Case Report

Increased Thyroid-Hormone Requirements Consistent With Type 3 Deiodinase Induction Related to Ibrutinib in a Thyroidectomized Woman

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Abstract

Objective: Tyrosine-kinase inhibitors (TKIs) are chemotherapeutic agents associated with increased thyroid-hormone requirements and altered deiodinase activity. We present the first case to link these findings to the TKI ibrutinib.

Methods: Serial thyroid-stimulating hormone (TSH), free-thyroxine (FT4), free-triiodothyronine (FT3), and reverse-triiodothyronine (rT3) levels were assessed.

Results: An 80-year-old, 62-kg woman with hypothyroidism secondary to total thyroidectomy for stage I papillary thyroid cancer, on maintenance levothyroxine (LT4) 137 mg daily, presented for follow-up. Compared to one year prior, the patient’s weight had increased by 2 kg and TSH from 2.58 to 27.60 μIU/mL (normal: 0.45-4.50 μIU/mL) while on pantoprazole. Ibrutinib, her other medication, had been started seven months prior for chronic lymphocytic leukemia. Despite sequential confirmation of proper LT4 adherence and self-administration, adjustment of LT4 to 150 mg, and discontinuation of pantoprazole, ibrutinib, her other medication, had been started seven months prior for chronic lymphocytic leukemia. Despite sequential confirmation of proper LT4 adherence and self-administration, adjustment of LT4 to 150 μg, and discontinuation of pantoprazole, the patient’s hypothyroid symptoms worsened, and the TSH was 73.90 μIU/mL six months later. LT4 was increased to 175 μg six days a week and 262.5 μg once weekly. Two months later, the TSH was 3.92 μIU/mL (steady-state condition), FT4 2.32 ng/dL (normal: 0.82-1.77 ng/dL), FT3 1.6 pg/mL (normal: 2.0-4.4 pg/mL), and rT3 69.6 ng/dL (normal: 9.2-24.1 ng/dL). Ibrutinib was discontinued the next month due to gastrointestinal side effects and elevated blood pressure. Four months later, LT4 had been reduced to 150 μg, and the FT4 reached 1.92 ng/dL, FT3 2.0 pg/mL, and rT3 26.6 ng/dL.

Conclusion: This report links ibrutinib to increased thyroid-hormone requirements in a thyroidectomized woman whose decreased T3:T4, T3:rT3, and T4:rT3 ratios suggested type 3 deiodinase induction and type 2 deiodinase inhibition.

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Introduction

Tyrosine-kinase inhibitors (TKIs) are a class of chemotherapeutic agents with a far-reaching impact. TKIs restrict angiogenesis through a variety of mechanisms, including the inhibition of vascular endothelial growth-factor receptor (VEGFR). Conceived as targeted therapy for chronic myeloid leukemia, TKIs have been integrated into the treatment of both hematologic and solid-organ malignancies.

As the clinical applications of TKIs have evolved, so has an awareness of their side effects, especially clinical and biochemical thyrotoxicosis and hypothyroidism. Such abnormalities can manifest as transient thyrotoxicosis or mild-to-severe hypothyroidism. Proposed mechanisms include impaired iodine uptake, VEGFR inhibition, and type 3 deiodinase (D3) induction. TKI-associated clinical and biochemical hypothyroid states, whether reported as hypothyroidism in patients with intact thyroid glands or increased thyroid-hormone (TH) requirements in...
An 80-year-old, 62-kg woman with hypothyroidism secondary to total thyroidectomy for stage I papillary thyroid cancer, stable on levothyroxine (LT4) 137 µg daily for the previous 21 months, presented with weight gain and a thyroid-stimulating hormone (TSH) elevation. Compared to one year prior, the patient had gained 2 kg, and the TSH had risen from 2.58 to 27.60 mIU/mL (normal: 0.45-4.50 mIU/mL). Seven months prior to presentation, ibrutinib had been started for recurrence of chronic lymphocytic leukemia/small lymphocytic lymphoma. The patient reported full adherence to and proper self-administration of LT4.

LT4 was increased from 137 µg to 150 µg daily; four months later, the TSH had increased to 47.50 mIU/mL. The TSH elevation was attributed to malabsorption of LT4 secondary to a recently increased dose of pantoprazole; medication reconciliation was unremarkable for other agents with known interactions with LT4. Pantoprazole was replaced with famotidine, and LT4 was continued unremarkable for other agents with known interactions with LT4. Given the persistent rise in TSH and her hypothyroid state, this association is reinforced by the normalization of the patient’s thyroid-function tests and decrease in LT4 dose needed to maintain a normal TSH after ibrutinib discontinuation, as depicted in the Table. Accordingly, the observed hypothyroid state was most likely ibrutinib induced.

