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Case Report
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Regorafenib-Related Myocardial Injury during Atrial Fibrillation

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Multikinase inhibitors with an anti-vascular endothelial growth factor effect have been reported to increase the risk of myocardial infarction or ischemia. We have presented the case of a 72-year-old male who had a metastatic gastrointestinal stromal tumor for which he received targeted therapy and who was admitted to our hospital for recurrent episodes of myocardial injury during atrial fibrillation. Coronary angiography showed insignificant coronary artery stenosis. We also reviewed the incidence of cardiovascular events in patients receiving regorafenib, and the current understanding of the mechanism of targeted therapy-induced myocardial ischemia/infarction.

Key Words: Multikinase inhibitor • Myocardial infarction • Myocardial ischemia • Vascular endothelial growth factor

INTRODUCTION

Regorafenib is an oral multikinase inhibitor which blocks the activity of protein kinases involved in tumor angiogenesis, oncogenesis, and the tumor microenvironment.[1] Randomized trials have shown that regorafenib therapy prolongs overall and progression-free survival in patients with metastatic colorectal cancer,[2] and progression-free survival in patients with a metastatic or unresectable gastrointestinal stream tumors (GISTs).[3] However, regorafenib has several relatively uncommon adverse effects including myocardial infarction and ischemia, the mechanism of which is not fully understood. Herein, we have presented a case of recurrent myocardial infarction/injury during atrial fibrillation in a patient receiving regorafenib.

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CASE REPORT

A 72-year-old male with a metastatic GIST presented to our hospital due to acute onset of chest pain for 30 minutes without elevated blood pressure. Palpitation, dizziness, cold sweating, and breathlessness were also reported. Electrocardiography (EKG) showed atrial fibrillation with a rapid ventricular rate, ST-segment elevation in lead aVR, and diffuse ST-segment depression in leads I, aVL, II, aVF, and V3-6 (Figure 1A). Initially, amiodarone was infused. However, due to unstable hemodynamics he was electrically cardioverted to a sinus rhythm. Blood tests showed a myocardial troponin-I level of 0.03 ng/mL initially, and 3.48 ng/mL 8 hours later. The peak total creatine phosphokinase level was 271 U/L with 6.6% of the MB form. Follow-up EKG showed a sinus rhythm and complete remission of the ischemic change (Figure 1B). Coronary angiography 5 days after presentation disclosed coronary artery disease without significant stenosis (Figure 2). Regorafenib was discontinued, and we prescribed aspirin, amiodarone, losartan, and lercanidipine after the patient was discharged.

A small bowel GIST with multiple liver metastases was first diagnosed in this patient in May 2009, present-

