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【 CASE REPORT 】

Destructive Thyroiditis Induced by Lenvatinib in Three Patients with Hepatocellular Carcinoma

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Abstract:
Hypothyroidism is a frequently occurring complication in patients on lenvatinib treatment. However, little is known about lenvatinib-induced thyrotoxicosis and destructive thyroiditis. We herein report the cases of three patients who developed hyperthyroidism during the course of lenvatinib treatment. All patients had multiple hepatocellular carcinoma of Child-Pugh class A. Two patients required beta blockers for the management of palpitations. One patient developed hyperthyroidism only one week after the initiation of lenvatinib treatment. Thus, the possibility of hyperthyroidism developing within one week after the first administration should be kept in mind, and periodic surveillance of the thyroid function should be performed during the early period of lenvatinib therapy (within the first two weeks or so after the initial administration).

Key words: hepatocellular carcinoma, lenvatinib, hyperthyroidism, destructive thyroiditis

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Introduction

Lenvatinib is an oral multi-target receptor tyrosine kinase inhibitor (TKI) for vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, and *KIT* and *RET* proto-oncogenes (1-4). Lenvatinib monotherapy has been approved for radioiodine-refractory differentiated thyroid cancer (5). Lenvatinib with everolimus has been approved for the treatment of advanced renal cell carcinoma (6). Recently, lenvatinib has been reported to be non-inferior to sorafenib with regard to the overall survival in cases of advanced hepatocellular carcinoma (HCC) (7). However, lenvatinib for HCC has only been approved in Japan. The most common reported adverse effects are hypertension, hand-foot syndrome, decreased appetite, proteinuria, and fatigue in patients with HCC (7, 8). While hypothyroidism reportedly occurred in 16% (7) and 21.7% of patients (8), it is unclear how many patients have experienced lenvatinib-induced hyperthyroidism.

To our knowledge, this is the first case report of lenvatinib-induced destructive thyroiditis in patients with HCC.

Case Reports

Case 1

A 69-year-old man with multiple HCC (Child-Pugh class A) received transarterial chemoembolization that was repeated every three months in order to achieve tumor reduction. He had no family history of thyroid disease. Due to his body weight of 74 kg, oral lenvatinib 12 mg/day was initiated. A baseline thyroid function test (TFT) revealed a euthyroid state [free thyroxine (FT4), 1.47 ng/dL (normal range 0.9-1.7); free triiodothyronine (FT3), 2.78 pg/mL (normal range 2.3-4.0); and thyroid-stimulating hormone (TSH), 4.95 μIU/mL (normal range 0.5-5.0)]. Laboratory test results also revealed positivity for anti-thyroid antibodies [anti-thyroglobulin antibody (TgAb), 129.0 IU/mL (normal range 0-27.9)] and negativity for other antibodies [anti-thyroid peroxidase antibody (TPOAb), 15.5 IU/mL (normal range 0-15.9); anti-human TSH receptor antibody, <0.3 IU/L

