Case Report

Acute aortic dissection caused by fruquintinib for metastatic colorectal cancer—a case report and literature review

Ya-Ya Deng[1,2], Yun-Wang Chen[1,2], Ming-Xing Wang[2,3], Peng-Fei Zhu[2,3], Shuan-Yue Pan[2,4], Ding-Yi Jiang[1,2], Zhe-Ling Chen[2], Liu Yang[1,2]

[1]The Qingdao University Medical College, Qingdao, China; [2]Cancer Center, Department of Medical Oncology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou, China; [3]Graduate School of Clinical Medicine, Bengbu Medical College, Bengbu, China; [4]Graduate School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, China

Contributions: (I) Conception and design: L Yang, ZL Chen; (II) Administrative support: None; (III) Provision of study materials or patients: L Yang; (IV) Collection and assembly of data: YY Deng, YW Chen, MX Wang, PF Zhu, SY Pan, DY Jiang; (V) Data analysis and interpretation: YY Deng, YW Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Liu Yang, MD, PhD. Professor, Cancer Center, Department of Medical Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310014, China. Email: yangliu@hmc.edu.cn; Zhe-Ling Chen, MD. Cancer Center, Department of Medical Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310014, China. Email: chenzheling@hmc.edu.cn.

Background: Fruquintinib is a highly selective tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR). At present, it has been approved for third-line therapy for advanced metastatic colorectal cancer in China. Like other small-molecule tyrosine kinase inhibitors, adverse reactions such as hand-foot syndrome, hypertension and cardiotoxicity may be seen. However, acute aortic dissection caused by fruquintinib has not been reported so far.

Case Description: Here, we report a case of aortic dissection. The patient, a 61-year-old man with advanced metastatic colorectal cancer, without history of hypertension or other risk factors for aortic dissection, received fruquintinib as the third line of treatment. Six weeks after oral fruquintinib treatment, the patient developed acute aortic dissection, and the occurrence of the adverse effect was determined to be probably related to the use of fruquintinib. This article focuses on the potential pathogenesis of fruquintinib-induced active dissection.

Conclusions: We reported the first case of fruquintinib-associated aortic dissection, and discussed the possible mechanism of vascular endothelial growth factor (VEGF)-VEGFR signal pathway (VSP) inhibitors leading to aortic dissection. As a new drug, fruquintinib brings not only clinical benefits, but also brings some adverse reactions. Clinicians must be vigilant to the cardiovascular toxicity caused by small molecular tyrosine kinase inhibitors, especially the severe cardiovascular toxicity, and strengthen monitoring and management.

Keywords: Fruquintinib; VEGFR TKIs; aortic dissection; cardiovascular toxicity; case report

Submitted Jul 12, 2022. Accepted for publication Nov 27, 2022. Published online Jan 16, 2023.
doi: 10.21037/tcr-22-1872
View this article at: https://dx.doi.org/10.21037/tcr-22-1872

Introduction

Colorectal cancer is the third most common malignant tumor in the world, with its mortality is only inferior to that of lung cancer (1). More than 20% of patients having distant metastasis at the time of diagnosis, with another 25% of patients will have metastasis after radical surgery (2). The standard therapies for patients with metastatic colorectal cancer are mainly cytotoxic drugs and targeted drugs, including chemotherapy based on fluorouracil, oxaliplatin and irinotecan, and targeted

therapy for vascular endothelial growth factor (VEGF) and epidermal growth factor receptors (EGFR). In recent years, the treatment of colorectal cancer has evolved into a multidisciplinary team (MDT) model. The quality of life of metastatic colorectal cancer patients has been significantly improved and their survival time has been significantly prolonged. Many patients have maintained good physical strength scores after the failure of first- and second-line treatment. However, at present, the drugs used in the third-line treatment of metastatic colorectal cancer are very limited. In China, fruquintinib has been approved for the third-line treatment of metastatic colorectal cancer. Fruquintinib is an efficient and highly selective oral tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), which has a strong inhibitory effect on a variety of metastatic tumors by inhibiting angiogenesis (3). The FRESCO study-a multicenter, randomized, double-blind, placebo-controlled phase III trial-showed that, compared with the placebo group, fruquintinib had dual benefits in overall survival (OS) (median OS 9.3 *vs.* 6.6 months, P<0.001) and progression-free survival (PFS) (median PFS 2.7 *vs.* 1.9 months, P<0.001), and safety was controllable (4). The common adverse reactions of fruquintinib include hypertension, hand-foot syndrome, albuminuria, hematuria and fatigue.

In this article, we report the first case of aortic dissection potentially caused by fruquintinib in advanced metastatic colorectal cancer and focus on the possible mechanism of fruquintinib leading to aortic dissection. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1872/rc).

