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Fulminant Vascular and Cardiac Toxicity Associated with Tyrosine Kinase Inhibitor Sorafenib

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Abstract

The use of vascular endothelial growth factor inhibitors such as sorafenib is limited by a risk of severe cardiovascular toxicity. A 28-year-old man with acute myeloid leukemia treated with prednisone, tacrolimus, and sorafenib following stem cell transplantation presented with severe bilateral lower extremity claudication. The patient was discharged against medical advice prior to finalizing a cardiovascular evaluation, but returned 1 week later with signs suggestive of septic shock. Laboratory tests revealed troponin I of 12.63 ng/mL, BNP of 1690 pg/mL, and negative infectious workup. Electrocardiogram showed sinus tachycardia and new pathologic Q waves in the anterior leads. Coronary angiography revealed severe multivessel coronary artery disease. Peripheral angiography revealed severely diseased left anterior and posterior tibial arteries, tibioperoneal trunk, and peroneal artery, and subtotal occlusion of the right posterior tibial artery. Multiple coronary and peripheral drug-eluting stents were implanted. An intra-aortic balloon pump was placed. Cardiac magnetic resonance imaging revealed chronic left ventricular infarction with some viability, 17% ejection fraction, and left ventricular mural thrombi. The patient opted for medical management. Persistent symptoms 9 months later led to repeat angiography, showing total occlusion of the second obtuse marginal artery due to in-stent restenosis with proximal stent fracture, and chronic total occlusion of the right internal iliac artery extending to the pudendal branch. Cardiac positron emission tomography/computed tomography viability study demonstrated viable myocardium, deeming revascularization appropriate. Symptom resolution was obtained with no recurrences. Sorafenib-associated vasculopathy may follow a fulminant course. Multimodality cardiovascular imaging is essential for optimal management.

Keywords Cardio-Oncology · Cardiotoxicity · Coronary artery disease · Sorafenib · Tyrosine kinase inhibitors · Vasculopathy

Introduction

Novel angiogenesis inhibitors, such as the tyrosine kinase and vascular endothelial growth factor (VEGF) inhibitor sorafenib, are increasingly and effectively used in the treatment of various types of cancer [1]. Unfortunately, these agents are associated with significant cardiovascular toxicity, including hypertension, heart failure, cardiomyopathy, arrhythmias, thromboembolic events, acute coronary syndromes, and myocardial infarction [1–5]. The proposed pathogenic mechanism of sorafenib cardiotoxicity is myocyte necrosis, an effect which amplifies the risk of death following a myocardial infarction [6]. Although it has been reported that the cardiac side effects associated with sorafenib may be transient and therapy can sometimes be resumed [7, 8], patients may also suffer from severe, life-threatening cardiotoxic events [9].

We present the case of a young man with acute myeloid leukemia (AML) who was treated with sorafenib following stem cell transplantation. He experienced severe cardiovascular toxicity, with diffuse coronary and peripheral arterial

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dysfunction which were resistant to treatment, despite the discontinuation of sorafenib.

Case Report

A 28-year-old man with a past medical history of AML (FLT3 positive with RUNX1 mutation) diagnosed 4 years ago presented for management of hypertension. His AML was initially treated with a "7 + 3" chemotherapy regimen (consisting of 7 days of standard-dose cytarabine plus 3 days of idarubicin, 12 mg/m^2). Due to persistent blasts, he received four cycles of high-dose cytarabine (3 g/m^2) as consolidation therapy. His AML recurred 9 months later and was treated with three cycles of azacitidine (75 mg/m^2) and quizartinib (60 mg) and matched-unrelated donor stem cell transplantation, conditioned with busulfan (6000 μMol min every 24 h for four consecutive days), fludarabine (40 mg/m^2 for four consecutive days), and anti-thymocyte globulin (0.5 mg/kg for 3 days). The transplant was complicated by graft-versus-host disease (GVHD) with gastrointestinal and cutaneous involvement, for which the patient received extracorporeal photophoresis twice weekly. He was also treated with tacrolimus (for 18 months), chronic prednisone (which led to the development of adrenal insufficiency, steroid-induced hyperglycemia, and bilateral femoral avascular necrosis requiring left total hip replacement), and maintenance sorafenib at a reduced dose of 200 mg/day (the maximum tolerated dose, due to the history of GVHD and concern for worsening of the rash). Hypertension was diagnosed several months after the transplant, while he was on high-dose prednisone for GVHD (which was controlled), and was treated with steroid tapering and amlodipine 10 mg/day. No other cardiac history or risk factors were present and baseline (1 month prior to starting sorafenib) chest computed tomography showed no coronary calcium. A few months later, the patient presented to the emergency department with complaints of bilateral lower extremity claudication after walking 50–75 yards and severe temporal and jaw pain while masticating. The Ankle-Brachial Index was 0.78 on the right and 0.74 on the left, while the Toe-Brachial Index was 0.82 on the right and 0.66 on the left, suggesting moderate bilateral arterial occlusive disease, but normal distal flow. Sorafenib was discontinued (after a total duration of 3 years of treatment) and conservative management was recommended, including aspirin, statin, and exercise. The patient was discharged against medical advice prior to finalizing a comprehensive cardiovascular evaluation.

