Sunitinib-Induced Thyrotoxicosis Followed by Persistent Hypothyroidism with Shrinkage of Thyroid Volume

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Sunitinib, a tyrosine kinase inhibitor, has been approved for the treatment of cancers, such as advanced renal cell carcinoma (RCC). On the other hand, sunitinib treatment is known to induce thyroid dysfunction in a substantial proportion of patients treated for advanced RCC; in fact, hypothyroidism is a frequent complication. However, little is known about sunitinib-induced thyrotoxicosis and destructive thyroiditis. Here, we report a patient with RCC who developed transient overt thyrotoxicosis followed by hypothyroidism due to sunitinib treatment. A 58-year-old woman, who had been treated with chronic thyroiditis, was diagnosed as having left RCC with bone metastasis to the rib. The patient underwent resection of the left kidney and the bone metastasis lesion. However, 3 months later, bone metastasis to the rib recurred, and sunitinib treatment was started. At 6 weeks of sunitinib therapy, the patient developed transient thyrotoxicosis, followed by persistent hypothyroidism. In the thyrotoxic phase, the patient was diagnosed as having destructive thyroiditis based on an increased thyroglobulin level, a low radioactive iodine uptake, increased free thyroxine level, and suppressed thyroid-stimulating hormone level. The thyroid volume in the hypothyroid phase was 68% of that in the thyrotoxic phase. In conclusion, the present report suggests that sunitinib-induced persistent hypothyroidism may be a consequence of preceding destructive thyroiditis with transient thyrotoxicosis. The decreased volume of the thyroid during the hypothyroid phase indicates irreversible organ damage in the present patient, thereby resulting in persistent hypothyroidism. Thus, periodic surveillance of thyroid function is mandatory during sunitinib therapy.

Keywords: sunitinib; thyrotoxicosis; hypothyroidism; chronic thyroiditis; destructive thyroiditis

Sunitinib is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR 1-3), platelet-derived growth factor receptor (PDGFRα and PDGFRβ), stem cell growth factor receptor (KIT), and ret proto-oncogene (RET), among others (Mendel et al. 2003; O’Farrell et al. 2003). Sunitinib has been shown to be a useful treatment for various cancers in vivo, as well as in vitro, with direct antitumor effects and anti-angiogenic effects (Mendel et al. 2003; O’Farrell et al. 2003). It has been approved for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumors (GIST).

Investigators have previously observed hypothyroidism in a number of sunitinib-treated patients. In RCC patients, hypothyroidism has been reported at rates of up to 85% (Desai et al. 2006; Rini et al. 2007; Wolter et al. 2007). However, little is known about sunitinib-induced thyrotoxicosis and destructive thyroiditis (Faris et al. 2007; Alexandrescu et al. 2008; Grossmann et al. 2008).

Destructive thyroiditis is diagnosed on the basis of an increased thyroglobulin level, a low radioactive iodine uptake, increased free thyroxine (FT4) level, and suppressed thyroid-stimulating hormone (TSH) level. It is characterized by transient thyrotoxicosis with complete recovery, and it is sometimes followed by transient or persistent hypothyroidism (Nikolai et al. 1980). It remains unclear whether sunitinib-induced destructive thyroiditis with transient thyrotoxicosis precedes persistent hypothyroidism.

Although sunitinib-induced hypothyroidism seems to be reversible in the majority of patients, some patients develop irreversible thyroid damage resulting in the need for long-term thyroid hormone replacement therapy (Wolter et al. 2008). In a recent report, sunitinib-induced shrinkage of the thyroid gland appears to have been a potential marker of irreversible organ damage, resulting in persistent hypothyroidism (Rogiers et al. 2010).

Here we report a female patient with RCC who developed destructive thyroiditis followed by persistent hypothy-
Clinicall Findings

As shown in Fig. 1, a 58-year-old woman who complained of chest pain was diagnosed as having left RCC with bone metastasis to the left rib. Ten years earlier, the patient was diagnosed as having chronic thyroiditis. At that time, thyroid ultrasonography demonstrated an inhomogeneous pattern in both lobes and a 2.0 × 2.0 cm hypoechoic nodule in the left lobe (data not shown). Ultrasound-guided fine-needle aspiration (FNA) cytology of the left lobe was performed. Cytological examination showed a benign nodule. Although anti-thyroid peroxidase antibodies (Abs), anti-thyroglobulin Abs, and anti-TSH receptor Abs were all negative, the patient was diagnosed as having chronic thyroiditis based on the ultrasonographic findings of the thyroid. She was treated with L-thyroxine (50 µg daily) for goiter (Fig. 1). The TSH level had been regulated to less than 0.4 µU/ml most of the time to avoid goiter enlargement (Table 1).

