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Case report

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 about this topic?

- Different mutations in the *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.
- The S891A mutation in the *RET* is a rare germline mutation associated with a moderate risk of medullary thyroid carcinoma (MTC).
- The use of sorafenib and other RET-targeting tyrosine kinase inhibitors (TKIs) in childhood thyroid cancers (DTC and MTC) are quiet rare.

What this study adds to the literature?

- Despite the well-defined genotype-phenotype correlation of moderate risk *RET* p.S891A germline mutation, we report an early-onset, inoperable MTC case.
- 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 related to the potential 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 aim to present the different features and difficulties in 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 according to ATA). As the tumor was inoperable, treatment with a tyrosine kinase inhibitor (sorafenib) was initiated. Sorafenib has prevented tumor progression for seven years. Whole exome sequencing (WES) did not identify additional mutations. Segregation analysis showed the same mutation in the asymptomatic mother and sister. In our case, 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 crucial in the clinical progression and prognosis of hereditary MTC (MEN2A, MEN2B, and familial MTC), which are autosomal dominant disorders. Different mutations in the *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 crucial in identifying patients at risk for familial MTC, as early diagnosis and prophylactic surgery can 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). Food and Drug Administration (FDA) recently approved Sorafenib. It inhibits RET, vascular endothelial growth factor receptor (VEGFR) (5). A meta-analysis by Vuong HG et al. shared 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 (4).

The S891A mutation in the *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 in *RET*. 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). This report also shares our experience with the treatment success and potential side effects of sorafenib.

Case Report/Case Presentation

A 4.2-year-old male patient was admitted to our outpatient clinic due to difficulty in breathing, stridor, loss of appetite, and weight loss. His medical history revealed that he was born to non-consanguineous parents. Before his current hospitalization, he had been hospitalized three times and was misdiagnosed with bronchiolitis. On his physical examination, he was 104 cm in length (-0.28 SD) with 13.87 kg/m^2 BMI (-1.48 SD) and had a goiter. Chest x-ray showed an apple core lesion around the trachea (shown in Fig.1.A). Further radiologic examination with the thorax CT 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 existence of several lymph nodes with metastatic involvement (shown in Fig.1.B).

The laboratory evaluation showed a normal thyroid function test. Although the levels of TSH and fT4 were within the normal range (3.24 mIU/ml (N:0.38-5.33 mIU/ml) and 17.95 pmol/L (N:11-22 pmol/L), respectively), the levels of hTg, calcitonin, and CEA were significantly elevated (54.2 ng/dl for hTg, 1093 pg/ml for calcitonin (normal range: 0-10 ng/ml), and 22.74 ng/ml for CEA (normal range: <0.3)). Following the biopsy of the lesions, pathological examination revealed the presence of medullary thyroid carcinoma (MTC). Molecular analysis revealed a heterogeneous pathogenic *RET* mutation[p.S891A (c.2671T>G) (rs75234356)]. According to ATA, it 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 periodical thyroid and thorax magnetic resonance imaging (MRI) annually. 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).

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, 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 (shown in Fig.2). Whole exome sequencing 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, presented a quite 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.

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

A remarkable slowing of growth velocity was observed under sorafenib treatment on the follow-up (shown in Fig.3) . Hemogram and biochemical parameters were normal, including liver and kidney function, blood glucose, tissue transglutaminase autoantibody Ig A, and serum total Ig A level. Additionally, his urine analysis was normal, too. This condition was considered a side effect of sorafenib. Somatamedin-C was 53.6 ng/ml (N: 76-499).At the age of 11, minimal elevation was detected in TSH (TSH: 11 mIU/ml) with normal fT4 (14 pmol/l) and elevated thyroglobulin (69 pg/ml). Thyroid peroxidase antibody (TPOAb) 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. This situation was associated with tyrosine kinase inhibition, and L-thyroxine (LT4) 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 (FSH: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 (shown in Fig.1.C.)

Discussion/Conclusion

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 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 above had a well-defined classification in moderate risk 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 the inoperable patient, 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.* It is commonly associated with paragangliomas and pheochromocytomas. 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 mutation may lead to increased succinate levels, which can activate HIF-1α and VEGF expression and promote tumor growth (10). However, the mutation as tier 3, corresponding to "variants with unknown clinical significance (VUS)(11) and the exact mechanism by which the *SDHA* c.1223C>T mutation contributes to MTC pathogenesis, is not fully understood. Since we excluded other germline mutations by WES, we hypothesised that this somatic mutation might have led to the aggressive tumor. In the study of Schulte KM 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 (median, 46 years; min.:17- max: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. They followed 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 had to be skipped because the pathological material was unsuitable for somatic mutation analysis. *SDHA* somatic mutation lacks substantial support in existing databases.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 trigger factors. Environmental factors and epigenetic modifications are other options that should be considered.