One week later, he returned with fever, headache, anorexia, nausea, vomiting, non-productive cough, and exertional substernal chest pressure. Vital signs were blood pressure of 89/54 mm Hg, heart rate of 112 beats per minute, and respiratory rate of 24 breaths per minute, non-responsive to volume resuscitation, suggestive of septic shock. He admitted to contact with his child, who recently had a viral upper respiratory tract infection. Blood tests revealed a white blood cell count of 6200 μL with left shift, platelet count of 93,000 μL, serum lactate of 0.6 mmol/L, troponin I of 12.63 ng/mL, BNP of 1690 pg/mL, and negative infectious workup (including blood, urine, and sputum culture, respiratory and cardiotropic viral panel, and opportunistic pathogen panel). Electrocardiogram showed sinus tachycardia and new pathologic Q waves in the anterior leads (Fig. 1a). A computed tomography angiogram was negative for pulmonary embolism and showed multilobar groundglass opacities. Transthoracic echocardiogram revealed dilated cardiomyopathy with severely reduced ejection fraction (EF) (< 20%), normal ventricular wall mass, and mid-to-distal wall akinesis. The patient was transferred to the intensive care unit and started on an acute coronary syndrome protocol with heparin drip, inotropic support with dopamine drip, and empiric broad-spectrum antimicrobials. Emergent coronary angiography revealed severe multivessel coronary artery disease with significant stenoses of the proximal-to-distal left anterior descending (LAD) artery, including the first diagonal (D1), and of a large bifurcating obtuse marginal (OM) 2 artery (Fig. 1b1–b2). Peripheral angiogram of the lower extremities revealed chronic total occlusion (CTO) of the left proximal anterior tibial artery, significant stenoses of the left tibioperoneal trunk and left proximal posterior tibial artery (Fig. 1d1), CTO of the left proximal peroneal artery, and 99% subtotal occlusion of the right posterior tibial artery. Right heart catheterization showed elevated intracardiac filling pressures (mean right atrial pressure 14 mm Hg, mean pulmonary artery pressure 32 mm Hg, pulmonary capillary wedge pressure 32 mm Hg) and Low Cardiac Index (2.12 L/min/m^2). Percutaneous coronary intervention with implantation of a 2.5 × 28 mm Synergy (Boston Scientific, Marlborough, MA) drug-eluting stent (DES) in the OM2 was performed. A 2.5 × 38 mm and a 2.5 × 20 mm Synergy DES were implanted in the left tibioperoneal trunk and posterior tibial artery, respectively (Fig. 1 d2). Two 2.5 × 20 mm Synergy DES were implanted in the right posterior tibial artery. An intra-aortic balloon pump (IABP) was placed and diuresis was initiated with furosemide drip. Cardiac magnetic resonance imaging was performed for myocardial viability testing and to evaluate for myocarditis, revealing chronic left ventricular (LV) infarction with some viability, an EF of 17%, and the presence of LV mural thrombi (Fig. 2a).

Over a prolonged hospital stay, the patient's condition decompensated twice after removal of the IABP and he remained inotrope dependent, New York Heart Association Class III-IV, and Interagency Registry for Mechanically Assisted Circulatory Support Profile 3. The Advanced Heart Failure service did not deem him to be a candidate for further revascularization, either percutaneously or surgically.

