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Lenvatinib – Induced Takotsubo Syndrome in Patient with Thyroid Cancer

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Abstract

As anti-Vascular Endothelial Growth Factor (VEGF) including Tyrosine Kinase Inhibitors (TKI) become more widely used for the treatment of a variety of malignancies including Thyroid Cancer (TC), it is important for oncologists and patients to understand the potential adverse effects associated with these drugs. This review presents a case of Takotsubo cardiomyopathy, associated with use of Lenvatinib therapy for thyroid cancer. It discusses the necessary interventions and treatment are needed to successfully resolve the complications that occur. This case illustrates the importance of close monitoring of patients under TKI therapy in order to identify early signs of congestive heart failure or myocardium damage.

Keywords: Lenvatinib; Takotsubo syndrome; Thyroid cancer; Myocardial dysfunction

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Abbreviations

VEGF: Vascular Endothelial Growth Factor; TKI: Tyrosine Kinase Inhibitor; TC: Thyroid Cancer; WHO: World Health Organization; ESMO: European Society for Medical Oncology; RUSSCO: Russian Society of Clinical Oncology; VEGFR-TKIs: Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors; MTKIs: Multitarget Tyrosine Kinase Inhibitors; CT: Computed Tomography; ECG: Electrocardiographic; LVEF: Left Ventricular Ejection Fraction; CMR: Cardiac Magnetic Resonance Imaging; NT-proBNP: N-Terminal Prohormone of Brain Natriuretic Peptide; TS: Takotsubo Syndrome; ACEi: Angiotensin-Converting-Enzyme inhibitors

Introduction

Thyroid Cancer (TC) is the most common detectable forms of malignant neoplasms. According to WHO database, 586,202 new cases of TC were detected worldwide in 2020 that resulted in, 43,646 deaths from this disease. TC is more prevalent in Asian countries that counts for 59.7% of all world annual cases [1]. The incidence of TC in Russian Federation is 183,495 cases for 2020, 1,205 cases per 100,000 population with mortality of 0.6% [2]. The targeted therapy with Vascular Endothelial Growth Factor (VEGF) inhibitors as the treatment for unresectable locally advanced or metastatic papillary or follicular TC which is radioiodine resistant according to European Society for Medical Oncology (ESMO), National comprehensive cancer Network Clinical Practice Guidelines in Oncology (NCCN) and Russian Society of Clinical Oncology (RUSSCO) guidelines [3,4]. Moreover, Anti-VEGF therapy, is an effective method of treating a large number of solid tumors, including lung cancer, epithelial ovarian cancer, colorectal cancer and breast cancer [5-8]. VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain [9]. Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors (VEGFR-TKIs) offer patients potential new treatment. Presently, four multitarget tyrosine kinase inhibitors (comprising sorafenib, Lenvatinib, vandetanib, and cabozantinib) (MTKIs) are licensed as critical therapeutic options for the treatment of thyroid cancer, and have improved survival of patients in clinical trials and real-world studies [10]. Thus, TKI are potent antitumor agents. However, their use have been associated with cardiotoxic events. TKI can cause hypertension [11], venous

thromboembolism [12], myocardial dysfunction in 3% to 15% of patients and heart failure in 1% to 10% of patients [13]. The case of Takotsubo cardiomyopathy following, using one of the VEGF-TKI drugs -Lenvatinib, in TC patient is presented.

Clinical Case

A 45-year-old female patient, with pT3N0M0 Ist TC. The disease was detected in 2008, afterward the right hemithyroidectomy was done, with following hormone replacement therapy. Follicular cancer was founded/In 2011- disease recurrence in the postoperative scar was revealed. The post-operative scar excision was performed, followed by thyroidectomy, radio-iodotherapy with the following suppressive hormone therapy prescription. By histological examination recurrence of follicular cancer was founded in the removed thyroid gland. In 2019, 11 years after the debut of TC, metastatic lung cancer was elicited. December 13th, 2019 by PET-CT Target lision have been selected:

1. S10 lower lobe right lung lision 14 mm × 11 mm (series 12, slice 418) RECIST total 14 mm non-Target lision: Multiple lision in the lungs, selected for control: 1.S10 lower lobe right lung lision max 7 mm (series 12, slice 429) 2. basal S3 upper lobe right lung lision max 5 mm (series 12, slice 309) 3. S4 upper lobe left lung paramediastinal lision max 5 mm (series 12, slice 374) 4. S9 lower lobe left lung peripheral lision max 6 mm (series 12, slice 450) 5. S10 lower lobe left lung lision nearby diaphragm max 8 mm (series 12, slice 504) nontumor lision: Multiple hepatic hemangioma, largest one located at SVII 25 mm × 15 mm a little amount osteosclerotic focus at bones varicose parametral veins, located mostly on the left side. In scintigraphy with iodine radioisotope, radiopharmaceutical accumulation wasn't detected. With the aim of tumor morphological verification, a marginal thoracoscopic resection of the lower left lung lobe was performed. As a result of the analysis, the clinical case was regarded as a progression of radioresistant thyroid cancer. Due to patient decision the start of treatment was delayed to October 2020. By CT scan just before treatment September 29th, 2020. Target lision: 1. S10 lower lobe right lung lision 26 mm × 18 mm (series 8, slice 160) RECIST total 26 mm by comparison with PET/CT at 13.12.2019 RECIST total increased by 12 mm /86% non-Target lision: Multiple lision in the lungs, selected for control: 1. S10 lower lobe right lung lision max 8 mm (series 8, slice 165), 0 mm 2. basal S3 upper lobe right lung lision max 6 mm (series 8, slice 94), + 1 mm 3. S4 upper lobe left lung paramediastinal lision max 5 mm (series 8, slice 141), 0 mm 4. we find new lision at this surgery area max 6 mm (series 8, slice 183), 0 mm 5. S10 lower lobe left lung lision nearby diaphragm max 6 mm (series 8, slice 205), - 2 mm. According to expert solution, a targeted therapy with Lenvatinib (Lenvima) at a dosage of 24 mg/day was prescribed starting from 10. 2020. According to the chest Computed Tomography (CT) scan June 26th, 2021, a significant positive response to treatment was noted; Target lision: 1. S10 lower lobe right lung lision 16 mm × 8 mm (series 8, slice 156) RECIST total 16 mm By comparison with PET/CT at 13.12.2019 RECIST total increased by 2 mm/14%. Non Target lision: Multiple lision in the lungs, selected for control: 1. S10 lower lobe right lung lision max 5 mm (series 8, slice 164), -2 mm 2. Basal S3 upper lobe right lung lision max 3 mm (series 8, slice 90), -2 mm 3. S4 upper lobe left lung paramediastinal lision max 3 mm (series 8, slice 134), -2 mm 4. we find new lision at

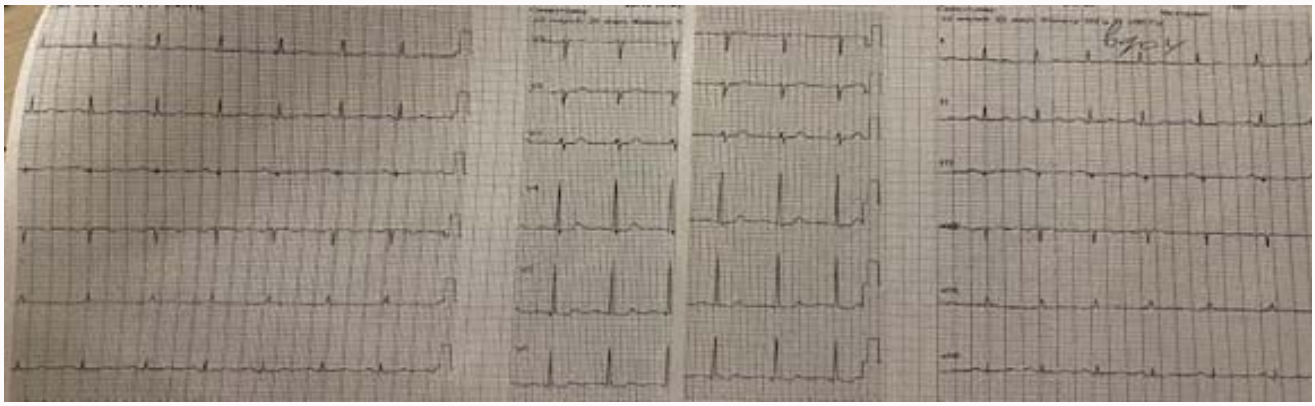

Figure 1: ECG - June 2021- Before TS developing.

