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Extreme hypothyroidism associated with sunitinib treatment for metastatic renal cancer

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Summary

Although thyroid abnormalities are reported with the use of tyrosine kinase inhibitors (TKI), patients rarely require replacement therapy. The initial multicenter studies of sunitinib for metastatic renal cancer did not report hypothyroidism in fatigued patients, and thyroid tests were not routinely monitored. More recent studies however, suggest up to 70% of patients develop thyroid test abnormalities during treatment with sunitinib. Despite these concerns, the clinical relevance of sunitinib-induced hypothyroidism is uncertain since thyroid gland recovery is the norm in most patients. We report a case of a patient with metastatic papillary renal cell cancer on combination anti-angiogenic therapy with sunitinib, who developed unusually high Thyroid Stimulating Hormone levels and severe symptoms despite receiving L-thyroxine. Our case also illustrates the complexity of managing sunitinib associated thyroid dysfunction, which may be accompanied by transient thyroiditis, hyperthyroidism and profound hypothyroidism.

Keywords

sunitinib; extreme hypothyroidism; symptoms

Introduction

Although thyroid abnormalities are reported with the use of tyrosine kinase inhibitors (TKI) such as imatinib, nilotinib, dasatinib¹, and pazopanib², patients rarely require replacement therapy and almost never need to discontinue the TKI. Sorafenib-induced hypothyroidism is reported to occur more frequently (in two thirds of patients with metastatic renal cancer), but only 5.8% develop clinically significant hypothyroidism requiring replacement therapy³.

There is evidence however, that sunitinib may induce thyroid atrophy, transient thyrotoxicosis,⁴ and possibly irreversible thyroid damage⁵. Despite these concerns, questions have also been raised as to the clinical relevance⁶ of sunitinib-induced hypothyroidism since

thyroid gland recovery is the norm in most patients,⁷ who may experience only transient iodine uptake blockade.⁸ In addition, few patients develop severe symptoms that can be attributed directly to hypothyroidism. We report a case of a patient on combination anti-angiogenic therapy containing sunitinib, who developed unusually high TSH levels and severe symptoms despite receiving L-thyroxine supplementation.

Case

A 41-year-old female was referred to a comprehensive cancer center for evaluation of progressive metastatic papillary renal cell cancer type II. 12 months after nephrectomy, MRI of the thoracic-spine showed extensive infiltration of the bone marrow and imaging of her chest, abdomen and pelvis showed liver and bone metastases. At presentation she had a low hemoglobin of 10.2 g/dL, placing her in the intermediate-risk category according to Motzer criteria⁹ (Karnofsky performance status, lactate dehydrogenase, hemoglobin, corrected serum calcium, and history of nephrectomy).

Over the preceding 6 months, she had reported a 5 pound weight loss, accompanied by insomnia and occasional fatigue. She had no family history of cancer or thyroid disease, but was found to be a carrier of a fumarate hydratase gene mutation (HIF1 α), responsible for hereditary leiomyomatosis and renal cell cancer. Renal cell cancers associated with this mutation are very aggressive and often metastatic at presentation, even when the primary lesion is <1 cm.¹⁰

Despite trials of bevacizumab, her disease progressed and she was referred for a phase I trial combining sunitinib and AMG-386. Sunitinib was given in courses of 50 mg daily for 4 weeks on, followed by 2 weeks off plus AMG-386 at 10mg/kg once weekly. AMG 386 is an investigational peptide-Fc fusion protein (peptibody) which inhibits angiogenesis by preventing the interaction of angiopoietin-1 and angiopoietin-2 with their receptor¹¹

Thyroid management

Her initial thyroid tests prior to sunitinib treatment (Figure 1 and 2) showed a marginally elevated thyroid stimulating hormone (TSH) level of 6.5 mU/mL with a normal free T4 and mild symptoms of fatigue. About 4 weeks after starting sunitinib, the TSH had increased to 34.18 mU/mL. Supplementation with 100mcg of L-thyroxine was initiated, but because of a progressively increasing T4 level and low TSH, her L-thyroxine dose was decreased to 75mcg about 4 months after starting sunitinib.