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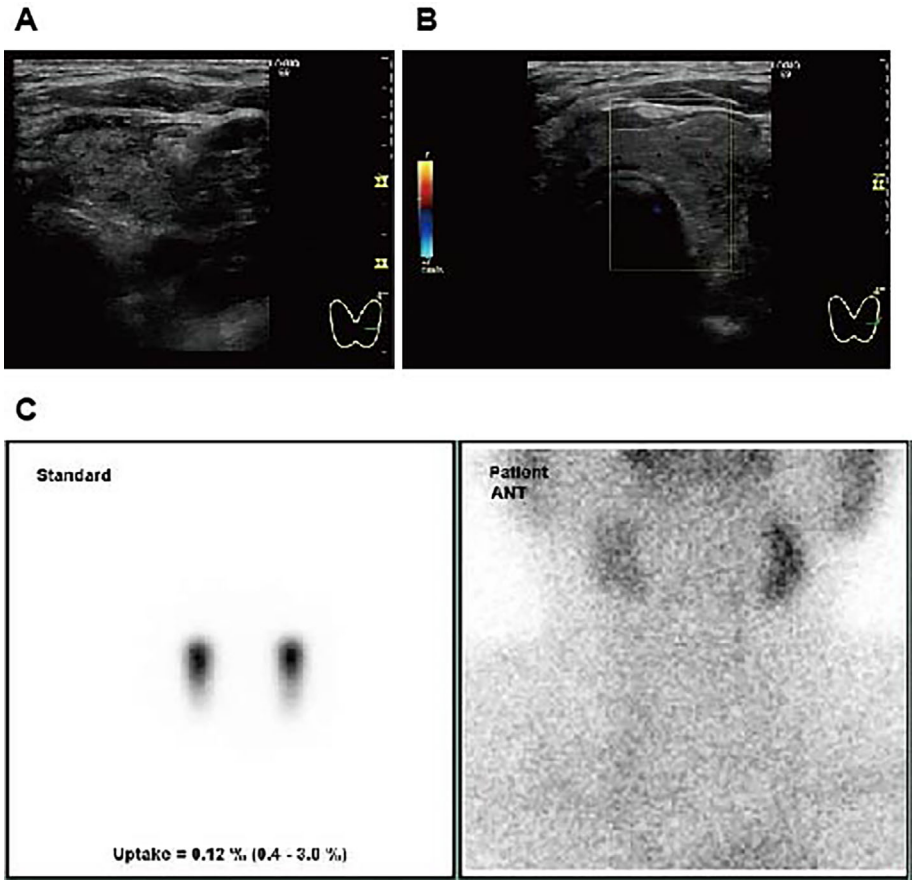

Figure 1. **Ultrasonography and ^{99m}Tc scintigraphy findings of Case 1. Ultrasonography revealed a hypoechogenic parenchymal pattern and decreased intrathyroidal blood flow (A, B); ^{99m}Tc scintigraphy demonstrated a markedly decreased radioactive uptake (C).**

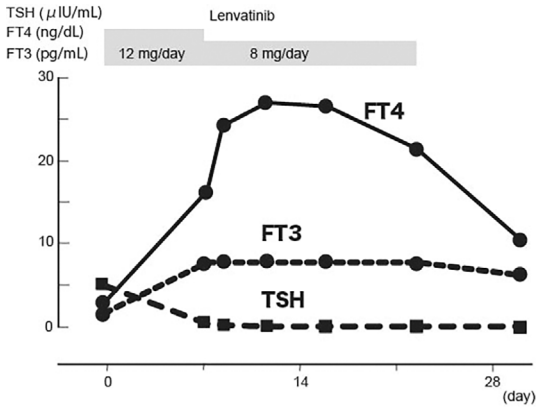

Figure 2. **Clinical course of Case 1.**

(normal range 0-2.0); and thyroid stimulating antibody (TSAb), 109% (normal range <120)]. Six days after the first administration of lenvatinib, he developed palpitations, and his TFT results revealed mild thyrotoxicosis (FT4, 7.76 ng/dL; FT3, 16.40 pg/mL; and TSH, 0.24 μIU/mL). Ultrasonography revealed a non-hypertrophic thyroid gland (size of the left lobe, 38.0×23.0×15.0 mm; right lobe, 45.3×29.0×17.8 mm), a hypoechogenic pattern of the parenchyma, and decreased intrathyroidal blood flow (Fig. 1A and B). In addition, 99m-technetium (^{99m}Tc) scintigraphy demonstrated a markedly decreased (0.12%) radioactive uptake (Fig. 1C). Thus, the thyroid dysfunction in this patient was diagnosed as lenvatinib-induced destructive thyroiditis. Treatment was initiated with a beta-blocker, and the dose of lenvatinib was reduced to 8 mg/day. About four weeks after the first dose of lenvatinib, his TFT results were improved (Fig. 2). Because general fatigue continued, lenvatinib was stopped at 21 days after the first administration.