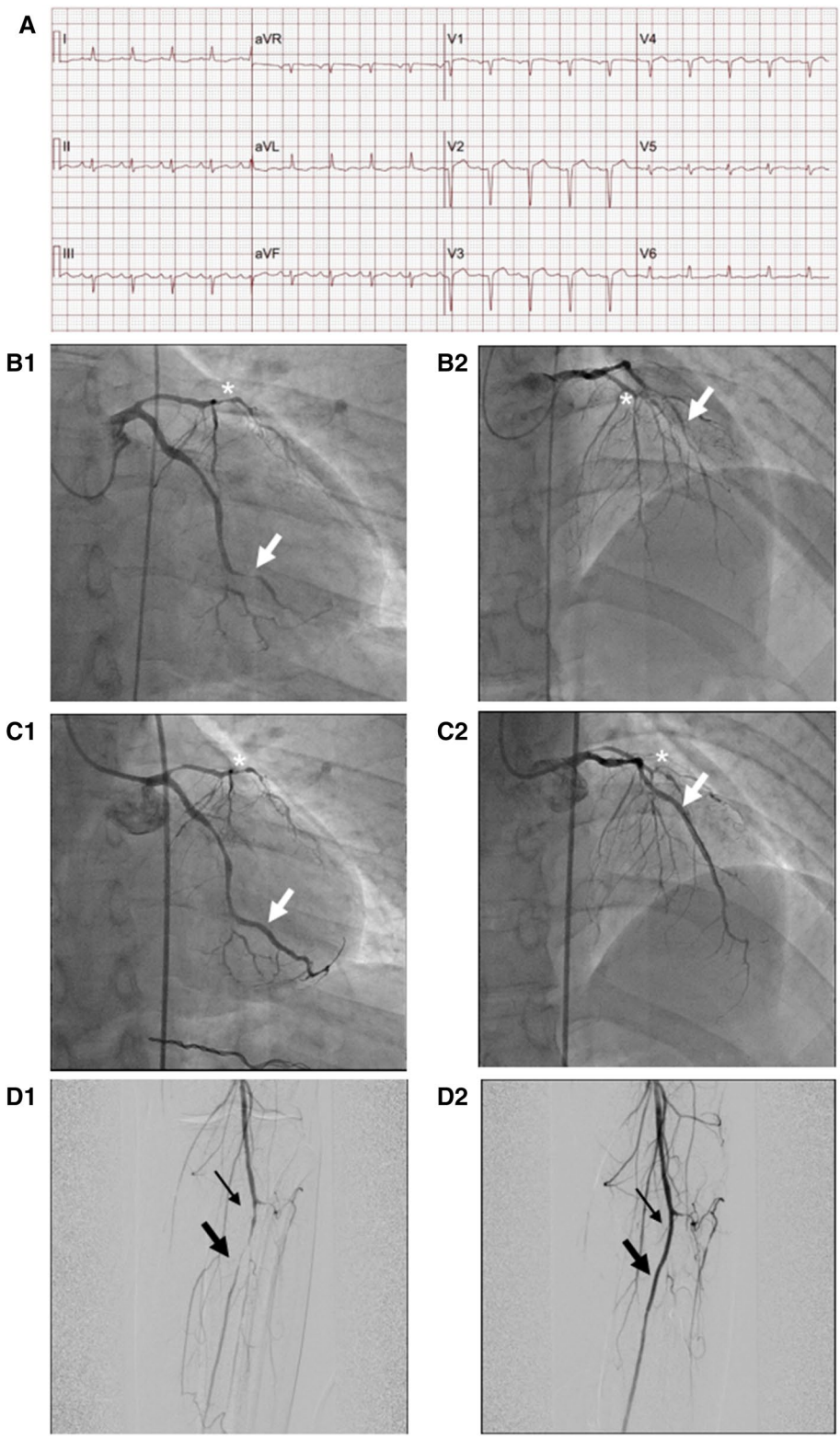

Fig. 1 Electrocardiogram and angiography in a young patient with sorafenib-induced vasculopathy. Electrocardiogram revealing sinus tachycardia and new pathologic Q waves in the anterior leads **a**. Coronary angiogram showing 70–85% stenosis of the proximal-to-distal left anterior descending (LAD) artery, including the first diagonal (asterisks), and a left circumflex (LCx) artery giving rise to a small obtuse marginal (OM) one artery and a long and large bifurcating OM2 with an 80–90% proximal stenosis and 85% tubular stenosis of the proximal right posterior atrioventricular and proximal posterolateral arteries (arrows) **b1, b2** Percutaneous coronary intervention with implantation of a 2.5 × 28 mm drug-eluting stent (DES) in the OM2 was performed (**c1, c2**) asterisks at LAD, arrows at stent. Peripheral angiogram of the lower extremities revealing chronic total occlusion of the left proximal anterior tibial artery, 80% stenosis of the left tibioperoneal trunk (thin arrow), 99% stenosis of the left proximal posterior tibial artery (thick arrow) (**d1**). A 2.5 × 38 mm DES was implanted in the left tibioperoneal trunk (thin arrow); a 2.5 × 20 mm DES was implanted in the posterior tibial artery (thick arrow) (**d2**)