As summarized in Fig. 1, the patient underwent resection of the left kidney and the bone metastasis affecting the rib. After 3 months, the rib bone metastasis recurred. She was then treated with sunitinib in repeated 6-week cycles (50 mg/day for 4 weeks, followed by 2 weeks off). The patient had also been treated for hypertension for 10 years. There was no history of neck pain, irradiation, trauma, recent fever, or viral illness. Her medication included ranitidine, valsartan, and L-thyroxine. She had never had iodine contrast medium injected intravenously. She had no history of allergy. There was no other known family history of autoimmune disease.

Since a thyroid function test (Table 1) showed elevated FT4 (1.87 ng/dl; normal range 0.70-1.48 ng/dl), free triiodothyronine (FT3) (4.31 pg/ml; normal range 1.71-3.71 pg/ml) and suppressed TSH (0.05 µU/ml; normal range 0.35-4.94 µU/ml) levels at 4 weeks of sunitinib therapy compared to initiation of sunitinib therapy, the patient was referred to our hospital (Fig. 1).

On physical examination at the first visit, her vital signs included temperature of 37.0-37.2°C, heart rate of 88-95 bpm, blood pressure of 152-181/75-83 mmHg, and respiratory rate of 22/min. Her thyroid was palpable without tenderness. Up to that time, she had been treated with L-thyroxine (50 µg daily) for goiter; treatment with L-thyroxine was then discontinued (Fig. 1).

At 6 weeks of sunitinib therapy, the patient complained of palpitations and fatigue without significant weight loss. Her thyroid function tests again showed elevated FT3 (5.11 ng/dl) and FT4 (1.87 ng/dl) levels. A diagnosis of destructive thyroiditis was made. At 10 weeks of sunitinib therapy, she developed hypothyroidism. L-thyroxine was then restarted.

Fig. 1. The patient’s clinical course.

Sunitinib treatment was started at 0 weeks. Ten years earlier, the patient was diagnosed as having chronic thyroiditis. L-thyroxine (50 µg daily) treatment was started to avoid goiter enlargement. Three months earlier, she was diagnosed as having left renal cell carcinoma with bone metastasis to the left rib. Left kidney and the bone metastasis affecting the rib were resected. At 0 weeks, the rib bone metastasis recurred. She was then treated with sunitinib. At 4 weeks of sunitinib therapy, L-thyroxine treatment was discontinued. At 6 weeks of sunitinib therapy, a diagnosis of destructive thyroiditis was made. At 15 weeks of sunitinib therapy, she developed hypothyroidism. L-thyroxine was then restarted.
Sunitinib-Induced Destructive Thyroiditis

Sunitinib-induced destructive thyroiditis (41 pg/ml) and FT4 (1.80 ng/dl) levels despite cessation of her L-thyroxine (Table 1). The 123I uptake at 24 h was low (1.2%). Serum C-reactive protein was normal (0.1 mg/dl; normal range < 0.3 mg/dl). Thyroglobulin was markedly increased (> 800 ng/ml; normal range < 30 ng/ml). Therefore, a diagnosis of destructive thyroiditis induced by sunitinib therapy was made, and the patient was treated with beta-blockers alone, but was not given anti-thyroid drugs.

At 15 weeks of sunitinib therapy, thyroid function tests showed hypothyroidism (Table 1). L-thyroxine (50 µg daily) was then restarted (Fig. 1), and it was found that L-thyroxine was needed to normalize her serum TSH levels. As shown in Table 1, the thyroglobulin level decreased (190 ng/ml) at 15 weeks of sunitinib therapy compared to the period of thyrotoxicosis. Anti-thyroid autoantibodies were both negative during the hypothyroid phase at 15 weeks of sunitinib therapy (Table 1).

Although FT4 had been in the normal range with L-thyroxine (50 µg/day) from 23 weeks to 37 weeks of sunitinib therapy, the TSH levels showed a transient, modest increase at 26 and 33 weeks (Fig. 2).

Thyroid ultrasonography demonstrated a diffuse goiter with heterogeneously reduced signal intensity in both lobes, and hypoechoic nodules in both lobes at 6 weeks of sunitinib therapy (Fig. 3). The estimated total thyroid volume (Brunn et al. 1981) was 31.9 cm³. The sizes of the nodules in the left and right lobes were 0.83 × 0.52 cm and 1.63 × 1.23 cm, respectively. Thyroid ultrasonography was repeated during the hypothyroid phase (at 26 weeks of sunitinib therapy). The estimated total thyroid volume was 21.85 cm³; it decreased to 68.4% of the volume at 6 weeks of sunitinib therapy. The size of the nodules in both lobes was slightly decreased.

After 37 weeks of sunitinib therapy, the patient stopped visiting our hospital for personal reasons; thus, we were unable to follow-up the patient thereafter.

