

Clinical Hypothyroidism in a Renal Cell Carcinoma Patient Treated With Sorafenib

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Case Presentation

A 54-year-old man presented to a local emergency room with gross hematuria. A computed tomography (CT) scan of the abdomen revealed a left renal mass. He underwent a left radical nephrectomy; pathology showed a 7.9 × 6.5 × 6.3-cm, grade 2 (out of 4) renal cell carcinoma, clear cell type. The tumor was confined to the kidney, but tumor thrombus was present in the renal vein (stage III, T3aN0M0). Serial follow-up was performed postoperatively with no clinical evidence of disease progression until 3 years later, when a 2.3-cm right hilar nodule and a 0.7-cm left lower lobe nodule were detected on imaging with no other clinical evidence of disease. The patient underwent video-assisted thoracic surgical resection of both nodules; both showed grade 2 renal cell carcinoma, clear cell type upon pathologic examination. Postmetastasectomy, the patient was monitored clinically with examinations and imaging. Eight months following his pulmonary metastasectomies, multiple new enlarging pulmonary nodules consistent with recurrent metastatic disease were detected.

The patient was initiated on treatment with sorafenib (Nexavar, Bayer) at 400 mg orally twice daily, which required dose reductions within the first 2 months for palmar-plantar erythrodysesthesia until a tolerable dose was reached at 200 mg twice daily. The patient responded with stabilization of disease for 6 months, at which time he developed abrupt onset of oral mucositis, worsening of palmar-plantar erythrodysesthesia, and fatigue. Temporary discontinuation of sorafenib for 2 weeks led to improvement in palmar-plantar erythrodysesthesia and mucositis, but fatigue worsened, and the patient developed periorbital and pretibial edema. Laboratory evaluation showed acute renal insufficiency with an increase of serum creatinine to 1.9 mg/dL from a baseline of 1.2 mg/dL (laboratory reference range, 0.8–1.3 mg/dL). In addition, the patient had elevations in aspartate transaminase (maximum 190 U/L;

laboratory reference, range 8–48 U/L) and alanine transaminase (maximum 92 U/L; laboratory reference range, 7–55 U/L), with no detectable abnormalities in alkaline phosphatase or bilirubin. Abdominal ultrasound showed no evidence of hepatic or renal involvement of renal cell carcinoma and no evidence of renal outflow obstruction. Urinalysis showed no proteinuria and no evidence of glomerulonephritis or nephrotic syndrome. A serum thyroid-stimulating hormone (TSH) level was measured at 87.7 mIU/L (Table 1). Free thyroxine was less than 0.2 ng/dL (laboratory reference range, 0.8–1.8 ng/dL), which, along with his presenting symptoms of unexplained fatigue, confirmed the diagnosis of clinical hypothyroidism. Serum thrombopoietin antibodies were not elevated.

The patient was initiated on oral levothyroxine 125 µg daily, during which time sorafenib was withheld. Four weeks later, the periorbital edema and fatigue had resolved, and creatinine and hepatic transaminases returned to baseline. Free thyroxine normalized to 1.2 ng/dL, and TSH improved to 5.2 mIU/L. In the interim, the patient's pulmonary nodules were noted as slightly enlarged on imaging. Sorafenib was reinitiated at his prior dose of 200 mg twice daily. He tolerated restarting sorafenib well, with grade 1 palmar-plantar erythrodysesthesia. Serial imaging with chest CT after 3 and 6 months on sorafenib showed no further progression of disease.

Discussion of Diagnosis and Management

Biochemical hypothyroidism, defined as an elevation of TSH, is frequently seen in patients treated with tyrosine kinase inhibitors (TKIs); however, symptomatic (clinical) hypothyroidism has less commonly been reported. Classic symptoms and signs of adult-onset hypothyroidism include fatigue, cold intolerance, weight gain, coarse or dry skin, periorbital and pretibial edema, bradycardia, and pleural and pericardial effusions.¹ Additionally, hypothyroidism can also lead to changes in metabolism, including renal insufficiency manifested by increased serum creatinine and decreased metabolism of medications. Our patient presented with classic hypothyroid symptoms of fatigue, and periorbital and pretibial edema, in addition

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Table 1. Time Course of Thyroid-Stimulating Hormone Variation

Date	Thyroid-Stimulating Hormone (0.3–5.0 mIU/L)	Clinical Course
4/21/08	2.3	Baseline (prior to metastasectomy)
8/13/09	87.7	Clinical hypothyroidism and increased sorafenib toxicity; discontinued sorafenib and started levothyroxine at 125 mg/day
9/8/09	5.2	Resolution of clinical hypothyroidism; mild disease progression; continued levothyroxine, re-initiated sorafenib
10/20/09	1.2	Asymptomatic; continued sorafenib and levothyroxine
12/1/09	0.7	Asymptomatic; no disease progression; continued sorafenib, reduced levothyroxine dose to 100 mg/day
1/12/10	10.8	Asymptomatic; continued sorafenib, increased levothyroxine dose back to 125 mg/day
2/23/10	6.6	Asymptomatic; no disease progression; continued sorafenib and levothyroxine