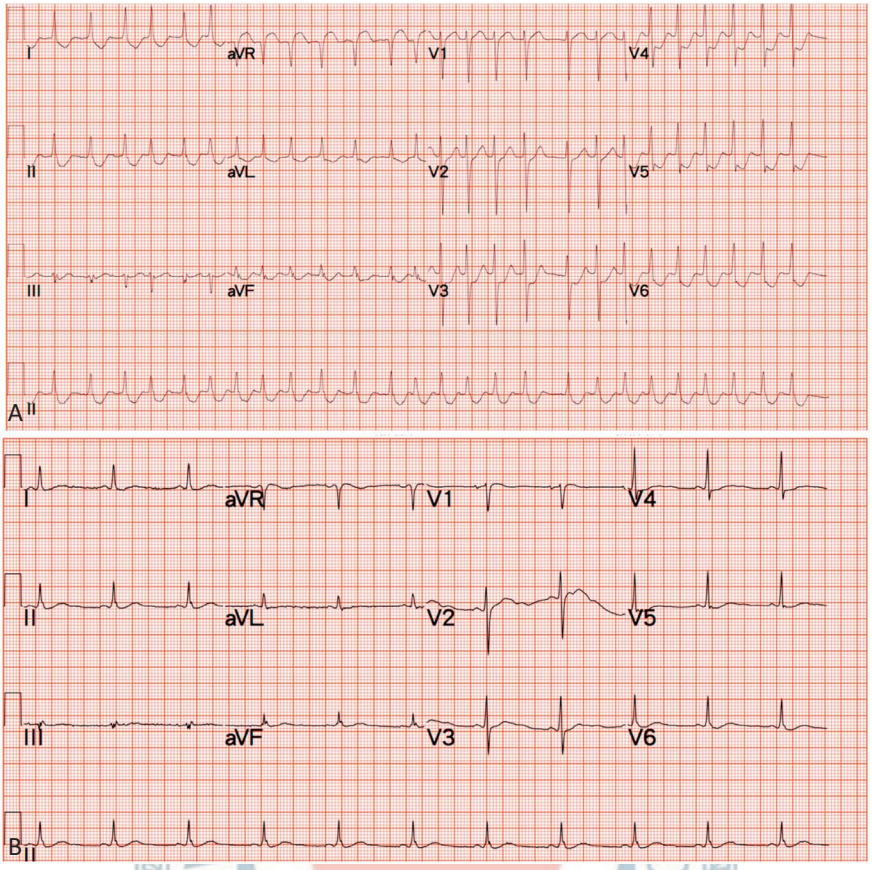

Figure 1. *(A) Electrocardiography on presentation showed atrial fibrillation with a rapid ventricular rate, ST segment elevation in lead aVR, diffuse ST segment depression and T wave inversion. (B) Remission of the ischemic change on electrocardiography before discharge.*

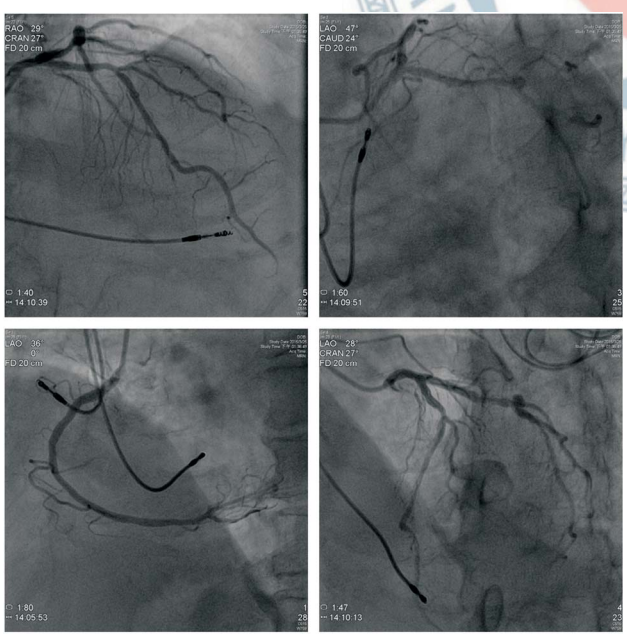

Figure 2. *Coronary angiography. Insignificant stenosis on proximal left anterior descending and left circumflex arteries.*

ing with tarry stools. Nilotinib therapy was commenced in July 2009, with a partial response initially. However, disease progression was documented 1 year later, and imatinib monotherapy was started in December 2010. Thereafter, the tumor regressed with stationary disease until 2014. Disease progression with recurrent gastrointestinal bleeding was reported in March 2014, and he then received laparoscopic jejunal tumor resection. Regorafenib monotherapy was started in May 2014, and his latest abdominal computed tomography scan in March 2015 showed disease progression.