His active malignancy made him ineligible for heart transplantation. Evaluation for implantation of a LV assist device as destination therapy was considered, but the patient opted instead for a trial of medical management. He was eventually successfully weaned off inotropic agents and discharged on guideline-directed medical therapy for heart failure and a LifeVest wearable defibrillator (Zoll Medical Corporation, Chelmsford, MA). As an outpatient, he maintained cardiac

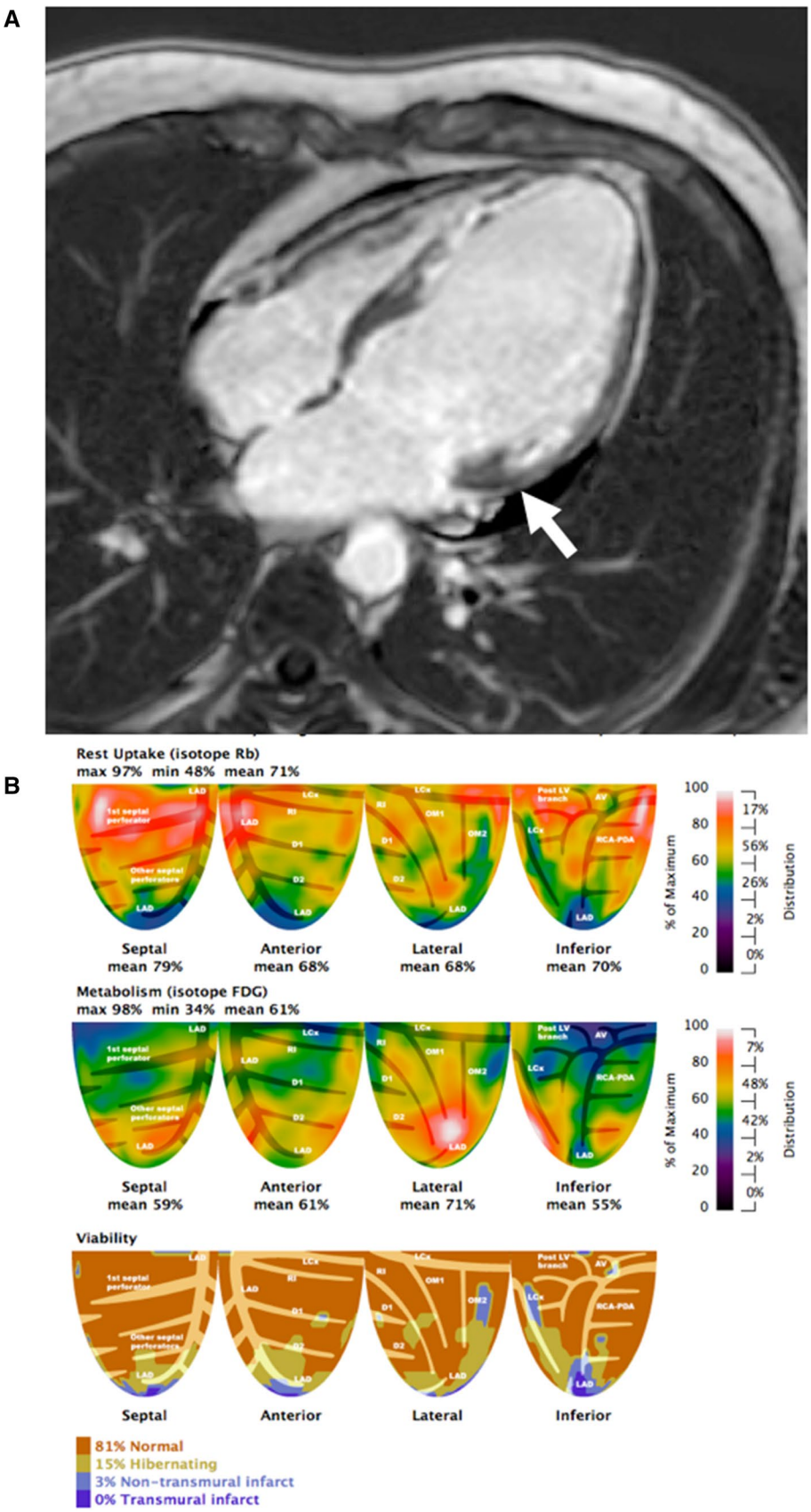

Fig. 2 Cardiac magnetic resonance imaging and cardiac positron emission tomography/computed tomography viability study in a young patient with sorafenib-induced vasculopathy. Cardiac magnetic resonance imaging revealed chronic left ventricular infarction with some viability, an ejection fraction of 17%, and the presence of LV mural thrombi (arrow) (**a**). Cardiac positron emission tomography/computed tomography viability study demonstrated viable myocardium, except for several small non-transmural scars (**b**)

