.1	3.17	102	19	**11****	14	200 + 200

Normal range for calcitonin: 5.2-11.7 pg/mL, FT4: 11-22 pmol/L, FT4*: 7-15.96 pmol/L, CEA: < 0.3 ng/mL.
**1.2 mcg/kg/day L-thyroxine treatment initiated.
CEA: carcinoembryonic antigen, Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathyroid hormone, TSH: thyroid stimulating hormone, FT4: free thyroxine

inhibition, and L-thyroxine (L-T4) treatment was initiated at a dose of 1.2 mcg/kg/day.

The patient is now 11 years of age and on 400 mg of sorafenib treatment. His height is 124 cm (-3.21 SD); his BMI is 14.5 kg/m^2 (-1.9 SD). Bone age is 6 years and 10 months. Throughout the follow-up period, it is important to note that the patient remained in a prepubertal state (follicle stimulating hormone 0.8 mIU/mL, LH < 0.3 mIU/mL, total testosteron 2.5 ng/dL). He has retarded growth and normal development (normal language, cognitive abilities, social skills, and fine motor development). He is on L-T4 1.2 µg/kg/day. Tumor markers are negative. He has no symptoms and signs of HPTH or PHEO. He is under close follow-up by physical examination every three months, with laboratory evaluation every six months and periodic MRI annually. The mass size remained stable, and no metastases were observed (Figure 1C).

Discussion

The varying clinical presentation in individuals with the same *RET* germline mutation is likely due to incomplete penetrance, allelic/chromosomal imbalance, a second hit mutation, and/or differences in the timing, location, and severity of somatic mutations during tumor development. It is also important to note that environmental factors and epigenetic modifications, such as DNA methylation, histone modification, and microRNA dysregulation, can influence gene expression and tumor development and contribute to differences in clinical presentation (6,7). Although the case presented herein had a well-defined classification of moderate risk with heterogeneous *RET* p.S891A, he had a rapid and severe onset tumor, contrary to expectations. The patient's sister and mother also had the same mutation with different clinical presentations. This variability in clinical presentation among family members highlights the importance of genetic testing and surveillance in families with a history of MTC. Genetic testing for *RET* mutations is recommended for individuals with a first-degree relative history of MTC or other related cancers (*HRAS, NRAS, KRAS*) and individuals with clinical features suggestive of MTC to enable earlier detection and intervention (2).

Additional somatic mutations, such as in the *KRAS, NRAS*, *CCND1, FGF3, FGF19* and *CDKN2A* genes, may be associated with more aggressive forms of MTC and poorer outcomes (8). Somatic mutations may influence the clinical course of MTC. In the case of this boy, it might be speculated that additional somatic mutations occurred early in tumor development, leading to a more aggressive and advanced form of MTC. In contrast, the healthy adult mother may have experienced fewer deleterious somatic mutations, resulting in a less severe form of MTC or a slower disease progression. Surprisingly, we identified a somatic mutation in *SDHA*. This has commonly been associated with paragangliomas and PHEOs. Both papillary and follicular thyroid tumors showed a significant reduction in *SDHC* and SDHD mRNA expression compared to normal thyroid tissues. Thyroid tumors with low *SDH* expression were associated with earlier age at diagnosis and higher pathological TNM stage (9). It has been suggested that the variant may lead to increased succinate levels, which can activate HIF-1α and VEGF expression and promote tumor growth (10). However, the mutation was

graded as tier 3, corresponding to "variants with unknown clinical significance" (11) and the exact mechanism by which this *SDHA* c.1223C>T mutation may have contributed to MTC pathogenesis is not clear. Since we excluded other germline mutations by WES, we hypothesized that this somatic mutation might have led to the more aggressive tumor. In the study of Schulte et al. (12), the youngest age at which MTC was observed to manifest in a cohort in which a large number of cases with S891A mutation were included was 17 years and the median (range) age was 46 (17-80) years. Within the literature, the clinical presentation of the index case and the laboratory and pathological findings (onset of high calcitonin levels and C-cell hyperplasia) of the sister manifested at a significantly younger age, suggesting a more aggressive clinical course. No somatic mutation was found in the mother's pathological samples. The mother's enduring clinical silence led to the investigation of additional mutations that might have caused the differences in the same family. The missing puzzle piece, in this case, might be the confirmation of the same *SDHA* somatic mutation in the sister's pathological material. The onset of MTC in the sister occurred earlier than expected. However, this important step was not taken because the pathological material was unsuitable for somatic mutation analysis. Currently, there is limited evidence or data in existing databases to support the association of SDHA somatic mutations with the condition. Functional studies are needed to establish the exact relationship. Even in the absence of conclusive evidence, cases with atypical clinical presentations should also be investigated for other potential pathogenic factors. Environmental factors and epigenetic modifications are other options that should be considered.

