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LETTER TO THE EDITOR

Hyperthyroidism and thyroid autoimmunity induced by sorafenib in metastatic renal cell cancer

Ceyla Konca Degertekin · Uğur Coşkun · Füsun Baloş Törüner · Müjde Aktürk · Umut Demirci

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Dear Editor,

Tyrosine kinase inhibitors (TKIs) are novel molecular-targeted agents used in the treatment of various cancers. Treatment with TKIs has been associated with changes in thyroid hormone status. While hypothyroidism had frequently been reported with the use of TKIs, thyroid-stimulating hormone (TSH) suppressing effect of TKIs is rare [1]. Here, we describe a case with metastatic renal cell cancer (RCC), who initially became hyperthyroid under sorafenib treatment and later long-term hypothyroid under sunitinib treatment.

A 58-year-old male with metastatic RCC presented with the complaints of weakness, palpitations, restlessness, and trembling in his hands for 4 weeks after starting his new cancer treatment using sorafenib. He did not have any other medication or recent iodinated-contrast exposure. On examination, he had tachycardia, fine tremor, hyperactive deep tendon reflexes, and a smooth, non-tender, slightly enlarged thyroid gland. His test results were compatible with overt hyperthyroidism [TSH: 0.011 μIU/ml (0.55–4.78); free thyroxine (fT4): 8.14 ng/dl (0.89–1.76); and free triiodothyronine (fT3): 17.3 pg/dl (2.3–4.2)], and he had high titers of thyroglobulin (anti-TG) (2,500 U/ml; normal <60), thyroid peroxidase (anti-TPO) (2,723 U/ml; normal <60), and TSH-receptor (TRAb) [24.6 U/L (0–14) antibodies; however, thyroglobulin levels were not elevated [4.76 (1.6–59.9 ng/mL)]. Thyroid function tests, anti-TG and anti-TPO, were normal before sorafenib treatment. His family history was negative for Graves disease. The ultrasonography revealed heterogeneous enlargement of the thyroid gland and the Tc-99 scintigraphy showed a homogeneously increased absorption; 4 and 24 h ^{131}I uptakes were 49.5 % (15–25 %) and 70.1 % (25–35 %), respectively. Graves disease, induced by sorafenib, was diagnosed based on positivity of anti-TSH receptor antibodies and high radio-iodine thyroid uptake and methimazole (20 mg/dl) and propranolol were prescribed. Completing his first cycle of sorafenib, the patient was switched to sunitinib. He had substantial improvement 1 month after the onset of antithyroid medication. Three months after starting methimazole, he developed features of hypothyroidism with low levels of fT4 (0.59 ng/dl) and fT3 (2.36 pg/dl) despite a sustained suppression of TSH (0.026 μIU/ml). Methimazole was stopped. Four weeks after, TSH increased to 11 μIU/ml and fT4 decreased to 0.47 ng/dl. Levothyroxine treatment was initiated and the patient achieved euthyroidism in 2 months. Currently, he is on follow-up with 150 mcg/day levothyroxine for the last 7 months without significant symptoms.

Few cases of thyroid hormone excess have been reported with sunitinib; however, they were whether mild and self-limiting or if overt, was associated with low uptake in thyroid scan and elevated thyroglobulins suggesting destructive thyroiditis [1]. There is even fewer data on the TSH-suppressing effect of sorafenib. Miyake et al. [2] reported that 23.9 % of patients with metastatic RCC receiving sorafenib had TSH suppression before the development of hypothyroidism. One case with overt hyperthyroidism was reported after sorafenib treatment in a

C. Konca Degertekin (✉) · F. Baloş Törüner · M. Aktürk
Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Gazi Üniversitesi Hastanesi, Endokrinoloji ve Metabolizma BD, 06100 Beşevler, Ankara, Turkey
e-mail: ceylakonca@hotmail.com

U. Coşkun · U. Demirci
Department of Medical Oncology, Faculty of Medicine, Gazi University, Gazi Üniversitesi Hastanesi, Onkoloji BD, 06100 Beşevler, Ankara, Turkey

group of 39 patients with RCC. However, the patient did not have baseline thyroid function tests or iodine uptake available and did not receive antithyroid medication [3].

Returning to our case, under sorafenib treatment, the patient developed overt hyperthyroidism and had increased radioiodine uptake, which is strikingly different than that of previously reported in the literature. Thyroglobulin levels were not elevated. These findings directed us to increased endogenous thyroid hormone production rather than destructive thyroiditis. It is of importance that the thyroid autoantibodies developed after TKIs in our case, which points out to an autoimmune etiology. There is evidence that different TKIs are able to modulate immune responses: increased T-helper 1 response and inhibition of regulatory T-cell proliferation had been reported with the use of TKIs [4]. We believe that the TKI treatment induced thyroid autoimmunity through triggering a subtle thyroiditis which in return activated the autoantibody production and subsequently increased thyroid hormone production as in the case of Graves disease. With the development of thyroid autoimmunity and other possible mechanisms induced by sunitinib, our patient consequently developed hypothyroidism.

In conclusion, thyroid dysfunction may frequently be seen, and thus should be monitored for under TKI therapy. While most frequent form of dysfunction is hypothyroidism, hyperthyroidism may as well be encountered. The increased iodine uptake, thus endogenous thyroid hormone production, in our case points out that destructive thyroiditis may not be the only mechanism that explains TSH suppression in these patients. Further studies on the mechanism of how TKIs lead to thyroid dysfunction and autoimmunity are needed.

Conflict of interest The authors declare that they have no conflict of interest.

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