Aortic Dissection and Cardiac Dysfunction Emerged Coincidentally During the Long-Term Treatment with Angiogenesis Inhibitors for Metastatic Renal Cell Carcinoma

A Case Report of Onco-Cardiology

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Summary

Angiogenesis inhibitors, such as sorafenib and axitinib, which target vascular endothelial growth factor (VEGF) signaling, are widely used for renal cell carcinoma, including metastasis. In this study, we report a case of cardiovascular adverse events of aortic dissection and cardiac dysfunction during treatment with sorafenib and axitinib for metastatic renal cell carcinoma. A 66-year-old man had been administered sorafenib for 2 years after nephrectomy due to renal cell carcinoma. To control the progression of metastatic lung tumor, axitinib was started after sorafenib for four years. During the treatment, angiotensin II type 1 receptor blockers and Ca antagonists were used to strictly control the axitinib-induced hypertension and proteinuria. Aortic dissection and cardiac dysfunction occurred coincidentally. Considering the critical role of VEGF signaling in the homeostasis of the cardiovascular system, we speculated that the long-term use of axitinib and sorafenib directly influenced the initiation of aortic dissection and cardiac dysfunction. Although the precise mechanisms underlying the aortic dissection and cardiac dysfunction induced by angiogenesis inhibition are still elusive, onco-cardiologists and oncologists should pay careful attention to cardiovascular toxicity and complications in patients with cancer, particularly patients undergoing long-term cancer treatment.

(Key words: Cardiovascular toxicity, Onco-cardiology/cardio-oncology, VEGF signaling pathway, Axitinib, Sorafenib, Cancer therapeutics-related cardiac dysfunction)

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ngiogenesis plays a critical role in the developmental process and pathological conditions of various diseases including cancer, cardiac hypertrophy, and heart failure. Angiogenesis inhibition has become a standard strategy for the treatment of solid tumors such as hepatocellular carcinoma, renal cell carcinoma, and their metastases. Angiogenesis inhibitors, which target vascular endothelial growth factor (VEGF) signaling, are composed of anti-VEGF antibody and small-molecule tyrosine kinase inhibitors. Tyrosine kinase inhibitors bind the tyrosine residues of the VEGF receptor (VEGFR) to inhibit the tyrosine kinase activities of VEGFR and block its downstream intracellular signaling for angiogenesis. Furthermore, most angiogenesis inhibitors have a variety of inhibitory activities not only for VEGFR but also for platelet-derived growth factor receptor, c-kit, and serine/threonine kinase Raf-1. These multiple inhibitory effects may be associated with cardiovascular toxicities and adverse events during cancer treatment.

Sorafenib and axitinib are small-molecule tyrosine kinase inhibitors that target VEGFR and are widely used for renal cell carcinoma, including metastasis. The common adverse cardiovascular side effects of these angiogenesis inhibitors are hypertension, proteinuria, and cardiac dysfunction. Sunitinib- or sorafenib-induced aortic dissection associated with hypertension has been reported, but axitinib-induced aortic dissection rarely occurs. Mechanistically, VEGF has acute vasodilating effects on the peripheral vessels stimulating the syntheses of nitric oxide and prostaglandin I2 via VEGFR2. Exposure to VEGFR inhibitors blocks these vasodilators, thus resulting in endothelial dysfunction and blood pressure (BP) elevation. VEGF signaling plays an important role in the angiogenesis and maintenance of capillaries. VEGF inhibition causes capillary rarefaction, which may contribute to the development of hypertension.
inhibitor-induced hypertension has been thought to induce aortic dissection\textsuperscript{3}; however, the precise role of VEGFR inhibitors in the initiation of aortic dissection remain unclear. In the present study, we reported the first case of aortic dissection and cardiac dysfunction coincidence in a patient with metastatic renal cell carcinoma after the serial treatment of sorafenib and axitinib for six years. We also discussed the underlying mechanisms of cardiovascular adverse events associated with angiogenesis inhibitors.