Case 2

A 69-year-old man with multiple HCC (Child-Pugh class A) received 8 mg/day of oral lenvatinib (body weight 58.2 kg). He had no family history of thyroid disease. Baseline TFT results showed a euthyroid state (FT4, 1.49 ng/dL; FT 3, 3.64 pg/mL; TSH, 0.04 μIU/mL) and negativity for antithyroid antibodies (TgAb, 13.4 IU/mL; TPOAb, 23.5 IU/mL). Although the patient was asymptomatic, his TFT results revealed mild hyperthyroidism 2 weeks after the first dose of lenvatinib (FT4, 2.81 ng/dL; FT3, 6.06 pg/mL; TSH, <0.03 μIU/mL). Ultrasonography revealed a hypoechogenic parenchymal pattern (Fig. 3). However, ^{99m}Tc scintigraphy was not performed, and no intervention was instituted. Due to the patient's complaints of severe fatigue, lenvatinib was transiently withdrawn. At 28 days after the start of treatment, lenvatinib was restarted at 4 mg/day. After four

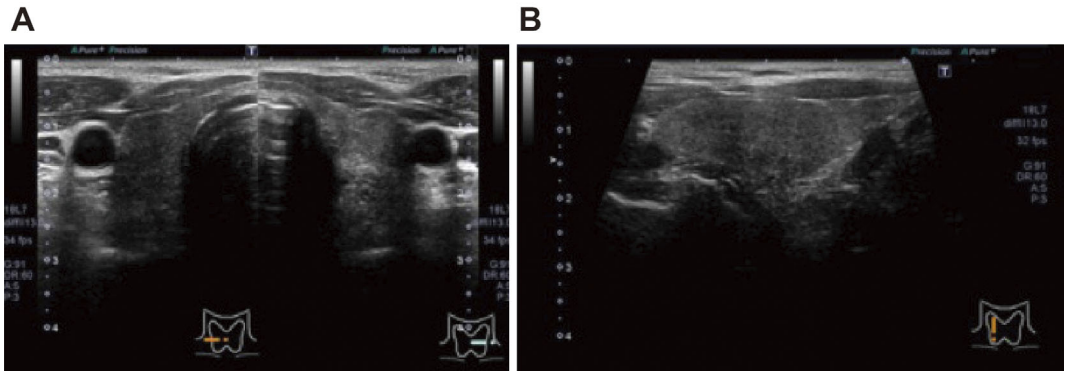

Figure 3. **Ultrasonography of Case 2. Ultrasonography revealed a hypoechogenic parenchymal pattern in transverse (A) and longitudinal (B) images.**

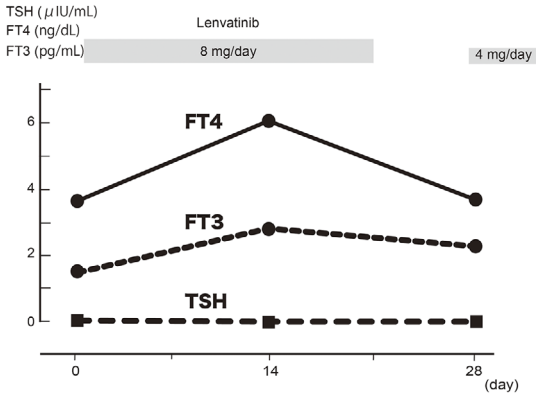

Figure 4. **Clinical course of Case 2.**

weeks, his TFT results were improved (Fig. 4).

Case 3

A 69-year-old man with multiple HCC (Child-Pugh class A) received 12 mg/day of oral lenvatinib. He had no family history of thyroid disease. Baseline TFT results revealed a euthyroid state (FT4, 1.13 ng/dL; FT3, 2.53 pg/mL; TSH, 1.62 μIU/mL). Ultrasonography revealed a non-hypertrophic thyroid gland, a hypoechogenic parenchymal pattern, and decreased intrathyroidal blood flow (Fig. 5); however, ^{99m}Tc scintigraphy was not performed. A beta-blocker was initiated for the management of palpitations. Lenvatinib was transiently stopped following the occurrence of palmar-plantar erythrodysesthesia. Lenvatinib is now being maintained at 12 mg/day because the palmar-plantar erythrodysesthesia improved and no other side effects appeared (Fig. 6).