Case presentation

A 61-year-old male patient with sigmoid cancer presented to our hospital for treatment in January 2017. He had quitted smoking for more than 20 years before hospitalization and had no history of drinking, hypertension, diabetes, coronary heart disease or Marfan syndrome. After diagnosis, he underwent radical sigmoidectomy. Lung metastasis was found 18 months after operation, then the patients received 10 cycles of bevacizumab with FOLFIRI (5-FU/leucovorin/irinotecan) first-line chemotherapy and 4 cycles of bevacizumab combined with ratetrexed second-line therapy. Nevertheless, none of them controlled the progress of the disease. The patient received three cycles of immunization combined with targeted third-line therapy (bevacizumab 260 mg + nivolumab 140 mg) in May 2021. Re-examination after 3 cycles indicated progressive disease (PD). In July 2021, fruquintinib (3 mg q.d.) was replaced with nivolumab. We assessed bleeding and cardiovascular risk factors before the replacement of fruquintinib, the baseline blood pressure fluctuated from 90 to 115/60 to 75 mmHg (Figure S1), and the electrocardiogram was not significantly abnormal. Furthermore, there were no signs of aortic dissection and thoracic aortic aneurysm in the baseline chest computed tomography (CT) (*Figure 1A*). During the treatment, the blood pressure was monitored regularly, and the highest blood pressure was in 142/80 mmHg. In September 2021, the patient experienced a sudden onset of tear-like chest pain, with back radiation pain and sweating, and his blood pressure rose to 183/100 mmHg (Figure S1), which could not be relieved after taking nitroglycerin. Emergency CT angiography showed aortic dissection (Stanford type B) (*Figure 1B*). Thereafter, the patient received nitroglycerin as anti-hypertensive medication in the emergency department and was transferred to vascular surgery to receive nifedipine combined with metoprolol to lower blood pressure, and stent-graft intervention was performed in September 2021 (*Figure 1C*). Using anticoagulants and antihypertensive drugs after operation, the blood pressure control was fair. Then, we evaluated the possible causal relationship between adverse events and drugs with reference to Naranjo probability scale, which was assessed as probable (Tables S1,S2), and therefore the patients discontinued the treatment with fruquintinib. Postoperative CT reexamination showed that the condition was stable (*Figure 1D*). In January 2022, the patient received 3 cycles of bevacizumab combined with S-1. By the last follow-up (February 16, 2022), the patient had no further arterial dissection. The patient's treatment timeline is as follows (*Figure 2*).

All procedures performed in this study were in accordance with the ethical standards of the Zhejiang Provincial People's Hospital research committee(s) (approval No. QT2022269) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

