Editorial

Tumor progression with thyrotoxicosis on differentiated thyroid carcinoma due to thyrotropin receptor stimulation: is tyrosine kinase inhibitors the cause of thyroid stimulating hormone receptor antibody positivity?

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Comment on: Toda S, Kadoya M, Matsui A, *et al.* Hyperthyroidism due to thyrotropin receptor antibody stimulation of metastatic thyroid carcinoma during lenvatinib treatment: a case report. Ann Palliat Med 2022. doi: 10.21037/apm-22-276.

Submitted Aug 17, 2022. Accepted for publication Sep 13, 2022.
doi: 10.21037/apm-22-971
View this article at: https://dx.doi.org/10.21037/apm-22-971

Multi-target tyrosine kinase inhibitors (mTKIs) are potential new options for the treatment of differentiated thyroid carcinoma (DTC). TKIs could inhibit the tyrosine kinase such as vascular endothelial growth factor (VEGF) receptors and their downstream kinases and subsequently suppress cancer proliferation. The beneficial therapeutic outcomes have been shown by mTKIs in radioactive iodine (RAI) refractory DTCs and improved survival rate (1). Despite their high efficacy and selectivity, TKI administration is associated with certain adverse events. Thyroid dysfunction, typically destructive thyroiditis and then hypothyroidism, is a well-known manageable side effect of TKIs. However, it is challenging when tumor progression with T3 thyrotoxicosis occurs during cancer treatment.

In recent publication, Toda *et al.* reported the potential link between TKI administration and appearance of thyroid stimulating hormone (TSH) receptor antibody (TRAb) (2). A 57-year-old male, with the history of total thyroidectomy for follicular thyroid carcinoma (FTC) 6 years ago, was treated with mTKI lenvatinib for metastatic thyroid cancer. At 83 weeks after lenvatinib initiation, he was hospitalized with thyrotoxicosis. Accumulation of RAI-131 scintigraphy at metastatic site with TRAb positivity suggested that cancer cells produced thyroid hormone and proliferation due to TSH receptor stimulation. Treatment with methimazole and restarted lenvatinib failed to prevent tumor growth. Authors concluded that "Hyperthyroidism may occur in advanced thyroid cancer after total thyroidectomy requiring lenvatinib treatment. Persistent TSH receptor stimulation caused by TRAb can be involved in tumor growth and thyroid hormone secretion from metastases".

Generally, TSH suppression therapy is recommend for high-risk DTC patients. TSH receptors expressed on DTC display the role on tumor growth via the cAMP cascade (3). Regard with this, TSH antagonist, K1-70, stabilized metastatic lesion of DTC (4). Therefore, in the management of DTC patients, avoiding TSH receptors activation is essential. Clinically, the induction of TSH receptor signaling could be happened by (I) the presence of activating mutation in the TSH receptor, or (II) the production of TSH receptor stimulating antibody (TSAb). Thyroid cancer cases with activating mutation of TSH receptor were reported (5). Other mechanisms by which TSH receptor is aberrantly activated is the presence of TSAb. TSAb can stimulate thyroid follicular epithelial cell proliferation and produce excessive thyroid hormone levels. VEGF expression is shown to be stimulated by TSH in

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thyroid cancer cell lines (6), and VEGF is associated with thyroid tumor aggressiveness *in vitro* and human study (7). The presented case by Toda *et al.* displayed the advanced metastasis accompanied with thyrotoxicosis via potentially aberrant activation of TSH and VEGF (2). Although there is no direct evidence, TSH receptor activation by TSAb in DTC cause vicious consequence via TSH-VEGF axis.

Another issue required consideration is the approach to thyrotoxicosis during cancer treatment. There are several causes of thyrotoxicosis during cancer treatment, destructive thyroiditis, drug-induced thyrotoxicosis, TSH receptor activating mutation and hyperthyroidism. In general, mTKI for thyroid cancer are used after total thyroidectomy. Therefore, typical destructive thyroiditis is often seen in non-thyroid carcinomas such as hepatocellular carcinoma (HCC). Ohki *et al.* reported that lenvatinib-induced thyroid dysfunction was occurred in 20/77 of HCC patients (25.9%) (8). Although the mechanism of thyroiditis associated with mTKI treatment has not elucidated yet, Makita *et al.* suggested mTKI-induced thyroid ischemia and thyrocyte apoptosis resulting in destructive thyroiditis (9). The thyrotoxicosis due to destruction of metastatic lesion is another important mechanism. As authors commented, low FT3/FT4 ratio and rapid increase in thyroglobulin would help to determine whether destructive thyroiditis is the cause of thyrotoxicosis in cancer patient treated with mTKI.