The fact that ibrutinib induced a hypothyroid state in this athyreotic patient provides important insight into the underlying mechanism. Previously proposed mechanisms for TKI-associated hypothyroid states that center on the thyroid per se, such as impaired iodine uptake and VEGFR inhibition, are unlikely in this thyroidecomized patient. We hypothesize that this patient’s hypothyroid state was caused by D3 induction, as seen with sunitinib and sorafenib. The patient exhibited a markedly elevated rT3, mildly elevated TT4, and decreased total triiodothyronine (TT3), estimated from a decreased FT3 and normal TBG. These values imply decreased TT3:TT4, TT3:rT3, and TT4:rT3 ratios, consistent with increased conversion of T4 into rT3 via D3 activation. This mechanism is corroborated by the high LT4 doses required to preserve normal TSH values during ibrutinib therapy, which indicate increased T4 metabolism with a concurrently elevated rT3. Given the low triiodothyronine (T3) and elevated TT4 and rT3, type 2 deiodinase (D2) inhibition yielding intracellular depletion of T3 is a possible concurrent mechanism, one potentially relevant to axitinib as well.

Prior literature on other TKIs has noted findings similar to those of the patient in this report. de Groot et al11 examined 8 athyreotic patients with medullary thyroid cancer receiving imatinib who also displayed significant elevations in LT4 doses and TSH levels, and whose hypothyroid symptoms did not reverse with augmented LT4 therapy. The authors deemed enhanced T4 and T3 clearance as the most likely cause. Abdulrahman et al7 conducted a prospective study on 21 athyreotic patients with nonmedullary thyroid carcinoma who received sorafenib for 26 weeks. As in the current report, the authors observed higher necessary LT4 doses and significantly decreased TT3:TT4, TT3:rT3, and TT4:rT3 ratios, consistent with D3 induction. Kappers et al12 also documented decreased TT3:rT3 ratios in 15 patients after 10 weeks of sunitinib therapy, with one athyreotic patient further requiring increased LT4. In addition, the authors measured increased hepatic D3 activity in rats exposed to
sunitinib for 8 days with corresponding decreases in T3 and T4 levels.6

Interestingly, the patient reported here featured a mildly elevated FT4 and T4, whereas low T4 levels are predicted with D3 induction.12 Given the patient’s athyreotic status and normal TBG, the elevated levels are likely from the high LT4 dose of 175 μg, which is substantially higher than the 1.6 μg/kg/day dosing traditionally employed. The dose intensity is further evidenced by the TSH reduction from 73.90 to 2.85 mIU/mL and the patient’s weight loss of 2 kg, although the latter may have been influenced by concurrent ibrutinib-related gastrointestinal side effects. Moreover, the FT4 normalized after ibrutinib discontinuation permitted lower LT4 doses to maintain the TSH within normal limits. Ibrutinib-induced D2 inhibition may have also contributed through decreased conversion of T4 to T3.

This case provides important insight into the evaluation and management of the hypothyroid state associated with sunitinib and other TKIs. For patients undergoing TKI therapy who present with an abnormal TSH, a complete thyroid panel, including TSH, FT4, T3, and T3, may help clarify the etiology and therapeutic expectations. The fact that the patient’s TSH and symptoms readily responded to high LT4 doses informs that therapeutic LT4 doses for patients on TKIs can be significantly higher than expected. Indeed, one study of 8 athyreotic patients receiving imatinib reported a mean increase of 206% (range: 100%-350%) from the pre-imatinib LT4 dose.11

Notably, this patient was not clinically euthyroid on her augmented LT4 therapy, as despite the normal TSH and high FT4, she continued to report hypothyroid symptoms. This hypothyroid state may have been influenced by low FT3 secondary to D3 induction and D2 inhibition. Accordingly, combined replacement therapy with LT4 and liothyronine may be beneficial in ibrutinib-induced hypothyroid states. Moreover, for this patient, the LT4 dose required to preserve a normal TSH level decreased following ibrutinib discontinuation, indicating that ibrutinib-induced hypothyroidism is reversible with cessation of the offending agent. This report and prior literature, however, are limited by small sample size and disparate measurements of TSH, thyroid hormones, LT4 doses, and deiodinase activity. Prospective research with large sample sizes is necessary to simultaneously measure the aforementioned biochemical and clinical parameters, clarify the molecular mechanism, and enumerate the intensity of LT4 and/or liothyronine therapy required to alleviate hypothyroid symptoms.

Disclosure

The authors have no multiplicity of interest to disclose.

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Table

Average Daily Levothyroxine Dose and Levels of Thyroid Hormones and TSH Before Ibrutinib, During Ibrutinib, and 4 Months After Ibrutinib Discontinuation.

| Parameter                        | Normal range | Before ibrutinib | During ibrutinib | After ibrutinib |
|----------------------------------|--------------|-----------------|-----------------|----------------|
| Thyroid-stimulating hormone (mU/mL) | 0.45-4.50    | 2.58            | 3.92            | 2.18           |
| Levothyroxine (µg)              | …            | 137             | 187.5           | 150            |
| Free triiodothyronine (ng/dL)   | 0.82-1.77    | …               | 2.32            | 1.92           |
| Reverse triiodothyronine (ng/dL)| 2.0-4.4      | …               | 1.6             | 2.0            |
| Free thyroxine (ng/mL)          | 9.2-24.1     | 69.6            | 26.6            |                |

a Values are weighted averages of daily levothyroxine doses over the course of a given week.