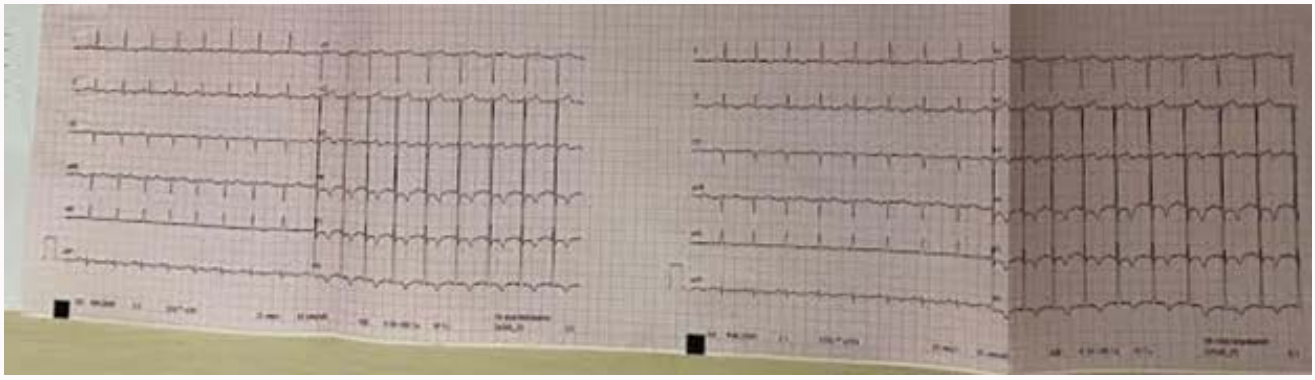

Figure 2: ECG - August 2021 - T-wave inversion.

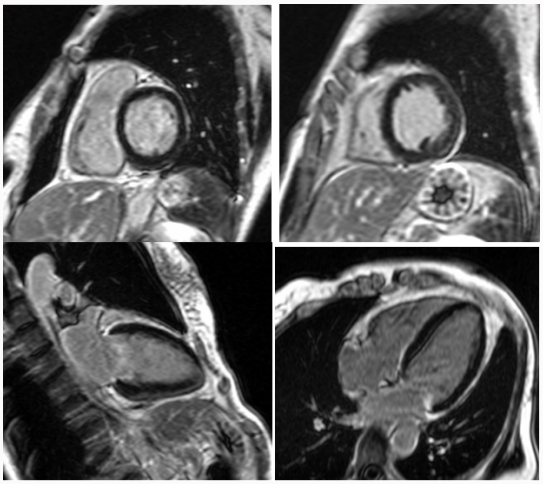

Figure 3: CT coronary angiography.

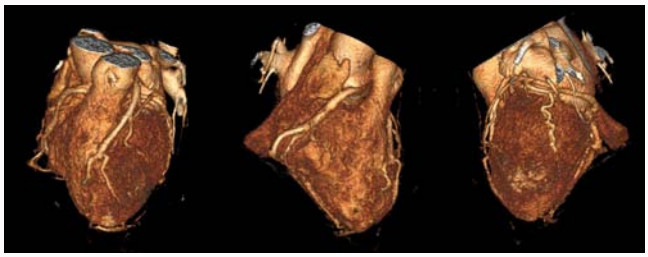

Figure 4: Cardiac Magnetic Resonance imaging (CMR).