The other remarkable point about our case presentation is that the mother carrying the *RET* p.S891A had papillary thyroid cancer and accompanying medullary microcarcinoma with no symptoms. There are two theories on histogenesis. The first theory is two types of tumor cells derived from the same transformed stem cells. The second theory is that triggering oncogenesis might encircle the normal thyroid tissue(13). It can be speculated that *RET* p.S891A mutation may have triggered the simultaneous formation of two tumors. A differentiated thyroid cancer formation that could accompany our patient's longitudinal monitoring would support this speculation. In this respect, the long-term follow-up of our patient 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 ensured a reduction in tumor size and a decrease in calcitonin and CEA levels in our case. However, as with any therapy, there are potential side effects and risks associated with TKI treatment. Studies have shown a deceleration in the growth velocity in pediatric patients who have been administered TKIs for at least six months(15-17).

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 involves 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 attributed to deficiencies in growth hormone (GH) and/or insulin-like growth factor-1 (IGF1), also(19). Our patient had an 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 situation. 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 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.

In conclusion, the varying clinical presentation of individuals with the same *RET* p.S891A can be due to somatic mutations, epigenetic modifications, and environmental factors. Additional somatic mutations, like *SDHA*, may worsen the disease. The presence of additional somatic mutations in patients with MTC can be important for treatment and monitoring purposes.TKIs such as sorafenib have shown promise in the treatment of advanced MTC. Genetic testing and surveillance are crucial. Long-term follow-up is necessary for understanding disease progression and treatment efficacy.

Statements

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Medical Practices:SC, ZA, ZS, EO, AC,KC, HD, EU, MB , Concept:SC, ZS, EO, , MB, Design: SC, EO, ZS, ZA MB, Data collection: SC, ZA, AC,KC, AK,HD, EU Analysis: : SC, ZA, AC,EU,HD, SC, EO, MB, Literature Search: SC, ZA, ZS, MB , Writing: SC, ZA, ZS, EO, MB.

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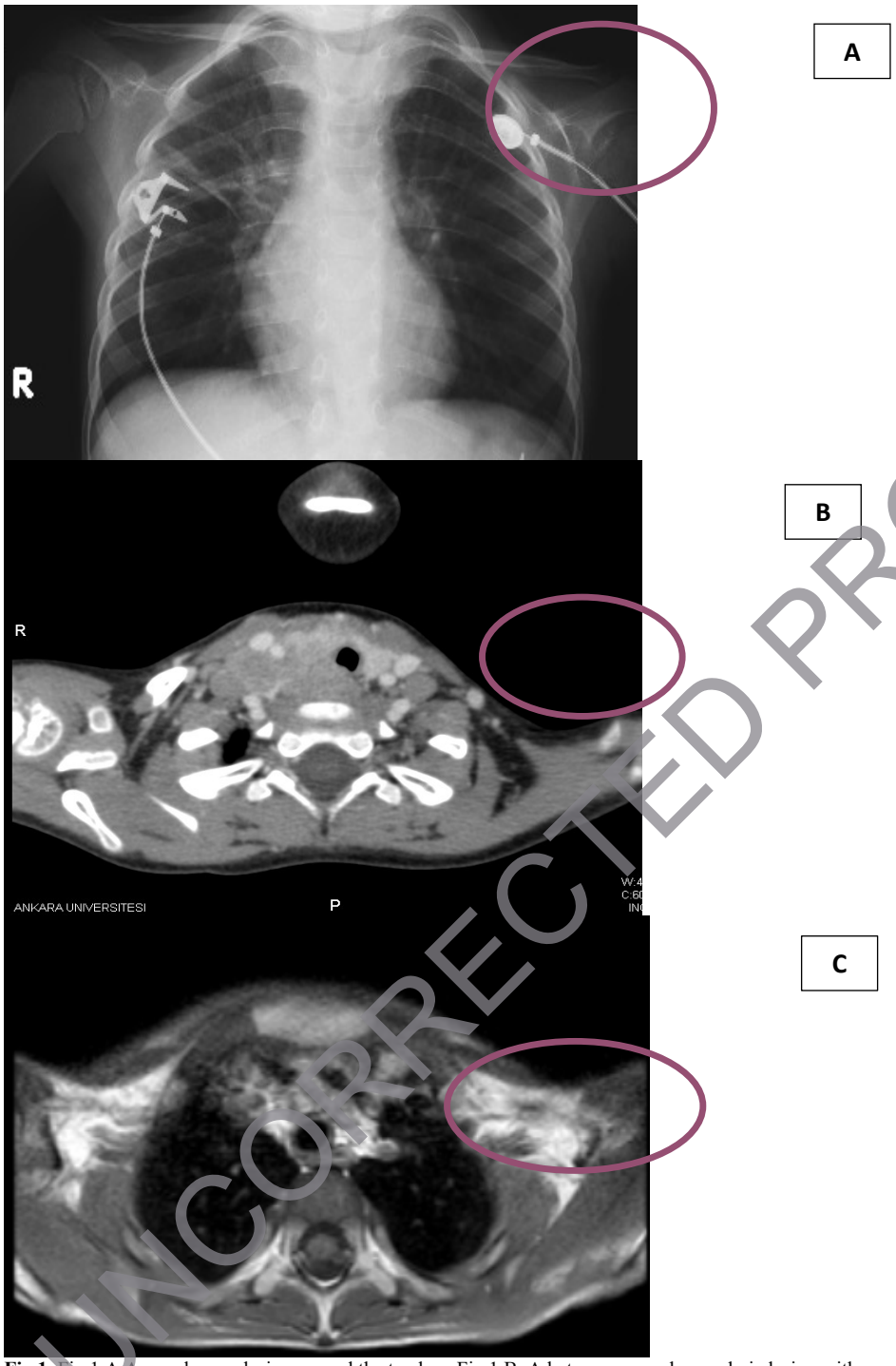