to a recently elevated creatinine, although no bradycardia or effusions were observed. He also had evidence of recent onset of sorafenib toxicity (oral mucositis, worsening palmar-plantar erythrodysesthesia, and elevated hepatic transaminases) despite receiving the same sorafenib dose, indicating that sorafenib metabolism may have been impaired during the time he was clinically hypothyroid. His presenting symptoms and laboratory abnormalities resolved with thyroid replacement and by withholding sorafenib. Thus, a patient of any age who presents with signs and symptoms of hypothyroidism and side effects of sorafenib toxicity—a clinical suspicion of hypothyroidism—while receiving a stable dose of sorafenib should prompt an evaluation of thyroid function, as appropriate medical management can reverse clinical deterioration. The time dependency for appearance of sorafenib toxicity or clinical hypothyroidism may not always correlate temporally with initiation of sorafenib, and may appear after prolonged exposure.

Iatrogenic hypothyroidism is a common adverse effect in patients with renal cell carcinoma treated with sunitinib (Sutent, Pfizer). A retrospective study of sunitinib in renal cell carcinoma found a prevalence of biochemical hypothyroidism (TSH increase) of 85%, with symptoms consistent with clinical hypothyroidism occurring in 84% of patients with biochemical hypothyroidism.² Prospective studies have also demonstrated hypothyroidism in renal cell carcinoma patients treated with sunitinib, albeit at a lower incidence (66% total, 33% requiring treatment).³ Hypothyroidism with sorafenib has been less frequently observed. In the initial studies of sorafenib in renal cell carcinoma, hypothyroidism was not reported, although nonspecific symptoms potentially attributable to hypothyroidism (fatigue, dry skin, anemia) were observed.^{4,5} The first case of clinical hypothyroidism in

a patient treated with sorafenib was reported in 2007.⁶ In another prospective study conducted in a Japanese patient cohort treated with sorafenib for metastatic renal cell carcinoma, abnormalities in thyroid function were recently reported.⁷ The results suggested a significantly higher incidence of biochemical hypothyroidism in patients receiving sorafenib (67.7%) compared to Western populations, and an association of hypothyroidism with older age (>65 years) was also observed in this study. A retrospective analysis of 39 North American patients treated with sorafenib for metastatic renal cell carcinoma who had undergone thyroid axis evaluation at least once during treatment showed that 8 patients (18%) had biochemical evidence of hypothyroidism.⁸ Of these, only 2 had clinical evidence of hypothyroidism and received treatment.

Sorafenib is approved by the US Food and Drug Administration (FDA) for the treatment of metastatic hepatocellular carcinoma, and it has also been clinically tested in advanced thyroid cancer. Hypothyroidism was not reported as an adverse event in the trials leading up to FDA approval of sorafenib for hepatocellular carcinoma, although fatigue, dry skin, and other symptoms that might have been due to hypothyroidism were noted.^{9,10} No studies directly addressing hypothyroidism in hepatocellular carcinoma have been performed. In thyroid cancer, however, sorafenib use in a phase II clinical trial resulted in 33% of patients requiring a dose adjustment in thyroid replacement therapy due to increases in TSH.¹¹ This difference in the effect of sorafenib on thyroid function based on tumor type may have been due to the fact that the vast majority of patients with advanced thyroid cancer require thyroid replacement at baseline, whereas this is much less common in patients with renal cell or hepatocellular carcinoma.

Based on the incidence of hypothyroidism in patients treated with sunitinib and, to a lesser extent, sorafenib and imatinib (Gleevec, Novartis), Torino and colleagues have recommended that patients initiating any TKI therapy for cancer treatment should undergo TSH evaluation prior to each cycle of therapy.¹² Clearly, thyroid axis surveillance is reasonable for patients treated with sunitinib, as they are at high risk for significant hypothyroidism. However, although thyroid cancer patients treated with sorafenib commonly require dosage adjustments in thyroid replacement therapy, the incidence of clinically significant hypothyroidism in sorafenib-treated renal cell and hepatocellular carcinoma patients appears to be fairly low in Caucasian patients, with no reports thus far in hepatocellular carcinoma and only a small percentage of renal cell carcinoma patients requiring thyroid replacement. Therefore, although we do not recommend routine TSH evaluation in renal cell and hepatocellular carcinoma patients receiving sorafenib, a careful assessment and awareness of signs and symptoms of clinical hypothyroidism at any time period of sorafenib treatment appears prudent, since appropriate management can reverse the morbidity from acquired hypothyroidism.

Conclusions

Hypothyroidism is frequently seen in patients treated for renal cell carcinoma with sunitinib, and is much less commonly noted in patients treated with sorafenib. We report a case of clinical hypothyroidism in a patient after several months of treatment with low doses of sorafenib. Though reports have suggested that the incidence of hypothyroidism in patients on sorafenib is influenced by advanced age, Japanese race, and the presence of underlying thyroid dysfunction, clinical hypothyroidism may occur even if none of these risk factors are present. Onset of symptoms may occur even after months of treatment at low doses. Thus, symptoms compatible with hypothyroidism or a decrease in sorafenib metabolism should trigger prompt evaluation of the thyroid axis regardless of dose, duration of treatment, or the presence of risk factors. In patients who require cessation of sorafenib due to toxicities related to hypothyroidism, sorafenib may be reintroduced safely following thyroid replacement.