Discussion

TKIs are small-molecule agents used in cancer therapy that target numerous cell proliferation and survival pathways. With the widespread application of these drugs, thyroid dysfunction is becoming an increasingly frequently recognized adverse event (9). Axitinib, pazopanib, sorafenib, sunitinib, and lenvatinib have been reported to cause thyroid-related adverse events (1, 7, 10-13).

Although understanding the etiology of TKI-induced thyroid dysfunction is a topic of considerable interest, the mechanism by which TKIs induce thyroiditis is unclear. However, several potential mechanisms have been proposed. First, TKIs cause apoptosis of the thyroid follicular cells, leading to destructive thyroiditis. Second, the prevention of VEGF binding to normal thyroid cells or inhibition of thyroid blood flow can cause destruction. Third, an as-yet-undescribed autoimmune mechanism affecting the thyroid function may result in hyperthyroidism. Thyrotoxicosis may have occurred in the present patients by any of these mechanisms.

It was believed that apoptosis of the thyroid follicular cells and a subsequent decrease in the thyroid blood flow might have occurred in our three cases, based on the ultrasonographic findings. Heterogeneity on B mode images reflects apoptosis of thyroid follicular cells. The reduction in blood flow on Doppler ultrasonography may reflect the decrease in the thyroid blood flow. The prevalence of TgAb or TPOAb positivity in patients with sunitinib-induced thyroid dysfunction was low (14). No correlation was observed between the presence of antibodies and the incidence and severity of thyroid dysfunction due to the autoimmune mechanism. One patient tested positive for antithyroid antibodies, while the other two patients tested negative. Therefore, autoimmune abnormalities did not appear to contribute to the TFT abnormalities caused by lenvatinib.

The onset of hyperthyroidism has not been well studied. Sato et al. reported one case in which the TSH level gradually increased at one week after the first administration lenvatinib (15). However, most patients experienced hyperthyroidism several months after the first administration of lenvatinib. Of our three patients who were treated with lenvatinib, only one experienced thyrotoxicosis at one week after the initiation of treatment. Thyrotoxicosis in the other two cases occurred more than four weeks after the first administration. Thus, TFTs should be performed as early as possible if symptoms due to destructive thyroiditis occur.

Destructive thyroiditis is diagnosed on the basis of an increased thyroglobulin level, a low radioactive iodine uptake, an increased FT4 level, and suppressed TSH level (13). Case

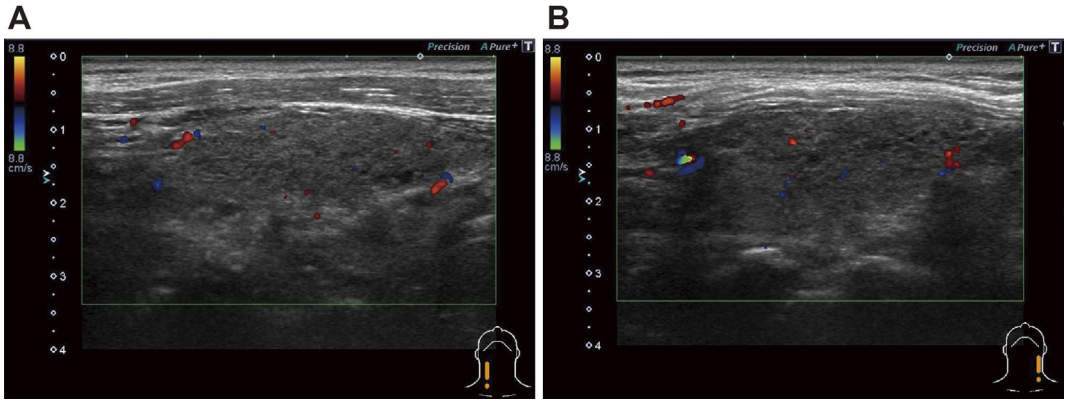

Figure 5. **Ultrasonography of Case 3. Ultrasonography revealed a hypoechogenic parenchymal pattern and decreased intrathyroidal blood flow in the right (A) and left (B) lobe.**