She had no prior history of thyroid disease or radiation therapy to the head and neck. On referral to the supportive care clinic after 6 months of therapy her TSH was 119 mU/mL, T4 was below normal (0.6 ng/dL) and she complained of cold intolerance. She reported compliance with her L-thyroxine replacement therapy at every visit to the clinic. Thyroglobulin levels were normal (41.4ng/mL) and anti-peroxidase antibodies <10 IU/mL. Her symptoms were evaluated using the Edmonton Symptom Assessment Scale (ESAS), a validated assessment tool quantifying a patient's response to symptoms scored for intensity between 0 (best) to 10 (worst). The ESAS scores for poor appetite, fatigue, insomnia and depression during her three visits to the supportive care clinic are shown in figure 2.

By her second supportive care clinic visit, the TSH had risen to 321 mU/mL, and she reported profound fatigue and cold intolerance. Her L-thyroxine dose was increased to 100mcg, and because of disease progression, sunitinib was discontinued.

By her third and final clinic visit, the TSH level had declined to 21mU/mL and her symptom burden had improved considerably. Over the next 4 weeks she remained on L-thyroxine and her TSH declined to normal levels. She died some 6 weeks later, just prior to entering another phase I trial.

Discussion

The clinical management of hypothyroidism is complicated by a lack of clinical data¹² since the majority of studies on hypothyroidism as an adverse effect of TKIs are small and observational¹³. In addition, because severe toxicities have been associated with better survival¹⁴, clinicians may be less inclined to investigate the etiology of side-effects associated with hypothyroidism such as fatigue.

Although TKI-related hypothyroidism is thought to be a long-term adverse effect¹², studies have reported a variable onset of sunitinib-induced hypothyroidism. A prospective study of Renal Cell Cancer and GIST found a median time to abnormal TSH of 4 weeks¹⁵ while another study restricted to those with GI stromal tumors reported a mean time of 50 weeks.¹⁶ Since sunitinib may cause fatigue even in the absence of thyroid abnormalities; there is some uncertainty about the frequency of clinically relevant hypothyroidism associated with sunitinib. The initial large multicenter studies¹⁷ of sunitinib for metastatic renal cancer did not report hypothyroidism in those patients with grade 3 or 4 fatigue and TSH was not monitored routinely. More recent studies however, suggest up to 70% of patients develop thyroid test abnormalities during treatment with sunitinib and between 9¹⁸ and 30% require thyroid replacement^{19, 13}. Although most patients may experience only transient hypothyroidism, our patient demonstrates that hypothyroidism associated with sunitinib may be severe, accompanied by a high symptom burden, and develop rapidly, even while receiving thyroxine replacement. In our patient, elevated TSH and decreased T4 correlated with symptom intensity, particularly fatigue and poor appetite as shown by the ESAS scores in table 3. Symptom burden was greatest when her TSH increased to an unusually high level of 324 mU/mL despite a dose of 75mcg thyroxine daily. When sunitinib was discontinued, the TSH declined and symptom intensity diminished, suggesting her symptoms were associated with drug-induced hypothyroidism.

Although one study¹⁶ reported a resolution of serum TSH abnormalities in all patients after replacement therapy, our case suggests some patients with thyroid dysfunction may be more challenging. Despite adjustments in dosing, figure 1 indicates normal values were difficult to achieve throughout her treatment course. Prior to developing profound hypothyroidism, she had an elevated T4 level suggesting either excessive replacement doses, altered T4 metabolism or even thyroiditis. Studies report thyroiditis accompanied by a low TSH may precede sunitinib^{14, 19} or sorafenib³ induced hypothyroidism in at least a third of patients. Occasionally patients can develop severe thyrotoxicosis²⁰ but at least one other study involving renal cancer patients^{9, 16} showed no abnormally low TSH levels. Although a

clinical algorithm^{12, 13} has been proposed to monitor thyroid function in patients on sunitinib, our case suggests the therapeutic management may be complicated by rapid fluctuations in TSH and T4 levels and sunitinib-induced transient hyperthyroidism.