Fig.1. Fig.1.A An apple core lesion around the trachea. Fig.1.B. A heterogeneous hypoechoic lesion with punctate calcifications measuring 32x25x34 mm in size involving the right anterior cervical region adjacent to the thyroid gland, invading the thyroid parenchyma and encompassing the right internal 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. Fig.1.C.

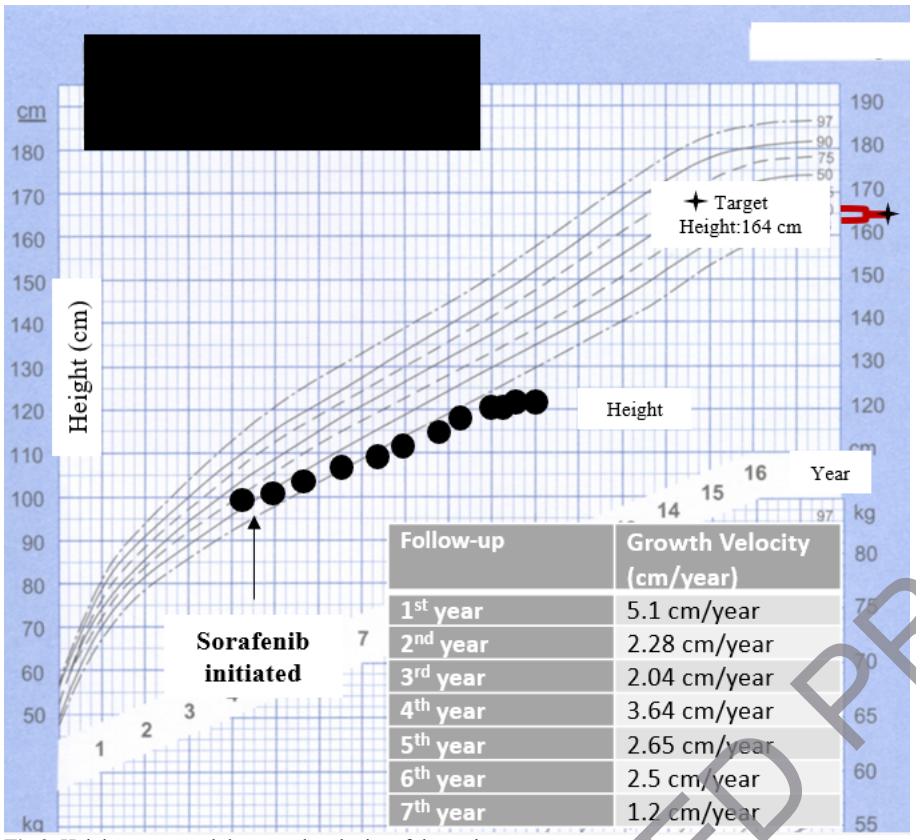

Fig.2. Height curves and the growth velocity of the patient

Age	Calcitonin (pg/mL)	CEA (ng/mL)	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	PTH (pg/mL)	TSH µıu/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

Table. Biochemical Monitoring of the Patient
CEA: carcinoembryonic antigen, Ca: calcium, P: phosphor, ALP: alkaline phosphatase, PTH: parathyroid hormone, TSH: thyroid stimulating hormone, FT4: free thyroxine
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.
**1.2mcg/kg/day L- thyroxine treatment initiated.