**Case Report**

A 66-year-old man was hospitalized with complaints of general fatigue and palpitation. He did not present with any comorbidity (e.g., coronary risk factors such as hypertension, diabetes, hyperlipidemia, and smoking). The patient was diagnosed with renal cell carcinoma of the right kidney in November 2007 and underwent right radical nephrectomy in January 2008. The pathological diagnosis of the nephrectomy was clear cell carcinoma, pT3bN0M1 with metastasis to the lung, and immunotherapy with interleukin-2 and interferon-\(\alpha\) was initiated after surgery (Figure 1). Despite the immunotherapy, lung metastatic tumor progressed in October 2010, and 800 mg/day of sorafenib, which is a multikinase inhibitor, was started. In March 2011, sorafenib was reduced to 400 mg/day because of grade 2 liver dysfunction. The lung tumor further invaded into the right primary bronchus, and 10 mg/day of axitinib was started in January 2013. Axitinib was once reduced to 6 mg/day because of severe hypertension of over 200 mmHg but was increased to 10 mg/day because of the lung tumor progression. Candesartan was administered at 8 mg/day to control the hypertension of the patient. To control the enlargement of the metastatic lung tumor, transcatheter arterial embolization was performed. Furthermore, axitinib was increased to 12 mg/day in May 2014, and 2.5 mg/day of amlopidine was added to manage the hypertension. In August 2015, proteinuria occurred, and 100 mg/day of irbesartan was started instead of candesartan and amlopidine. In December 2015, axitinib was increased to 14 mg/day because of bone metastasis. To control the hypertension, 4 mg/day of azelnidipine was added to irbesartan, and the BP was controlled at approximately 130/80 mmHg. Although no abnormality was observed at the regular checkup on January 6, 2017, the patient experienced severe back pain on January 20, 2017 (Figure 1), which was controlled by loxoprofen. In April 2017, he started to experience general fatigue and palpitation. The onco-cardiologist detected moderate cardiac dysfunction with an ejection fraction (EF) of 48%, slightly progressed aortic regurgitation, and no evidence of diastolic dysfunction by echocardiography (Figure 1, Table I). Brain natriuretic peptide (BNP) and troponin I (TnI) did not markedly change during the patient’s treatment and clinical course.\textsuperscript{11} Thereafter, the patient was hospitalized for cancer therapeutics-related cardiac dysfunction.
Contrast-enhanced CT performed on April 14, 2017. CT showed the aortic dissection from the ascending to descending aorta with thrombosed false lumen.

Figure 3. A: Anterior planar images of $^{123}$I-MIBG scintigraphy. The heart (H) and mediastinum (M) were selected to measure the H/M ratio. The cardiac $^{123}$I-MIBG washout rate was calculated from the early (left) and delayed images (right). B: Short-axis slices of $^{201}$Tl myocardial SPECT.

In this study, we report a case of aortic dissection and cardiac dysfunction, both of which occurred coincidentally in a patient with metastatic renal cell carcinoma treated with serial angiogenesis inhibitors sorafenib and axitinib for six years. Although sorafenib and axitinib have been reported to have cardiovascular toxicities such as hypertension, proteinuria, aortic dissection, and cardiac dysfunction, this case is the first reported occurrence of both aortic dissection and cardiac dysfunction to our
knowledge. The long-term use of sorafenib and axitinib has been speculated to detrimentally contribute to these cardiovascular adverse events.

The Common Terminology Criteria for Adverse Event version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14QuickReference_8.5x11.pdf) shows the stratification of cardiac disorders, including heart failure and LV systolic dysfunction, according to the patient’s symptoms. On the contrary, expert consensus by the American Society of Echocardiography/European Association of Cardiovascular Imaging defined CTRCD as a ≥ 5% reduction in EF from baseline to ≤ 53% with accompanying signs or symptoms of heart failure or as a ≥ 10% reduction in EF from baseline to ≤ 53% without accompanying signs or symptoms of heart failure.12,13 Our case may correspond to the latter definition. As shown in Figure 1, the levels of BNP and TnI were within the normal range during the axitinib treatment, thus indicating that these biomarkers are not reliable indicators of cardiac dysfunction or cardiac damage for this case. BNP frequently does not work as a biomarker of cardiac dysfunction in cancer treatment. Although LVEF with echocardiography is not sensitive enough to detect the initial change of CTRCD and is not a predictor of CTRCD prognosis, LVEF measurements are practically and clinically helpful in diagnosing CTRCD. LVEF is used to assess CTRCD when patients are suspected to have cardiac dysfunction. Measuring the baseline LVEF before cancer treatment is desirable to compare the LVEF values after treatment.

VEGF controls angiogenesis and plays a critical role in organ homeostasis, particularly in the cardiovascular system.15 Heterozygous VEGF knockout mice14,15 and homozygous Flt-1 (also known as VEGFR-1) knockout mice16 showed embryonic lethality due to abnormal vessel formation, thus indicating that the VEGF signaling pathway is indispensable for vascular formation during embryogenesis. In the adult heart, VEGF has been reported to play important roles in cardiac hypertrophy and in maintaining cardiac function via angiogenesis in the myocardium.17 Cardiac myocytes themselves control VEGF expression at transcriptional levels in response to pressure overload and/or hypoxia of the myocardium to induce angiogenesis in mice.17,18 In heart failure, the number of capillaries is decreased in the myocardium because of the inhibition of hypoxia-inducible factor-1 activity and the suppression of VEGF expression.19 Whether VEGFs directly interact with cardiac myocytes remains unclear, but the rarefaction of capillary density via the genetic manipulation of VEGF signaling in the heart is closely associated with cardiac dysfunction.20 Although myocardial ischemia was not clearly detected using 201T1 scintigraphy in our case, numerous basic studies strongly suggest that long-term exposure to sorafenib and axitinib could induce capillary density rarefaction and relative hypoxia in the myocardium, which may lead to cardiac dysfunction.