VEGF, VEGFR, c-kit, platelet-derived growth factor

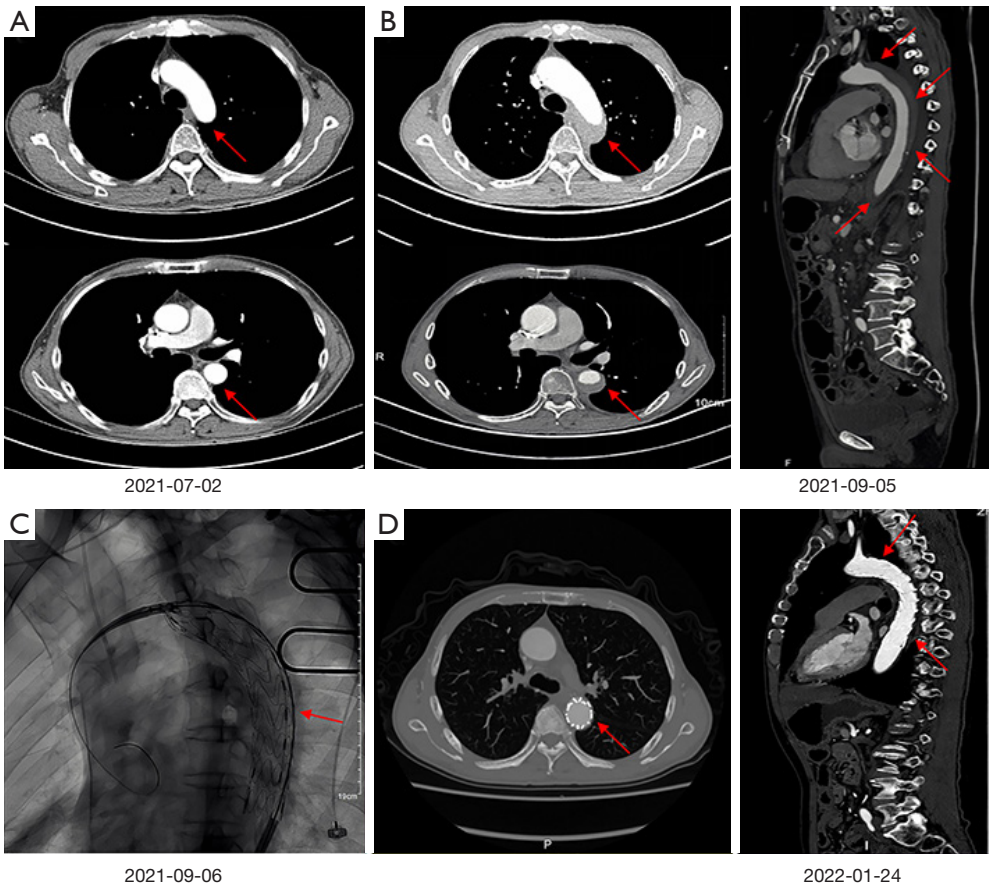

Figure 1 Chest CT before and after fruquintinib treatment. (A) Aortic dissection and aortic aneurysm were not observed in CT scan at baseline. (B) Descending TAD with intramural hematoma occurred 6 weeks after fruquintinib treatment. (C) Stent-graft implanted into the aorta. (D) Reexamination after aortic dissection stent implantation. The red arrows indicate the lesion. CT, computed tomography; TAD, thoracic aortic dissection.

receptor (PDGFR) and fibroblast growth factor receptor (FGFR) expressed on the surface of vascular endothelial cells play an important role in maintaining normal vascular endothelial cell development and homoeostasis (5-8). Targeting these molecules can inhibit the formation of new blood vessels, and also produce different side effects. Aortic dissection associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) has been reported in Japan as early as 2017 that increases the risk of aortic dissection during systemic exposure to vascular endothelial growth factor receptor pathway inhibitors (VPIs) (9). In December 2018, Health Canada also issued a warning of the potential risk of abnormal structural changes (dissection and aneurysm, including ruptured) in the arterial wall of VEGFR TKIs, and updated product safety information for all VEGFR TKIs drugs in June 2020 to inform them of this risk (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/june-2020.html). However, as far as we know, this is the first report of fruquintinib-associated aortic dissection.

Aortic dissection is a very serious cardiovascular disease. Within 48 hours after onset, the mortality rate of untreated aortic dissection is close to 1% per hour (10). Even after surgical repair, the mortality rate of acute aortic dissection is still high. Hypertension is one of the main causes of aortic dissection (11). Meanwhile, hypertension is also the main adverse reaction of vascular endothelial growth factor inhibitors (VEGFIs). VEGFIs can increase hypertension in a variety of ways (*Figure 3*). It is reported that up to 80% of patients who use VEGFIs for the first time have elevated blood pressure (12). In order to find out the relationship

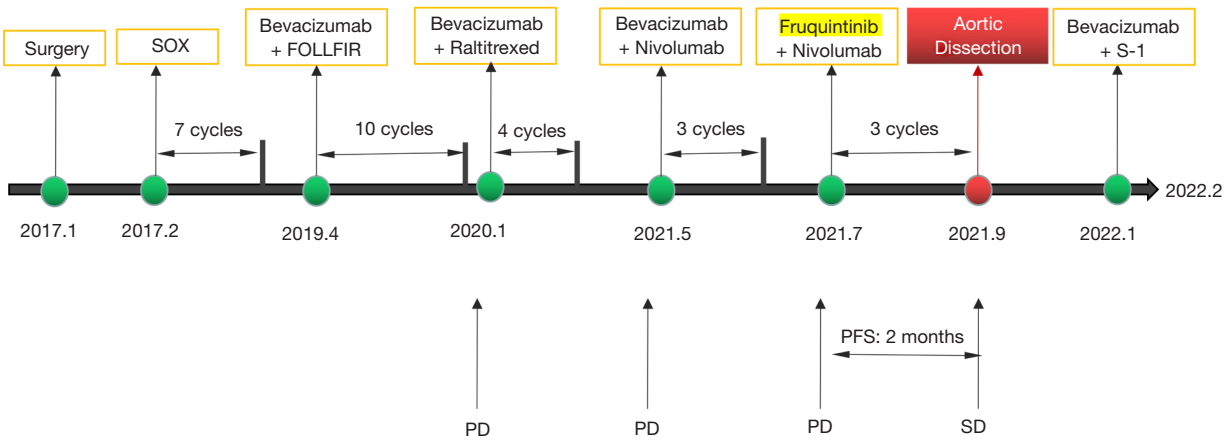

Figure 2 Timeline of therapy regimen. SOX, S-1/oxaliplatin; FOLLFIRI, folinic acid/fluorouracil/irinotecan; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

between these factors, we reviewed all reports of VEGFI-associated aortic dissection and found that not all cases describing TKI-induced aortic dissection had hypertension before the onset of aortic dissection (*Table 1*), which was consistent with this case we reported. Based on this fact, we speculated that VEGF-VEGFR signal pathway (VSP) may also play an important role in fruquintinib-related aortic dissection in addition to hypertension.