The other remarkable point about this case is that the mother carrying the *RET* p.S891A had papillary thyroid cancer and accompanying medullary microcarcinoma with no symptoms. There are two hypotheses on histogenesis. The first is two types of tumor cells derived from the same transformed stem cells. The second is that triggering oncogenesis may pathogenetically affect the normal thyroid tissue (13). It can be speculated that *RET* p.S891A mutation may have triggered the simultaneous formation of two tumors. The detection of a differentiated thyroid cancer during follow-up of the index case would support this speculation. In this respect, long-term follow-up will be instructive.

The treatment of advanced MTC is challenging. Systemic therapy with TKIs, such as cabozantinib and vandetanib, has been approved for treating advanced MTC but is not widely available in all countries (2). Studies showed that sorafenib could be considered a first-line medical treatment for advanced cases (14). Sorafenib controlled the progression and metastases of the disease and resulted in a reduction in tumor size and a decrease in calcitonin and CEA levels in the index case. However, as with any therapy, there are potential side effects and risks associated with TKI treatment. Studies have shown a deceleration in growth velocity in pediatric patients who have been administered TKIs for at least six months (15,16,17).

Neovascularization is essential in the normal physiological growth of a developing skeleton. The administration of TKIs, such as sorafenib, has been associated with cartilage abnormalities and growth plate alterations, which was related to the anti-VEGF effect. A typical progression involved the gradual narrowing of normal growth plates; however, it has been reported that a distinct widening is observed during therapy. Due to the limited number of patients in studies, any correlation between growth plate toxicity and factors such as "treatment dose, age, gender, or tumor type" could not be reported (18). Thus far, we have not observed this effect in our patient, although radiological evidence may emerge in the future. The growth retardation impact of TKIs is also attributed to deficiencies in growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) (19). Our patient had IGF-1 deficiency. Recombinant GH therapy was not considered appropriate due to an underlying malignancy and associated metastases. It suggests the potential involvement of as-yet-unexplained mechanisms contributing to this growth inhibition. Further research is warranted to elucidate the intricate interplay between TKIs, cancer treatment, and growth dynamics in pediatric patients.

It is well-documented that sorafenib can lead to hypothyroidism. The mechanism of inducing hypothyroidism involves the upregulation of T4 and T3 metabolism through deiodinase type 3 (18,20). Treatment was initiated at the age of 11.2 years when TSH levels reached 11 IU/mL, while T4 levels remained within normal limits. Although closer patient monitoring without treatment could be a management option, the family's inability to comply with more frequent follow-up appointments made it clear that closer monitoring would not be feasible. Typically, hypothyroidism develops sooner with sorafenib treatment (18). Our evaluation did not reveal non-pharmacological factors, such as iodine deficiency or autoimmune factors, that could explain the observed mildly elevated TSH. Surprisingly, TSH elevation presented in the seventh year of sorafenib treatment. A long-term follow-up of the patient's thyroid function will likely provide a more definitive etiological explanation.

Conclusion

In conclusion, the varying clinical presentation of closely related individuals with the same *RET* p.S891A may be due to somatic mutations, epigenetic modifications, and environmental factors. Additional somatic mutations, like *SDHA* present in the index case, may worsen the disease. The presence of additional somatic mutations in patients with MTC may also be important for treatment and monitoring purposes. TKIs, such as sorafenib, have shown promise in the treatment of advanced MTC although growth abnormalities have been reported in pediatric patients, including in the present case. Genetic testing and surveillance are important and long-term follow-up is necessary for understanding disease progression and treatment efficacy.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Zehra Aycan, Handan Dinçaslan, Emel Ünal, Merih Berberoğlu, Concept: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Zehra Aycan, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Zehra Aycan, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Handan Dinçaslan, Emel Ünal, Analysis or Interpretation: Sirmen Kızılcan Çetin, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Handan Dinçaslan, Emel Ünal, Literature Search: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Ayşegül Ceran, Merih Berberoğlu, Writing: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Merih Berberoğlu.

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