this surgery area max 4 mm (series 8, slice 183), -2 mm. 5. S10 lower lobe left lung lision nearby diaphragm max 4 mm (series 8, slice 205), -4 mm. The tolerability of the drug was satisfying. During the first year of medication, a 3rd degree single episode intestinal toxicity was noted. Due to the ineffectiveness of dosage reduction, a temporary withdrawal of the drug was undertaken for 3 weeks. After elimination of intestinal toxicity, the drug was resumed at a reduced dose of 20 mg/day. Subsequently, episodes of increased blood pressure at 145 mmHg to 150 mmHg were observed, and consequently losartan was prescribed at a 50 mg/day, the effect was positive. Every 2 to 3 months, the patient underwent an echocardiographic and Electrocardiographic (ECG) examination. T-wave inversion on ECG were noted In August 2021 during regular screening (Figure 1, 2) accompanying decreased control of arterial hypertension. Echocardiography revealed moderate hypokinesia of the apical segment of the interventricular septum, the apical anterolateral segment of the left ventricle with a slight decrease in Left Ventricular Ejection Fraction (LVEF) up to 52% (previous LVEF from 06. 2021 was 62%). Increase in NT-proBNP up to 680.0 pg/ml was measured with normal troponin level. The patient denies any symptoms of chest pain or exercise intolerance. The existing changes occurred in the time window between the first days of June and the end of August 2021. Due to the low pre-test probability of coronary artery disease CT coronary angiography was performed and excluded coronary artery disease or coronary anomalies (Figure 3). Cardiac Magnetic Resonance imaging (CMR) was performed with no late gadolinium enhancement patterns or myocardial edema (Figure 4). The Takotsubo Syndrome (TS) was mentioned as the cause. However, the patient denies physical or emotional stress during that period. Lenvatinib was the possible cause of TS. However, the patient experienced TS during the timeframe of almost 2 months taking the drug and the drug benefit for cancer progression in her case was unquestionable. Thus, we decided to start cardioprotective treatment without withholding Lenvatinib. Treatment with ACEi fosinopril, beta-blocker metoprolol succinate, torasemide and amlodipine was initiated and resulted in good blood pressure control. A complete restoration of the kinetics of the left ventricle was revealed pursuant to the serial echocardiography and ECG within a month.

Discussion

Takotsubo syndrome is a rare cardiotoxicity manifestation in Lenvatinib treating. The pathogenesis of stress cardiomyopathy is unclear, but animal studies demonstrate, that catecholamine surges during periods of physical or emotional stress can deteriorate cardiac dysfunction, either by causing vasoconstriction of the coronary vascular network, or by direct cytotoxic effects on cardiomyocytes [14]. It was suggested takotsubo syndrome may develop due to catecholamine surges and stress associated with the process of undergoing treatment for malignant neoplasms. Furthermore, for some VEGF antagonists, such as pazopanib, it is possible to increase the response to catecholamines in some organs by modulating the effects of nitric oxide and catecholamines, while VEGF antagonists reduce the level of nitric oxide [15]. Now, numerous studies describe cardiomyopathy development and myocardial dysfunction related to VEGF antagonist intake, although in some studies there was no mention of patients who had any Takotsubo syndrome specific signs [16-18]. In one of these studies, when using Lenvatinib, cardiovascular damage was described in 7% of patients, compared with 2% in the placebo group in the third stage of the clinical trial. However, in this study there is no observations of takotsubo syndrome development [19]. In 2018, Young Kwang Chae presented in their article a similar clinical case of a patient with thyroid cancer, who received targeted therapy with Lenvatinib, due to the medication acute cardiac insufficiency (Takotsubo syndrome) and Posterior reversible encephalopathy syndrome developed, because of that Lenvatinib was withdrew. The patient ultimately died under hospice-care one week later [20]. In our case Lenvatinib treatment was continued together with ACEi and beta-blockers that resulted in compete resolution of TS.

Conclusion

Targeted therapy with VEGF antagonists is a highly effective method of treating advanced thyroid cancer. This drug therapy is relatively safe. The presented clinical observation describes the cardiotoxic development of takotsubo syndrome with reverse restoration of cardiac function in association with ACEI and beta-blocker therapy intake without Lenvatinib withdrawal.

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