The histopathological features of aortic dissection are mainly media degeneration, which is composed of smooth muscle cells (SMCs) and extracellular matrix (ECM), which mainly produces aortic tension and elasticity. The pathological process of aortic dissection includes the decrease of vascular SMCs, the rupture of elastic fibers and the degradation of ECM (21). These processes are related to oxidative stress involved in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (22,23). Recent research has found that inhibition of VSP may increase the production of reactive oxygen species (ROS) by inducing the activation of NADPH oxidase (NOX) and down-regulation of antioxidants in endothelial cells (7). The continuously increasing level of ROS will eventually induce apoptosis of vascular SMCs (24). NOX1 can inhibit TIMP-1 expression induced by angiotensin II (Ang-II), change the balance of protease/antiprotease, promote the degradation of elastin and basement membrane of vascular wall, and negatively regulate the expression of Fibulin-5 (25). Fibulin-5 is an extracellular protein, which is reported to be related to the polymerization and assembly of elastin (26). Previous study has found that decreased expression of Fibulin-5 in patients with thoracic aortic dissection (TAD) may lead to elastic fiber breakage and reduced elastin content, which in turn promotes the progression of aortic dissection (27). Furthermore, the production of ROS can inhibit the binding of Fibulin-5 and elastin, so it is easy to cause disordered arrangement of elastic fibers, loose structure, which can affect the structure of aortic media, and make the weakened aorta easy to spontaneously tear and form aortic dissection (25). VSP can not only affect the formation of elastic fibers through Fibulin-5, but also degrade ECM through matrix metalloproteinases (MMPs), destroy elastic fibers and vascular SMCs, damage aortic media and induce aortic dissection (28). The normal physiological structure of ECM must rely on the balance and coordination of MMPs and tissue inhibitors of metalloproteinases (TIMPs), and the imbalance between MMPs and TIMPs will lead to excessive degradation of ECM (29). MMPs is a kind of zinc-dependent endopeptidase protein (30). Only after being activated by enzyme can various components of ECM begin to be degraded, which are secreted in vascular endothelial cells, SMCs, macrophages, neutrophils and so on. MMP2 and MMP9 have been found to be key factors in the occurrence of aortic dissection (31). The expression of MMP9 is regulated by fork head box protein O1 (FOXO1). The expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) is regulated by GATA1. Protein Kinase B (AKT) can phosphorylate FOXO1 and GATA1 and regulate their transcriptional activity to MMP9 and