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Review

Thyroid Function Abnormalities in Patients Receiving VEGF-Targeted Therapy

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Block and Kohli¹ describe a case of metastatic renal cell carcinoma (RCC) treated with sorafenib (Nexavar, Bayer) in which the patient developed drug-induced clinical and biochemical hypothyroidism after 6 months of therapy. This was accompanied by a sudden increase in other drug toxicities including mucositis, fatigue, and hand-foot syndrome. In addition, acute laboratory abnormalities at this time included serum creatinine and transaminase elevation. The patient clinically improved with thyroid hormone replacement, and was successfully restarted on sorafenib with resumption of clinical benefit. Unfortunately, no baseline thyroid function tests (TFTs) were drawn, although presumably the patient was clinically euthyroid and the subsequent abnormalities can be presumed to be sorafenib-induced. Further, thyroid function tests were not obtained until the onset of significant clinical symptoms, and therefore the timeline for development of this toxicity is not known.

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This case highlights a relatively common class effect of small molecule tyrosine kinase inhibitors (TKIs) of the vascular endothelial growth factor receptor (VEGFR), namely biochemical abnormalities consistent with hypothyroidism, sometimes accompanied by signs and symptoms of reduced thyroid function. As the authors detail, several previous retrospective case series have documented thyroid function abnormalities induced by VEGFR-inhibiting drugs in RCC and other malignancies.²⁻⁵ These series, although very limited by their small size and retrospective nature, document that: 1) such abnormalities are relatively common, occurring in up to 85% of patients if any biochemical thyroid abnormality is included; 2) clinically-significant hypothyroidism and the requirement for replacement hormone therapy is much less common, ranging from 3–23% in the largest RCC series published to date; and 3) thyroid abnormalities appear to be more frequent with sunitinib (Sutent, Pfizer) compared to sorafenib.⁶ Unfortunately, the large, prospective clinical trials that led to regulatory approval of these agents did not carefully measure thyroid function, and, as a consequence, likely underreported this toxicity.^{7,8}

The precise mechanism of this phenomenon is not well understood. Various authors have reported decreased intrathyroidal blood flow during VEGFR TKI therapy as measured by ultrasound, with concomitant thyroiditis preceding the development of hypothyroidism.⁹ Other series have focused on drug-induced effects on thyroid volume. One recent report looked at 17 sunitinib-treated RCC patients, and measured thyroid volume by computed tomography volumetry along with biochemical thyroid function.¹⁰ The median reduction rate in thyroid volume at last evaluation during sunitinib treatment was 30%. The incidence of hypothyroidism during sunitinib treatment was significantly higher in those patients with a greater reduction in thyroid volume. Histologic evaluation at autopsy in 4 patients demonstrated atrophy of thyroid follicles and degeneration of follicular epithelial cells without critical diminution of vascular volume in the thyroid gland. The authors concluded that thyroid atrophy, either as a direct or indirect sunitinib effect, may underlie thyroid gland dysfunction in this setting. Other reports have documented reduced thyroid volume along with preceding thyroiditis, suggesting a destructive effect of sunitinib on the thyroid gland, leading to reduced function.⁵ The precise mechanism of thyroid gland volume reduction, whether or not related to alterations in blood flow and/or other mechanisms, is not completely defined.

Another unanswered question is whether or not thyroid abnormalities are a potential biomarker of response to treatment. Initial reports have specifically not shown an association between the development of hypothyroidism during therapy with sunitinib and sorafenib, and any mea-

surement of clinical outcome.²⁻⁴ Other, more recent series have suggested that the occurrence of biochemical thyroid abnormalities is associated with clinical outcome to either sunitinib or sorafenib in metastatic RCC patients.^{5,11}

It is important to measure thyroid function both at baseline and throughout treatment with sunitinib and sorafenib, given the notable incidence of TFT abnormalities during treatment with these agents. The patient reported here is unusual in that several other clinical and laboratory abnormalities developed concurrently with thyroid dysfunction. Thyroid abnormalities with VEGFR inhibitors usually develop first biochemically, and are not always followed with clinical symptoms or necessitate replacement therapy. The authors put forth an interesting hypothesis regarding sorafenib metabolism in the face of this severe clinical hypothyroidism. It may be true that this particular patient may have encountered the concomitant abnormalities as a result of the lack of TFT monitoring throughout treatment, leading to severe hypothyroidism, a condition not usually seen with routine monitoring. Ongoing prospective trials with additional VEGFR inhibitors are more carefully monitoring thyroid function and may provide further clarification and insight into the true incidence of this toxicity and any association with clinical outcome. Further studies are required to clarify the proper timing of thyroid replacement therapy in patients receiving VEGFR inhibitors for RCC, and whether such therapy mitigates treatment-induced fatigue or affects clinical response to this class of agents.

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