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Case Report

Multimodality imaging approach in a case of vascular toxicity caused by cabozantinib ☆

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ABSTRACT

Vascular toxicity caused by cancer treatment can present as vasospasm, arterial thrombosis, and accelerated atherosclerosis. We report a case of a 60-year-old man with metastatic renal cell carcinoma under cabozantinib treatment for 3 years who presented to the hospital with relapsing episodes of rest angina. Due to the presence of ST depression in the 12-lead electrocardiogram and elevated troponin, a non-ST-segment elevation myocardial infarction was suspected. The patient underwent invasive coronary angiography, which revealed extended coronary artery spasm, and it subsided totally after nitrate administration. One year later, the patient presented again at the cardio-oncology outpatient clinic, reporting relapsing episodes of angina during the previous month. Coronary computed tomography angiography was performed, and it revealed 2 subsequent 70%-99% stenosis in OM1. To our knowledge, this is the first case of a patient treated with cabozantinib presenting with coronary artery spasm and accelerated atherosclerosis, in which a multimodality imaging approach was followed.

Abbreviations: CAS, coronary artery spasm; ccRCC, clear cell renal cell carcinoma; CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; TKI, tyrosine kinase receptor inhibitor; TTE, transthoracic echocardiogram.

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Introduction

Cabozantinib is a multitarget tyrosine kinase receptor inhibitor (TKI) used as a second-line treatment of advanced clear cell renal cell carcinoma (ccRCC) alone and as a first-line treatment in combination with nivolumab [1]. Several TKIs, such as imatinib, ponatinib, pazopanib, have been linked with vascular toxicity [2].

We describe a case of cabozantinib-induced vascular toxicity in a patient with metastatic renal cell carcinoma, highlighting the role of multimodality imaging in the diagnosis of vascular toxicity.

Case presentation

A 60-year-old man presented to the emergency department due to 3 relapsing episodes of rest angina on a background of metastatic renal cell carcinoma. He was originally diagnosed with renal cell carcinoma 16 years ago, and underwent left nephrectomy. Eight years later, the patient developed lung and pleura metastases, and in 2018, he underwent pleurodesis due to recurrent pleural effusions. He also had multiple episodes of hemoptysis and atelectasia due to a left main bronchi metastasis. Except for pleurodesis, he also underwent bronchoscopic palliative therapy, and he has been under therapy with cabozantinib the last 3 years. He has hypothyroidism, no cardiovascular risk factors, and no known intracardiac metastases.

At presentation, the patient was hemodynamic stable and asymptomatic. A 12-lead electrocardiogram revealed ST depression in leads III and avF. Laboratory results showed elevated troponin. Transthoracic echocardiogram (TTE) revealed hypokinesia of the inferior and posterior wall, and a left ventricular ejection fraction (LVEF) of 45%-50%. Given the previous results, a non-ST-segment elevation myocardial infarction (NSTEMI) was diagnosed, and the patient underwent invasive coronary angiography (ICA) within 12 hours. ICA revealed extended coronary artery spasm (CAS) (Figs. 1A-, video 2), which subsided totally after nitrate administration (Figs. 1B , video 3), and the patient was discharged with the diagnosis of vasospastic angina. At discharge, nifedipine controlled-release (CR) 30 mg, aspirin 80 mg, and sublingual nitroglycerin on demand were prescribed.

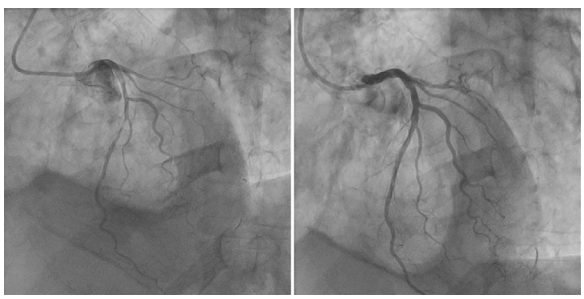

Fig. 1 – Left coronary artery before (left) and after nitrate administration (right). Invasive coronary angiography revealed extended coronary artery spasm, which subsided totally after nitrate administration.