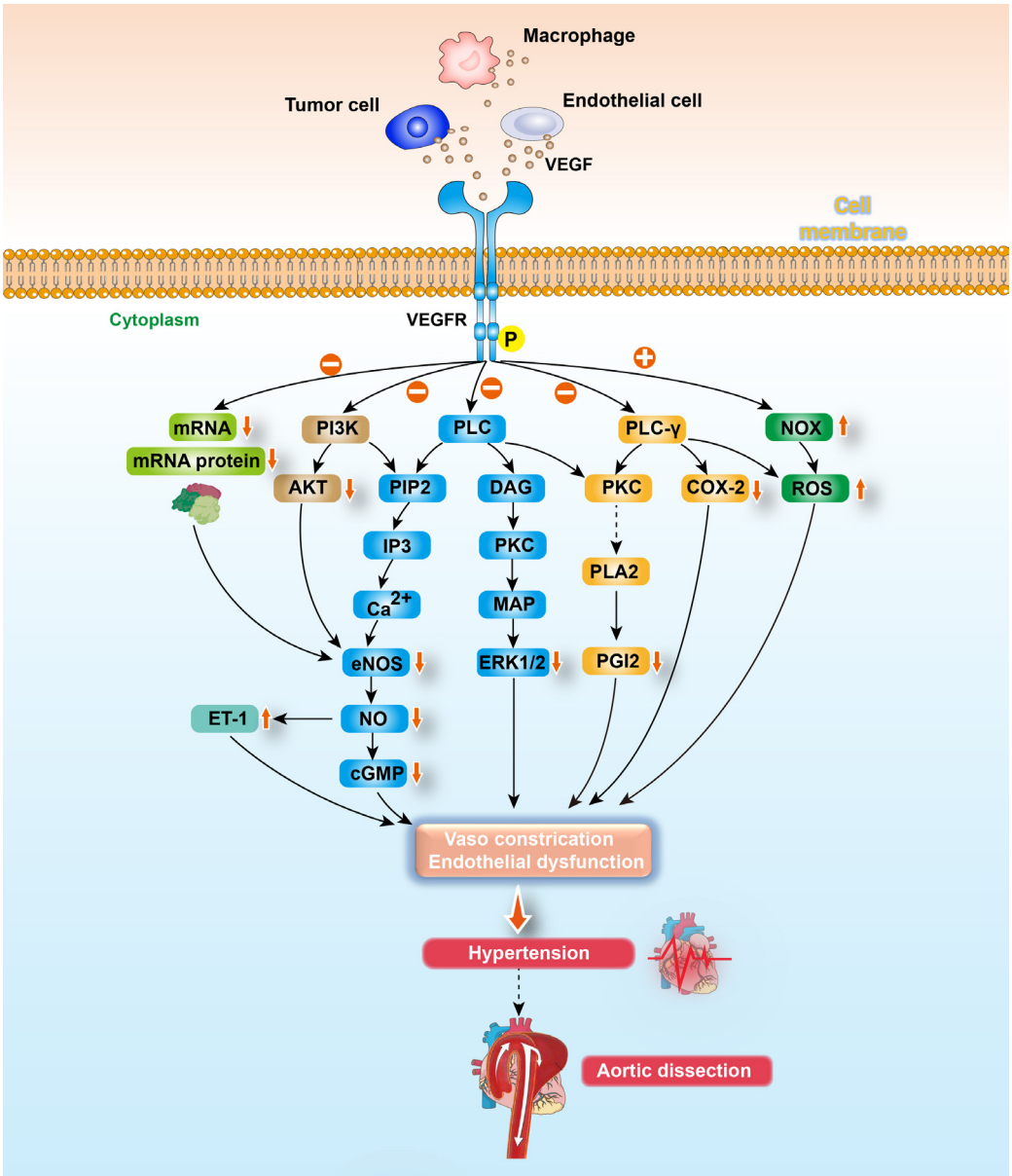

Figure 3 The pathogenesis of VEGF signal inhibition-related hypertension. VEGFR-TKIs can inhibit the activation of many kinases induced by VEGF, decrease the mRNA and protein levels of eNOS, reduce the synthesis of eNOS, PGI2 and COX2, lead to decreased vasodilation, and increase the expression of ET-1 and ROS, leading to vasoconstriction and vascular endothelial cell dysfunction. These signal pathways will eventually lead to hypertension. VEGF, vascular endothelial growth factor; VEGFR-TKIs, vascular endothelial growth factor receptor-tyrosine kinase inhibits; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PGI2, prostacyclin; COX2, cyclooxygenase-2; ET-1, endothelin-1; ROS, reactive oxygen species.

TIMP-1 (*Figure 4*). In Akt-2 gene deficient mice, the expression of MMP9 was significantly increased, the expression of TIMP-1 was significantly decreased, the elastic fibers of aortic wall were abnormal, and the medial thickness was decreased. When challenged with Ang-II, these mice developed aortic aneurysms, dissections, and ruptures similar to those in the human thorax and abdomen (32). At the same time, targeting AKT signal can also inhibit the proliferation and migration of vascular SMCs (33). In addition, inhibition of VSP would impair

Table 1 Cases of aortic dissection during antiangiogenic therapy

Drug class	Agent	Publication time	Region	Authors	Tumor type	History of hypertension	Blood pressure during TKI treatment	Target(s)	Indications	Reference
Tyrosine kinase inhibitor	Sunitinib	2015	Brazil	Formiga *et al.*	Renal cell carcinoma	No	<140/90 mmHg	VEGFR-1, -2, -3; PDGFR; c-Kit; RET; FLT3	Gastrointestinal stromal tumour, renal cell carcinoma, pancreatic neuroendocrine tumour	(13)
	Sunitinib	2010	France	Edeline *et al.*	Renal cell carcinoma	Yes	>140/90 mmHg; long-term control of blood pressure with nebivolol	VEGFR-1, -2, -3; PDGFR; c-Kit; RET; FLT3	Gastrointestinal stromal tumour, renal cell carcinoma, pancreatic neuroendocrine tumour	(14)
	Axitinib	2015	Japan	Niwa *et al.*	Renal cell carcinoma	No	<140/90 mmHg	VEGFR-1, -2, -3; PDGFR; c-Kit	Renal cell carcinoma	(15)
	Anlotinib	2020	China	Jiang *et al.*	Lung squamous cell carcinoma	No	<140/90 mmHg	VEGFR-2, -3; PDGFR; FGFR1-4; c-Kit; RET	Thyroid cancer, renal cell carcinoma, gastric cancer, esophageal squamous cell carcinoma	(16)
	Sorafenib	2017	China	Xu *et al.*	Hepatocellular carcinoma	Yes	>140/90 mmHg; long-term use of calcium channel blockers to lower blood pressure	VEGFR-2, -3; PDGFR; FIT3; c-Kit; Raf	Hepatocellular carcinoma, renal cell carcinoma, melanoma	(17)
	Sunitinib	2017	Canada	Hatem *et al.*	Gastrointestinal stromal tumor	No	<140 mmHg	VEGFR-1, -2, -3; PDGFR; c-Kit; RET; FLT3	Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumour	(18)
	Sorafenib and axitinib	2018	Japan	Takada *et al.*	Renal cell carcinoma	No	<140/90 mmHg; control of blood pressure by irbesartan and azelnidipine	VEGFR-2, -3; PDGFR; FIT3; c-Kit; Raf	Hepatocellular carcinoma, renal cell carcinoma, melanoma	(19)
Monoclonal antibody	Bevacizumab (+ docetaxel, thalidomide, and prednisone)	2008	USA	Aragon-Ching *et al.*	Prostate cancer	Yes	>160/100 mmHg; blood pressure is controlled by diuretics, calcium channel blockers and hydrazine	VEGF-A	Colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical carcinoma	(20)

TKI, tyrosine kinase inhibit.