rehabilitation and was adherent to medical therapy, but had persistent systolic dysfunction, which imposed placement of a single-chamber implantable cardioverter defibrillator for primary prevention of sudden cardiac death.

Nine months later, the patient complained of persistent exertional dyspnea and claudication after walking 30 feet. Coronary and peripheral angiographies were repeated, showing CTO of the distal LAD, 85% stenosis of the D1, total occlusion of OM2 due to in-stent restenosis with proximal stent fracture, and CTO of the right internal iliac artery extending to the pudendal branch. Cardiac positron emission tomography/computed tomography (PET/CT) viability study demonstrated viable myocardium, except for several small non-transmural scars (Fig. 2b). Severe hypokinesis of the inferolateral wall and apex was observed, with an EF of 30%. Given the systolic dysfunction with primarily viable myocardium, revascularization was deemed appropriate. The patient underwent laser atherectomy and balloon angioplasty of the OM2 and the right internal iliac and pudendal arteries. The procedure was followed by symptom resolution, with no further recurrences after 4 months.

Discussion

Although VEGF inhibitor-associated vascular damage is established, this is, to the best of our knowledge, the first report of a fulminant evolution, with severely diseased, multiple vascular territories leading to ischemic cardiomyopathy in a young patient with no risk factors. Despite discontinuation of sorafenib and complex cardiovascular therapy with multiple DES implantations, his condition was resistant and recurred. A comprehensive cardiovascular evaluation, which included cardiac PET/CT, guided clinical decision-making and allowed for optimal risk assessment and management, eventually leading to symptom resolution.

Despite a theoretical concern for endothelial dysfunction associated with GVHD that could translate to vasculopathy, data on this issue are limited. Sorafenib, on the other hand, has well-described vascular toxicities imposing cardiovascular assessment. Cardiovascular comorbidities in cancer patients are multifactorial and often attributed to the cancer itself or the anti-cancer treatment. In our patient, it is likely that both GVHD and the history of multiple chemotherapies augmented the role of sorafenib as a vascular offender. Sorafenib is currently approved for the treatment of advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and radioactive iodine-resistant thyroid carcinoma. Its off-label use as maintenance therapy in AML post-allogeneic stem cell transplantation (as was the case for our patient) is derived from its ability to inhibit FLT3 tyrosine kinase, in which mutations are associated with higher relapse rates even after transplantation [10]. The mechanism of action is inducing vasculopathy in tumor vessels, causing ischemia and eventual tumor necrosis [11, 12]. It can also increase vascular tone leading to dysregulated vasoconstriction and endothelial injury over time [13]. Among TK inhibitors, sorafenib may be associated with a higher relative risk of cardiac ischemia [14]. Reports of acute coronary vasospasm associated with sorafenib resulting in myocardial infarction have been published [15]. As it remains on the market and is being prescribed as long-term cancer therapy, there is increasing recognition of its cardiovascular toxicity, even with lower doses and especially in patients with pre-existing cardiac disease [1]. Vasodilator agents such as nifedipine may be useful for managing some sorafenib-associated events, such as hypertension or cutaneous vasculopathy, and may even prevent the development of coronary and peripheral arterial disease [16]. If baseline risk is high, it is appropriate to consider early cardiac follow-up in the first 2–4 weeks after therapy initiation, with regular cardiac biomarker measurement and biannual echocardiography [5].

Conclusion

The vasculopathy associated with sorafenib (and possibly other VEGF inhibitors) may follow a fulminant course, even in young patients with otherwise no cardiovascular risk. This condition may be recurrent and resistant to treatment, requiring multiple interventions and complex cardiovascular therapy. A multidisciplinary approach and multimodality cardiovascular imaging aid in risk assessment and guide optimal management. The use of multiple cardiotoxic drugs should be accompanied by regular cardiac monitoring, even in patients otherwise at low-risk for cardiovascular disease.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from the patient presented in this work.

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