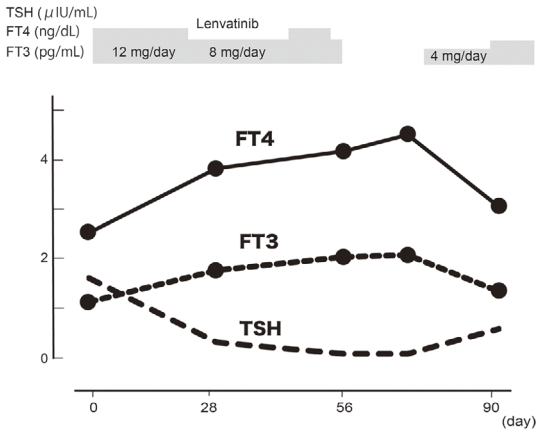

Figure 6. **Clinical course of Case 3.**

1 was a typical case of destructive thyroiditis, while cases 2 and 3 were virtually diagnostic of destructive thyroiditis. Whether or not TKI-induced destructive thyroiditis with transient thyrotoxicosis precedes persistent hypothyroidism remains unclear. Sunitinib-induced hypothyroidism appears to be reversible in the majority of patients; some patients, however, develop irreversible thyroid damage resulting in the need for long-term thyroid hormone replacement therapy (13, 16). Not all cases experienced thus far have developed hypothyroidism, as the follow up periods have been very short. Follow-up should thus be continued carefully. In the hyperthyroid state, only beta-blockers should be administered. When hypothyroidism is symptomatic (with palpitations, fatigue, or appetite loss), L-thyroxine should be administered as soon as possible.

In summary, this is the first case report of lenvatinib-induced destructive thyroiditis in patients with HCC. Lenvatinib-induced thyrotoxicosis can occur in any patient. Further studies are required to elucidate the underlying mechanism and risk factors.

The authors state that they have no Conflict of Interest (COI).

References

1. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol **52**: 512-519, 2017.
2. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res **14**: 5459-5465, 2008.
3. Tohyama O, Matsui J, Kodama K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res **2014**: 638747, 2014.
4. Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell **6**: 18, 2014.
5. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med **372**: 621-630, 2015.
6. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol **16**: 1473-1482, 2015.
7. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet **391**: 1163-1173, 2018.
8. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol **52**: 512-519, 2017.
9. Lechner MG, Vyas CM, Hamnvik OR, et al. Risk factors for new hypothyroidism during tyrosine kinase inhibitor therapy in advanced nonthyroidal cancer patients. Thyroid **28**: 437-444, 2018.
10. Ohba K, Takayama T, Matsunaga H, et al. Inappropriate elevation of serum thyrotropin levels in patients treated with axitinib. Thyroid **23**: 443-448, 2018.
11. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med **369**: 722-731, 2013.
12. van Doorn L, Eskens FA, Visser TJ, van der Lugt A, Mathijssen RH, Peeters RP. Sorafenib induced thyroiditis in two patients with hepatocellular carcinoma. Thyroid **21**: 197-202, 2011.
13. Sakurai K, Fukazawa H, Arihara Z, Yoshida K. Sunitinib-induced thyrotoxicosis followed by persistent hypothyroidism with shrinkage of thyroid volume. Tohoku J Exp Med **222**: 39-44, 2010.

14. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med **145**: 660-664, 2006.

15. Sato S, Muraishi K, Tani J, et al. Clinical characteristics of thyroid abnormalities induced by sunitinib treatment in Japanese patients with renal cell carcinoma. Endocr J **57**: 873-880, 2010.

16. Rogiers A, Wolter P, Op de Beeck K, Thijs M, Decallonne B, Schöffski P. Shrinkage of thyroid volume in sunitinib-treated patients with renal-cell carcinoma: a potential marker of irreversible thyroid dysfunction? Thyroid **20**: 317-322, 2010.