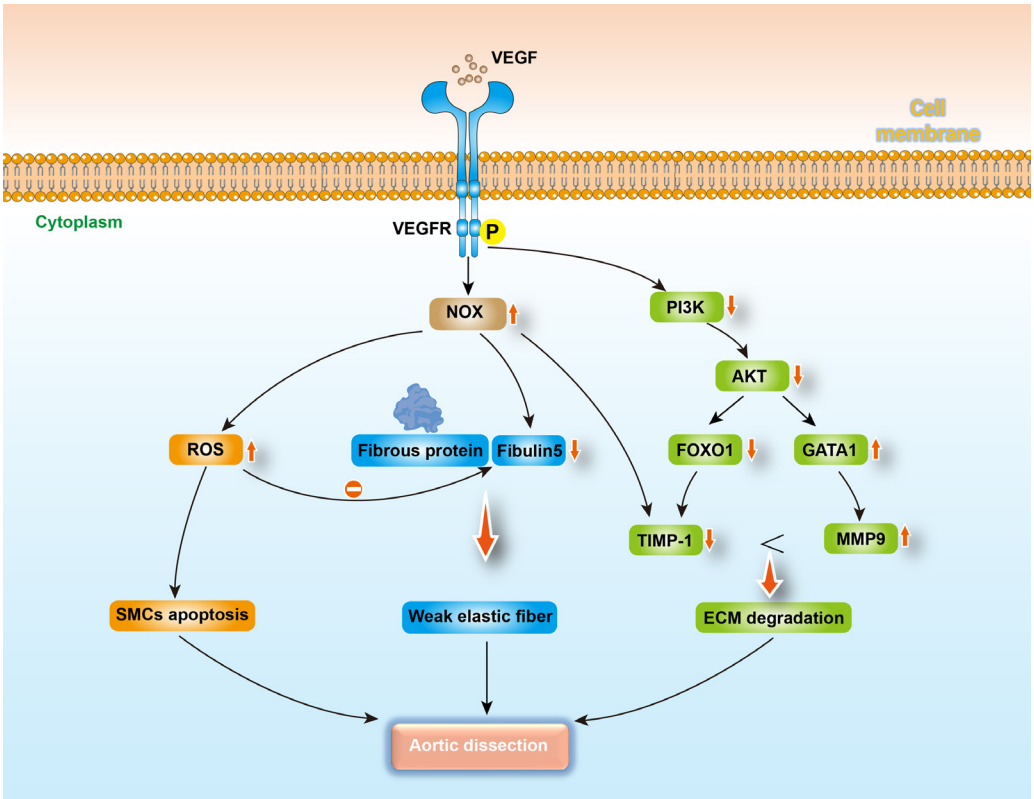

Figure 4 Possible mechanism of aortic dissection induced by VEGF inhibitor. TKIs inhibit the PI3K-AKT signaling pathway and increase the expression of MMP9, thereby breaking the balance of TIMP-1 and MMP9, leading to ECM degradation; inhibiting the VEGF signaling pathway can also induce the activation of NOX and increase the production of ROS, leading to apoptosis of SMCs, and at the same time ROS can also inhibit the binding of Fibulin-5 and elastin, causing the elastic fibers to become weak. VEGF, vascular endothelial growth factor; TKIs, tyrosine kinase inhibits; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; FOXO1, fork head box protein O1; MMP9, matrix metalloproteinase 9; TIMP-1, tissue inhibitor of metalloproteinase-1; ECM, extracellular matrix; NOX, nitric oxide; ROS, reactive oxygen species; SMCs, smooth muscle cell.

nitric oxide-mediated vasodilation, leading to arterial stiffness and making it more prone to aortic dissection (34).

Conclusions

Here, we reported the first case of fruquintinib-associated aortic dissection, and discussed the possible mechanism of VSP inhibitors leading to aortic dissection. As a new drug, fruquintinib brings not only clinical benefits, but also brings some adverse reactions. How to manage these adverse reactions, especially serious cardiovascular toxicity, such as aortic dissection, is still a problem that needs further exploration.

Acknowledgments

Funding: This work was supported by the Key Medical and Health Science and Technology Plan of Zhejiang Province (No. 2023552922).