His risk factors for atherosclerotic cardiovascular disease included male gender, age, well-controlled hypertension, and smoking, of which hypertension was noted after receiving targeted therapy. He stated that none of his close relatives suffered from cardiovascular disease. Tracing back his medical history, we found another two episodes with similar presentations, the first in April 2010 with acute onset of chest pain, paroxysmal

atrial fibrillation with a rapid ventricular rate and positive cardiac biomarkers (Table 1) while receiving nilotinib; the second episode occurred in June 2014 while receiving regorafenib. Coronary angiography at that time also showed no significant coronary stenosis. In addition, a long pause was documented in June 2014 following termination of atrial fibrillation, for which a dual chamber pacemaker had been implanted. Myocardial perfusion studies with dipyridamole pharmacological stress were negative for ischemia or infarction in May 2010 and March 2014.

Table 1. Creatine phosphokinase and MB form level in the three cardiac events

March 2015	0 hour	8 hours	16 hours
Total CPK (U/L)	156	271	198
MB	0%	6.6%	10.4%
June 2014	0 hour	8 hours	16 hours
Total CPK (U/L)	232	320	285
MB	7.2%	7.7%	6.0%
April 2010	0 hour	8 hours	16 hours
Total CPK (U/L)	126	213	162
MB	9.3%	2.6%	2.8%

CPK, creatine phosphokinase.

DISCUSSION

Regorafenib is a multikinase inhibitor that targets various types of kinases including VEGFR1-3, PDGFR-beta, TIE2, and RTKs.[1] After the CORRECT[2] and the GRID[3] trials, regorafenib was approved for previously treated metastatic colorectal cancer and unresectable or imatinib/sunitinib refractory GISTs. As with other anti-angiogenic agents, regorafenib is cardiotoxic,[4] with the most common cardiovascularly adverse event being hypertension. The reported incidence rates of all-grade and high-grade hypertension are 44.4% and 12.5%, respectively.[5] Myocardial ischemia and infarction are uncommon adverse effects. A recent meta-analysis found that the use of vascular endothelial growth factor receptor tyrosine kinase inhibitor (including sorafenib, sunitinib, axitinib, pazopanib, and vandetanib) significantly increase the risk of cardiac ischemia/infarction.[6] In the CORRECT[2] trial, regorafenib was also reported to increase the incidence of myocardial ischemia and infarction (1.2% for regorafenib-treated patients vs. 0.4% for placebo-treated patients). Nilotinib has also been reported to be associated with myocardial infarction.[7] Koch's postulates are typically used to prove this strongly relationship between regorafenib and myocardial injury.

The mechanism of regorafenib and other multikinase inhibitor-related myocardial infarction or ischemia is not completely understood. Endothelial dysfunction, vasoconstriction, promotion of thromboembolism, induction of hypertension, reduction in cardiac capillary density, local tissue hypoxia, and micro-thromboembolism may all be involved in the pathophysiology.[8] At the molecular level, complex on-target and off-target effects involving calcium handling, nitric oxide synthesis, metabolic homeostasis, mitochondrial function, and cellular apoptosis have been reported.[9,10]

In the present case, recurrent myocardial ischemia and injury were confirmed by clinical symptoms, electrocardiography, and positive cardiac biomarkers.

Electrocardiographic testing indicated that the involved myocardial segment was extensive, suggesting global ischemia. In the absence of significant coronary stenosis, the recurrent myocardial ischemia/injury may have been related to myocardial microvascular thrombosis or coronary spasms, which may have been related to the targeted therapy. In addition, the sinus node dysfunction requiring a pacemaker may have resulted from micro-thromboembolism involving the sinoatrial nodal artery. These pathophysiological changes probably led to his heart being in a more vulnerable status to increased oxygen demand, such as tachyarrhythmia. The myocardial perfusion study was negative, probably arising from the global natural myocardial involvement but not coronary artery stenosis-related regional ischemia.

In conclusion, myocardial infarction or ischemia is an uncommon side effect of multikinase inhibitor treatment. It can lead to deterioration in the health status of cancer patients and also to the discontinuation of cancer treatment. Cardiologists should be aware that myocardial infarction or ischemia with angiographically normal coronary arteries could be an adverse effect of targeted therapy.

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