Replacement therapy related T3 thyrotoxicosis is potentially lead to a critical event. Most patients after total thyroidectomy are on replacement therapy with T4 agent. Miyauchi *et al.* reported cases with thyrotoxicosis due to increased conversion of administered levothyroxine (10). They showed that type 1 and type 2 iodothyronine deiodinase activities were high in the tumor tissue of cases with thyrotoxicosis. In these cases, both Free T3 and Free T4 levels were decreased by the cessation of levothyroxine. Other groups have also reported similar cases in follicular cancer patients on lenvatinib treatment (11). This mechanism should be considered when T3 thyrotoxicosis develops in patients receiving mTKIs while on thyroid hormone replacement without TRAb. If the T3 toxicosis is induced by this mechanism, associated symptoms would be expected to be gone with the cessation of levothyroxine.

In Toda's presented case, TRAb was positive and suggested to stimulate both hormone production and tumor progression via TRAb-induced TSH receptor activation. On the other hand, we and others reported thyroid hormone producing cancer cases without TRAb (12,13). Activating mutations in TSH receptor genes stimulate the intracellular cyclic adenosine monophosphate cascade, which is the most considerable cause of hyperthyroidism due to thyroid cancer without TRAb. Among hyperfunctioning thyroid cancers, FTC has been shown to have a markedly higher prevalence than papillary thyroid carcinoma (14). Metastatic hyperfunctioning thyroid cancer is characterized by extensive or massive metastatic disease (12,13), yet there was no direct evidence that metastatic lesion could produce thyroid hormones via TSH receptor activation mutation.

Finally, there are several DTC cases that become TRAb positive in clinical course. The mechanism by which TRAb is produced during treatment of DTC has not been elucidated. Aoyama *et al.* reported DTC patients with TRAb positivity during the treatment course of RAI treatment (15). They suggest two mechanisms of TRAb production, the one is an autoimmune response triggered by radioiodine therapy and another is alteration of immunological homeostasis due to stress. According to the review by Bhattacharya *et al.*, mTKI-associated Grave's disease would be minor case (16). The replacement dose of levothyroxine is sometimes increased associated with TKI treatment. Increased type 3 deiodinase activity and decreased pituitary type 2 deiodinase activity could be the possible mechanisms (17).

Association between TKI and appearance TRAb is unclear. There are several reports that assessed their effects on the immune systems (18). TKIs could affect humoral immunity and potentially influence the production of TRAb. TKI could affect plasma immunoglobulin levels (19). Sunitinib, another TKI, has shown to induce trigger/exacerbate thyroid autoimmunity in some patients, (20), and also linked to worsening the membranous nephropathy, the disease associated with anti-PLA2R antibody IgG (21). Concerning the association with the TK deficiency and autoimmune-thyroid disease, the stop mutation in Fms-Related Receptor Tyrosine Kinase 3 (FLT3), the TK associated with various hematologic cancers, has been shown to increase the risk of autoimmune thyroid diseases (22). The underlying mechanism associated with FLT3 deficiency and autoimmune thyroid disease is hypothesized that stop-mutation in FLT3 in certain cells induces feedback elevation of FLT3 ligand; such elevated FLT3 ligand stimulates remaining normal FLT3 in dendritic cells, consequently inducing autoimmune thyroid disease. Whether these mechanisms would be relevant to the TKI and appearance TRAb is not clear yet; indeed, the FLT3 ligand has been shown to augment severe autoimmune thyroiditis in mice (23). In addition to thyroid disorders, various endocrine abnormalities may be induced by TKI treatment.

Recent study reported lenvatinib induced primary adrenal insufficiency (24). Evaluation and management of endocrine related adverse event associated with mTKI may become essential in the treatment of DTC patients and could be linked to autoimmunity.

In conclusion, the first DTC case with TRAb during the mTKI treatment was reported by Toda and his colleagues. Whether/how TKIs are involved in TRAb production has not been elucidated yet; therefore, close monitoring of thyroid function with auto-antibody before and after treatment of TKI would be required.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-971/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Notsu M, Kanasaki K. Tumor progression with thyrotoxicosis on differentiated thyroid carcinoma due to thyrotropin receptor stimulation: is tyrosine kinase inhibitors the cause of thyroid stimulating hormone receptor antibody positivity? Ann Palliat Med 2022;11(9):2806-2809. doi: 10.21037/apm-22-971