Footnote

Reporting Checklist: The authors have completed the CARE

reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1872/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1872/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1872/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. All procedures performed in this study were in accordance with the ethical standards of the Zhejiang Provincial People's Hospital research committee(s) (approval No. QT2022269) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin 2017;67:177-93.
3. Sun Q, Zhou J, Zhang Z, et al. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. Cancer Biol Ther 2014;15:1635-45.
4. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA 2018;319:2486-96.
5. Herrera A, Herrera M, Guerra-Perez N, et al. Endothelial cell activation on 3D-matrices derived from PDGF-BB-stimulated fibroblasts is mediated by Snail1. Oncogenesis 2018;7:76.
6. Ronca R, Giacomini A, Rusnati M, et al. The potential of fibroblast growth factor/fibroblast growth factor receptor signaling as a therapeutic target in tumor angiogenesis. Expert Opin Ther Targets 2015;19:1361-77.
7. Neves KB, Rios FJ, van der Mey L, et al. VEGFR (Vascular Endothelial Growth Factor Receptor) Inhibition Induces Cardiovascular Damage via Redox-Sensitive Processes. Hypertension 2018;71:638-47.
8. Liu Q, Huang X, Zhang H, et al. c-kit(+) cells adopt vascular endothelial but not epithelial cell fates during lung maintenance and repair. Nat Med 2015;21:866-8.
9. Oshima Y, Tanimoto T, Yuji K, et al. Association Between Aortic Dissection and Systemic Exposure of Vascular Endothelial Growth Factor Pathway Inhibitors in the Japanese Adverse Drug Event Report Database. Circulation 2017;135:815-7.
10. HIRST AE Jr, JOHNS VJ Jr, KIME SW Jr. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine (Baltimore) 1958;37:217-79.
11. Nienaber CA, Clough RE, Sakalihasan N, et al. Aortic dissection. Nat Rev Dis Primers 2016;2:16053.
12. Olsson AK, Dimberg A, Kreuger J, et al. VEGF receptor signalling - in control of vascular function. Nat Rev Mol Cell Biol 2006;7:359-71.
13. Formiga MN, Fanelli MF. Aortic dissection during antiangiogenic therapy with sunitinib. A case report. Sao Paulo Med J 2015;133:275-7.
14. Edeline J, Laguerre B, Rolland Y, et al. Aortic dissection in a patient treated by sunitinib for metastatic renal cell carcinoma. Ann Oncol 2010;21:186-7.
15. Niwa N, Nishiyama T, Ozu C, et al. Acute aortic dissection in a patient with metastatic renal cell carcinoma treated with axitinib. Acta Oncol 2015;54:561-2.
16. Jiang B, Li J, Chen J, et al. Aortic dissection in a patient treated with anlotinib for metastatic lung squamous cell carcinoma. Thorac Cancer 2020;11:461-4.
17. Xu L, Wang B, Ding W. Abdominal aortic dissection during sorafenib therapy for hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2017;41:e24-5.
18. Hatem R, Bebawi E, Schampaert E. Potential Sunitinib-Induced Coronary Artery and Aortic Dissections. Can J Cardiol 2017;33:830.e17-8.

19. Takada M, Yasui T, Oka T, et al. Aortic Dissection and Cardiac Dysfunction Emerged Coincidentally During the Long-Term Treatment with Angiogenesis Inhibitors for Metastatic Renal Cell Carcinoma. Int Heart J 2018;59:1174-9.
20. Aragon-Ching JB, Ning YM, Dahut WL. Acute aortic dissection in a hypertensive patient with prostate cancer undergoing chemotherapy containing bevacizumab. Acta Oncol 2008;47:1600-1.
21. He R, Guo DC, Estrera AL, et al. Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. J Thorac Cardiovasc Surg 2006;131:671-8.
22. Guzik B, Sagan A, Ludew D, et al. Mechanisms of oxidative stress in human aortic aneurysms--association with clinical risk factors for atherosclerosis and disease severity. Int J Cardiol 2013;168:2389-96.
23. Thomas M, Gavrila D, McCormick ML, et al. Deletion of p47phox attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein E-deficient mice. Circulation 2006;114:404-13.
24. Griendling KK, Ushio-Fukai M. Redox control of vascular smooth muscle proliferation. J Lab Clin Med 1998;132:9-15.
25. Hu X, Jiang W, Wang Z, et al. NOX1 Negatively Modulates Fibulin-5 in Vascular Smooth Muscle Cells to Affect Aortic Dissection. Biol Pharm Bull 2019;42:1464-70.
26. Nakamura T, Lozano PR, Ikeda Y, et al. Fibulin-5/DANCE is essential for elastogenesis in vivo. Nature 2002;415:171-5.
27. Wang X, LeMaire SA, Chen L, et al. Decreased expression of fibulin-5 correlates with reduced elastin in thoracic aortic dissection. Surgery 2005;138:352-9.
28. Kim J, Lee J. Matrix metalloproteinase and tissue inhibitor of metalloproteinase responses to muscle damage after eccentric exercise. J Exerc Rehabil 2016;12:260-5.
29. Vianello E, Dozio E, Rigolini R, et al. Acute phase of aortic dissection: a pilot study on CD40L, MPO, and MMP-1, -2, 9 and TIMP-1 circulating levels in elderly patients. Immun Ageing 2016;13:9.
30. Aziz F, Kuivaniemi H. Role of matrix metalloproteinase inhibitors in preventing abdominal aortic aneurysm. Ann Vasc Surg 2007;21:392-401.
31. Maguire EM, Pearce SWA, Xiao R, et al. Matrix Metalloproteinase in Abdominal Aortic Aneurysm and Aortic Dissection. Pharmaceuticals (Basel) 2019;12:118.
32. Shen YH, Zhang L, Ren P, et al. AKT2 confers protection against aortic aneurysms and dissections. Circ Res 2013;112:618-32.
33. Poon M, Marx SO, Gallo R, et al. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277-83.
34. Bonnet C, Sibon I. Potential role of anti-VEGF targeted therapies in cervical artery dissection: A case report. Rev Neurol (Paris) 2015;171:677-9.