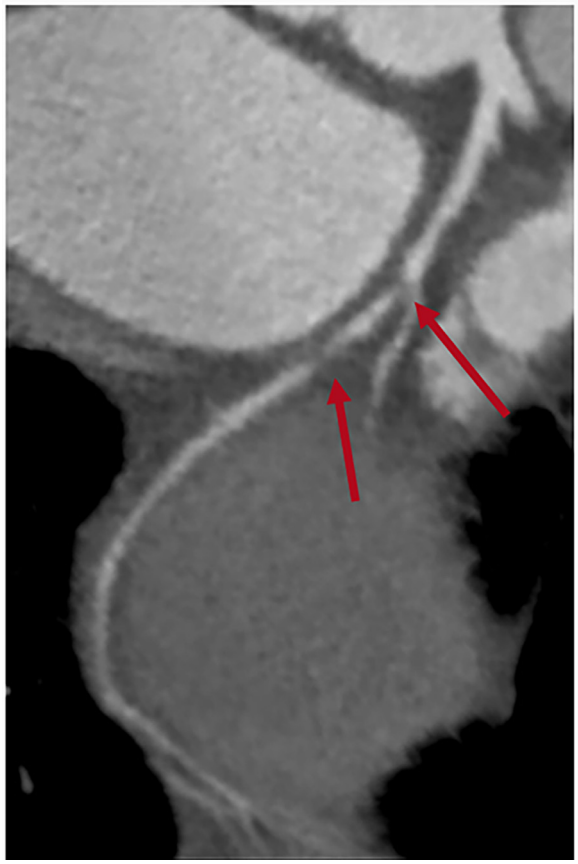

Fig. 2 – Coronary computed tomography angiography revealing stenosis of coronary arteries. Coronary computed tomography angiography revealed 2 subsequent 70%-99% stenosis in OM1 (red arrows).

Almost one year later, the patient presented again at the cardio-oncology outpatient clinic, reporting relapsing episodes of angina (both at rest and by effort) during the previous month, which subsided completely after sublingual nitrate administration. He also reported having elevated blood pressure measurements of 150/90 mmHg at home during the previous month. The year before, the patient was free of anginal episodes without any antianginal treatment, since he did not receive nifedipine due to low blood pressure measurements. Physical examination and electrocardiogram were normal, while TTE showed normal LVEF with no hypokinesia. Coronary computed tomography angiography (CCTA) revealed stenosis free left anterior descending, right coronary artery and left circumflex artery, and 2 subsequent 70%-99% stenosis in OM1 (Fig. 2, video 1).

Cardiooncology team decided for cabozantinib continuation and conservative management of atherosclerotic disease. Specifically, nifedipine CR 60 mg and isosorbide mononitrate 60 mg were prescribed. However, nifedipine was stopped due to gum hypertrophy and bleeding, and the dose of isosorbide mononitrate was reduced to 30 mg due to headache. The patient remains free of symptoms the last one year under ther-

apy with aspirin 80 mg and isosorbide mononitrate 30 mg, while receiving cabozantinib.

Discussion

Cabozantinib is a multitarget TKI, which inhibits the activity of B-RAF, MET, VEGFRs, AXL, RET, ROS1, c-KIT, TrkB, and FLT-3 [3]. A common adverse effect of cabozantinib is hypertension, which occurs in 36% of cabozantinib-treated patients. Venous thromboembolism occurs in 7%, while arterial thromboembolism occurs in 2% of patients receiving cabozantinib [3]. Except for vascular thrombosis, cabozantinib-induced vascular toxicity can also present as CAS and accelerated atherosclerosis, and these types of vascular toxicity can overlap in the same patient, as shown in this case report.

The fact that our patient had no cardiovascular risk factors before cabozantinib treatment supports the hypothesis that there is an association between development of CAS and treatment with cabozantinib. CAS is a known adverse effect of a lot of anticancer therapies, such as bleomycin, fluoropyrimidines, taxanes, vinca alkaloids, platinum-containing chemotherapy and TKI [2]. Specifically, sorafenib, which is a multitargeted TKI that inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, platelet-derived growth factor receptor β (PDGFR-β), Raf-1 and B-Raf, may also induce coronary vasospasm, as demonstrated in 3 case-reports, possibly due to inhibition of VEFG production, downregulation of MEK activity and upregulation of Rho activity [4]. Furthermore, cases of patients with coronary artery spasm induced by BCR-ABL TKIs (nilotinib, dasatinib, and bosutinib) have been described [5]. The exact mechanisms underlying the vascular toxicity of cabozantinib remain unclear, although it is known that the major mechanisms involved in CAS are oxidative stress, endothelial dysfunction with decreased NO release and impaired vasodilation, chronic inflammation, excessive vascular smooth muscle contractility with enhanced Rho-kinase activity, and overactivity of the autonomic nervous system [6].