The mechanism for sunitinib-induced thyroid dysfunction is unclear, but may be due to atrophy as a result of decreased capillary blood flow induced by VEGF inhibition²¹ or anti-peroxidase activity²². Besides the direct effect on the thyroid gland, other mechanisms²³ may be responsible for the increased requirements of L-thyroxine in our patient. The major mechanisms leading to an increased need for thyroxine are predominantly drug induced⁶ and can include decreased absorption of L-thyroxine, altered transport of T3 and T4 in the serum or altered metabolism of T3 and T4. The induction of microsomal enzymes that increase the clearance of fT4 and fT3 is proposed as a possible mechanism of persistent hypothyroidism in patients on imatinib and sunitinib already receiving replacement L-thyroxine^{9, 16, 12, 21}. Postthyroidectomy patients on L-thyroxine have been reported to develop symptoms of hypothyroidism during imatinib²⁴ or motesanib therapy²⁵.

While studies suggest there may be a survival advantage for patients with renal cancer on TKI's who experience hypothyroidism, our patient with papillary renal cell cancer died only 6 weeks after discontinuing sunitinib. Progression free survival and overall survival of patients with subclinical (elevated TSH only) or clinical hypothyroidism (elevated TSH, decreased T4 and T3) on sunitinib are reported to be better,^{26,16} however, it should be emphasized that the histologic subtype in these studies is almost exclusively renal clear cell. The survival benefit persists even in those receiving L-thyroxine replacement^{27, 28} perhaps because many remain in a persistent hypothyroid state despite replacement therapy²⁴. Even patients with head and neck cancer not on sunitinib are reported to have improved survival associated with hypothyroidism, possibly due to a modulating effect on proliferation and apoptosis.²⁹ Recommendations by some authors²³ suggest TSH should be measured in all patients on sunitinib to validate TSH as a potential prognostic marker. Our patient's symptoms of overt hypothyroidism and poor prognosis suggest that patients with extreme hypothyroidism might have worse outcomes than their counterparts with mildly elevated TSH levels or subclinical hypothyroidism. Future studies should determine whether the relationship between survival and TSH is affected by severe hypothyroid symptoms, the degree of elevated TSH levels or by histologic subtype. Our patient's FH gene mutation-associated papillary renal cell cancer is known to be associated with worse prognosis and may have increased her susceptibility to clinical toxicities and thyroid abnormalities via an unexplained mechanism. Kidney cancer is a heterogeneous disease with markedly different clinical courses, is caused by different genes, and may have different responses to therapies³⁰.

Even though our case of extreme hypothyroidism appears to be associated with sunitinib we cannot exclude the possibility that combination anti-angiogenic therapy (sunitinib plus AMG-386) may have contributed to the pronounced thyroid abnormalities.³¹ Although fatigue is reported as the most common side-effect of AMG-386, thyroid abnormalities have not been identified in animal studies or preliminary phase I and phase II trials, even when AMG-386 is combined with other small molecule TKI's such as sorafenib³².

Ultimately, the patient's poor response and marked thyroid dysfunction may have been multifactorial including her genetic FH mutation, papillary renal cell cancer histologic subtype^{33, 34}, or possibly combination therapy with another anti-angiogenic agent.

In summary, the case presented illustrates the potential for TKI's to cause extreme hypothyroidism, and unusually high serum TSH levels even while patients are on thyroxine replacement. Severe clinical toxicity is not necessarily accompanied by prolonged survival, and can contribute to substantial symptom burden which abates after TKI treatment is withdrawn. In addition the profound hypothyroidism may be complicated by thyroiditis and transiently elevated thyroxine levels. Clinicians should monitor serum levels and consider early referral to their endocrinology colleagues if thyroid replacement is considered.

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Figure 1.
Temporal relationship between TSH, T4, L-thyroxine dose, and sunitinib cycles.

Figure 2.
ESAS scores relative to clinic visit and TSH.