Cite this article as: Deng YY, Chen YW, Wang MX, Zhu PF, Pan SY, Jiang DY, Chen ZL, Yang L. Acute aortic dissection caused by fruquintinib for metastatic colorectal cancer—a case report and literature review. Transl Cancer Res 2023;12(1):177-185. doi: 10.21037/tcr-22-1872

Supplementary

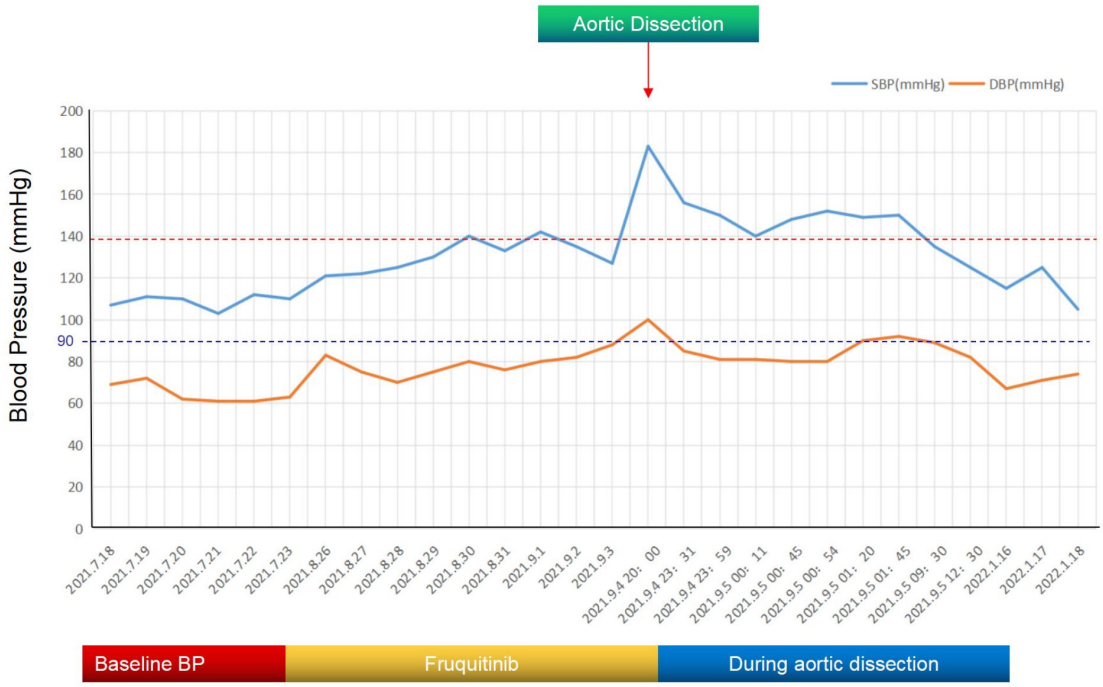

Figure S1 Blood pressure fluctuation during treatment (red dotted line: upper limit of normal systolic blood pressure; blue dotted line: upper limit of normal diastolic pressure). BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S1 The probability of fruquintinib and aortic dissection was scored by Naranjo probability scale

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	–1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	–1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	–1	+2	0	2
6. Did the reaction reappear when a placebo was given?	–1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
			Total score: 6	

https://dx.doi.org/10.21037/tcr-22-1872

Table S2 Adverse drug reaction probability classification

Score	Interpretation of scores
Total score ≥9	Definite. The reaction (I) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (II) followed a recognized response to the suspected drug, and (III) was confirmed by improvement on withdrawing the drug and reappeared on reexposure
Total score 5 to 8	Probable. The reaction (I) followed a reasonable temporal sequence after a drug, (II) followed a recognized response to the suspected drug, (III) was confirmed by withdrawal but not by exposure to the drug, and (IV) could not be reasonably explained by the known characteristics of the patient's clinical state
Total score 1 to 4	Possible. The reaction (I) followed a temporal sequence after a drug, (II) possibly followed a recognized pattern to the suspected drug, and (III) could be explained by characteristics of the patient's disease
Total score ≤0	Doubtful. The reaction was likely related to factors other than a drug

https://dx.doi.org/10.21037/tcr-22-1872