We also hypothesize that there is an association between acceleration of atherosclerosis and treatment with cabozantinib, due to the emergence of 2 subsequent 70%-99% stenosis in OM1 in 1 year in our patient despite the absence of pre-existing cardiovascular risk factors. It is known that acceleration of atherosclerosis can be caused by anticancer therapy, such as BCR-ABL TKI, VEGF inhibitors, gonadotropin-releasing hormone (GnRH) agonists, and radiation therapy, and can provoke stable angina [2]. Specifically, nilotinib and ponatinib inhibit kinases, such as c-KIT, and PDGFR, which play an important role in endothelial function and regulation of vascular tone [5]. Moreover, nilotinib causes elevated production of cytokines, such as Interleukin 6 (IL6), C-X-C motif chemokine ligand 8 (CXCL8), C-C motif chemokine ligand 2 (CCL2), superoxide dismutase 2 (SOD2), NFKB inhibitor alpha (NFKBIA), baculoviral IAP repeat containing 3 (BIRC3), C-C motif chemokine ligand 20 (CCL20), and C-X-C motif chemokine ligand 2 (CXCL2), leading to complex cascades that results in the formation and disruption of atherosclerotic plaques [7]. VEFG inhibitors have also been associated with accelerating atherosclerosis, as in vivo experiments with pan-VEGF inhibition demonstrate significant increase in atherosclerotic lesions yet without increase in features of plaque vulnerability in thoracoabdominal aortae and aortic arches of mice, while in human endothelial cells, VEGF inhibition reduces NO availability and decreases proliferation due to a dose-dependent increase in mitochondrial superoxide generation [8]. Thus, inhibition of c-KIT and VEGF signaling pathways may play a role in the progress of atherosclerosis induced by cabozantinib, as well.

Regarding the imaging techniques used, when a NSTEMI was suspected at the patient's first presentation, the patient underwent ICA, which revealed CAS. At his second presentation after one year, CCTA was preferred, since the patient had a low-to-intermediate likelihood of coronary artery disease (CAD) and normal ECG. According to 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, CCTA is considered as an alternative to ICA to exclude ACS in patients with these characteristics (Class 1 recommendation with level of evidence of A) [9]. Except for atherosclerotic cardiovascular disease, CCTA can also be used in the evaluation of cardiac tumors, pericardial conditions, and valvular heart diseases in cancer patients [10]. Thus, CCTA is an emerging alternative in cardio-oncology patients with high diagnostic accuracy.

Conclusion

Our patient developed CAS and accelerated atherosclerosis after long-term treatment with cabozantinib, although he did not have any pre-existing cardiovascular risk factors. These findings suggest that long-term treatment with cabozantinib may be associated with an increased risk for vascular toxicity. ICA and CCTA revealed CAS at patient's first presentation and stenosis of coronary arteries due to accelerated atherosclerosis at patient's second presentation, respectively. CCTA is an emerging alternative in cardio-oncology patients with high diagnostic accuracy. To our knowledge, this is the first case of a patient treated with cabozantinib presenting with CAS and accelerated atherosclerosis, in which a multimodality imaging approach was followed.

Patient consent

This is to certify that patient consent has been obtained and can be uploaded whenever necessary.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2023.09.062.

REFERENCES

[1] eUpdate – Renal cell carcinoma treatment recommendations | ESMO. https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-treatment-recommendations-4 Accessed January 24, 2023.

[2] Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar M, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022;43(41):4229–361. doi:10.1093/EURHEARTJ/EHAC244.

[3] Jin Y, Xu Z, Yan H, He Q, Yang X, Luo P. A comprehensive review of clinical cardiotoxicity incidence of FDA-approved small-molecule kinase inhibitors. Front Pharmacol 2020;11:891. doi:10.3389/FPHAR.2020.00891/BIBTEX.

[4] Naib T, Steingart RM, Chen CL. Sorafenib-associated multivessel coronary artery vasospasm. Herz 2011;36(4):348–51. doi:10.1007/S00059-011-3444-5.

[5] Fiets RB, Staal AHJ, Cramer GE, Blijlevens NMA. Coronary artery spasms due to tyrosine kinase inhibitors used in chronic myeloid leukemia. Neth J Med 2018;76(7):330–5.

[6] Lanza GA, Careri G, Crea F. Mechanisms of coronary artery spasm. Circulation 2011;124(16):1774–82. doi:10.1161/CIRCULATIONAHA.111.037283.

[7] Li S, He J, Zhang X, Cai Y, Liu J, Nie X, et al. Cardiovascular adverse events in chronic myeloid leukemia patients treated with nilotinib or imatinib: a systematic review, meta-analysis and integrative bioinformatics analysis. Front Cardiovasc Med 2022;9:3201. doi:10.3389/FCVM.2022.966182/BIBTEX.

[8] Winnik S, Lohmann C, Siciliani G, von Lukowicz T, Kuschnerus K, Kraenkel N, et al. Systemic VEGF inhibition accelerates experimental atherosclerosis and disrupts endothelial homeostasis: implications for cardiovascular safety. Int J Cardiol 2013;168(3):2453–61. doi:10.1016/J.IJCARD.2013.03.010.

[9] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt D, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42(14):1289–367. doi:10.1093/EURHEARTJ/EHAA575.

[10] Lopez-Mattei JC, Yang EH, Ferencik M, Baldassarre LA, Dent S, Budoff MJ. Cardiac computed tomography in cardio-oncology: JACC: CardioOncology primer. JACC CardioOncol 2021;3(5):635. doi:10.1016/J.JACCAO.2021.09.010.