Several case reports exist on the association between aortic dissection and the use of VEGF inhibitors (Table II),19,20 but no coincidental case of aortic dissection and cardiac dysfunction during VEGF inhibitor treatment has been found. The Japanese Adverse Drug Event Report database showed that the occurrence rate of aortic dissection in the VEGF pathway inhibitors of patients with cancer was 0.3%.21 The median time to onset was 105 days (range: 4-1363 days) after the administration of VEGF inhibitors; therefore, the present case could be the latest on-set case of VEGF inhibitor-induced aortic dissection. Niwa, et al. reported the first case of axitinib-associated acute aortic dissection (Stanford type A) in a patient with metastatic renal cell carcinoma. In their case, axitinib administration following 2 cycles of sunitinib treatment without an episode of hypertension (Table II).22 In the present case, sorafenib and axitinib were administered for two and four years, respectively, before the occurrence of cardiovascular events. Hypertension is a major cause of aortic dissection, and half of aortic dissection cases have been reported to have hypertension at baseline.23 However, in the current case, BP elevation was well controlled by angiotensin II type 1 receptor blockers and Ca antagonists. This finding indicates that additional mechanisms and/or multiple hits may contribute to aortic dissection. Ischemic heart disease and severe valvular disease, such as aortic regurgitation, which could induce cardiac dysfunction, were ruled out using coronary CT and echocardiographic analysis. These data support our hypothesis that multitarget kinase inhibitors are directly associated with the occurrence of aortic dissection and cardiac dysfunction.

Although aortic dissection is a fatal disease and causes sudden death, the underlying pathological and molecular mechanisms involved in the initiation of the disease remain elusive. In aortic dissection, the histological feature is characterized by medial degeneration containing cystic medial necrosis in the chronically damaged aorta associated with aging, as well as hypertension and aortic aneurysm. However, the precise cellular and molecular
mechanisms of medial degeneration and the onset of dissection have not been fully investigated. Bevacizumab, a VEGF antibody, was reported to induce microvascular angina by reducing coronary flow and was shown to reduce the capillary density of the mucosal surface of the lip and significantly increase mean aortic pulse wave velocity (PWV) after six weeks of treatment. Furthermore, analyses of carotid PWV in patients with cancer treated with sunitinib or sorafenib revealed the BP-independent effects of these drugs on arterial stiffness. This study adjusted the angiogenesis inhibitor-induced changes of BP and showed a BP-independent increase in carotid PWV, thus suggesting the possibility that the long-term inhibition of angiogenesis due to sorafenib and axitinib could detrimentally and BP independently increase aortic stiffness and develop arteriosclerosis in our patient.

In the aortic wall, VEGF is predominantly expressed in the smooth muscle cells in vessel walls and is highly expressed in atherogenic lesions. Although the vasa vasorum supplies oxygen and nutrients to the medial layer and is associated with the progression of atherosclerotic plaque, a correlation was not found between the expression of VEGF and the degree of vasa vasorum neovascularization. Given that VEGF colocalized with inflammatory cells in atherosclerotic lesions, VEGF played inflammatory roles rather than angiogenic roles in the large vessel walls in human tissue. This result indicates that VEGF signaling is vital to the maintenance of vessel walls and that sorafenib and axitinib possibly contribute to the vulnerability of the aortic wall. The balance between collagen synthesis and degradation is important to the elasticity and vulnerability of vessel walls. Recent studies have demonstrated that the overexpression of matrix metalloproteinase 9 (MMP9) was associated with various vascular diseases, including aortic dissection. MMP9, which degenerates collagen tissue, is elevated in the peripheral blood of patients with acute aortic dissection. MMP9 is produced from fibroblasts, smooth muscle cells, inflammatory neutrophils, and macrophages in the vessel wall and is thought to play an important role in the onset of aortic dissection. MMP9 expression was regulated by forkhead box protein O1 (FOXO1), and tissue inhibitor of metalloproteinase-1 (TIMP-1) expression, which is an inhibitor of MMP9 activity, was regulated by GATA1. Both MMP9 and TIMP-1 expressions were regulated by Akt2. Akt-2-deficient mice showed a significantly increased expression of MMP9 and a decreased expression of TIMP-1. In Akt-2-deficient mice, abnormal elastic fibers were detected, and aortic dissection was induced by the angiotensin II-administered hypertension model. This study showed that Akt phosphorylated FOXO1 and GATA1 and regulated their transcriptional activity for MMP9 and TIMP-1, thus resulting in abnormal elastic fibers in the mice. Akt is known as a downstream signaling molecule of VEGFR1, and PI3K modulates the angiogenic process, thus suggesting that the tyrosine kinase inhibitor of VEGFR may be associated with medial degeneration via Akt inactivation, MMP9 induction, and TIMP-1 inhibition in the aortic media in patients with cancer (Figure 4).

Angiogenesis inhibitors that target the VEGF signaling pathway are widely and regularly administered to patients with solid cancer for a relatively long duration. Given that VEGF also plays a critical role in the homeo-
stasis of the cardiovascular system, the inhibition of VEGF signaling can lead to cardiovascular adverse events such as aortic dissection and cardiac dysfunction. Therefore, onco-cardiologists and oncologists should pay more attention to cardiovascular toxicity and complications in patients during cancer treatment.

Disclosures

Conflicts of interest: None.

References