Discussion

Destructive thyroiditis is the term usually used to describe transient thyrotoxicosis with reduced thyroid radioactive iodine uptake (Nikolai et al. 1980). Some drugs, such as amiodarone (Roti et al. 1993), interferon-alpha (Preziati et al. 1995), and lithium (Miller and Daniels 2001), apparently cause a sudden onset of inflammation, damaging thyroid follicles and releasing preformed thyroid hormone into the circulation. This causes transient thyrotoxicosis, often followed by a subsequent hypothyroid phase. Most disorders causing destructive thyroiditis do not cause permanent hypothyroidism, but a persistent or even a permanent state of hypothyroidism is not without precedent.

There have been several clinical reports about sunitinib-induced thyrotoxicosis (Faris et al. 2007; Alexandrescu et al. 2008; Grossmann et al. 2008). Desai et al. (2006) published a prospective study of 42 patients treated with sunitinib for GIST and found that 15 (36%) developed primary hypothyroidism, and 7 (17%) had transient, mild TSH

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<th>Tg (ng/ml)</th>
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Sunitinib treatment was started at 0 weeks. −149 weeks and −2 weeks indicate 149 weeks and 2 weeks before starting sunitinib therapy, respectively. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; L-thyroxine, levothyroxine; Tg, thyroglobulin; Anti-TPO Abs, anti-thyroid peroxidase antibodies; Anti-Tg Abs, anti-thyroglobulin antibodies.
They also noted that 6 of 15 (40%) hypothyroid patients had suppressed TSH before developing hypothyroidism. These data suggest that in some patients, sunitinib-induced hypothyroidism may be a consequence of preceding destructive thyroiditis with transient thyrotoxicosis.

We postulate that the sunitinib-induced thyrotoxicosis in the present case was due to destructive thyroiditis because of the high thyroglobulin levels and the decreased uptake on the thyroid scan. Grossmann et al. (2008) indicated that thyroglobulin levels were more specific and useful in assessing the extent of thyroid destruction. Faris et al. (2007) reported a case of sunitinib-induced thyrotoxicosis due to destructive thyroiditis, and thyroglobulin levels in their case were also high. The present case is consistent
with these previous reports. Therefore, the patient was treated with beta-blockers alone and not with anti-thyroid drugs during the hyperthyroid phase. In fact, the rapid, self-limiting resolution of the thyrotoxicosis is typical of destructive thyroiditis.

Whether the use of sunitinib causes reversible or irreversible changes in the thyroid gland remains unclear. Grossmann et al. (2008) reported that 3 of 6 patients experienced recurrent episodes of thyrotoxicosis in a temporal relationship to sunitinib treatment. These data suggest that sunitinib induced reversible changes in the thyroid gland. In contrast, Wolter et al. (2008) reported that 16 of 59 patients (27%) developed persistent hypothyroidism and required hormone replacement in RCC or GIST patients receiving sunitinib.

In the present patient, TSH levels had been regulated to less than 0.4 \( \mu U/ml \) in order to avoid goiter enlargement before sunitinib treatment. The TSH levels had been low and stable. After L-thyroxine treatment for hypothyroidism, the TSH levels, which ranged from 0.12 to 6.15 \( \mu U/ml \), fluctuated with sunitinib treatment. TSH levels were slightly elevated at 26 and 33 weeks despite the L-thyroxine treatment (Fig. 2 and Table 1). We assumed that these elevations of TSH at 26 and 33 weeks implied persistent or even permanent hypothyroidism with sunitinib therapy.

As described above, Rogiers et al. (2010) reported two cancer patients with a pre-existing nodular thyroid gland who developed hypothyroidism and showed marked shrinkage of the thyroid during treatment with sunitinib, necessitating permanent thyroid hormone replacement therapy even after discontinuation of sunitinib. They suggested the possibility that shrinkage of thyroid volume in sunitinib-treated patients could be a potential marker of irreversible organ damage. In the present case, the estimated total thyroid volume at 26 weeks of sunitinib therapy was decreased to 68.4% of the volume at 6 weeks. The result might indicate the possibility of persistent or even permanent hypothyroidism in the present case.

It remains unclear whether sunitinib-induced thyroid dysfunction is mediated by an autoimmune mechanism such as IL-2 and interferon-alpha (Atkins et al. 1988; Franzke et al. 1999; Mandac et al. 2006). Mannavola et al. (2007) and
Rini et al. (2007) reported that none of 11 patients and 5 of 44 patients (11%) with sunitinib-induced hypothyroidism, respectively, had positive thyroid antibodies. Taken together with the present patient, we suggest that sunitinib-induced thyroid dysfunction can occur in the absence of predisposing thyroid autoimmunity.

In summary, sunitinib-induced hypothyroidism may be a consequence of preceding sunitinib-induced destructive thyroiditis associated with transient thyrotoxicosis. The decreased volume of the thyroid during the hypothyroid phase in the present patient might indicate the possibility of persistent hypothyroidism. Further studies are required to elucidate the mechanisms of sunitinib-induced thyroiditis. Regardless of the mechanism, periodic surveillance of thyroid function during sunitinib therapy is mandatory.

**Disclosure Statement**

The authors declare that no competing financial interests exist.

**References**


