Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine

A 73-year-old woman was admitted with fatigue, nausea, cold-intolerance, hair-loss, brittle nails, progressive weakness and impressive facial oedema 6 months after starting imatinib (600 mg daily) for metastatic gastrointestinal stromal tumour (GIST, Figure 1) elsewhere. Previously, she had thyroidectomy and 131I-ablation for follicular thyroid carcinoma. She always had normal thyroid function using 200 μg levothyroxine daily. She also used alendronic acid, hydrochlorothiazide and quinapril. We attributed her complaints to imatinib. However, thyroid function (reference values in parenthesis) was abnormal: thyrotropin (TSH) 74 mU/l (0.42–7.20), free thyroxine (fT4) 13.5 pmol/l (6.3–18.2) and free triiodothyronine (fT3) 4.2 pmol/l (2.4–6.7). We increased levothyroxine to 250 μg and stopped imatinib because of intolerance (Figure 2). Four weeks after admission all complaints had disappeared and except for a period of oversubstitution with levothyroxine, the patient remained euthyroid using 175 μg levothyroxine. Seven months later, GIST metastases progressed and were proven irresectable. Therefore, she restarted with 400 mg imatinib; this time with instantaneous increase of levothyroxine to 300 μg (Figure 2). We increased levothyroxine to 250 μg and stopped imatinib because of intolerance (Figure 2). Although she remained euthyroid using 175 μg levothyroxine, the patient experienced extreme fatigue and periorbital oedema. Therefore, imatinib was discontinued and levothyroxine decreased to 175 μg.

Five months later the patient started with sunitinib 50 mg daily (Pfizer A6181036 protocol) for 4 weeks of a 6 weeks cycle. After 3 days, TSH levels rose (23 mU/l), whereas fT4 (16.0 pmol/l) and fT3 (3.9 pmol/l) were normal. We increased levothyroxine to 300 μg and TSH levels declined but failed to return to normal (13.0 mU/l). The patient again experienced hair loss, brittle nails and oedema. Furthermore, she developed leukocytopenia (2.4 × 10^9/l), thrombocytopenia (33 × 10^9/l) and extreme fatigue. We withheld treatment until she recovered to 3.7 × 10^9/l leukocytes and 100 × 10^9/l thrombocytes and restarted sunitinib from the first day of the second cycle at 37.5 mg. On this cycle she remained euthyroid (TSH 5.7 mU/l, fT4 22.9 pmol/l) using 300 μg levothyroxine without serious haematological toxicity. After three courses, sunitinib was stopped because of progressive disease.

Imatinib and sunitinib are used against various cancers. Although generally well tolerated, common side-effects are fatigue and (periorbital) oedema [1]. Symptoms of hypothyroidism are almost undistinguishable from these side-effects. We attributed the first increase in TSH levels to imatinib because there was no evidence of non-compliance to levothyroxine and hypothyroidism resolved once imatinib was stopped and returned once imatinib was restarted. Besides, the patient took her levothyroxine before any other medication, reducing the possibility of drug-related absorption problems. Given the normal levels of free thyroid hormones, the levothyroxine was probably adequately absorbed. Since the patient was euthyroid in the period that she was not on tyrosine kinase inhibitors, it is unlikely that GIST could have interfered with levothyroxine absorption. The marked increase in TSH suggests interference of tyrosine kinase inhibitors with thyroid hormone action at pituitary level.

It has been described that a sudden rise of TSH with normal fT4 and fT3 levels leads to complaints of hypothyroidism [2]. Recently, we reported on imatinib-induced hypothyroidism in patients receiving levothyroxine after thyroidectomy [3].
study, TSH levels rose in patients on imatinib and levothyroxine but not in patients with a normal functioning thyroid.

This case demonstrates intrusion of two tyrosine kinase inhibitors with levothyroxine therapy. This pitfall could have severe consequences if unnoticed and left untreated. Increasing levothyroxine dosage at the start of imatinib and sunitinib treatment can prevent hypothyroidism. The mechanism by which hypothyroidism arises is unclear and whereas imatinib apparently only causes hypothyroidism in thyroidectomized patients, sunitinib can also cause hypothyroidism in patients with a normal functioning thyroid [3, 4]. Nevertheless, it is important to evaluate thyroid function in hypothyroid patients on tyrosine kinase inhibitors.

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Figure 2. Time course of the serum concentrations of thyrotropin (TSH) and free thyroxine (fT4) after treatment with tyrosine kinase inhibitors. — = upper and lower reference limit for TSH; - - - = upper and lower reference limit for fT4. Start imatinib 600 mg/day at t = 0 weeks; → stop imatinib; ↓ restart imatinib 400 mg/day with instantaneous increase of levothyroxine to 300 µg/day; ↑ start sunitinib 50 mg/day.